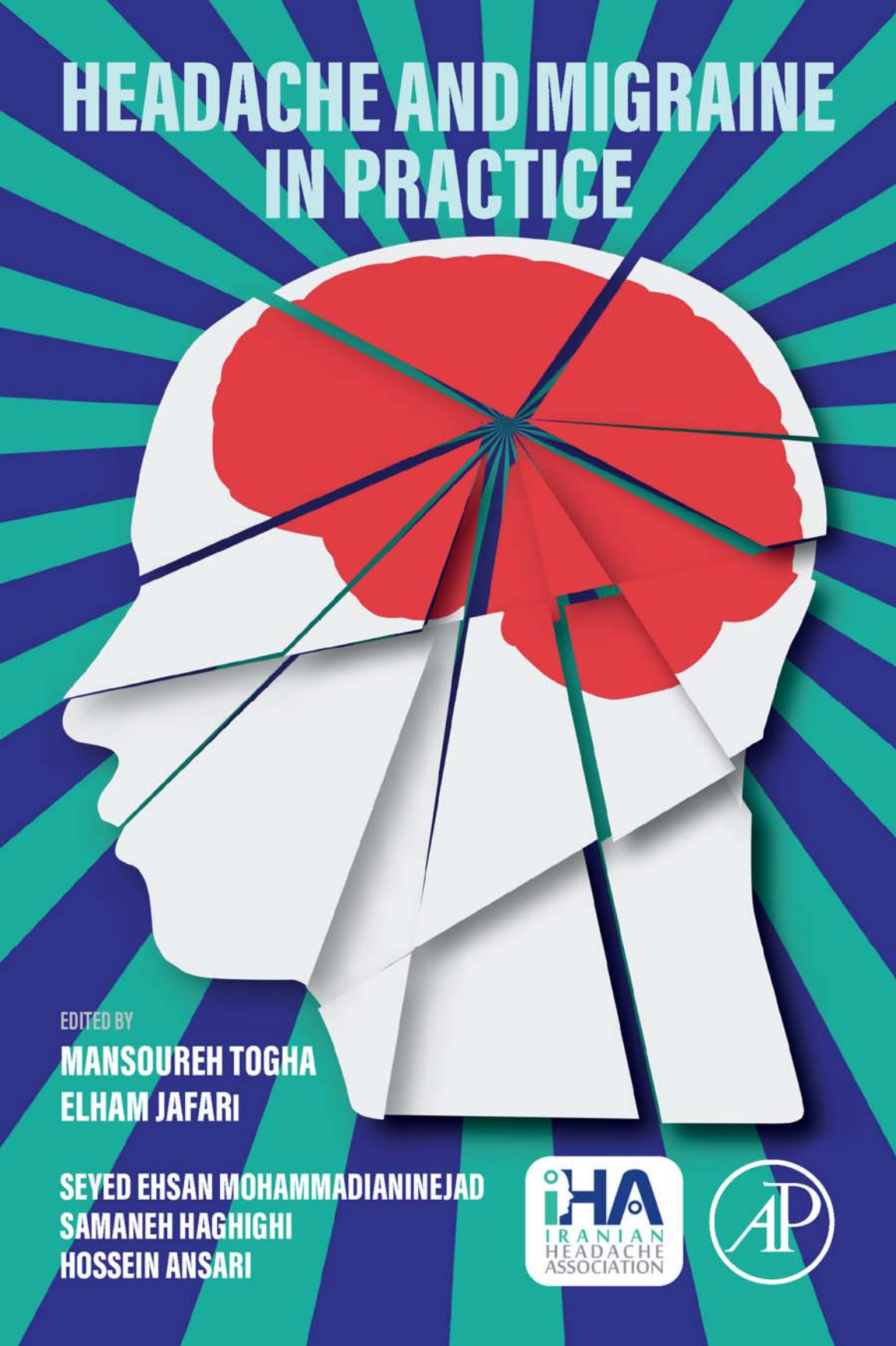
HEADACHE AND MIGRAINE IN PRACTICE



EDITED BY
MANSOUREH TOGHA
ELHAM JAFARI

SEYED EHSAN MOHAMMADIANINEJAD
SAMANEH HAGHIGHI
HOSSEIN ANSARI

IHA
IRANIAN HEADACHE ASSOCIATION

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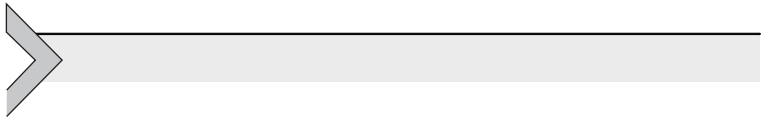

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Edited by

MANSOUREH TOGHA, Editor-in-Chief
Professor of Neurology, Tehran University of Medical Sciences, Tehran, Iran

ELHAM JAFARI, Co-Editor-in-Chief
Neurologist, Science manager of Iranian Headache Association website, Tehran, Iran

SEYED EHSAN MOHAMMADIANINEJAD, Associate Editor
Associate professor of Neurology, Tehran University of Medical Sciences, Tehran, Iran

SAMANEH HAGHIGHI, Associate Editor
Assistant professor of Neurology, Tehran University of Medical Sciences Tehran, Iran

HOSSEIN ANSARI, Associate Editor
Associate professor of Neurology, University of California, San Diego, USA

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Cover Designer: Matthew Limbert

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Dedication

The book is dedicated to all physicians that refer to it and use the information to help their patients.

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Contents

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Contributors

Maryam Abolhasani
Sports Medicine Department, Tehran University of Medical Sciences, Tehran, Iran

Hossein Ansari
Headache and Facial Pain Clinic, Kaizen Brain Center, San Diego, CA, United States

Behnaz Ansari
Neurology, Isfahan University of Medical Science, Isfahan, Iran

Mahsa Arzani
TUMS, Neurology, Tehran, Iran

Hoda Asefi, MD
Radiologic image preparer, Assistant Professor of Radiology, Sina Hospital, Tehran University of Medical Sciences, Tehran, Iran

Mohaddeseh Azadvari
Physical Medicine and Rehabilitation, Sina Hospital, Tehran University of Medical Science, Tehran, Iran

Hayrunnisa Bolay
Faculty of Medicine, Department of Neurology and Algology, Gazi University, Ankara, Turkey; Neuropsychiatry Center, Gazi University, Ankara, Turkey; Neuroscience and Neurotechnology Center of Excellence (NÖROM), Ankara, Turkey

Farnaz Etesam
Psychosomatic Medicine, Psychiatry, Tehran University of Medical Sciences, Tehran, Iran

Fardin Faraji
Neurology Department, Arak University of Medical Sciences, Arak, Iran

Majid Ghafarpour
Tehran University of Medical Sciences, Neurology, Imam Khomeini Hospital, Tehran, Iran

Samaneh Haghighi
Neurology Department, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran

Elham Jafari
Tehran University of Medical Sciences, Iranian Headache Association, Sina Hospital, Tehran, Iran

Seyed Ehsan Mohammadianinejad
Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

Fereshteh Naderi Behdani
Department of Neurology, Ziaeeyan Hospital, Tehran, Iran

Somayeh Nasergivehchi
Neurology, Tehran University of Medical Sciences, Tehran, Iran

Ali Asghar Okhovat
Neurology, Tehran University of Medical Sciences, Tehran, Iran

Aynur Ozge
Faculty of Medicine, Department of Neurology and Algology, Mersin University, Mersin, Turkey

Soodeh Razeghi Jahromi
Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran; Headache Department, Iranian Center of Neurological Research, Neuroscience Institute, Tehran, Iran

Mansoureh Togha
Iranian Center of Neurological Research, Headache Department, Neuroscience Institute, Tehran, Iran; Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran

Zahra Vahabi
Geriatric Department, Tehran University of Medical Sciences, Tehran, Iran; Psychiatry Department, Tehran University of Medical Sciences, Tehran, Iran

Doga Vuralli
Faculty of Medicine, Department of Neurology and Algology, Gazi University, Ankara, Turkey; Neuropsychiatry Center, Gazi University, Ankara, Turkey; Neuroscience and Neurotechnology Center of Excellence (NÖROM), Ankara, Turkey

Editor-in-chief

Dear respectful readers,

This book aims to help physicians interested in headaches with a practical approach.

We tried to suggest answers to the common questions in dealing with headache patients of different ages with a variety of presentations in emergency ward, inpatient situations, and outpatient clinics.

Our colleagues in the Iranian Headache Association with various specialties in physical medicine, sports, nutrition, and psychiatry collaborated in writing the relevant parts of the book. I would like to sincerely thank every one of them who accepted my invitation and actively participated in writing the different chapters of the book.

My special thanks go to Dr. Elham Jafari, Dr. Ehsan Mohammadianinejad, Dr. Samaneh Haghighi, and Dr. Hossein Ansari for their efforts in the scientific editing of the book.

I should have my deep gratitude to Dr. Elham Jafari for her help in all stages of preparing the book and its long process for publication with the valuable Elsevier publisher.

Mansoureh Togha,
Professor of Neurology,
Tehran University of Medical Sciences,
Founder and president of Iranian Headache Association.

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Introduction

This wonderful, new headache book for doctors and nurses covers everything anyone would want to know about headache and does so in an innovative style. The multiple authors follow the ICHD 3 diagnostic criteria from beginning to end and delve into every single category of headache; but they take out important topics and cover them separately utilizing a special teaching method. For example, they discuss what positive points help to make a diagnosis and what negative points negate a diagnosis. This is rarely discussed in a textbook. Each chapter has numerous useful references, and the reader does not have to go to multiple sources to learn all about headache.

This book accurately teaches the reader to diagnose headache by very careful history taking; in fact, it gives the reader the exact questions to ask. It carefully distinguishes adults, older adults, and children from each other. It then dissects each question you ask in the history and explains why one patient answer will lead to a different diagnosis from another. It is very hard to get this information in other formats. We know the diagnostic criteria for each headache according to IHS criteria; but how do we obtain the accurate information to make that diagnosis? For example, in the section on frequency and duration of episodes, it teaches how each headache is diagnosed differently depending on the details and helps tremendously with making the diagnosis. It has numerous informative tables that contrast aura with transient ischemic attack or side-locked migraine with cluster headache. These nuances in understanding headache types are hard to find in other textbooks and journals.

Professor Togha's chapter on migraine goes into all types of this ubiquitous headache disorder and lists in great detail older and newer treatments in a very comprehensive way. It is followed by an informative section on types of vertigo which discusses vestibular migraine and how Meniere's disease may overlap with migraine and how to tell the difference between the two.

After all areas of ICHD 3 are covered, there is an excellent chapter on headache in women. It covers all phases of the female cycle, how to treat, what role hormones play in the cause and therapy of headache, and what to do about treating during pregnancy and breastfeeding. There are numerous helpful tables in this chapter and others. This is a most helpful

chapter for anyone treating women, especially if they are pregnant, breastfeeding, or going through menopause.

Rather than ending abruptly, the last four chapters cover the all-important topics of headache in the elderly, rehabilitation and headache, headache and exercise, which suggests useful tips about posture and lays out helpful exercise programs and finally one of the most novel topics covered by the well-known expert on nutrition and headache, Soodeh Razeghi Jahromi. She starts with the helpful topic of explaining that weight loss may be the key to helping headache and then teaches the reader what is to be avoided and goes on to discuss vitamins, supplements, probiotics, and fiber. Everyone can benefit from the expertise documented here, especially those who suffer with headache.

In summary, this is a complete, informative, easy-to-read textbook on headache. The authors should be proud of their accomplishment.

Alan M. Rapoport, M.D.
Professor of Neurology
The David Geffen School of Medicine at UCLA
Los Angeles, California, USA
Past President of the International Headache Society

CHAPTER ONE

Approach to a patient with headache

Seyed Ehsan Mohammadianinejad
Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Headache (HA) is a common symptom in many systemic and neurologic disorders. The third edition of International Classification of Headache Disorders (ICHD-3) lists more than 200 primary and secondary HA disorders that can be differentiated mostly by history and physical examination [1].

ICHD classifies HA disorders into two types

1. Primary HAs that lack an underlying structural disorder. The cornerstone of diagnosis is a good history taking, since neurological examination and para clinical investigations are characteristically normal. Primary HAs consist of four groups, including migraine, tension-type HA (TTH), trigeminal autonomic cephalalgias (TACs), and other primary HA disorders. These benign conditions can be mimicked by secondary causes. There is no definitive diagnostic test for primary HAs; therefore, secondary causes should be excluded to make a diagnosis.
2. Secondary HAs that have an underlying cause that should be discovered by red flags found in history or physical examination or a relevant abnormality found in investigations including imaging or laboratory tests. Therefore, a normal examination alone does not exclude secondary HA disorder. In practice, approximately 90% of patients with HA have primary HAs [2].

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Therefore, the diagnosis of a primary HA disorders requires the following stages:

1. There are no red flags or better explanations for the symptoms. This is actually an important negative point for the diagnosis of a primary HA.
2. There are typical features supporting the diagnosis according to criteria. This is actually an important positive point for the diagnosis of a primary HA.
   - The symptoms of migraine HA such as nausea, vomiting, photophobia, or phonophobia are not specific and several primary and secondary HA disorders can superficially mimic migraine HA (Table 1.1) [3,4].
   - HAs resembling TTH are a common phenotype in brain tumors.
   - In almost all of these mimickers, there is one or more atypical features in detailed history taking or physical examination that is not compatible with typical primary HA [4]. Meanwhile, the primary and secondary HA disorders could occur simultaneously in a patient.

In conclusion, all patients with HA, even those that seem to have a primary benign disorder initially, should first have a negative diagnosis by excluding secondary causes. This is mainly performed by detailed history taking and completed by a targeted systemic and neurologic examination to search for red flags (Table 1.2). Imaging and laboratory work up completes the investigation in cases where a secondary cause is in consideration (**Algorithm 1.1**). The presence of red flags, as shown in Table 1.2, mandates patient evaluation for a secondary HA disorder [5–9].

Table 1.1 HA disorders that mimic migraine HA.

Primary HA disorders	Secondary HA disorders
Hemicrania continua	Vascular malformations
Cluster HA	Cerebral vein thrombosis
	Cervical artery dissection
	Giant cell arteritis
	Hypertension
	Brain tumors
	Hydrocephalus
	Pseudotumor cerebri sphenoid sinusitis
	CADASIL

Table 1.2 Red flags that may indicate a secondary HA disorder.

Acute onset severe HA
The worst HA of life
Thunderclap HA
Split-second onset HA
The first occurrence of a new type of HA
A change in the pattern of HA
Progressive or worsening HA
Onset of HA at age 50 or more
Chronic daily HA that has a clearly remembered onset (NDPH)
HA that remains focal over time
Recent onset of a side-locked HA
HA present immediately after sleep
HA that awakens patient from sleep (nocturnal headache)
Vomiting precedes HA
Neurologic symptoms and/or signs
Systemic symptoms and/or signs
HA with changes in behavior/personality
Acute HA following cough, sneeze, straining or any valsalva maneuver
Acute HA after bending
Acute HA after exercise
Acute HA during sexual intercourse
Acute HA in pregnancy or postpartum period
Underlying cancer, diabetes or immunocompromised state
HA in patients on anticoagulants
HA in patients with dementia
HA occurring or exacerbating with postural changes
HA does not respond adequately to treatment
Recent history of head or neck trauma
Onset of HA < 6 years

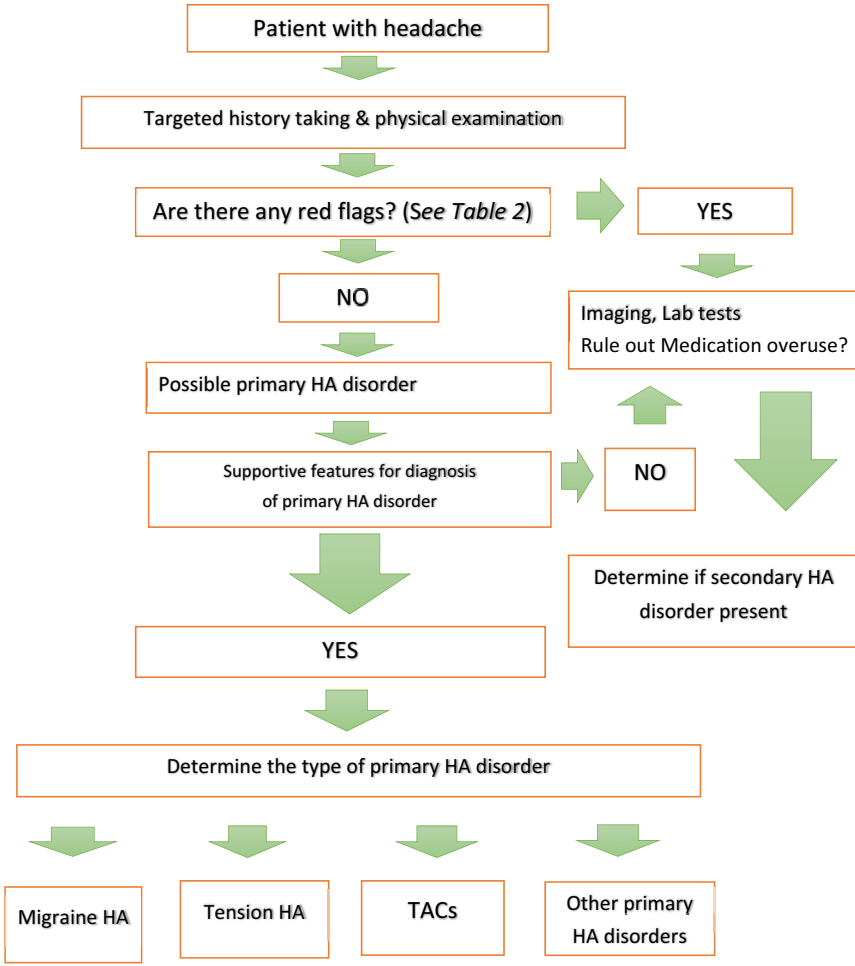
Most of the patients with HA can be diagnosed with history alone. Obviously, more time is usually given to history taking compared to physical examination in patients with HA. It is not possible to diagnose primary HA disorders without history taking. History taking reveals many red flags for secondary HAs and also guides the physician as to the order of imaging or laboratory investigations. It also provides a background for treatment plans.

The following parts of this chapter discuss the use of targeted history taking, physical examination, and finally imaging and laboratory investigations to approach a patient with HA. Elements of history taking are shown in Table 1.3 and explained in the following sections.

Table 1.3 History taking in a patient with headache.

1	What was your age when HA started?
2	Temporal profile of HA episode(s) **a.** How long have you been having HA? **b.** How does it start and how long does it take from onset to peak? **c.** What is the duration and frequency of episodes? **d.** Has there been a change in the pattern of episodes recently or is your recent HA like your previous ones?
3	Have you ever had similar HA before?
4	Where is the location of pain and where does it radiate?
5	How is the pain quality?
6	How do you score the severity of pain from 1 to 10?
7	What are the accompanying symptoms?
8	Do you experience premonitory symptoms before the onset of HA?
9	How do you behave during the attack?
10	Do HA episodes occur in particular times?
11	Do the attacks awaken you from sleep?
12	What are exacerbating and relieving factors?
13	Is the HA related to postural change?
14	Is there a change in behavior and personality?
15	Does the patient have a family history of migraine or neurologic disorder?
16	Is there one or more types of headache?
17	Is there a history of head or neck trauma?
18	Is there acute pain following Valsalva (cough, straining, lifting)?
20	Is there acute pain after exercise?
21	Is HA related to sexual activity and how?
22	Is there a history of any systemic disease like hypothyroidism, connective tissue disorder (CTD), hypertension, glaucoma, HIV, cancer, immunosuppression.
23	What is the amount of analgesics you consume in a week?
24	What are personal habits?
25	Did the HA start during pregnancy or in the postpartum period?

Algorithm 1.1. Primary approach to patient with headache.



History taking in patients with headache

What was your age when HA started?

The patient's age has significant diagnostic and therapeutic implications in HA.

- HA is the most common neurologic complaint in children. Most cases are due to primary benign disorders, but concerns do exist for

secondary disorders. The SNOOOPPPPY red flags have recently been suggested to determine children with HA who require evaluation for secondary causes (Table 1.4) [9,10]. Although there is general agreement about most of the included features, there is no consensus for some, including age and occipital pain [11,12].

The onset of HA in less than 6 years is considered a red flag, because the history and physical examination may not be very reliable in this age group. However, it probably depends on the case. Obviously if the patient's age does not allow an adequate evaluation, further evaluation seems reasonable.

The ICHD-3 considers that occipital pain is rare in childhood migraine and calls for more evaluation. However, a recent study showed that occipital HA as the only symptom in children without associated warning features is rarely related to brain tumors and therefore may be investigated similar to the pain in other locations [11,12].

- Childhood migraine is different from adults in some clinical aspects [13]. It affects boys more often than girls before puberty. Attacks are typically shorter in children (30 min−2 h). They are more often bilateral, non-throbbing, and located in frontal or temporal areas compared to adults. Vomiting may be more prominent and symptoms such as nausea and sensitivity to light and sound may be more obvious from the function and behavior of the patient than direct questions in the history. Migraine equivalents are characteristically more common in children.

Migraine most commonly starts at 15−25 years and attenuates after 50. It should not be considered as a first diagnosis in headaches starting after age 50.

- TTH does not respect to any period of life. It is more common in middle-aged people but is also the most common cause of HA in

Table 1.4 SNOOOPPPPY red flags for headache in children.

Systemic symptom or illness
Neurologic symptom or signs
Acute onset
Recent onset
Occipital location
Precipitated by Valsalva
Positional
Progressive
Parents not involved (negative family history)
Year < 6

elderly, while children, especially adolescents, are not uncommonly affected. Adolescents with intractable primary headaches and normal investigations who do not respond adequately to treatment probably suffer from TTH and benefit from a psychiatric consultation [14,15].

- HA in older adults (practically after age 50) is most commonly caused by primary HAs such as TTH or migraine, but the risk of secondary disorders increases in this age group (Table 1.5) [16,17]. This is why new onset HA after age 50 is a red flag and mandates evaluation for secondary causes.
- Giant cell arteritis (GCA) starts after 50 and should be excluded in every older adult patient with new onset HA.
- Ischemic strokes, particularly when they occur in the posterior circulation, are commonly associated with headaches. A severe headache with an acute onset may be due to an ischemic infarct of the cerebellum or occipital lobe. Focal neurologic deficits are often present.
- ICH should be considered in an older adult presenting with acute severe HA. It could be in the form of intraparenchymal, subdural or epidural hematoma. Altered consciousness and vomiting are often associated. This diagnosis should be particularly considered in hypertensive patients or those on anticoagulants.
- Brain tumors do not have a characteristic type of HA; most patients have a clinical picture like a TTH. There is a red flag often in history and less often in physical examination to guide the physician.
- In older adults, especially those with vascular risk factors, HA that occurs upon exercise and is relieved by rest may be due to cardiac ischemia. Unlike other HAs, cardiac cephalalgia is uniquely relieved by nitroglycerine.
- Cervicogenic HA is more common in older adults. The pain is typically unilateral, starts with neck pain, and extends to the head on the same

Table 1.5 Common causes of HA in older adults.

Primary causes:
Tension type HA, Migraine, Hypnic HA
Secondary causes:
Giant cell arteritis, intracranial hemorrhage, subdural hematoma, ischemic stroke, brain tumors, cervicogenic HA, posttraumatic HA, glaucoma, hypertension, cardiac cephalalgia, sleep apnea, medication overuse HA

side. Neck stiffness and limited range of motion are commonly present. Neck movement or pressure on the greater occipital nerve may provoke the pain. Migraine features such as nausea, vomiting, photophobia, or phonophobia may be present although to a lesser extent compared to migraine [18].

- Sleep apnea may present with morning or wake up HA in older patients. This should not be forgotten in this age group, since the prevalence of sleep apnea increases with age.
- Acute angle closure glaucoma is easily diagnosed because of the prominent eye symptoms such as red eye and blurred vision, while it is not the case with subacute angle-closure glaucoma that typically presents with no red eye. It may present with intermittent short HA episodes. They last usually less than 4 h (usually less than 1 h) and are often associated with blurred vision. The episodes typically occur in the evening when dim light results in mydriasis leading to increases intraocular pressure [19]. It needs a high index of suspicion as a cause of intermittent unilateral HA in older people.
- Older patients with HA most often suffer from TTH compared to migraine. The clinical profile of TTH in older adults is the same as younger people but this may not be true for migraine. Interestingly, symptoms such as nausea, vomiting, photophobia, and phonophobia are less prominent in older adults with migraine but neck pain is more common [20].
- Hypnic HA is a particular type of primary HA disorder that typically occurs after age 50. It occurs exclusively at night and awakens the patient from nocturnal sleep. The bilateral location and absence of autonomic features differentiate it from cluster HA [21,22].

What is the time course of HA?

This is actually the most informative part of history in a patient with HA. It should be asked in detail very accurately.

How long have you been having HA?

A recent onset HA is more likely to be secondary to a serious disease than a stable pattern of a chronic headache. The longer the time HA has been present (>12 months), the greater the chance that it is a primary benign type. This is while the more recent the HA onset (<6 months), the higher is the risk of a worrisome cause.

How does it start and how long does it take from onset to peak?

- Acute HA with maximal severity within seconds to minutes of onset should always be considered serious, particularly if not experienced before.

The onset to peak time of HA is very important. The shorter is the time, the higher is the risk of a serious disease. If the HA peaks in less than 1 minute, it is referred to as a thunderclap HA (TCH), which is a serious red flag, with a vascular cause in most secondary cases. Although a period of 1 min is proposed for defining TCH, every severe HA that starts acutely and peaks in a short time (not necessarily 1 min) is considered as a red flag [23]. This is particularly true when it is described as "the worst HA of life."

Common causes of TCH are shown in Table 1.6. The same list is considered for sudden onset severe HA regardless of the proposed 1 minute. The details are discussed in the next chapters.

- Subarachnoid hemorrhage (SAH) is actually the most important cause of TCH. Timely treatment can prevent rebleeding, which is associated with a mortality rate of up to 70% [24]. Isolated HA is the most common presentation. Nothing is characteristic for HA to differentiate from other conditions except the severity and acuteness. The duration of pain is usually more than 2 h and the pain typically lasts for hours to days [25].

An unruptured aneurysm may also produce a severe sudden onset HA in the form of TCH. This sentinel HA, which is seen in 10%–43%, may occur days to weeks (usually within 2 weeks) before the rupture of aneurysm and SAH. It is probably due to acute expansion or aneurysm leak [26]. Sentinel HA is of utmost importance since it is an alarm for aneurysm rupture in the

Table 1.6 Causes of thunderclap HA.

Vascular causes	Nonvascular causes
SAH	Spontaneous intracranial hypotension
Unruptured intracranial aneurysm	Colloid cyst of third ventricle
Dissection of cervico-cerebral arteries	Cardiac cephalalgia
Cerebral venous thrombosis	Primary cough HA
RCVS	Primary exertional HA
Pituitary apoplexy	Primary HA with sexual activity
Cerebral infarct	Primary TCH
Intracranial hemorrhage	
PRES	
Acute hypertensive crisis	

near future. A specific time course for patients with SAH as "split-second onset HA" probably results from such a scenario. The patient experiences a severe and transient sentinel HA, enjoys remission for a short time (may be hours to days) unexpectedly, and then again suffers from a more persistent severe HA resulting from the aneurysm rupture.

- Dissection of cervical arteries including internal carotid artery (ICA) or vertebral artery (VA) is easily misdiagnosed due to variable and sometimes nonspecific presentations. HA and neck pain are the most common and often the only symptoms. Most patients experience ischemic events in the territory of the dissected artery during or after the HA phase. Up to 80% of dissections follow a trauma to the head or neck, which may be minor and not significant [27]. Dissection usually occurs immediately after trauma but may occur with a latency of 1 week [28].

ICA dissection presents typically with HA (mainly frontotemporal) and/or facial pain. Neck pain in the anterolateral area up to the jaw may be present. Partial Horner syndrome (ptosis and miosis without anhydrosis) is present in 1/3 of the cases [29]. Ischemic stroke in the territory of the middle or anterior cerebral arteries may follow.

VA dissection has a more stereotyped clinical profile. It typically presents with unilateral posterior neck pain or occipital pain commonly followed by lateral medullary infarction.

The diagnosis of cervical artery dissection should be considered when a combination of acute neck pain, HA, and facial pain occurs shortly a trauma. This is particularly the case when complete Horner syndrome, transient monocular blindness, or ischemic events accompany or follow the pain. Obviously, this diagnosis is easily missed in cases with isolated pain when there is no or minor trauma or the HA is of a subacute or more chronic course similar to previous migraine episodes.

- Cerebral vein thrombosis (CVT) most commonly presents with a subacute progressive HA but may less commonly present with acute HA. A significant minority of the patients present with TCH that is similar to SAH [30]. HA is the most common symptom of CVT. It may be the only symptoms but is often associated with other CVT suggestive features (see chap vascular).
- Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by a specific pattern of recurrent short-lived TCHs. The patient experiences an acute severe HA that peaks rapidly in less than a minute, making the patient agitated for minutes to few hours. The patient experiences a temporary remission and then suffers from further episodes.

It is a uniphasic disorder with a spectrum of clinical manifestations ranging from isolated HA episodes to ischemic or hemorrhagic complications, all lasting less than 3 months [31].

- Pituitary apoplexy results from an infarct or hemorrhage in the pituitary gland. Most cases occur in the setting of pituitary adenoma although they may not be aware of the adenoma at the time of presentation. Acute-onset severe HA is the main symptom. It is sometimes associated with varying degrees of visual impairment and ophthalmoplegia. Pituitary dysfunction may occur to a variable extent.
- Cerebral infarcts, mainly in the posterior circulation, may present with acute severe HA. The same is true for different types of ICHs.
- Acute hypertensive crisis may be associated with acute severe HA, mainly in the back of the head. It may be associated with symptoms such as dizziness, agitation, chest pain, dyspnea, epistaxis, and even focal neurologic deficits, which are reversible upon blood pressure control.
- Posterior reversible encephalopathy syndrome (PRES) occurs in the setting of acute hypertension, eclampsia, or administration of some drugs. It presents with acute severe HA associated with nausea, vomiting, confusion, blurred vision, seizure, and/or focal deficits. It is confirmed by reversible clinical and MRI findings.
- Among nonvascular causes of TCH, spontaneous intracranial hypotension (SIH) requires a high index of suspicion. It typically presents as orthostatic HA; however, it presents as TCH, which is very similar to rupture of aneurysm, in almost 15% of cases [32]. It often follows Valsalva maneuver such as lifting, straining, cough, bending over, or sport activities. The pattern of orthostatic HA may become less obvious after the initial phase.
- Patients with colloid cysts of the third ventricle may experience acute HA following bending over. This is due to obstruction of the Monro foramen and acute reversible obstructive hydrocephalus following a position change. It may even result in altered consciousness that improves upon position change.
- Myocardial infarction should be considered as a rare but important cause of TCH. It should be suspected in acute onset severe HA in older patients with vascular risk factors.
- Cough HA, exertional HA, and HA associated with sexual activity have primary and secondary types and all may present with TCH. They are discussed in Chapter 5.

- Among primary HA disorders, TACs have the shortest onset to peak time. They can last for only seconds to minutes. Cranial neuralgias, especially trigeminal neuralgia (TN), also have a very short onset to peak time.
- Migraine HA usually peaks in 1–2 h. However, migraine episodes may have an onset to peak time of minutes [33]. The diagnosis of migraine should not be accepted easily in this unusually acute condition unless a similar history is present and there is no other red flag in the assessment.

What is the frequency and duration of episodes?

- The frequency and duration of HA episodes is helpful for diagnostic and therapeutic purposes.
- HAs are arbitrarily divided into short duration (less than 4 h) and long duration (more than 4 h). Migraine HA lasts 4–72 h if untreated and is of long duration, but TACs are characteristically of short duration.
- Subacute closed angle glaucoma may present with intermittent short episodes of HA in the evening as discussed before. New-onset pain in older adults and pain duration are main differentiating features from benign primary HAs.
- Subacute progression or worsening of HA in terms of the frequency or duration of episodes over weeks to months is a red flag indicating an intracranial pathology such as space occupying lesions, cerebral venous thrombosis, intracranial hypertension, and giant cell arthritis.
- Chronic daily headache (CDH) is defined as HA episodes in 15 or more days per month for three or more consecutive months.
- Chronic migraine (CM) is considered when a patient with CDH has HA with migraine features for eight or more days in the month. Medication overuse is seen in many cases of CM. Prognosis and treatment strategy are different from episodic migraine.
- Chronic Tension-Type Headache (CTTH) is defined as a CDH that fulfills the criteria for TTH. It is commonly associated with psychiatric comorbidities and requires multidisciplinary management.
- In chronic cluster HA (CH), CH episodes continue for more than 1 year without remission or with remissions of less than 3 months. The treatment may be rather different from patients with episodic CH.
- New daily persistent HA (NDPH) is a CDH with a clearly remembered onset. The patient remembers the exact time of HA onset, which becomes daily and continuous in less than 24 h. It is a red flag, even if the HA has migraine or tension-type features [34]. It has different causes, the

most important of which include intracranial hypertension, intracranial hypotension from CSF leak, dissection of cervical arteries, and posttraumatic headache. This emphasizes the importance of asking specifically how the HA started from onset.

Have you experienced a recent change in the pattern of HAs?

In a patient with a stable pattern of headache for more than 6 months, a serious cause is less likely. A recent change in the pattern of a previously stable HA is a red flag and requires investigation. This change can be in the temporal course, quality, duration, severity, location, and/or accompanying symptoms of HA.

- An example would be a patient with a previous migraine HA that experiences acute to subacute progressive HA of different duration and severity after a course of oral contraceptive (OCP) use. It may be wrongly attributed to exacerbation of migraine from OCP use, but CVT or alternative possibilities should be ruled out first.
- Another example is a patient with a previous history of occasional severe attacks of migraine who is referred with severe persistent HA in frontal and vertex areas since 10 days ago; imaging shows sphenoid sinusitis.

For headaches that have begun recently, particularly when the pattern is unstable and episodes are progressive in terms of frequency and or severity, further evaluation is mandatory.

Have you ever had similar HAs before?

If the answer to the question is "No," the HA should be interpreted with caution. This is not necessarily considered a red flag but the patient should be interpreted more cautiously according to associated clinical features and the setting in which the pain has started.

- An example is a patient with a new severe and persistent pain in the neck and back of head for 10 days following trauma and more investigation reveals dissection of the VA.

Where is the location of pain and where does it radiate to?

Migraine HA is most commonly located in the eye or frontal or temporal areas, but it can involve any part of head such as the vertex, back of the head, the neck, or the whole ahead. Pain in the occipital or neck each occurs in almost 40% of the patients with migraine [35]. Episodes of migraine are often unilateral, but bilateral pain is not uncommon. Tension headaches

are typically generalized and bilateral or may be felt in the back of the head, vertex, or neck. TACs are side-locked HAs that are centered most severely in the V1 territory of trigeminal nerve (orbit and nearby around). They commonly radiate to the temple or face.

Neck pain is a common complaint in patients with HA and is not specific for cervicogenic HA. It is common in primary HAs such as TTH and migraine and is seen in many secondary HA disorders. However, acute neck pain associated with HA should be considered important, particularly following trauma, since dissection of cervical arteries may be the cause.

The term sinus HA is used by patients and sometimes general physicians to note pain over the paranasal sinuses in the face and frontal areas. It is associated with nausea, vomiting, photophobia, or phonophobia most of the time and is actually due to migraine. Nasal symptoms such as nasal stuffiness or rhinorrhea are not uncommon in migraine and should not be simply attributed to rhinogenic pain.

HA is nonspecific in brain tumors. It is not located in a specific part of the head except for infratentorial tumors, which mostly present with occipital pain. Tumor HA is more often like TTH than other types of HA [36,37].

Sphenoid sinusitis is an underdiagnosed cause of HA. The pain is often in the vertex and or retro-orbital area but may be felt in other parts of the head including the frontal or even the neck region. It requires a high index of suspicion because the nasal symptoms are often absent [38]. One should think of this diagnosis when there is a subacute progressive HA in the vertex and/or retro orbital area.

Side-locked HA is defined as an HA that is always on the same side. Some experts define it when more than 90% of episodes occur on the same side. Two thirds of the cases have primary HA disorders, while about 1/3 suffer from a secondary disorder or cranial neuralgia. It is considered as a red flag requiring investigation to rule out secondary causes [39].

TACs are characteristically side-locked, which is a mandatory feature for diagnosis. Migraine is rarely side-locked, but it is a diagnosis by exclusion. Side-locked HA with or without neck pain with an acute to subacute course should be taken seriously, since cervico-cerebral arterial dissection is a possibility.

HAs that remain focal without any changes in the location over the expected time are a red flag requiring more evaluation. Primary headaches do not usually remain focal over time and typically shift to adjacent areas or to the other side.

Unilateral or occipital HA that becomes generalized after the Valsalva maneuver is suggestive of intracranial lesions and increased intracranial pressure (ICP).

What is the quality of pain?

Throbbing or pulsating headache is characteristic for migraine and is a feature of migraine in ICHD; however, the following points should be considered:

1. Nonthrobbing HA is not uncommon in migraine. Therefore, ICHD allows a diagnosis of migraine in the absence of pulsatile pain when other criteria are fulfilled.
2. Many other HA types (including serious causes) may also present with throbbing pain. Therefore, the throbbing quality of pain is not a reliable symptom to differentiate primary from secondary HAs and should be interpreted using accompanying symptoms and the clinical setting.

TTH is described as a pressing, pressure like, or band like pain, feeling something heavy on the head, or a dull headache.

Brief sharp pain in different parts of the head is referred to as icepick or stabbing pain. It is commonly reported by patients with migraine or may be an idiopathic entity known as "idiopathic stabbing HA."

Patients with TACs, particularly cluster HA, may experience a very severe deep, boring, or burning pain that may be described as a hot poker in one eye. The patient is usually agitated and restless during the episode.

TN is characterized by paroxysmal sharp and jab-like pain episodes that the patient describes as repeated shocks to the face.

Persistent dull pain in the mid-face without any objective findings is compatible with persistent idiopathic facial pain, previously known as atypical facial pain. It might be due to underlying psychopathologies although other causes such as posttraumatic pain or comorbid pain conditions should also be considered.

How does the patient score the pain severity?

The severity of HA is assessed by a numeric rating scale from 0 to 10 in which 0 means no pain and 10 indicates the worst pain. Cluster HA or severe migraine episodes are usually given a score of 8–10, but patients with TTH usually give a score of less than 5; hence, the pain does not typically interfere with routine physical activities.

Therefore, the severity of HA per se is not a reliable indicator for differentiating benign from serious headaches since the most common primary HAs may be as severe as the pain in SAH. It is the mode of onset, evolution of pain (onset to peak time), history of similar episodes, associated symptoms, and the clinical setting that are much more diagnostic. An acute severe HA that peaks in a short time requires investigation when occurring for the first time, but it might be taken as a primary HA disorder when there is a history of similar previous episodes. On the other hand, a mild to moderate intensity of HA does not guarantee a benign cause. Most patients with brain tumors present with HA of mild to moderate intensity that may respond well to analgesics in early stages.

What are the accompanying symptoms with HA?

Symptoms that are associated with HA are key to diagnosis. Migraine is a complex disease with many associated symptoms such as nausea, vomiting, and sensitivity to light, sound, or odor.

On the contrary, TTH is famous for lack of associated symptoms and is therefore known as featureless HA. ICHD has proposed the presence of photophobia or phonophobia (not both) for a diagnosis of TTH. Nausea or vomiting is not compatible with TTH, but nausea of mild severity is accepted for diagnosis of TTH.

TACs are characterized by at least one cranial autonomic symptom ipsilateral to the HA although ICHD-3 allows a diagnosis of cluster HA and hemicranias continua (two types of TACs) in the absence of autonomic symptom when there is agitation or restlessness.

TACs (especially cluster HA and paroxysmal hemicranias) and side-locked migraine may mimic each other. Migraine patients may experience cranial autonomic symptoms such as lacrimation, conjunctival injection, facial or eyelid edema, and nasal congestion or rhinorrhea mimicking TAC [40]. Migraine features such as nausea, vomiting, photophobia, or phonophobia have also been reported with cluster HA [41]. It is sometimes difficult to differentiate at the first glance, but there are some reliable differentiating features (Table 1.7).

Photophobia and phonophobia are not specific for migraine and may be present in many HA disorders, including some serious causes such as SAH and meningitis in addition to primary HA disorders. Vomiting is most commonly associated with migraine, but intracranial lesions should be ruled

Table 1.7 Comparing side-locked migraine with cluster HA.

Feature	Side-locked migraine	Cluster HA
Sex	More females	More males
Circadian rhythm	Absent	Present
Autonomic symptoms	May be present (usually bilateral)	Prominent (ipsilateral)
Photophobia	Prominent	May be present
Duration of attack	Longer (4–72 h)	Shorter (< 3 h)
Behavior during the attack	Rest in a dark, quiet room	Agitation and restlessness
Laterality of photophobia	Bilateral	Unilateral

out by clinical judgment. This is particularly true for vomiting without preceding nausea (projectile vomiting) or when vomiting proceeds HA, which are both considered as red flags.

Tinnitus and transient visual obscuration (TVO) may herald increased ICP in a patient with recent HA. Unilateral or bilateral TVO, especially with bending or Valsalva maneuver, may be a sign of increased ICP, which can be due to intracranial lesions or pseudotumor cerebri syndrome (PTCS). Acute to subacute unilateral severe HA with ipsilateral transient monocular blindness or Horner syndrome is highly suggestive of dissection of craniocervial arteries.

Do you have premonitory symptoms before the onset of HA?

Aura is a reversible neurological disturbance that may precede or accompany migraine HA. It may last from 5 min to 1 h, but it usually lasts 10–30 min [42]. Prolonged aura is defined as aura of more than 1 hour but less than a week and is usually in the form of nonvisual symptoms [43]. Aura typically evolves and fades within minutes and has positive features. Visual aura is the most common type, with positive, negative, or both types of visual phenomena. It usually involves both eyes and is sometimes in black and white. If it is multicolored and of a shorter duration (usually less than 3 minutes), an occipital lobe seizure should be considered [44]. Patients with migraine with aura may experience more than one type of aura. In this setting, symptoms usually occur in a sequential order and are not simultaneous (for example, visual aura followed by somatosensory aura).

Somatosensory aura presents with paresthesia, numbness, or other odd sensations in the limbs, face, or other parts of body. Speech aura manifests as variable dysphasic errors. These less common aura types produce diagnostic challenges for transient ischemic attack (TIA). TIA shows itself as negative symptoms that start and fade suddenly and occur simultaneously at presentation (Table 1.8).

- To clarify by example; the simultaneous occurrence of transient monocular blindness in left eye and numbness in right extremities that evolves and fades acutely is compatible with TIA.
- On the other side a patient who experiences transient blurred vision associated with zig-zag lines or sparkling in the left hemifield and then paresthesia or numbness in the extremities, face, or throughout the body in succession, which develops within minutes, suffers from migraine with polysymptomatic aura.

Migraine with brainstem aura (formerly known as vertebrobasilar migraine) presents with different combinations of bilateral symptoms including dizziness, ataxia, blurred vision, dysarthria, diplopia, and perioral numbness/paresthesia, followed by occipital or generalized HA.

How is the patient's behavior during the pain episode?

This is sometimes a very informative data. Patients with migraine prefer to rest in a dark and quiet room because any activity may worsen the symptoms. This is in contrast to patients with TAC (particularly cluster HA) that become restless and agitated during the episodes. The pain is so severe in cluster HA that the patient paces the floor and tends to strike the head to sense a very mild and transient attenuation of pain. This feature is so characteristic for patients with cluster HA and hemicrania continua among TACs that ICHD-3 has proposed a diagnosis is possible even in the absence of cranial autonomic symptoms in a patient with side-locked HA.

Table 1.8 Comparison of migraine aura with TIA.

Feature	Migraine aura	TIA
Type of symptoms	Positive symptoms (fortification spectra, paresthesia)	Negative symptoms (scotoma, numbness)
Evolution of symptoms	Gradual (at least 5 min)	Typically less than 5 min
Succession of symptoms	Sequential	Simultaneous

Do episodes of HA occur at particular times in the day or year?

HA episodes may occur at particular times in the day (circadian rhythm) or during certain months or seasons in the year (circannual rhythm). This indicates the role of hypothalamus in developing HA syndrome and is a characteristic feature of cluster HA. Migraine HA may also have a seasonal pattern.

Do the HA episodes awaken the patient from sleep?

"Does the HA awaken you from sleep?" This question is commonly asked in practice. HA that awakens the patient from sleep (sometimes called "wake up or morning headache") is usually considered as a red flag. This is while both primary and secondary causes may have this presentation (Table 1.9).

Primary HA disorders including migraine and TTH are the most common causes of morning headaches along with disturbed sleep, caffeine withdrawal, and alcohol consumption [45]. TTH is present throughout the day. The patient sleeps with pain and wakes up with pain. Patients with migraine commonly wake up with HA that gets worse within the following minutes to hours. This is in contrast to patients with increased ICP that wake up with HA and then feel better in the upright position. The same is true for patients with sleep apnea or chronic lung disease that feel better after waking up and getting out of bed. Patients with medication overuse HA (MOH) wake up with HA and feel better after analgesic consumption. Patients with cervicogenic HA may have HA upon waking up due to positional stimulation of trigger zones during sleep associated with pain and stiffness of the neck. The neck range of motion is limited and painful. It may also get better after a short time [46]. HA related to paranasal sinus/nose disorders may be associated with morning HA or facial pain that improves after getting up. Rhinogenic causes are often overestimated in practice by patients and primary care physicians in patients who actually have migraine HA [47,48].

Table 1.9 Causes of morning headache.

Primary causes
Migraine, TACs, hypnic HA,
Secondary causes
Sleep apnea, increased ICP, cervicogenic HA, HA related to sinus/nose disorders, HTN
Bruxism

Severe HTN may awaken the patient with HA, mainly in the back of the head. Patients with overnight bruxism may wake up with pain in the jaw that may extend to adjacent areas in the head [49]. There may be tenderness over temporo-mandibular joint (TMJ) with provoked pain on jaw movements.

1. If there is a long history of morning HA in a patient who is otherwise typical for migraine without any red flags, the patient may be followed without more investigation.
2. The same may be true for a typical patient with mood disorder and TTH or one with typical MOH.
3. Conditions associated with hypoxia or hypercarbia including obstructive sleep apnea, chronic lung disease, or asthma might be easily missed as TTH or depression. Symptoms such as snoring, daytime fatigue or sleepiness, and poor concentration should not be neglected in the history of patients with morning HA.
4. Otherwise, wake-up morning HA is a red flag, which should be investigated for a secondary cause.

Pain episodes that exclusively occur at night suggest TACs and hypnic HA. TACs (particularly cluster HA) are characterized by clockwise episodes that occur mostly and sometimes exclusively at night. The episodes of cluster HA are predictable in time, often occurring within 1–2 h after falling sleep at night or within daytime naps. Some patients fear or avoid going to bed because they anticipate a severe attack. It may not be very prominent or may even be absent in other types of TACs.

Hypnic HA is a particular type of HA that usually occurs after age 50. It occurs exclusively at night and awakens the patient like cluster HA. The patient's age, bilateral location of pain, and lack of autonomic symptoms are differentiating features.

1. What worsens and/or improves the HA?

This may be a very informative part of history in some patients. Common triggers of migraine HA are shown in Table 1.10.

- A diagnosis of TTH should not be solely based on preceding stressful events because a significant number of migraineurs may also have stressful events as the headache trigger. On the other hand, a serious secondary HA disorder may come to attention after a stressful event.
- Most HAs that occurred upon exposure to cold weather or cold drinks are actually migraine and not disorders of paranasal sinuses.

Table 1.10 Common triggers of migraine HA.

Stress
Fatigue
Menstrual cycle
Cold weather or drinking
Some diet habits
Strong odors
Sleep habits
Alcohol
Estrogen containing agents
Bright sunlight
Travel
Tyramine containing foods
Caffeine withdrawal
Aspartame, monosodium glutamate (MSG)
Nitrates.

- HA episodes that occur regularly during the menstrual cycle are assumed to be of primary benign type. They should not be always attributed to migraine since they may be actually TTH as part of the premenstrual syndrome.

Estrogen containing compounds such as OCPs may exacerbate or even complicate migraine. They should be avoided in some patients with migraine and additional risk factors due to increased risk of stroke (Table 1.11) [50,51].

It is important to consider that OCPs may lead to CVT or stroke. Therefore, a new onset HA disorder or any changes in the pattern of a previously known migraine HA following the use of OCP should not be attributed to migraine unless a diagnosis of CVT or stroke is excluded. Patients with underlying hereditary coagulopathy are susceptible to CVT or stroke even following a short course of estrogen containing agents.

Table 1.11 Contraindications of estrogen containing contraceptives in migraine.

Migraine with aura
Age>35 with vascular risk factors (diabetes, HTN, smoking, hyperlipidemia)
Hereditary thrombophilia

Is HA related to postural change?

Asking for the relationship between HA and postural change is a very important part of history that may be missed. HA that starts in a short time after assuming an upright position (sitting or standing) and improves upon lying down is known as orthostatic HA and is characteristic for intracranial hypotension. It most commonly follows lumbar puncture but may occur spontaneously known as SIH. Trivial trauma including flexion or extension of the neck or even Valsalva or cough may be the antecedent events. The diagnosis requires a brain MRI with contrast to look for dural enhancement. The pattern of orthostatic HA may start acutely in patients with SIH and may be present in the first weeks to months. It gradually converts to a nonspecific chronic daily HA without any postural change. Here the diagnosis of SIH is easily missed in a patient with CDH, unless one asks the patient about postural HA in the beginning of the disease course. This again emphasizes the importance of asking the question "how did your HA start from the beginning?" from any patient including those with subacute to chronic HA.

Acute HA after bending could be due to a colloid cyst of the third ventricle, causing obstruction of the interventricular foramina (foramina of Monro) resulting in acute hydrocephalus.

Has there been a change in behavior or personality?

Behavior or personality changes accompanying HA should not be ignored. This is particularly true when there is no history of a psychiatric disorder. Intracranial lesions (including brain tumors) involving the frontal and temporal areas may present in this way. Decreased initiation, flattened affect, emotional lability, disinhibition, and childish behavior are among the symptoms that may be more obvious to the family or caregiver. Sometimes the altered behavior or personality is more prominent than HA [52].

Significant changes in behavior or personality in older patients may be due to dementia. This is more probable when there is no previous history of psychiatric disorders. HA in a demented patient is considered a red flag and should be investigated for secondary causes. This is because history is not very reliable in patients with dementia.

Does the patient have a family history of migraine or neurologic disorders?

Family history is positive in many patients with migraine. A negative history of migraine in the parents of a child with HA has been considered as

a red flag [53]. A positive family history is essential for diagnosis of familial hemiplegic migraine. A personal or strong family history of stroke or dementia is a clue for CADASIL. Migraine is often the earliest symptom of CADASIL, usually in the form of migraine with aura [54].

Does the patient have one or more types of HA?

HA is a common disorder, especially in young women. A detailed history will reveal if the patient with a previous benign HA has developed a new HA recently. One or more changes in the pain pattern in terms of duration, frequency, location, and accompanying symptoms should be considered as red flags for secondary headaches.

Is there a history of head or neck trauma?

A new onset or different type of HA following head or neck trauma should be interpreted with caution as it may be a life threatening condition. Dissection of cervical arteries, ICH, and CVT is among the most serious causes. Therefore, the history of trauma preceding a recent HA disorder can be a red flag even in cases of minor trauma, especially in the elderly.

Some clinical points that should be considered when evaluating HA following trauma include the following:

1. HA may exist for a short time or continue for weeks to months after head or neck trauma.
2. Elderly patients, those who are on antiplatelet or anticoagulant agents, and patients who suffer from hereditary connective tissue disorders are more susceptible to complications.

In these conditions, even a minor preceding trauma in weeks before might be considered significant.

3. Flexion and/or extension of the neck during chiropractic manipulations, dental procedures, or other situations may cause dissection of cervical arteries.
4. CVT is an underestimated cause of HA after trauma. Head trauma could be the only cause of CVT and HA could be the only symptom of CVT.
5. Subdural or even epidural hematoma can develop with a lucid interval. This should be considered in patients with delayed worsening or onset of HA after trauma (Table 1.12).

Table 1.12 The most common causes of HA following head or neck trauma.

Cervico-cerebral arterial dissection
Intracranial hemorrhage (including subdural, epidural, and subarachnoid hemorrhage)
Cerebral vein thrombosis
Posttraumatic headaches

Is HA related to cough or Valsalva maneuver and how?

The term cough HA is used when a patient develops a sudden and short-lived HA only after a form of Valsalva maneuver but not with prolonged physical exercise. This particular form of HA can occur immediately after coughing, sneezing, straining, laughing, crying, or even singing loudly or any form of Valsalva maneuver; hence, its alternative name is "Valsalva maneuver HA." Cough HA starts acutely and lasts for 1 s to 2 h. It has a secondary cause in almost 50% of the cases, so it is considered a red flag. The most common secondary cause is type 1 Arnold Chiari malformation. Diagnosis of primary cough HA is by exclusion. It is typically a bilateral HA that may last for even seconds in a patient more than 40 years old, whereas secondary cough HA usually lasts longer in a younger patient [55,56].

Patients with sinusitis or other conditions whose underlying HA is worsened by coughing or sneezing should not be regarded as cough HA, since the background HA is present also in the absence of Valsalva maneuver.

Is HA related to exertion and how?

The term exertional HA is used when HA occurs during or after strenuous physical activity. The duration of HA is less than 48 h by definition. When occurring for the first time, it should be considered as a red flag. Compared with cough HA, most patients (almost 80%) have the primary type and are younger. The diagnosis of primary exercise HA is by exclusion. It occurs typically in a man (younger than 40) as a pulsatile HA with migraine features. Secondary causes such as intracranial aneurysms, ICH, dissection of cervical or intracranial arteries, pheochromocytoma, and cardiac cephalalgia should be excluded in all cases [55,56]. To memorize easier, "*older people primarily cough in seconds and younger people exercise for hours*".

Is HA related to sexual activity and how?

HA associated with sexual activity is a primary benign disorder in most of the time (almost 80%) [55]. An acute HA that occurs immediately before or just

during orgasm for the first time should be always considered as an important red flag. ICHs (including SAH), dissection of cervical or cerebral vessels, and RCVS are the most common secondary causes that should be ruled out [56]. For a valid diagnosis of primary HA associated with sexual activity, at least two attacks should have occurred with a benign course.

Recurrent TCH within a few weeks is characteristic for RCVS. Recent use of SSRIs or sympathomimetic agents may make patient susceptible for developing RCVS with sexual activity.

Is there history of systemic diseases?

Systemic disorders might be simply ignored as a cause of HA or exacerbation of an existing primary HA disorder. Systemic disorders may result in HA by several mechanisms: 1. They can produce a new type of HA, 2. They can exacerbate an existing primary disorder such as migraine, 3. They can indirectly cause HA by a superimposed infection, bleeding diathesis, thrombotic vascular event, adverse effects of treatment, etc., 4. They may lead to PTCS.

- Among endocrine disorders, hypothyroidism is most commonly associated with HA. It can produce a chronic bilateral nonthrobbing HA that resembles TTH [57,58]. Even subclinical hypothyroidism can exacerbate an existing migraine HA or make it resistant to treatment [59]. Hyperthyroidism may produce a migraine like HA or may exacerbate a previous migraine HA [60]. Other symptoms of hyperthyroidism are usually present.
- Hematologic disorders commonly cause HA. Anemia could be associated with HA or may exacerbate an existing migraine HA. Polycythemia vera and essential thrombocytosis are commonly associated with HA.
- Pulmonary disorders associated with hypoxia or hypercarbia can produce HA, especially in the form of morning HA. This can be the case with chronic obstructive pulmonary disease (COPD), asthma, or sleep apnea.
- Ischemic heart diseases are an important cause of HA. Most patients are over 50 and have vascular risk factors. It is typically in the form of a migraineous HA (pulsatile HA accompanied by photophobia or phonophobia) after exercise of varying degrees. HA can be the only symptom of ischemic heart disease and chest pain may be absent, causing a diagnostic challenge. Use of triptans or ergots due to a misdiagnosis of migraine may result in worsening of cardiac ischemia [61,62]. Cardiac

HA can occur at rest such as angina and needs a high index of suspicion in susceptible patients [63].

- Severe arterial hypertension (HTN) (SBP $\geq$ 180 and/or DBP $\geq$ 110) can cause HA, which is typically bilateral and pulsatile. Evidence suggests that chronic mild (140–159/90–99) and moderate HTN (160–179/100–109) do not usually cause HA unless they develop acutely [64–66].
- Pheochromocytoma is a rare chromaffin cell tumor that secretes catecholamine leading to HTN. Acute HTN crises result in severe HA attacks of short duration (usually less than 1 h) that are bilateral and pulsatile and associated with symptoms such as sweating, palpitation, pallor or anxiety [66,67]. Patients often lose weight [68] and typically have a persistent HTN with superimposed crises concurrent with HA episodes.
- HA occurring in a patient with diabetes, malignancy, or an immunodeficiency state is considered as a red flag because there is a higher risk of infections.
- Disorders associated with autonomic dysfunction may result in HA or neck pain after assuming an upright position because of orthostatic hypotension.

What is the amount of analgesics the patient consumes in a week?

Frequent use of analgesics may lead to MOH. This requires the use of medication for more than 10–15 times per month (depending on the type of the analgesic) for 3 months or more [69]. Most patients have underlying migraine.

Analgesic withdrawal may also cause HA. The diagnosis requires a relationship between skipping a dose and occurrence of episodes. It could also awaken the patient from sleep and could be a cause of morning HA as discussed before.

What are the personal habits and lifestyle?

Some habits and lifestyle patterns may be the cause of HA or exacerbate previous migraine HA (Table 1.13). These may be simply missed or underestimated as the cause of HA worsening when the physician is searching for a more sophisticated cause.

Table 1.13 Questions that may reveal habits or lifestyle patterns producing or exacerbating HA.

How much alcohol do you consume in a day?
How much caffeine do you consume in a day?
How many cigarettes do you smoke in a day?
Do you use illicit drugs or substances?
How many times do you eat per day?
How do you sleep throughout the day?
Are you usually highly stressed?
How much do you exercise?

Did the HA start during pregnancy or postpartum period?

An acute HA or a new-onset HA during pregnancy and postpartum (within 6 weeks after delivery) is considered as a red flag and requires assessment for secondary causes. Most patients with HA in this period have a benign primary HA, but there is a higher risk of secondary causes. This depends largely on the trimester in which the HA starts. Most HAs in the first trimester have a primary benign cause, while there is a higher risk of secondary causes in the third trimester and postpartum period [70,71].

Physical examination in patients with headache

Although the diagnosis of HA is mostly made by history alone, the significance of physical examination should not be underestimated, even in patients who seem to have a primary benign disorder.

The examination is suggested to be targeted, according to the information obtained from the history. Some parts of physical examination are essential in most patients with headache (Table 1.14) [72]. Some parts of assessment such as mental state, motor, and gait assessment might be performed during conversation or while the patient is moving to sit next to the examiner.

- Blood pressure measurement is essential in any HA patient, as acute hypertension might cause HA, although some patients with migraine or tension HA have low or low normal BP [73].
- Manual examination is an essential part of assessment in all patients with HA. The aim is mainly to look for tender points in muscles, ligaments, or tendons of the head, face, or neck. These myofascial tender points are commonly present in patients with migraine and TTH. HA can be

Table 1.14 Essential examinations in most patients with headache.

Measurement of blood pressure and temperature
Examination for tender points in head, face, and or neck
Examination of nose, ears, mouth, and temporo-mandibular joints
Examination of mental status
Examination of cranial nerves (focus on ophthalmoscopy)
Motor examination
Gait examination

provoked by palpation of these myofascial triggers; if so, it may be assumed to some degrees that HA is of a primary benign type. The examiner should firmly palpate muscles such as trapezius, sternocleidomastoid, levator scapulae, posterior superior cervical, and masticatory muscles. Both sides should be compared to determine the muscles that are more involved in that patient [74,75]. Tender points in patients with primary HA disorders may be a guide to alternative therapies, since these patients may respond better to local therapies including injection and manual interventions. Migraine patients may have scalp tenderness or allodynia. This could be due to central sensitization, which indicates development of CM.

- Examination of the TMJ is an important part of examination in patients with pain in or around the TMJ. The TMJ pain may extend to the ear, postauricular zone, temporal area, or downward toward the maxilla. It should be particularly considered when the pain is produced or exacerbated by chewing, yawning, talking, or even swallowing.
- The Cottle sign is evaluated by a simple maneuver to check for obstruction of nasal airways. The examiner uses the index finger to draw the patient's cheek laterally away from the midline, opening the nasal opening away from the septum. If the patient appreciates an improvement in nasal breathing, nasal airway obstruction is present. This may be due to turbinate hypertrophy or deviated septum or other pathologies. In this case, an ENT consultation and/or a paranasal sinus CT scan may be considered.
- Mental status examination is usually started during physical and completed thereafter if required. HA associated with mental clouding indicates encephalopathy, which may have an infectious, inflammatory,

toxic, or metabolic cause. Migraine with brainstem aura may be associated with decreased levels of consciousness.

- Cranial nerve assessment is the most important part of examination in patients with HA, which provides the most informative data for secondary disorders by an abnormality found in cranial nerves. Cranial nerves 2–7 are the most important nerves in this regard (Table 1.15).
- Fundoscopic examination to search for increased ICP may be the one examination that should be performed in every patient with HA. Disc hyperemia and absent venous pulsation are seen in the earliest stages of papilledema, which may be ignored. Spontaneous venous pulsation is absent in up to 20% of the normal population, so its absence may not have diagnostic value, while its presence is against increased ICP. With worsening of papilledema, the classic findings such as blurring of vessels at disc margins and elevation of disc borders become obvious and hemorrhages or exudates may appear on or near the disc edge. If increased ICP and papilledema are untreated and become chronic, secondary optic atrophy ensues. In this condition, some disc pallor is superimposed on the blurred disc and retinal arterioles become narrower. This stage is an alarm for the risk of persistent visual loss. Papilledema is not associated with reduced visual acuity until the late stages of optic atrophy. This is in contrast to papillitis (optic neuritis), which is accompanied by early and rapid central visual loss. The same is true for pupillary reaction that is spared in papilledema but is characteristically impaired in optic neuritis. Papilledema should be monitored closely in patients with increased ICP to prevent permanent visual loss.
- Examination of pupils is of particular significance. The pupillary size and reactivity to light (direct and consensual response) should be checked. Optic nerve lesions, even when causing unilateral blindness, do not cause significant anisocoria. The consensual response is better than the direct

Table 1.15 Most important parts of cranial nerve examination in patient with headache.

Visual acuity, Fundoscopy (cranial nerve 2)
Pupillary size and reactivity (cranial nerves 2 and 3)
Extraocular movements (cranial nerves 3, 4, and 6)
Facial sensation and movements (cranial nerves 5 and 7)

response in unilateral optic neuropathy, which is known as afferent pupillary defect or Marcus Gunn pupil. Anisocoria could be a physiologic phenomenon in 20% of the people. Here the difference in pupillary size is 1 mm or less with an equal size in light and dim rooms and both react well to light.

- Horner's syndrome is an important finding in a patient presenting with HA. The full triad is a combination of ptosis, miosis, and facial anhydrosis on the same side. Ptosis is mild and less than 3 mm. Dark or dim rooms make anisocoria more prominent because the meiotic pupil does not dilate as do normal pupils. The association of headache or neck pain with Horner's syndrome (painful Horner's) is particularly suggestive of the dissection of ICA or VA, but other causes should also be considered according to the location of the sympathetic pathways lesion (Table 1.16).

The full triad may not be present in all cases of painful Horner syndrome. Facial anhydrosis is associated with involvement of the first and second order neurons (before the level of superior cervical ganglion). Therefore, it is not seen in patients with lesions in third order neurons such as ICA dissection. The full triad of Horner syndrome is present in conditions such as VA

Table 1.16 Causes of Horner syndrome.

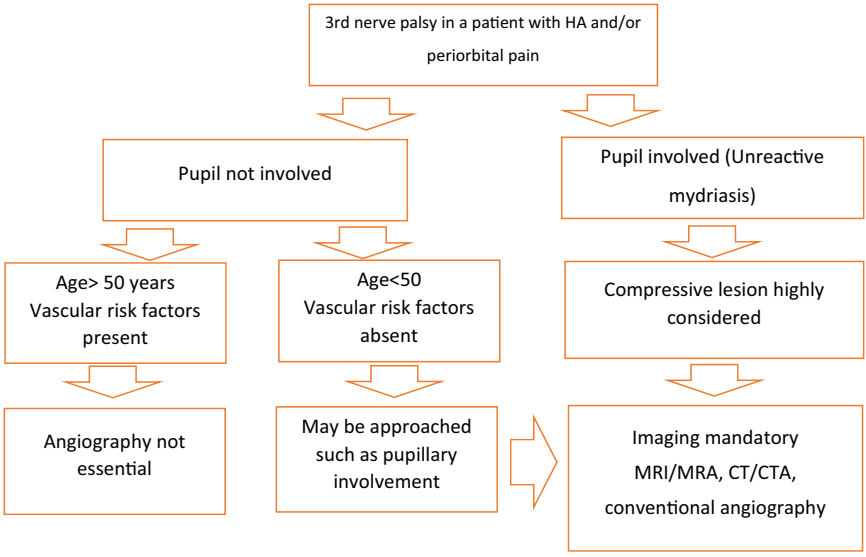
Localization of Horner syndrome	Anatomical distribution	Causes
First order neuron	From hypothalamus to spinal cord sympathetic chain at C8-T2.	Brainstem strokes VA dissection Chiari malformation Skull base tumors
Second order neuron (preganglionic)	From spinal cord to superior cervical ganglion.	Lung apex lesions Thyroid or other cervical cancers Mediastinal tumors Subclavian aneurysm
Third order neuron (postganglionic)	From cervical ganglion to targets	ICA dissection Cavernous sinus lesions Cluster HA Tolosa hunt syndrome GCA

dissection, lung tumors, or other pathologies of the first- and second-order neurons.

- Third nerve palsy causes a more severe ptosis (6—7 mm) with paresis of extraocular movements. Acute third nerve palsy with mydriasis indicates a compressive pathology (tumor or aneurysm) and mandates further investigation. The approach to cases with pupillary sparing depends on the age and the presence or absence of vascular risk factors (**Algorithm 1.2**). The approach to acute painful third nerve palsy without pupillary involvement in patients under 50 who do not have vascular risk factors is similar to approach to patients with pupillary involvement. Microvascular third nerve palsy typically occurs in patients above 50 years with vascular risk factors. It often starts with periorbital pain or HA (sometimes severe) for several days and usually resolves spontaneously within a few months.
- A serious cause of recent onset HA and third nerve palsy that may be underdiagnosed is GCA. There is pupillary sparing as described for microvascular causes. Painful third nerve palsy is often simply attributed to a more benign microvascular ischemic cause in older patients and the diagnosis of GCA might be missed [76].
- A kind of palsy similar to microvascular ischemic sixth nerve palsy associated with pain may occur in patients above 50 years or those with vascular risk factors.
- Examination of trigeminal and facial nerves is very important in patients with facial pain. Trigeminal nerve innervates the temporalis, masseter, and pterygoid muscles that are responsible for clenching and lateral movements of the jaw and provide sensation to the face (V1, V2, V3 territories). The examination of the fifth nerve should be completely normal in idiopathic TN. Any sensory and or motor abnormality indicates a secondary trigeminal neuropathy rather than TN.
- Numbness or paresthesia in the chin is described as numb chin syndrome (NCS). Lip and gingiva may also be involved. NCS should be treated as a warning symptom for malignancy. It is unilateral in 90% of the cases and may be due to invasion or infiltration of inferior alveolar nerve by systemic or local tumors as it passes into the

mandible. Breast cancer and lymphoma are the most common systemic cancers [77].

Algorithm 1.2. Approach to patient with painful third nerve palsy.



- Head and neck cancers (involving the skin, oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, and salivary glands) may spread via the peripheral nerves along with other forms of spreading. The pathology may be squamous cell carcinoma, basal cell carcinoma, melanoma, lymphoma, or other types. This perineural spread most commonly involves the trigeminal and facial nerves. It is manifested by pain, paresthesia, and numbness in trigeminal nerve territory (especially V3) and facial weakness [78]. Facial weakness may be wrongly attributed to an old Bell's palsy in a patient presenting with facial pain [72].

Imaging in HA

Primary HAs are characterized by the absence of an identifiable cause including structural lesions. The diagnosis is made by history taking and there should not be any relevant lesions in imaging studies. Therefore, brain imaging is not indicated in patients with typical primary HA who have stable patterns.

- In a group of patents, HA looks like migraine, while it has atypical features or accompanying symptoms that do not fulfill the ICHD criteria. More investigation is required to exclude mimicking conditions in this group of patients with migraine like HA (Table 1.17).
- Similarly, patients with typical TTH do not require imaging. However, imaging is justified if there are unexpected findings such as progression of symptoms or inadequate response to treatment. This is because HA associated with brain tumors is more similar to TTH.
- Patients with TACs are exceptional among primary HA disorders because imaging is recommended in all cases. The most common pathologies in secondary TACs are intracranial tumors, particularly pituitary adenomas. Other less common but important causes such as vascular etiologies (aneurysm or dissection) and infections (sphenoid sinusitis) should not be missed [79].
- Therefore, it is not the phenotype of HA but the presence or absence of red flags and clinical judgment that determines the need for imaging. Investigation of patients with HA is an individualized decision based on what is obtained in history taking and clinical examination of an individual patient. The aim should be to investigate "*The RIGHT patient by the RIGHT imaging modality in the RIGHT time with the RIGHT sequence*" [80].

Table 1.17 Atypical features that mandate imaging in patients with migraine like HA.

Atypical feature of migraineous HA	Some alternative causes to consider
Change in the pattern	CVT, structural lesions, sinus, or CNS infections
Clearly remembered onset	New daily persistent HA (NDPH); consider secondary causes
Side locked HA	Cervical artery dissection, structural lesions, TACs
Personal or strong family history of dementia	CADASIL
History of stroke like episodes	MELAS, CADASIL
Prolonged aura (>1 h)	Structural lesions
Motor aura	Structural lesions

Table 1.18 Identification and investigation of acute severe onset HA.

Clinical presentation	Etiologies	Most helpful imaging modalities
Acute severe HA not experienced before	Subarachnoid hemorrhage	Brain CT in the first 24 h Brain MRI (FLAIR) after day 1 Brain CTA/MRA/DSA Repeat angiography if negative
Acute HA and neck pain Side locked HA and neck pain Stroke in younger adults Head or neck trauma in recent days Painful horner syndrome	Dissection of cervical arteries	T1 axial fat suppressed MRI of skull base Cervical CTA/MRA Carotid duplex sonography
Acute or subacute progressive HA in appropriate setting	Cerebral vein thrombosis	Brain MRI (GRE, T2) and with contrast MRV with contrast
TCH Orthostatic HA	Spontaneous intracranial hypotension	Brain MRI with contrast Spinal MRI w/o contrast or CT myelography to detect leak site
Recurrent TCH Ischemic or hemorrhagic stroke in appropriate clinical setting	RCVS	Plain brain MRI Brain CTA/MRA/DSA Repeat MRI or angiography as needed
Acute onset severe HA ± ocular motor nerve involvement	Pituitary apoplexy	Brain CT/MRI (especially flair and with contrast)
Acute HA after positional change ± altered consciousness	Colloid cyst of 3rd ventricle	Most easily seen on CT scan
Acute HA ± neurological deficits	Cerebral infarction	Brain MRI (especially DWI/ADC sequences)
Acute HA AND blurred vision, seizure or confusion	Acute hypertensive crisis, PRES	Brain MRI (FLAIR)

Table 1.18 Identification and investigation of acute severe onset HA.—cont'd

Clinical presentation	Etiologies	Most helpful imaging modalities
Acute onset transient severe HA (sentinel HA)	Unruptured intracranial aneurysm	Brain CTA, MRA, or DSA
Subacute progressive HA (mainly retro-orbital or vertex pain)	Sphenoid sinusitis	Paranasal sinus CT scan Brain MRI
Acute HA + fever ± neurological findings	Meningitis, encephalitis	Brain MRI ± contrast
Acute HA after Valsalva maneuver	Cough HA	Brain MRI Brain MRA, CTA, DSA
Acute HA after exercise	Exertional HA	Brain MRI MRA, CTA, DSA
Acute HA after sexual activity	HA with sexual activity	Brain CT Brain MRI Brain MRA, CTA, DSA

- Appropriate selection of the imaging modality for patients with acute severe onset HA or TCH depends on the impression according to the initial clinical assessment (Table 1.18).

In patients with acute severe HA or TCH, the priority is to rule out SAH. In the first 24 h, a brain CT scan has a very high sensitivity in detecting SAH, so it is the first imaging modality in the emergency setting. After 3 days, the sensitivity of the CT scan for detection of SAH decreases markedly and MRI is preferred. Conditions where CT or MRI is preferred for

Table 1.19 Conditions where CT is preferred over MRI in patients with HA.

TCH in the first 24 h (suspected SAH)
Acute trauma
Paranasal sinus infections (including sphenoid sinusitis)
Rhinogenic HA
MRI contraindicated
Evaluation of bone

Table 1.20 Conditions when MRI is preferred over CT scan in patients with HA.

Dissection of cervical or cerebral arteries
SAH after 3 days (subacute stage)
Cerebral vein thrombosis
Spontaneous intracranial hypertension
Space occupying lesions
Pseudotumor cerebri syndrome
Infective disorders (meningitis, encephalitis, abscess)
Inflammatory disorders (CNS vasculitis)
Multiple sclerosis, antiphospholipid antibody syndrome
Arnold Chiari malformation
CADASIL, MELAS
Pregnancy
Children

Table 1.21 Standard MRI protocol in patients with HA.

Axial 5 mm T1-T2-FLAIR and DWI
Sagittal T2 and FLAIR
Coronal T2, 3 mm through circle of Willis

investigation in patients with HA are shown in Tables 1.19 and 1.20. A standard MRI protocol is shown in Table 1.21.

There are some conditions when a CT scan is the preferred modality (Table 1.19). A brain MRI with a standard protocol is the modality of choice in most patients (Table 1.20). It lacks the risk of radiation and can reveal many pathologies that may be missed in CT scan if performed according to the standard protocol (Table 1.21). Contrast-enhanced MRI is requested when initial impression predicts a chance of yielding positive findings (Table 1.22). It may be the first or the next modality based on the condition.

Laboratory and other investigations in headache

There are some important secondary HA disorders in which imaging is normal and specific laboratory tests are diagnostic.

Table 1.22 Indications for MRI with contrast in primary and secondary HA disorders.

Trigeminal autonomic cephalalgias
Primary headaches with atypical features
Cough headache
Space occupying lesions
CSF leak syndrome (SIH)
Infective disorders
Inflammatory disorders
Known history of cancer, AIDS, or infectious disease
Facial neuralgias (including trigeminal neuralgia)

- Erythrocyte sedimentation rate (ESR) is an essential study in every patient with new-onset HA after age 50 to exclude GCA. A normal ESR is estimated by the formula of age/2 in men and age+10/2 in women. It is usually increased to more than 50 in patients with GCA. It is important to consider that the value of a normal ESR for excluding GCA may be overestimated and a minority of patients may have normal ESR levels. Increased C reactive protein (CRP) might be a more sensitive index of inflammation in GCA with a sensitivity of up to 97.5%. The sensitivity increases when both ESR and CRP are checked. Therefore, a normal ESR may not exclude GCA, but a combination of a normal ESR and CRP can be considered as a reliable marker for excluding GCA with a high degree of certainty. Normocytic anemia and thrombocytosis are other probable findings in GCA [81–83].
- Thyroid function tests are suggested in patients with chronic HA or patients with migraine who experience exacerbations without an obvious cause or those who do not respond adequately to treatment [57–59].
- The serum prolactin level should be checked in men or women with HA who have decreased libido, impotence, infertility, galactorrhea, or oligomenorrhea. A prolactin secreting pituitary adenoma may be the cause, but there are many other conditions associated with hyperprolactinemia. Physiologic conditions (pregnancy, lactation, breast stimulation, and stress), drugs (such as antipsychotics, H2 blockers, SSRIs, SNRIs), OCPs, chronic renal or liver diseases, and hypothalamic lesions are among other causes of hyperprolactinemia [84,85]. The diagnosis of prolactin secreting pituitary adenoma is suspected when the prolactin level is significantly elevated (usually above 200 ng/mL) [86]. Less increase in

prolactin levels is usually due to other causes such as drugs and chronic renal disease rather than pituitary adenoma. Many types of HA are seen in pituitary adenoma including TACs, migraine, and sometimes TTH. In practice, most headaches associated with pituitary microadenomas and hyperprolactinemia are of migraine type and may respond to antimigraine prophylactic treatment. It seems that increased prolactin levels can also exacerbate an existing migraine HA [87].

- In patients with episodes of HA associated with unusual behavior and impaired consciousness, increased levels of insulin and c-peptide are compatible with a diagnosis of insulinoma [88].
- Pheochromocytoma is a probable diagnosis in hypertensive patients who have paroxysmal short duration pulsatile HA often in association with sweating, palpitation, or anxiety. Increased levels of plasma metanephrine and 24-hour urine total catecholamines, vanillylmandelic acid, and metanephrines are diagnostic.
- Preeclampsia and eclampsia are diagnosed by increased urinary protein excretion of more than 300 mg per 24 h and hypertension.
- When a patient has recurrent attacks of migraine type headaches along with seizures or stroke-like episodes, the possibility of a mitochondrial disorder should be suspected. Mitochondrial encephalopathy with lactic acidosis and stroke (MELAS) is a disorder with maternal inheritance. The serum levels of lactate and pyruvate may be elevated on initial screening; however, genetic testing on leukocytes, skeletal muscle, hair follicles, urine sediment, or mucosal biopsies is needed to demonstrate abnormalities in mitochondrial DNA to confirm the diagnosis [89].
- A clinical combination of migraine with aura, recurrent strokes, dementia, and positive family history suggests CADASIL. There are characteristic multiple confluent white matter lesions on brain MRI. Genetic testing for NOTCH3 mutations on chromosome 19 or skin biopsy for the characteristic nodules on arterial walls due to the presence of abnormal protein confirms the diagnosis. The specificity and sensitivity of the skin biopsy are above 90% [90].
- Assessment of CSF is part of HA investigation in certain conditions. It is abnormal and diagnostic in almost all patients with CNS infections. It may be the diagnostic test in patients with SAH and carcinomatous or lymphomatous leptomeningeal involvement. CSF examination, when done in the right time frame of 12 h−2 weeks, is useful for the diagnosis of SAH. It may reveal xanthochromia by visual inspection or spectrophotometry in the second week when imaging is not sensitive enough

for detecting SAH. Headache and Neurological Deficits with CSF Lymphocytosis (HaNDL syndrome) is a self-limited disorder characterized by recurrent attacks of migraine-like HA and transient neurological deficits. Most patients are confused during the episodes. CSF analysis reveals lymphocytosis, which is diagnostically very helpful along with the clinical picture [91].

- Polysomnography is indicated in patients with morning or wake-up HA who have symptoms such as snoring, fatigue, poor concentration, or excessive daytime somnolence to evaluate obstructive sleep apnea. This investigation should be especially considered with a low threshold in obese men with short necks who snore. Treatment can prevent long-term complications such as hypertension and increased cardiovascular morbidities and mortality.
- Other paraclinical investigations may be indicated in certain conditions. EKG and or exercise tolerance test can confirm cardiac ischemia in a patient with HA after exercise (cardiac cephalalgia). EEG may show evidence of epilepsy in a patient with morning HA and suspected seizure attacks during overnight sleep.

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CHAPTER TWO

Migraine

Mansoureh Togha[1,2]
[1]Iranian Center of Neurological Research, Headache Department, Neuroscience Institute, Tehran, Iran
[2]Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran

Introduction

Migraine headache is now a hot topic among different types of headache and is on the WHO list of 10 debilitating diseases. There is now a shift of attention toward its physiological and pathophysiological basis as well as new treatments.

Its prevalence varies from 9 to more than 20% in different communities and is higher in women than men [1]. The high prevalence of this headache and the resulting disability mandate special attention. In practice, migraine is divided to two types: migraine with aura and migraine without aura. Patients suffering from migraine with aura commonly experience attacks without aura. Pure migraine with aura is much less prevalent.

Clinical signs: typical migraine attack may have four phases:

1 **Prodromal phase:** It occurs hours to days before headache and may be associated with hyperactivity, hypoactivity, craving for particular foods, repetitive yawning, neck stiffness or pain, and fatigue. Craving for particular foods, like potato chips, cocoa, etc., is more common in children, which may trigger headache.
2 **Aura**: An aura is transient neurological symptoms usually lasting a few minutes to an hour before headache. It does not appear suddenly and is complete within 5 min or more. An aura may accompany the headache and should not necessarily precede it. An aura may manifest as visual, sensory, brainstem, motor, or retinal disturbances or a speech and/or language problems. It is not uncommon for sufferers to experience more than one type of aura.

Visual aura is the most common form of aura that is often perceived as defects, bright lines, or blobs in the visual field. The lines are usually black and white. Sensory aura is less common than visual aura followed by aphasia. The usual duration of an aura is about 30 min up to 1 h but it might be even longer than 3 days and overlap the headache. One aura is commonly shorter

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than two or more consecutive auras [2]. Aphasic aura and visual aura are usually shorter than sensory or motor auras. In hemiplegic migraine, motor aura may even last more than 1 week [3].

Red flags for aura symptoms

- If a visual aura manifests as colorful circles, secondary causes like AVM in the occipital region should be ruled out.
- If an aura is very short or very long, if it reaches its peak intensity in less than a minute, or if it starts after the age of 40 years, other causes, especially ischemia, should be considered.
- Negative aura symptoms like hemianopia should raise suspicion of other causes.
- It is recommended that motor auras be considered a red flag and secondary causes be investigated.

3 **Headache:** This phase lasts for 4—72 h in adults and from 1 to 2 to 72 h in children. The headache

A. is usually unilateral or is more intense on one side.
B. is pulsatile in part of its duration or during activities like bending.
C. is moderate to severe in intensity.
D. worsens by walking, physical activity, and climbing up or down the stairs.

If a person experiences a headache with similar features meeting at least two of the above characteristics and duration for at least five times that is associated with nausea and/or photophobia and phonophobia, it is a migraine headache.

Important notes

- The headache is usually bilateral in children and felt in the frontotemporal region.
- Caution should be exercised about occipital headaches.
- Although autonomic signs like tearing, red eye, and rhinorrhea are not characteristic features of migraine, they may be seen in a number of migraine attacks and are usually bilateral. However, they may be present only in the affected side, as well.
- Migraine without aura may markedly worsen before or around menstruation, which is a useful sign for diagnosis of migraine headache.

4 **Postdrome:** This phase occurs once the headache has resolved. The person may feel tired or have diarrhea and/or urinary frequency. Phases 1, 2, and four are not necessarily seen in all migraine sufferers.

Migraine with brainstem aura

It is a type of migraine that was previously known as basilar migraine. In this type of migraine, in addition to sensory or visual aura, other disturbances like dysarthria, vertigo, ataxia, tinnitus, hypacusis, diplopia, or decreased consciousness may be present. TIA should be ruled out. Aura should be completely reversible and have all the aforementioned characteristics [4]. Motor or retinal symptoms are not categorized as brainstem aura. In the majority of migraine attacks with brainstem aura, typical auras, mainly visual aura, are also present. The patients may also experience other migraine attacks with typical auras without brainstem symptoms.

Hemiplegic migraine

In this type of headache, other auras such as hemiplegia accompany common visual or speech disturbances. Common auras have the above-mentioned characteristics and last for 60 min but motor auras may continue for 72 h to some weeks [4].

If an aura precedes the headache or occurs with it, attention should be paid to rule out cerebral ischemia. Patients suffering from hemiplegic migraine may experience migraine attacks without motor aura.

Hemiplegic migraine is considered sporadic if it is not seen in other first- and second-degree relatives. It may be familial and other family members may also have migraine with brainstem aura. Most of the affected cases experience the first attack during their childhood or adolescence although it may occur in a wide age range of 1−51 years. About half of the patients experience progressive cerebellar ataxia not associated with headache attacks.

Impaired consciousness, fever, and CSF pleocytosis may be seen in rare cases of hemiplegic migraine [5].

Vascular diseases and epilepsy are the main differential diagnosis.

Retinal migraine

Retinal migraine is defined as frequent attacks of visual impairment in the form of positive phenomena such as scintillation or negative ones such as

dark spots or regions or even blindness together with migraine headache that is reversible and has the characteristics previously described for an aura [4]. Other causes of visual impairment like ischemic disorders should be ruled out to make a diagnosis of retinal aura. There are rare case reports of persistent monocular visual impairment with migraine headache but it is necessary to assess and rule out other possible causes before making such a diagnosis.

Periodic syndromes associated with migraine

Periodic disorders are usually more common in children but they may start in adulthood. These disorders occur in patients suffering from migraine with or without aura and usually occur in the background of a positive family history.

1 Abdominal Migraine: It is defined as a periodic abdominal pain or discomfort with vomiting or anorexia that may last for 2–72 h [4]. This diagnosis can be proposed when the results of gastrointestinal evaluations are negative.
2 Cyclic vomiting syndrome: This condition is defined by severe attacks of nausea and vomiting that repeat occasionally. Its timing is sometimes predictable. The attacks may be associated with pallor and weakness. The patients are symptom-free between attacks. According to the diagnostic criteria, nausea and vomiting should repeat at least 4 times per hour and each attack lasts for 1 h to 10 days with an interval of at least 1 week between attacks. Gastrointestinal assessment should be unremarkable [4]. These patients may experience episodes of motion sickness and periodic sleep disorders like sleep bruxism, night terrors, sleep talking, and sleep walking.

Migraine triggers and their management

The first step to headache management is determining the triggers for the headache attacks and their avoidance for susceptible persons. Migraine attacks can be initiated by several extrinsic and intrinsic factors which must be pinned down, as abstaining or restraining exposure to them is a crucial aspect of nonpharmacological migraine control. A combination of triggers can initiate, worsen, or even prolong a headache attack and the physicians should direct their patients to recognize and record triggers in a headache diary. Common examples of such combinations are long work hours

without breaks for meals or for a change in posture. Other triggers can be lack of sleep, especially during menstruation, a prolonged fixed posture in front of an electronic device, and insufficient consumption of liquids. Although some triggers, such as menstruation, are by themselves sufficient to evoke a migraine attack, the addition of other triggers may induce even more severe headache attacks and should be taken into account [6].

A trigger such as emotional stress during the daytime could lead to a headache attack at night while sleeping and a food trigger may not produce an effect for 1 or 2 days. Persons with high frequency or severe headaches, those who have only a slight response to or sensitivity to abortive medications, as well as pregnant or breast-feeding mothers, are highly recommended to record all possible trigger factors for their headaches and manage them as much as possible [7].

Some common, but manageable, triggers or stimulating factors can be found here [8].

- Changes in climate or in the weather, such as extreme high or low temperatures, an atmospheric pressure change, and elevated humidity, can induce migraine headache attacks in susceptible persons [9].
- Sleep disorders, insufficient or excessive sleep duration, sleep deprivation, irregular sleeping times, sleep apnea, or insomnia all can be triggers for a migraine attack [10,11]. It is evident that improving the quality of life could alleviate migraine headaches [12].
- Dietary issues are important with respect to migraine triggers. Irregular meals, fasting, high-carbohydrate or high-fat diets, insufficient liquid intake, high caffeine consumption, reliance on unhealthy snack foods, and those rich in tyramine are common migraine triggers [13].
- Additionally, low levels of activity, obesity, anxiety, and depression are factors that can induce or worsen migraines. Migraineurs should strive for regular exercise, to maintain or achieve a normal weight, and seek of psychological issues. These actions all can lead to improvement in the frequency and severity of migraine [14,15].

Headache diaries can help uncover triggers and aid in better management of migraines. Lifestyle modifications, such as proper sleep, exercise, regular meals, maintaining an ideal weight, avoidance of prolonged fixed or incorrect neck posture while at work and while using electronic devices, as well as stress management, are recommended for headache control.

Treatment of acute migraine attack

Mild to moderate headache

NSAIDs and Acetaminophen: Acetaminophen might be the drug of choice in this group, which should be taken with an antiemetic drug if there is excessive vomiting. It seems that the effect of acetaminophen 1000 mg plus metoclopramide 10 mg is equal to sumatriptan. Ibuprofen and diclofenac have a faster absorption and a shorter half-life; therefore, they are better options in patients whose headache reaches its peak intensity sooner. Naproxen has a longer half-life and is more suitable for patients with prolonged headaches. The soluble and powder form of ibuprofen and diclofenac is absorbed faster than their tablets. The effervescent form of ASA 1000 mg has a rapid absorption rate, too.

- Acetaminophen has hepatotoxic side effects at doses exceeding 4000 mg per 24 h [16].
- Ibuprofen is a good drug but has a short half-life of 2 h. It seems that taking more than 400 mg ibuprofen at each dose is not more effective than 400 mg. There is good evidence regarding the use of acetaminophen in migraine headache. It is associated with less gastric irritation, and since it does not block prostaglandin synthesis in platelets, it does not affect the platelet function.
- Diclofenac has a half-life of 2 h and can be administered at a dose of 50–100 mg/day safely [17].
- Ketorolac is not well studied but it seems to be a good choice due to its rapid absorption (less than an hour) and long half-life (5 h). It is usually administered at a dose of 10 mg, but doses up to 40 mg/day can be used. It is recommended to not administer the drug for more than 5–7 consecutive days to minimize the risk of renal and GI toxicity.
- Parenteral ketorolac has been studied for severe migraine headache in the emergency department setting with good results (Table 2.1).
- Antiemetic drugs are recommended for patients with nausea/vomiting. Metoclopramide, domperidone, and prochlorperazine can each be added to all acute treatment strategies discussed above [18–24] (13).

Combined Pills: Acetaminophen/aspirin/caffeine or acetaminophen/ibuprofen/caffeine tablets are more effective than each drug alone. Considering the shorter time to induce MOH, serious advice should be given to patients regarding limiting the number of administration days in a month.

Table 2.1 Analgesics dosage for treatment of migraine attacks.

Medication	Usual dose	Maximum dose per day
Acetaminophen	1000 mg	4000 mg/d
Ibuprofen tablets	400 mg	2400 mg/d
Ibuprofen solubilized (liquid) tablets	400 mg	2400 mg/d
Diclofenac potassium tablets	50 mg	100 mg/d
Diclofenac powder for oral solution	50 mg	Maximum single dose/ d recommended
Naproxen sodium	250–500 mg (up to 825 mg)	1375 mg/d
Acetylsalicylic acid	500–1000 mg	4000 mg/d
Effervescent acetylsalicylic acid	500–1000 mg	2000 mg/d
Indomethacin cap/tab	50–75 mg	200 mg/d
Indomethacin suppository	50–100	200 mg/d
Ketorolac IM injection	30 mg	60–120 mg

Moderate to severe headache

Triptans: Triptans are serotonergic agonists with greater effects on 5-HT1b and 5-HT1d receptors. Triptans are believed to be more effective than NSAIDs in migraine attacks and are advised especially in moderate to severe headache.

Although the effect of ergotamines is similar to triptans, they are less specific and affect other receptors, thus having more side effects. There are currently seven oral triptans with similar molecules but slightly different pharmacokinetic properties. If the patient develops side effects or fails to respond to one type of triptans, another triptan may be tried. Subcutaneous sumatriptan has the best and fastest effect although it can induce more nausea and vomiting. Zolmitriptan nasal spray also acts rapidly and can be used in children and adolescents as well. Melt forms of zolmitriptan and rizatriptan induce less vomiting.

If headache is associated with marked vomiting, oral metoclopramide 10 mg, prochlorperazine 10 mg oral or 10–25 mg suppository, domperidone 10 mg oral, or promethazine 25 mg oral can be administered with NSAIDs or triptans. Except for domperidone, other drugs are also effective

in controlling migraine headache but extrapyramidal side effects are always a concern. Because domperidone does not cross the BBB, it does not cause extrapyramidal symptoms. Metoclopramide enhances the absorption of other abortive drugs through its prokinetic effect and is thus helpful in this regard.

The effect of ondansetron in migraine has not been evaluated well.

A combination of NSAID and triptan is more effective in providing a higher 2-h headache relief rate, a higher 24-h sustained pain-free period, and a lower 24-h recurrence rate. A combination of sumatriptan 50 mg and naproxen 500 mg is now available in the market and is a good choice in severe migraine attacks.

- Patients who have recurrent headache attacks can take a triptan or NSAID as the next dose.
- Taking abortive drugs exactly at the onset of headache is important to prevent recurrence. A lower recurrence rate is expected with eletriptan and frovatriptan.
- Dihydroergotamine subcutaneous injection or nasal spray is the most effective drug in prevention of recurrence but possible side effects limit its use.

If the first dose of a triptan is not effective at all, the next dose might also be ineffective. However, if the first dose partially resolves the attack, the next dose in 2 h is probably more effective.

Migraine sufferers may experience different attacks in terms of duration and intensity, so different drugs may be needed according to the type of each attack. If a patient cannot take triptans for any reason, acetaminophen/ASA/caffeine or acetaminophen/ibuprofen/caffeine tablets are a good option.

- If a patient wakes up with a headache, does not respond to oral triptans, or has nausea and vomiting, subcutaneous sumatriptan may be the best choice.

Eletriptan acts fast and has a prolonged efficacy. Almotriptan, frovatriptan, and naratriptan have a prolonged efficacy, as well (Table 2.2).

- Opioids should be strictly avoided; however, codeine or tramadol may be occasionally used (in combination with other analgesics) in refractory attacks [17].
- In the acute phase of hemiplegic migraine, retinal migraine, or migraine with brainstem aura, it is better to use adequate doses of simple analgesics like aspirin or NSAIDs as triptans may not be safe.
- Serotonin 5-HT1F agonists (ditans):

Table 2.2 Pharmacodynamics and dosage of triptans.

Triptan	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan
Onset of action	++	++			Melt form is especially helpful if headache is associated with nausea	Six milligram SC produces response	Five milligram nasal is more effective than oral and is recommended in young adults.
Dose in 24 h	12.5–25	40–80 mg	2.5–7.5 mg	2.5–5 mg	10–30 mg	50–200	5–10
Onset of action	++	+++	+	+	+++ No difference between melt and common form	++ Melt or nasal form	++ (Nasal)
Half-life	+	+	++	++	+	+	+
Recurrence prevention in 24 h		+++	+++		+	+	
Side effects	+					++	

Lasmiditan (COL-144), a new interesting drug, is a selective 5-HT1F agonist at the receptor site. It seems that the drug is safe and has good efficacy as an abortive drug for migraine attacks. Activation of 5-HT1F receptors decreases the expression of c-Fos, a marker of neuronal activation, in the trigeminal nucleus caudalis. This drug does not have vascular effects. Therefore, the superiority of this new drug to triptans is its safety for patients with cardiovascular diseases. It can be used at a single dose of 50, 100, or 200 mg orally in 24 h as needed. The most common adverse effects are dizziness, paresthesia, somnolence, fatigue, and nausea that usually are mild [25].

- Gepants, anti-CGRP receptors:

The first oral anti-CGRP receptor, Ubrogepant, has been approved for migraine headache attacks. It improves the headache and the associated symptoms including photophobia, phonophobia, and nausea. This drug is safe in patients with cardiovascular diseases. A dose of 50−100 mg is effective to abort the attack and the second dose might be used at least after 2 h with a maximum dose of 200 mg per attack. The rate of adverse effects with this drug, including nausea, somnolence, and dry mouth, is usually low and mild [26,27]. It is contraindicated for coadministration with strong CYP3A4 inhibitors such as clarithromycin, erythromycin, diltiazem, ketoconazole, and verapamil.

- New drugs are being tested in different trials such as new gepants, glutamate receptor antagonists, nitric oxide synthase inhibitors, orexin receptor antagonists, which might be proposed for acute migraine attacks in the future (Table 2.3).

Status migrainosus treatment

It is a migraine headache lasting for more than 72 h. Its treatment includes the following:

1 IV dihydroergotamine (DHE): It is very effective with few side effects and results in full recovery in two-thirds of the patients and relative recovery in the rest. Studies have shown that it can be safely used in adolescents. According to the literature, seven doses are required to achieve optimal results. The usual dose is 0.5−1 mg every 8 h until the attack has abated or the maximum dose has been given plus an additional dose to prevent recurrence. Oral or parenteral metoclopramide or prochlorperazine can be used to relieve nausea associated with its administration. It seems that prochlorperazine is also effective in controlling headache and its

Table 2.3 Recommendation for abortive drug selection.

Severity of attacks	Medications
Mild to moderate	Acetaminophen, acetylsalicylic acid, ibuprofen, naproxen sodium, diclofenac potassium
Moderate to severe	Sumatriptan, rizatriptan, eletriptan, zolmitriptan, almotriptan, frovatriptan, naratriptan
Refractory	Combination of triptan and nonsteroidal antiinflammatory drugs, combination of dihydroergotamin and various rescue medications (e.g., dopamine antagonists), combination analgesics without opioids, combination analgesics with opioids (not for routine use)
Strategies for patients with contraindication to triptans or refractory to other abortive drugs	Combination analgesics without opioids, combination analgesics with opioids (not for routine use)
New drugs for patients with contraindication to triptans or refractory to other abortive drugs	Lasmiditan, ubrogepant

recurrence although it may cause extrapyramidal symptoms. Three doses of prochlorperazine 10 mg are usually given. Chlorpromazine 0.1 mg/kg IV up to a maximum dose of 25 mg may be prescribed instead of prochlorperazine. Diphenhydramine 12.5 mg or benztropine 1 mg might be used before these antiemetics to prevent extrapyramidal side effects. Other antiemetics like ondansetron and domperidone do not have extrapyramidal side effects; however, they have no proven effects on headache. Possible Q-T prolongation following the use of domperidone is a concern.

2 Sodium valproate: If the response achieved with DHE is not satisfactory, sodium valproate may be administered at a dose of 15 mg/kg given as an IV bolus and then 5 mg/kg every 8 h until the attack abates or for a maximum of 10 doses [28]. Using valproate in divided doses every 6 h may be preferred to ensure a steady serum level (up-to-date). Its use has not been evaluated in children but it is reported to be effective in 80% of the adults [29].

3 Magnesium sulfate: IV magnesium infusion at a dose of 1−2 g can be used in adolescents and adults [30]. It seems that it is most effective when the

initial level of ionized magnesium is below normal. It is probably more effective in migraine with aura [31]. There is not enough evidence for its use in children.

4 Corticosteroids:
- Dexamethasone at a dose of 10–30 mg is safe and effective.
- Methylprednisolone at a dose of 1 mg/kg is safe and may be effective.
- Dexamethasone 8 mg or prednisolone 60 mg on the first day followed by rapid tapering in 3–4 days can be used in severe migraine attacks.
- There is not enough evidence for corticosteroids in children.

Treatment of severe headache in emergency setting

When the headache is severe enough to oblige the patient to seek an emergency visit, oral treatments are not usually effective. Intravenous (IV) NSAIDs such as ketorolac or ibuprofen, suppository or subcutaneous sumatriptan, and nasal zolmitriptan with or without intravenous antiemetics according to the patient's symptoms are recommended and might be repeated if the headache and associated symptoms recur. In the second step, intravenous administration of corticosteroids, sodium valproate, or opioids with or without antiemetics is recommended (Table 2.4) [16].

Prophylactic treatment of migraine

It seems that about 38.8% of migraine sufferers need prophylactic treatment, while only 13% of them receive it.

1 Prophylactic treatment is considered when:
2 Frequent migraine attacks impair the quality of life.
3 Migraine attacks occur 4 times or more or for a total of 8 days in a month, predisposing progression to chronic migraine.
4 Analgesic or antimigraine drugs have a little effect on attacks or their use is contraindicated [16].

The following factors should be considered when selecting a drug for migraine prophylaxis:

1 Patient's condition like age and sex
2 Coexisting diseases like PCO or psychiatric problems
3 Type of migraine (with aura, without aura, with brainstem aura, vestibular migraine) [16].
4 Social or occupational conditions of the patient including the need for more attention and concentration
5 Probable effect of the drug

Table 2.4 Less common suggested drugs and their possible side effects.

Medication	Usual dose	Selected side effects	Comments
Prochlorperazine suppository	10–25 mg Maximum 50 mg/d	Extrapyramidal symptoms, drowsiness	Dopamine antagonist, helpful for severe nausea or vomiting
Chlorpromazine tablet	10–50 mg Maximum 200 mg/d	Extrapyramidal symptoms, drowsiness	Limited evidence for efficacy
Ketorolac by IM self-injection	60 mg Maximum 120 mg/d	Gastrointestinal disturbance, renal toxicity, injection site pain	Patients must be adequately trained
Indomethacin tablet	50–75 mg Maximum 200 mg/d	Nausea, vomiting, heartburn, diarrhea, stomach pain, constipation, dizziness	Limited evidence for efficacy
Indomethacin suppository	50–100 mg Maximum 200 mg/d	Nausea, vomiting, heartburn, diarrhea, stomach pain, constipation, dizziness	Limited evidence for efficacy
Prednisone tablet	60 mg on the first day, with rapid taper over several days	Insomnia, behavioral change, other steroid side effects	Only for occasional use in prolonged attacks
Dexamethasone tablet	8 mg on the first day, with rapid taper over several days Individualized dosing	Insomnia, behavioral change, other steroid side effects	Only for occasional use in prolonged attacks

(*Continued*)

Table 2.4 Less common suggested drugs and their possible side effects.—cont'd

Medication	Usual dose	Selected side effects	Comments
Combination of analgesics with isometheptene		Depends on tablet ingredients	Isometheptene is a vasoconstrictor and should be avoided in vascular disease
Combination of analgesics with tramadol or codeine	Individualized dosing	Drowsiness, constipation	Monitor frequency of use for risk of medication overuse headache
Butorphanol intranasal	1 mg (1 spray) in one nostril, repeat once in 60–90 min if necessary; repeat two-dose sequence in 6 h if necessary	CNS depression, sedation, respiratory depression, dependence, abuse, possible addiction	Use only in exceptional circumstances and limit use to fewer than 8 days per month to avoid medication-overuse headache
Butalbital-containing combination analgesics	Avoid if possible		
Strong opiates (e.g., morphine, oxycodone)	Avoid if possible		
Acetylsalicylic acid, acetaminophen, and caffeine combination analgesics	Individualized dosing	Gastric irritation (acetylsalicylic acid), liver toxicity at high doses (acetaminophen), insomnia (caffeine)	Combinations may be more effective than individual drugs alone

6 Possible side effects of the drug
7 Patient's inclination for gaining or losing weight (Table 2.5).

Classes of medications used for migraine prevention:

1. Antiepileptics: topiramate and sodium valproate are the most acceptable drugs in this category.
   Both of these drugs have good efficacy but their side effects limit their use in the majority of migraine sufferers.
   Sodium valproate is not a good choice in overweight subjects who are of the productive age, but it could be a good drug in older women and in men.
   Topiramate is not a good selection for patients with jobs requiring high levels of concentration and those who have a history of renal stones.
2. Beta blockers: Propranolol and metoprolol are the most effective drugs in this group. The possible complications such as fatigue, cold hands, and bradycardia should be the points of concern in prescription.
3. Tricyclic antidepressants: Amitriptyline and nortriptyline are the main drugs for migraine prophylaxis in this category. They are not recommended in old or overweight patients, but they might be good choices in adolescents and in anxious or depressed patients with insomnia.
4. Serotonin Norepinephrine Reuptake Inhibitors (SNRIs): Venlafaxine and duloxetine are known SNRI drugs. Most of the studies have evaluated venlafaxine for migraine prophylaxis and showed its efficacy that is possibly higher than TCAs. It usually induces nausea, anxiety, and insomnia in the first days of its use. Therefore, it is recommended to start it at a low dose and titer it up to the optimum state.
5. Calcium channel blockers or calcium antagonists: Verapamil, flunarizine, and cinnarizine are the drugs in this group with prophylactic effects in migraine headaches. Flunarizine could be a good choice in adolescents without significant side effects and cinnarizine might be a good choice in children and in migraine associated vertigo. There is not much interest in verapamil for migraine prophylaxis, mainly because of its side effects.
6. Calcitonin Gene—Related Peptide (CGRP) antibodies: CGRP is a potent vasodilator and an important transmitter in the trigeminovascular system that is released during migraine attacks (Table 2.6).

Four monoclonal antibodies (mAbs) have been registered for migraine prophylaxis: one targets the CGRP receptor (erenumab) and three act on the CGRP peptide (fremanezumab, eptinezumab, and galcanezumab). Currently three drugs, i.e., erenumub, frenumub, and galcanezemub, with a half-life of about 1 month have been approved for treatment of migraine.

Table 2.5 Recommendations for prophylactic drug selection in different situations.

Patient group	Recommended	Not recommended
Old age	Divalproex sodium, topiramate	TCA, Ca channel blocker, beta blocker
Migraine + depression	TCA, SNRIs, SSRI	Beta blockers
Menstrual migraine	Short course NSAID Short course triptans	
Obese patients	Topiramate	TCA, sodium valproate
Slim patients	TCA, sodium valproate	Topiramate
Patients with insomnia	TCA	SNRIs, SSRIs
Hemiplegic migraine Migraine with brainstem aura	Flunarizine, acetazolamide	Amitriptyline, propranolol
Epilepsy	Topiramate, sodium valproate	TCA, SNRI
Asthma, COPD A.V block Raynaud's disease Peripheral vascular disease Severe diabetes Impotence		Beta blocker
Urinary retention Constipation Palpitation Epilepsy		TCA

Table 2.6 Overview of anti-CGRP MABs [32].

Generic name	Dose/frequency	Side effects
Erenumab	70 mg X 1 or 2 subcutaneous injections/monthly	Constipation, injection site reactions, latex allergy, upper respiratory symptoms
Fremanezumab	225 mg monthly or 675 mg quarterly	Injection site reactions, upper respiratory symptoms
Galcanezumab	240 mg (2 injections) 1st month, then 120 mg (1 injection thereafter) monthly	Injection site reactions, upper respiratory symptoms
Eptinezumab	100 mg or 300 mg intravenous/ Quarterly	Sore throat, stuffy or runny nose, muscle aches, Hypersensitivity reaction

Erenumab and galcanezumab are administered monthly. Erenumab is administered once a month using one or two 70-mg autoinjectors. Fremanezumab is available in prefilled syringes. It can be administered monthly using a single injection of 225 mg or three injections at once every 3 months. Galcanezumab can be injected monthly using an autoinjector but it is also available in prefilled syringe, depending on preference. The first month of galcanezumab requires two injections of 120 mg each, one on each side of the body as a loading dose. Then, only one injection at a dose of 120 mg is given monthly thereafter (Table 2.7).

The guideline suggested by European Headache Federation seems to be a good guide for neurologists (Table 2.8) [16,32].

Short-term preventive treatment: In certain situations, like menstrual migraine or migraine due to ascend to a high altitude, NSAIDs or triptans can be taken for 3—5 days. A single dose of indomethacin is prescribed for exercise-induced headache.

Key points on preventive treatment

1 The drug should be initiated at a low dose and increased slowly to the target dose.
2 Attention should be paid to coexisting diseases.

Table 2.7 Recommendations on the use of CGRP MABs for prevention of episodic and chronic migraine [32].

Setting	Drug
Patients with episodic migraine	Eptinezumab 100 mg or 300 mg quarterly
	Erenumab 70 mg monthly
	Erenumab 140 mg monthly
	Fremanezumab 225 mg monthly
	Fremanezumab 675 mg quarterly
	Galcanezumab 240 mg loading dose + 120 mg monthly
	Galcanezumab 240 mg monthly
Patients with chronic migraine	Erenumab 70 mg monthly
	Erenumab 140 mg monthly
	Fremanezumab 675 mg quarterly
	Fremanezumab 675 mg loading dose + 225 mg monthly
	Galcanezumab 240 mg loading dose + 120 mg monthly
	Galcanezumab 240 mg monthly
	Eptinezumab 100 mg or 300 mg quarterly

Table 2.8 Suggestions on the use of anti-CGRP MABs in subjects with migraine [32].

1. Anti-CGRP MABs are suggested in patients with episodic or chronic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects, or poor compliance.
2. In patients with episodic migraine, before starting anti-CGRP MABs, it is suggested that oral preventive drugs be stopped unless the patient has a previous history of chronic migraine before prevention; in this case, the anti-CGRP monoclonal antibody can be added to the ongoing treatment and the need of treatment withdrawal should be assessed again.
3. In patients with chronic migraine who are on treatment with any oral drug with inadequate treatment response, anti-CGRP MABs can be added to the regimen and later withdrawal of the oral drug be considered in evaluations.
4. In patients with chronic migraine who are on treatment with onabotulinumtoxin A with inadequate treatment response, onabotulinumtoxin A can be stopped before initiation of anti-CGRP MABs.
5. Oral preventive drugs may be added to the regimen in patients with chronic migraine who are on treatment with anti-CGRP MABs and may benefit from additional prevention.
6. In patients with episodic or chronic migraine, it should be considered whether treatment with anti-CGRP MABs can be stopped after 6–12 months of treatments.
7. In patients with chronic migraine and medication overuse, erenumab, fremanezumab, and galcanezumab can be used before or after withdrawal of acute medications.
8. Anti-CGRP monoclonal antibodies should be avoided in pregnant or nursing women as well as patients with alcohol or drug abuse, cardiovascular and cerebrovascular disease, and with severe mental disorders.
9. In patients with migraine on treatment with anti-CGRP monoclonal antibodies, binding and/or neutralizing antibodies should not be tested in daily clinical practice.

3 Adequate time, about 3 months, should be allowed for the administered drug to achieve the optimum effect [16]. A 50% reduction in the headache frequency indicates success. This point should be reminded to the patients at the start of prophylactic treatment [33]. The headache may subside on its own, for example, at older ages. Therefore, reevaluation is necessary during treatment.

4 Although monotherapy is the best method, a combination of two drugs may sometimes produce better results. Nonetheless, caution should be exercised regarding the dosage and side effects of the drugs; for example,

in migraine patients that are depressed, a low-dose SSRI or SNRI may be administered instead of increasing the dose of TCA.

5 The recommended duration of prophylactic treatment is 6–9 months in migraine headache although longer durations may be required [16].

6 Clomipramine and sertraline might not be effective in prevention of migraine headache.

7 Gabapentin may be effective at high doses of 1800–2400 mg/day [24] (21) although it might not be a good choice according to a systematic review [34,35].

8 Divalproex sodium and valproic acid are associated with tremor and alopecia and increase the risk of liver failure, pancreatitis, teratogenicity, thrombocytopenia, and other blood dyscrasias. They may cause hyperandrogenism, polycystic ovary disease, and obesity in young women. Therefore, although they offer effective prophylaxis, they should be prescribed and administered with caution [36].

9 Although few studies have evaluated drugs like Feverfew (an herbal medicine) and magnesium, they may be useful in some patients. Magnesium at a dose of 400–600 mg can be administered especially in patients suffering from constipation, menstrual-related headaches [37–40], or gestational headaches There is a debate over the use of IV magnesium during pregnancy [41].

10 Riboflavin and coenzyme Q10 may be effective in prevention of migraine headache.

11 Cyproheptadine, an antagonist of H_1 and 5-HT_2 receptors, is effective, especially in children, but prolonged use may hinder normal growth (Table 2.9) [16].

Guidelines for stopping preventive therapy

Preventive treatment can be stopped if

1 Intolerance or marked adverse reactions are observed.

Table 2.9 Miscellaneous medications for preventive treatment of migraine.

Agent	Daily dose	Comments
Lisinopril	10–40 mg	Positive small controlled trials
Candesartan	16–32 mg	Positive small controlled trials
Feverfew	50–300 mg	Controversial evidence
Riboflavin	400 mg	Positive small controlled trial
Coenzyme Q10	300 mg	Two positive controlled trials
Magnesium citrate	400–600 mg	Controversial evidence

2 No partial efficacy is seen after 2 months

The drug may be slowly tapered and stopped if adequate response is achieved and the headache is controlled for 6 months [16].

Chronic migraine

According to the ICHD-3, chronic migraine is a headache occurring on 15 or more days per month for at least 3 months, which, on at least 8 days per month, has the features of migraine headache or responds to ergotamine compounds or triptans. Chronic migraine is a disabling condition affecting 1.4%–2.2% of the population [42]. When it is stated that someone has a chronic migraine, it indicates that the person had a positive history of episodic migraine previously. On average, 2%–3% of the patients suffering from episodic migraine develop chronic migraine every year [43]. The headache does not often have the features of migraine headache and resembles tension headache. This type of headache cannot be easily treated. It is often associated with medication overuse headache (MOH) and does not respond favorably to prophylactic treatments. The only confirmed treatment is botulinum toxin injection that is undertaken if oral treatments are not effective. None of the oral treatments used for migraine prevention are approved for chronic migraine although more studies have evaluated topiramate and its probables effects.

Treatment of chronic migraine

1 The first step is to treat MOH if it is associated with CM. MOH is a headache occurring on 15 or more days per month for at least 3 months and is associated with overuse of analgesics or antimigraine drugs.
2 The second step is to find the underlying cause of the chronic headache and treat it. Among these causes are psychiatric problems or diseases like hypothyroidism, hyperprolactinemia, and morbid obesity.
3 The next step is lifestyle modification and removing simple stimulants like irregular sleep or eating patterns, or correction of head and neck position, especially while sitting.
4 Patients may benefit from oral migraine prophylactic medications used in episodic migraine although the success rate is far less than episodic migraine.
5 In case of inadequate response to oral treatments, botulinum toxin injection is suggested. It is recommended to use both "fixed point" and "follow the pain" approaches (Fig. 2.1).

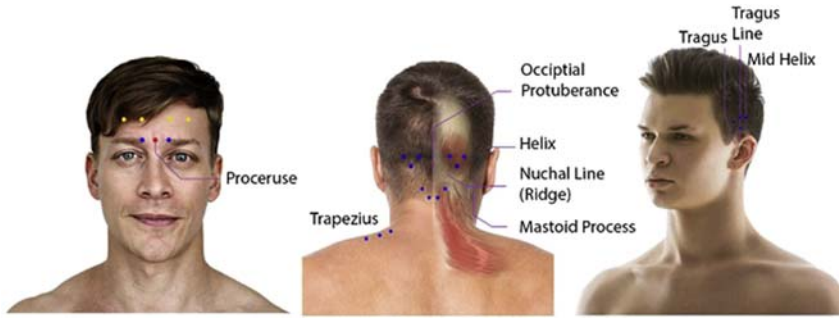

Figure 2.1 Injection sites of botulinum toxin.

6 Because it is necessary to interrupt the headache cycle in chronic migraine headache, different nerve blocks in the head and face using anesthetics or steroids or a combination of both may be helpful [44]. Blocking one or more of supratrochlear, supraorbital, auriculotemporal, greater occipital, and zygomaticotemporal nerves is recommended. The nerve/nerves selection might be done by the headache start point ± - presence of tenderness. Blockade of other nerves is rarely effective (Fig. 2.2).

7 Available studies indicate that erenumab, fremanezumab, and galcanezumab are effective for prevention in patients with CM. They reduce the

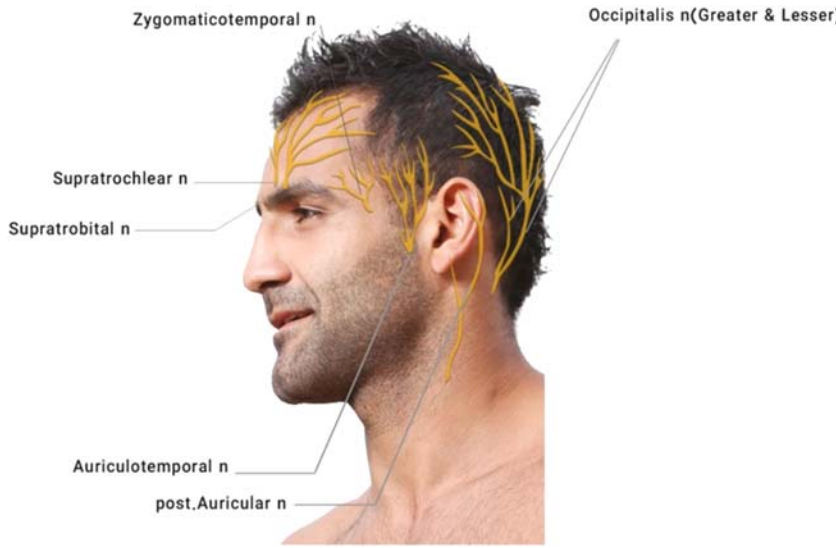

Figure 2.2 Different nerve blocks for treatment of migraine.

number of headache days, reduce the number of days using acute medications, improve disability, and are safe.

8 The next suggestion is a sphenopalatine ganglion (SPG) block through invasive and less invasive methods. The SPG block is especially effective when the headache is associated with autonomic symptoms like lacrimation and rhinorrhea.

9 If treatment is not effective, SPG stimulator for the SPG may be helpful.

10 Physical therapy including TENS, cervical manipulation, etc., may be effective in subsiding or resolving chronic migraine headaches.

11 Behavioral therapy, biofeedback relaxation, and mindfulness are among the recommended therapies, especially for those who are resistant to treatment or who have psychological obstacles.

The last recommended method is migraine surgery, a very new and challenging method, which may be useful in carefully selected chronic migraine patients whose pain starts from one or few fixed points in the skull.

Migraine and vertigo

Introduction

Migraine and vertigo are two common disorders in the general population that tend to occur together. Dizziness or vertigo is reported in 30%—50% of migraine sufferers in different studies [45]. It seems that pathophysiological similarities lead to both migraine headache and vestibular symptoms. These accompanying symptoms are more common in chronic migraine and migraine with aura, which may result in disability, especially because of bouts of vertigo [46]. The exact cause of vertigo in terms of peripheral or central pathways involved is not well defined [47]. Although it is not clear whether the central or peripheral vestibular system is involved in migraine, bouts of vertigo may accompany migraine attacks due to synapses between the vestibular neurons and the trigeminovascular system. Moreover, it has been elucidated that the trigeminovascular system is responsible for migraine headache. Furthermore, the neurotransmitters involved in migraine headache may have a role in vestibular system activation [46].

Vertigo could be the aura of migraine headache and occur in a time frame of 5—60 min, but this presentation is only seen in a very limited number of patients [48]. Benign positional vertigo, a syndrome characterized by attacks of vertigo mainly in changing head position, is more prevalent in migraine headache subjects [49]. Vestibular migraine (VM) (or migrainous

vertigo) and migraine with brainstem aura (BM) (previously known as basilar-type migraine) are two principal clinical syndromes that are associated with vertigo. The International Headache Society (IHS) has accepted both VM and BM as migraine variants. On the other hand, IHS requires an aura with two or more brainstem symptoms in addition to visual, sensory, or dysphasic symptoms to qualify as BM [50]. Thus, these variants should be considered as two different migraine types. Few studies have investigated the treatment of migraine-associated vertigo in vestibular migraine or migraine with brainstem aura, but it seems that response to medication is somehow different in the above migraine variants. Several studies have shown that prophylactic migraine drugs usually used for episodic migraine might be effective in vestibular migraine and migraine with brainstem aura.

At this point, there are not enough data to show any preference between drugs although lamotrigine and calcium channel blockers might be more effective [51]. Our studies on cinnarizine (CIN), which is a well-tolerated L-type calcium channel blocker, showed that it could be an acceptable treatment for migraine, especially when it is associated with vertigo [52–54]. It directly inhibits vestibular hair cells stimulation and has antihistaminic actions [55].

Vertigo and headache, different types

1 **Benign paroxysmal vertigo:** According to ICHD-3, this entity is categorized as an episodic syndrome that may be associated with migraine. It is mostly seen in children but its occurrence is also reported in adults. It may occur in migraine sufferers or in people who are prone to developing migraine later in life. The vertigo starts suddenly and resolves spontaneously. The attacks resolve after minutes to several hours without loss of consciousness. Neurological, audiometric, and vestibular examinations are normal between attacks. At least one of the signs and symptoms of nystagmus, ataxia, vomiting, pallor, and ear fullness should be present during the attacks. Other causes of vertigo such as vestibular disorders, seizures, and posterior fossa tumors should be excluded to establish a diagnosis. Drugs used to treat migraine may reduce the attacks.
2 **Migraine with brainstem aura:** Vertigo is a main component in 60% of the patients suffering from migraine with brainstem aura, previously known as basilar migraine. According to ICHD, the diagnostic criteria for migraine with brainstem aura are:

A Fully reversible aura of 5–60 min before or accompanied by headache.

B At least two of the following brainstem symptoms

I. Dysarthria, that should be distinguished from dysphasia
II. Vertigo
III. Tinnitus
IV. Hypoacusis
V. Diplopia
VI. Ataxia
VII. Decreased Level of Consciousness (GCS≤13)

C No motor or retinal symptom [50].

A brain MRI with or without contrast, brain MRA, or brain CTA should be done at least in the first attack to exclude vascular and nonvascular disorders of the posterior fossa.

3 **Vestibular migraine:** Vestibular migraine is considered a disease with an important effect on the quality of life for the sufferers, with several attacks of spontaneous or positional vertigo [56,57].

Vestibular migraine (VM) could be one of the most common causes of episodic vertigo in the general population [58].

The pathophysiology of vestibular migraine has not been established yet. Eye movement studies during the attacks and in the interictal phase are in favor of central vestibular abnormalities, but peripheral causes are also mentioned [47,51].

In this type of migraine, which may occur at any age, attacks of vertigo may last for 5 min to 72 h and is of moderate to severe intensity. As the diagnostic criteria, the patient has a present or past history of migraine headaches and episodes of vertigo accompanies one or more of these three characteristics: (Fig. 2.3)

- Headaches with migraines features,
- Photophobia and phonophobia,
- Visual aura

Moreover, the bouts of vertigo should accompany at least 50% of the headache attacks [50]. Sometimes the episodes of vertigo are associated with transient tinnitus, nausea, or vomiting (Fig. 2.4).

Effective drugs in vestibular migraine have not been studied extensively. According to the literature, calcium channel blockers [59–61] and lamotrigine may be more effective for vestibular migraine prophylaxis compared to other drugs [50,51,62] (Fig. 2.5).

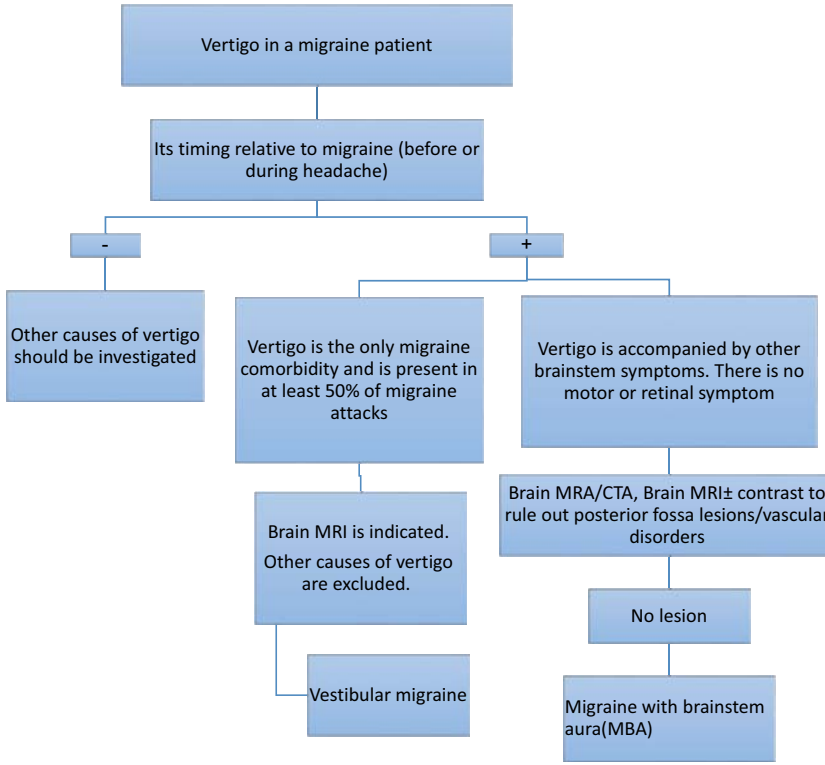

Figure 2.3 Approach to a patient with headache and vertigo.

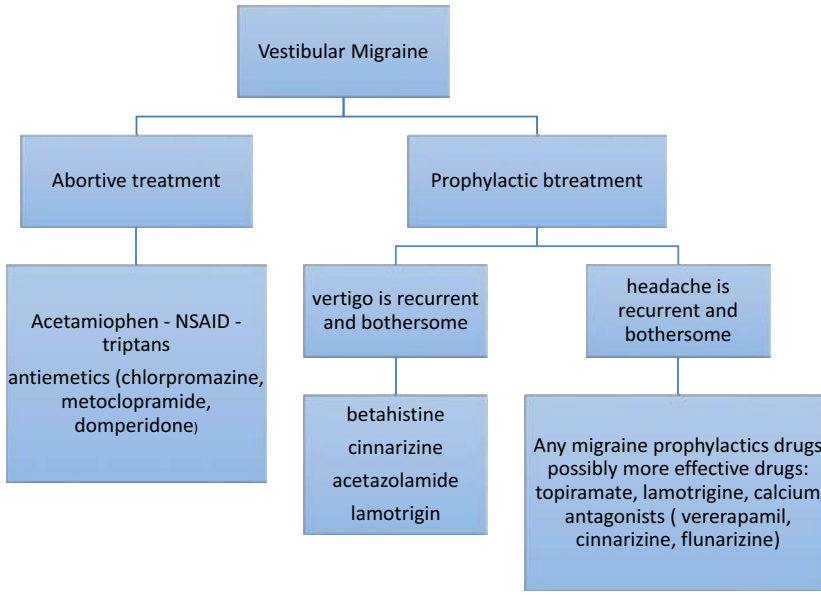

Figure 2.4 Approach to a patient with vestibular migraine.

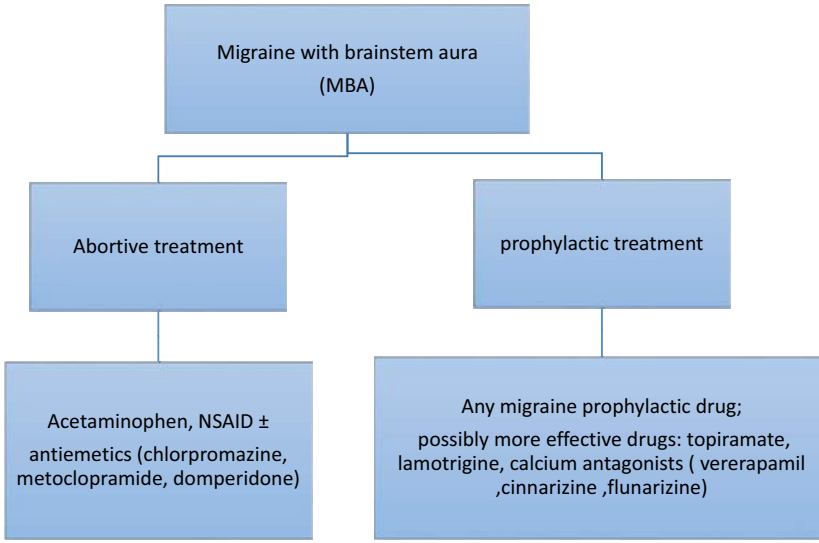

Figure 2.5 Approach to a patient with migraine with brainstem aura.

Meniere's disease and migraine

Meniere's disease is characterized by episodic vertigo associated with cochlear problems including tinnitus, ear fullness, and/or decreased hearing. Its prevalence is much less than vestibular migraine and it lacks a marked sex preference. The disease usually presents in a wide age range of 30—70 years. Vertigo is usually the main complaint although hearing loss may accompany it. It should be noted that the first presenting symptoms might be related to hearing problems before vertigo is noticed. The best diagnostic approach is delicate history taking and examination. Audiologic tests, especially during attacks, are usually helpful to differentiate between vestibular migraine and Meniere's disease [63].

Migraine and Meniere's disease may coincide, making it more complicated to make a diagnosis. Studies have shown that the prevalence of migraine is about two times higher in patients with Meniere's disease compared to the normal population [63]. On the other hand, Meniere's disease is more common in migraine patients.

Another point that needs more attention is that migraine patients, especially those suffering from vestibular migraine and migraine with brainstem aura, may experience vertigo, tinnitus, ear fullness, and even a mild hearing loss in the course of time.

It is very important to differentiate these two diseases for treatment purposes. The following features may be helpful in this regard:

1 Very brief vertigo attacks, from seconds to 15 min, and attacks longer than 24 h are more common in migraine.
2 If spontaneous vertigo attacks are accompanied by migraine manifestations like photophobia and visual aura, migraine is a more likely diagnosis.
3 Progressive hearing impairment is necessary to establish a diagnosis of Meniere's disease.
4 Hearing loss in Meniere's disease is usually unilateral and more severe compared to a bilateral mild hearing loss in a minority of migraine patients [63].
5 Although audiometric and vestibular tests may be abnormal in migraine, the impairment is usually mild with no marked progression.
6 Vertigo relief with antimigraine drugs indicates that vertigo is a component of migraine.
7 Meniere's disease and migraine sometimes coexist in a patient. In this case, exclusive treatment for each disease is necessary.

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CHAPTER THREE

Tension-type headache

Fardin Faraji
Neurology Department, Arak University of Medical Sciences, Arak, Iran

Introduction

Tension-type headache (TTH) is a chronic headache and the most common type of primary headache in the general population. Although TTH affects 30%–70% of the general population, its prevalence is lower than migraine headache in headache clinics because many patients do not seek treatment. TTH may start at any age but is more prevalent in the middle-aged population and is rarely seen in children and adolescents.

The pain in TTH is usually described as a mild to moderate pressure or tightness that is present on both sides of the head. Its prevalence is higher in women as they comprise about 65% of the patients. It was supposed to have a psychologic etiology in the past, but recent studies suggest a neurobiological basis, especially in more severe types [1,2,11].

Classification

A diagnosis of TTH is usually made based on the presence of some symptoms (positive diagnosis) and lack of some other symptoms and exclusion of other primary and secondary headaches (negative diagnosis). Based on the recurrence pattern of headache episodes, TTH is divided into three categories: infrequent episodic TTH, frequent episodic TTH, and chronic TTH (Tables 3.1 and 3.2).

Frequent episodic TTH is similar to infrequent TTH, except for the following:

A- At least 10 episodes in 1–14 days per month ($\geq$1 day and $<$15 days per month or $\geq$ 12 and $<$ 180 days per year on average) for at least 3 months that fulfill the criteria B to D.

These definitions are useful in different ways. The importance of the definitions lies in the fact that TTH subtypes have different pathophysiologic

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Table 3.1 ICHD3 criteria for infrequent episodic TTH.

A.	At least 10 episodes, less than 1 day per month on average (less than 12 days per year), that fulfill the criteria B to D
B.	Lasting between 30 min and 7 days
C.	At least two of the following four characteristics:
	1. bilateral location
	2. pressing or tightening (nonpulsating) quality
	3. mild or moderate intensity
	4. not aggravated by routine physical activity such as walking or climbing stairs
D.	Both of the following:
	1. no nausea or vomiting
	2. no more than one of photophobia or phonophobia
E.	Not better accounted for by another ICHD-3 diagnosis.

Table 3.2 ICHD3 criteria for chronic TTH.

A.	Headache $\geq$15 days per month on average (at least 180 days in a year) for more than 3 months that fulfills the criteria B to D.
B.	Lasting hours to days, or unremitting
C.	At least two of the following four characteristics:
	1. bilateral location
	2. pressing or tightening (nonpulsating) quality
	3. mild or moderate intensity
	4. not aggravated by routine physical activity such as walking or climbing stairs
D.	Both of the following:
	1. no more than one of photophobia, phonophobia, or mild nausea
	2. neither moderate or severe nausea nor vomiting
E.	Not better accounted for by another ICHD-3 diagnosis.

backgrounds, different effects on the quality of life, and different treatments. While symptomatic treatment is preferred in episodic TTH, prophylactic treatment is necessary in the chronic type.

Pathophysiology

Although the exact mechanism of TTH is not clear, the pathogenesis is probably multifactorial. Increased sensitivity of the central and possibly peripheral pain pathways may play a key role in the pathogenesis of TTH. Recent studies have also implicated genetic and environmental factors.

Environmental factors and peripheral myofascial nociceptive sensitization seem to play important roles in the pathogenesis of ETTH, while genetic factors and central sensitization may be more important in transformation of ETTH to CTTH [3–6].

Signs and symptoms

A TTH usually lasts between 30 min and 7 days in the episodic type and hours to days in the chronic type. The pain is bilateral, nonpulsatile, and mild to moderate in intensity. Nausea and vomiting, photophobia, and phonophobia are not usually present. Due to lack of associated symptoms, it is usually referred to as featureless headache. However, chronic TTH may be associated with mild nausea, photophobia, or phonophobia. Loss of appetite is sometimes noticed. Moreover, the pain is squeezing and band-like and does not worsen with activity. Head, neck, and shoulder muscles may be tender [7,8]. Therefore, frontal, temporal, masseter, pterygoid, sternocleidomastoid, and trapezius muscles should be palpated with index and middle fingers in all patients. The tenderness of these muscles increases during attacks and in frequent episodes. According to the International Classification of Headache Disorders, TTH has two subcategories, TTH associated with pericranial tenderness and TTH not associated with pericranial tenderness, because their pathophysiology might be different. TTH may be associated with anxiety, fatigue, and depression [11–14].

Differentiation between migraine and TTH:

- Sumatriptan is effective in migraine attacks but has no effect in pure TTH. However, in migraine patients who have TTH attacks, sumatriptan is effective in both types of attacks
- Osmophobia and vomiting are not seen in TTH
- There is no aura in TTH
- Autonomic features are not usual in TTH
- Headache is of mild to moderate intensity

TTH in children

In children, TTH usually starts at the age of 7 years and has a male to female ratio of 1:1. It has a slight female preponderance in adolescents. There are two attacks per months on average each lasting about 2 h. TTH attacks

are less intense and frequent, are shorter, and require less medication than migraine attacks. It should be noted that since the duration of migraine attacks is shorter in children compared to adults and may even last for less than 2 h and because the headache is usually bilateral, it might be mistaken for TTH in children and other associated features should be used for differentiation.

TTH in the elderly

Several studies suggest that TTH is the most common headache in the elderly accounting for more than 40% of the cases. However, secondary causes of headache such as brain tumors, temporal arthritis, and chronic subdural hematoma must be ruled out in the elderly with new onset TTH; therefore, a brain MRI with and without contrast is necessary in these patients (Table 3.3).

Aggravating factors

Although TTH is not caused by tension and stress, they may worsen TTH. Common migraine triggers like the menstrual cycle, climate change, inadequate rest, intense light or noise, strong odors, and alcoholic drinks worsen TTH in some patients.

Diagnosis

Since there is no definite diagnostic test for TTH, it is diagnosed based on clinical criteria and physical examination. Physical examination should be done to rule out other causes of secondary headache. A brain CT/MRI is used to exclude other structural causes of headache. It may also be required to evaluate the cervical vertebrae [9].

Table 3.3 Differential diagnosis of TTH.

Diagnosis	Especial feature
Giant cell arteritis	A new-onset persistent progressive headache in individuals above 50 years
Pseudotumor cerebri	Worsens with position changes and Valsalva maneuver
Low-pressure headache	History of lumbar puncture, trauma, and surgery Worsens in the upright position; however, this characteristic is lost in time as the headache becomes chronic

Acute treatment

In patients with infrequent ETTH, the treatment of choice for acute headache is simple analgesics or NSAIDs and combined analgesics are the second choice. Despite fewer GI complications than other NSAIDs, acetaminophen is associated with hepatic adverse effects if misused. However, irrational use of NSAIDs is associated with serious renal complications. Among NSAIDs, ibuprofen has the fewest side effects.

Caffeine in combination with simple analgesics like acetaminophen, aspirin, and ibuprofen is suggested if the response is not adequate, although the risk of side effects and MOH is higher [13].

Simple analgesics with codeine should not be combined with barbiturates due to a marked risk of MOH. Triptans are not effective in acute TTH. Opioids are not recommended for the treatment of TTH (Table 3.4).

Prophylactic treatment

Prophylaxis may be required for patients with CTTH and frequent ETTH due to the performance disturbance and risk of analgesic abuse, while milder cases that respond well to analgesic treatment and are not at risk of analgesic abuse may benefit from the treatment strategies of acute TTH.

Table 3.4 Treatment of TTH.

Acute treatment	Ibuprofen	200–400 mg
	Naproxen	375–550 mg
	Ketorolac	60 mg IM
	Aspirin–acetaminophen–caffeine	250 mg/250 mg/65 mg
Prophylactic treatment	Amitriptyline protriptyline	10–100 mg
	Tizanidine	20 mg
	Mirtazapine venlafaxine	4 mg 15–30 mg 150 mg
Nonpharmacological treatments	Behavioral therapy Physical therapies Acupuncture	Relaxation, biofeedback, and cervical massage posture improvement, massage, vertebral manipulation, exercise,…

- Amitriptyline is the most effective drug but its side effects should be weighed against benefits. It is better to start amitriptyline at a dose of 10 mg per night and increase its dose gradually according to the patient's response and tolerance. Its effect in TTH is independent of its antidepressant properties and is even seen at low doses. Patients with pericranial tenderness respond better to amitriptyline compared to patients without pericranial tenderness.
- To compensate for the latency in response to amitriptyline, tizanidine 4 mg daily may be administered together with amitriptyline for the first 3 weeks, especially in patients with pericranial muscle tenderness.
- The minimum time required to evaluate the response to amitriptyline is 3 weeks. If effective, treatment is continued for at least 6 months considering the patient's conditions and then gradually tapered. In the meantime, nonpharmacological treatments and treatment of coexisting diseases, especially depression, improve the results.
- Amitriptyline adverse effects include dry mouth, urinary retention, decreased sweating, weight gain, confusion, nausea, orthostatic hypotension, and tremor. Amitriptyline should not be used in the elderly with hypotension, seizures, and glaucoma.
- Other tricyclic antidepressants like clomipramine and tetracyclic drugs like maprotiline and mianserin are also effective. It is interesting that some tetracyclic antidepressants are equally or more effective than amitriptyline.
- Mirtazapine 15–30 mg at night is effective in patients not responding to amitriptyline.
- Venlafaxine, a serotonin–norepinephrine reuptake inhibitor (SNRI), 150 mg daily has been shown to be effective.
- Some studies have shown that SSRIs like sertraline and citalopram are not more effective than placebo; therefore, the effect of SNRIs may be due to norepinephrine reuptake inhibition.
- Since higher doses of mirtazapine and venlafaxine are well tolerated compared to amitriptyline, they may be better choices in patients with depression and TTH.
- Open-label studies have also shown that topiramate and buspirone are effective in TTH.
- Botulinum toxin has no effect on CTTH according to systematic studies [10–12].

Nonpharmacological TTH treatments

Nonpharmacological treatments should be tried in all TTH patients although little evidence supports the effectiveness of the majority of these techniques.

- Triggering factors should be recognized in order to develop strategies to cope with them. The most common triggers TTH are stress (mental or physical), irregular or inappropriate diets, caffeine overuse or abstinence, dehydration, sleep disorders, improper or low physical activity, psycho-behavioral problems, menstrual irregularities, and hormonal therapy.
- Many psycho-behavioral approaches have been used for TTH treatment. Behavioral therapy, including relaxation, biofeedback, and cervical massage, are effective. Biofeedback, cognitive-behavioral therapy (CBT), and relaxation have been evaluated more than other nonpharmacological approaches. Hypnotherapy has been reported effective but there is no convincing evidence regarding its effect.

Electromyographic biofeedback

In this method, the patient is trained to control and decrease muscle tension through continuous feedback on muscular activity. Then, the patient learns how to control muscle stretching without feedback during multiple sessions. A large metaanalysis showed that the effect of biofeedback was moderate to high and lasted for a long time. The results of this metaanalysis also indicated that the effect of biofeedback increased if combined with relaxation training.

Cognitive-behavioral therapy

The aim of CBT is to train the patient to identify and recognize thoughts and beliefs that cause stress and worsen headache. Then, these thoughts and beliefs are challenged and coping strategies are offered. CBT may be effective, but there is lack of convincing evidence.

Relaxation training

This technique helps the patient to recognize and control the tensions resulting from daily activities. It includes a spectrum of behavioral, cognitive, and emotional techniques like deep breathing meditation techniques.

In general, among different behavioral therapies for TTH, EMG biofeedback may be most acceptable although CBT is probably more effective in patients with psycho-behavioral problems.

Other physical therapies

Physical skills that are used in TTH include posture improvement, massage, vertebral manipulation, exercise, hot and cold packs, ultrasound, and electrical muscle stimulation. There are controversies about the effects of these techniques and high-quality studies are required to support these modalities.

Acupuncture

The results of the available studies on the effect of acupuncture are controversial. However, it can be considered a treatment modality in patients with frequent ETTH, but more studies are needed to reach a definite conclusion.

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CHAPTER FOUR

Trigeminal autonomic cephalalgia

Seyed Ehsan Mohammadianinejad
Iranian Center of Neurological Research, Neuroscience Institute,Tehran University of Medical Sciences, Tehran, Iran

Introduction

Trigeminal autonomic cephalalgias (TACs) are a group of severe and disabling primary headache disorders with unique diagnostic and therapeutic considerations, including cluster headache (CH), PHs, short-lasting unilateral neuralgiform headaches, and hemicrania continua (HC). They are characterized by a unilateral (side locked) cranio-facial pain associated with an ipsilateral autonomic symptom. In the absence of autonomic symptoms, the presence of agitation or restlessness in a patient with side-locked cranio-facial pain might suffice for a diagnosis.

The pain is most severe in the orbital, supraorbital, or temporal area or V1 territory of the trigeminal nerve. A side-locked severe pain in the head and face, centered most severely in and around the eye, should be considered as a TAC and prompt further investigation for the presence of any autonomic symptom on that side.

The autonomic symptoms are in the form of parasympathetic overactivity or sympathetic underactivity, including ptosis, miosis, lacrimation, eye injection, eyelid edema, forehead and/or facial flushing or sweating, and ear fullness. A detailed history taking for each of the autonomic symptoms from the patient, spouse, or family members is important since it may confirm the diagnosis of TAC. A slight ptosis due to Horner syndrome, facial or forehead flushing, or edema might be evident for an observer and not for someone who is suffering from a very severe pain. Ear fullness was added to the list of autonomic symptoms in ICHD-3. The patient is typically agitated and restless during the headache episode and urges to move and walk, pacing the floor to relieve the pain to some extent. This feature is most obvious in patients with CH and can be used to differentiate TAC from migraine headaches in which the patient prefers to rest in a dark and quiet place.

TAC should not be the final diagnosis since the treatment options and modalities are completely different and unique among different types.

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Therefore, the next step should be to determine the type of TAC, which is mainly done based on the duration and frequency of headache episodes and the presence or absence of pain-free days. The spectrum ranges from the longest duration and lowest frequency (hemicrania continua) to the shortest duration and highest frequency (short-onset unilateral neuralgiform headache). Between these two ends are CH and PH.

An exact diagnosis of the type of TAC is important because they are severe and disabling disorders with different and unique treatment options. There is a higher risk of underlying structural brain disorders in patients with TAC compared to other primary headache disorders. This is while mistakes in diagnosis and treatment are not uncommon.

Imaging is mandatory once a diagnosis of TAC is made, since a significant minority of the patients has intracranial lesions, more commonly pituitary tumors. This is not the case in other primary disorders such as migraine or tension headache in which imaging is not essential when the ICHD criteria are fulfilled on the first visit.

Cluster headache

CH is the most common and also the most severe and disabling TAC. The term suicide headache is sometimes used denoting the severity of episodes. It usually starts in 20–40-year-olds and is about three times more common in men with a prevalence of 0.1% in the general population [1].

The term "cluster" comes from the pattern of headache episodes as a cluster of active bouts for several weeks and then a phase of remission for several months putting the patient on hold for the next cluster over the following months. The active bout lasts for 1–2 months in almost 60% and less than 1 month in 30% of the cases. Hence, it is not common for the active phase of severe headache episodes to last more for than 2 months. The attacks of unilateral cranio-facial pain last for 15–180 min (typically 45–90 min) with a frequency that ranges from one every other day to eight per day. They typically occur in a circannual (certain times in the year) and circadian (certain times in the day) rhythm. Attacks typically occur in the night within 2 h of falling sleep, awakening the patient and making them restless and agitated. Ipsilateral autonomic symptoms may be felt by the patient or observer. Agitation is present in more than 90% of the patients and could replace autonomic symptoms for diagnosis [2].

Factors such as alcohol, pungent odors, nitroglycerine, and daytime naps are among the triggers of episodes during the cluster phase but not in the

remission phase. The patient may avoid naps during the day to avoid severe attacks.

A diagnosis of CH should be considered when the syndrome of TAC occurs in a man with typical duration and frequency, particularly if it has a circadian rhythm, awakes the patient at night, or occurs in particular times of the day (Table 4.1).

CH is divided into two subtypes:

1. Episodic CH: This is the usual subtype characterized by cluster periods of weeks to months (7 days to 1 year) separated by remission periods of months to years. Studies have shown that about 25% of the patients have only one cluster period.
2. Chronic CH: Chronic CH affects 10%–15% of the patients and is considered when the cluster period lasts for more than 1 year without a remission period or a remission period of less than 1 month.

Almost all patients with CH should be investigated by imaging since secondary causes have been found even in typical cases. The most common reported pathologies are tumors of the hypophysis followed by posterior fossa lesions. Other secondary causes include dissection of cervical arteries, intracranial aneurysms, and AVMs. Hence, a brain MRI with and without contrast and a brain and cervical MRA or CTA might be indicated according to the case. Cervical artery dissection should be considered especially in cases with Horner syndrome. There are reports of refractory patients with CH who improve after treatment of associated sleep apnea; therefore, this assessment should be considered, particularly in obese men with short necks, nocturnal snoring or patients who are refractory to treatment [3].

Table 4.1 ICHD3 criteria for cluster headache.

A.	At least five attacks fulfilling criteria B–D
B.	Severe or very severe unilateral orbital, supra orbital and/or temporal pain lasting 15–180 min (when untreated)
C.	Either or both of the following:
	1 At least one of the following symptoms or signs, ipsilateral to the headache:
	(a) Conjunctival injection and/or lacrimation
	(b) Nasal congestion and/or rhinorrhea
	(c) Eyelid edema
	(d) Forehead and facial sweating
	(e) Miosis and/or ptosis
	(f) A sense of restlessness or agitation
D.	Occurring with a frequency between one every other day and eight per day
E.	Not better accounted for by another ICHD-3 diagnosis.

Table 4.2 Treatment stages of cluster headache.

	Drugs
Acute treatment	Sumatriptan (6 mg) S.C injection
	Zolmitriptan (5–10 mg) intranasal
	Dihydroergotamine (1–2 mg) IV
	Oxygen 100% 12–15 L/min
	Lidocaine intranasal
Bridge therapy	Prednisolone 60 mg tapered within 10–14 days
	Greater occipital nerve block naratriptan 2.5 mg BID
Prophylactic treatment	Verapamil 320–480 mg/day
	Lithium 300–900 mg/day
	Topiramate 100–200 mg/day
	Melatonin 3–24 mg at night
	Neuromodulation

Treatment of CH includes three stages of acute, bridge, and prophylactic treatment. Most of the patients require all stages for satisfactory results; however, patients with short cluster periods may only need acute and bridge therapies (Table 4.2).

1. Acute treatment is indicated because of the severity of the episode that is not tolerable to the patient. The most effective agents are triptans. Subcutaneous injection of sumatriptan is the first line and works best. A 6 mg injection relieves the attack most rapidly within 15 min. Pure oxygen by a high flow mask is another first line acute symptomatic treatment known for many years to be safe and effective in two thirds of the patients. Oxygen should be administered in the sitting position. The dose is 7–15 L per minute. It usually provides relief in about 15–20 min and can be repeated because of safety. Alternatively, and as a second line, intranasal zolmitriptan 5–10 mg may provide relief within 30 min. Oral triptans are not suggested because of delayed onset of action. Use of intranasal lidocaine in the ipsilateral nostril is used with the head in the backward position and tilted to the side. It may relieve the pain in about one third of the patients.
2. Bridge or transitional therapy is a treatment course of short duration to provide improvement in a more rapid time until the effect of prophylactic medications starts. Oral steroids are commonly used in this phase. A suggested regimen is oral prednisolone 60, 45, 30, and 15 mg each for 3 days. Alternately, greater occipital nerve (GON) block may be applied ipsilateral to the pain. This option may be more effective in patients that

have tenderness over the GON and is performed with a combination of lidocaine or bupivacaine and steroid. A long-acting oral triptan such as naratriptan 2.5 mg BID may also be used as a bridge therapy.

3. Prophylactic treatment should start simultaneously with bridge therapy. Verapamil is considered the most effective prophylactic treatment for CH. The effective dose is higher than the dose used for migraine, mostly in the range of 240–480 mg per day. It is started at a dose of 40–80 mg TDS and titrated by 80–120 mg every 1–2 weeks as tolerated. The risk of cardiac rhythm disorders is obviously higher at these large doses and ECG before and 1 week after each dose increment should be performed to monitor the patient closely. The dose may be increased to 960 mg per day by some experts. Adverse effects such as fatigue, constipation, nausea, vomiting, ankle edema, bradycardia, and hypotension may occur, especially at higher doses. ECG monitoring should be continued even after a stable dose since the side effect may be delayed for months. Interaction with grapefruit should be noted since it may boost the effects of verapamil leading to unexpected complications at lower doses [4].

Lithium is another first-line treatment for CH. The dose is usually lower than what is used for bipolar disorder, in the range of 300–900 mg per day. It is particularly effective in patients with chronic CH and could be the first choice in these cases. Renal and cardiac function should be checked before starting lithium and the drug level should be maintained in the range of 0.8–1.2 mmol/lit.

In patients who do not respond to the above first-line therapies, topiramate may be added with gradual titration to 100–200 mg per day according to response and tolerability. Melatonin may be added as a third-line drug in unresponsive patients at a dose of 3–24 mg at night. Gabapentin and valproate are other options with uncertain values that can be tried as add-on drugs in some unresponsive patients.

The duration of prophylactic treatment could be about 2–3 months in episodic CH since the active bout period will terminate after this time in almost all patients. In patients who have experienced a period of CH, the duration of treatment is planned rather longer than the previous cluster period. Patients with chronic form usually require longer or unlimited periods of maintenance treatment using the lowest effective dose.

Most of the patients with episodic CH live with their episodic nature of disease. They may enjoy long remissions for months to years. A small number of patients convert to chronic type of CH. Patients with chronic CH usually live with their disease but a minority may convert to the episodic form. Prolonged remission is likely but is less possible than the episodic type.

Neuromodulatory therapies are available in patients that are refractory to medical treatment. Neurostimulation can be performed on peripheral nerves (occipital, supraorbital, supratrochlear, vagus), sphenopalatine ganglion, or deep brain structures (such as hypothalamus) and has been reported to be effective in intractable CH [5].

Paroxysmal hemicrania

Similar to CH, PH is a severe side-locked craniofacial pain centered in the V1 territory and associated with at least one autonomic feature. The main differential feature is a higher frequency (1–40 attacks per day) and shorter duration (2–30 min) of episodes compared to CH. In fact, according to the ICHD-3, more than five attacks per day in more than 50% of the days is necessary for a diagnosis, while this frequency is not usual in CH. PH is also divided into episodic and chronic subtypes similar to the time course defined for CH (Table 4.3).

Other differentiating features to distinguish PH from CH are as follows:

1. The chronic subtype is more common than the episodic subtype.
2. The chronic subtype is more common in women, while there is no sex predilection in the episodic form. In fact, when a woman presents with cluster like headache, other features of PH should be investigated in her past history.
3. The circadian rhythm and nocturnal attacks of headache, although possible, are not prominent as CH.

Table 4.3 ICHD3 criteria for paroxysmal hemicranias.

- **A.** At least 20 attacks fulfilling criteria B–E
- **B.** Severe unilateral orbital, supraorbital, and/or temporal pain lasting 2–30 min
- **C.** Either or both of the following:
  - **1.** At least one of the following symptoms or signs, ipsilateral to the headache:
    - (a) Conjunctival injection and/or lacrimation
    - (b) Nasal congestion and/or rhinorrhea
    - (c) Eyelid edema
    - (d) Forehead and facial sweating
    - (e) Miosis and/or ptosis
  - **2.** A sense of restlessness or agitation
- **D.** Occurring with a frequency of >5 per day
- **E.** Prevented absolutely by therapeutic doses of indomethacin
- **F.** Not better accounted for by another ICHD-3 diagnosis.

4. Agitation or restlessness, although present in almost 80% of the cases, is not prominent as in CH.
5. Alcohol is not a common trigger as in CH.
6. PH episodes are typically provoked by neck movement or rotation or pressure on the neck over the C2 root or transverse process of the C4–5 vertebrae. This mechanical trigger is not reported in CH.

In conclusion, PH should be considered in practice when a CH like headache has one or more of the following features:

1. Attacks have a higher frequency (>5) and shorter duration (<30 min)
2. Headache does not exactly follow a circadian or nocturnal rhythm.
3. Headache is triggered by mechanical stimuli and not by alcohol.
4. Headache does not respond expectedly to treatment of CH.

A brain MRI is mandatory as in all TACs to exclude intracranial pathologies.

Once a diagnosis of PH is made, a trial of indomethacin should be considered. According to ICHD-3, absolute response to indomethacin is essential for diagnosis. This is while there are reports of patients with typical PH who do not follow this rule. It is started at a dose of 25 mg TDS and increased by 75 mg per week until response to treatment or a maximum dose of 225 mg per day is achieved. The response is often seen in a couple of days, but it may take up to 2 weeks in some of patients. The maximum dose should be maintained for 2 weeks to consider the patient as unresponsive to indomethacin.

The duration of treatment could be somewhat longer than the previous episodes in the episodic type and may be continued for an indefinite time in the chronic type. Periodic attempts to lower the dose are rational since some cases may respond to lower maintenance doses.

In cases that do not respond or tolerate indomethacin, other NSAIDs such as celecoxib, naproxen, or piroxicam may be used. Patients who do not tolerate indomethacin or other NSAIDs despite a favorable response may benefit from verapamil and topiramate alone or in combination, which have shown positive results in some case series. Melatonin has also been administered with promising results. Since there are not adequate controlled studies, the above agents may be used in different combinations to obtain an acceptable response with good tolerability in particular patients. These agents may allow the patient to use lower but tolerable doses of indomethacin or other NSAIDs to boost the effect of treatment. Alternatively, nerve blocks, particularly GON block (combined anesthetic and steroid), can help

the patient in almost half of the cases. This simple procedure can be repeated in the outpatient clinic every 3 months [6].

As in other TACs, interventional or neuromodulatory therapies may be indicated in refractory and disabling cases.

Hemicrania continua

HC is the second most common TAC after CH. As the name implies, it is characterized by a constant unilateral pain without any pain-free intervals. This is in contrast to other TACs in which the patients could have periods of pain-free days (Table 4.4).

Moderate to severe headache episodes with migraine features (nausea, photophonophobia) are superimposed on the consistent mild to moderate background pain. Some patients may only report exacerbations and do not point to the persistent background pain. In these cases, the diagnosis may be missed as an episodic migraine. In fact, HC is commonly misdiagnosed as chronic side-locked migraine even by experienced neurologists. This is because migraine symptoms are common in HC and autonomic symptoms are not uncommon in patients with migraine.

In a patient with chronic side-locked headache lasting more than 3 months, it is diagnostically helpful to ask if they have any pain-free days instead of only asking for painful times. If the patient claims the pain is constant without any pain-free days but with superimposed episodic exacerbations, a diagnosis of HC should be considered.

Table 4.4 ICHD3 criteria for hemicranias continua.

A. Unilateral headache fulfilling criteria B–D
B. Present for >3 months, with exacerbations of moderate or greater intensity
C. Either or both of the following:
  1. At least one of the following symptoms or signs, ipsilateral to the headache:
    (a) Conjunctival injection and/or lacrimation
    (b) Nasal congestion and/or rhinorrhea
    (c) Eyelid edema
    (d) Forehead and facial sweating
    (e) Miosis and/or ptosis
  2. A sense of restlessness or agitation, or aggravation of the pain by movement
D. Responds absolutely to therapeutic doses of indomethacin
E. Not better accounted for by another ICHD-3 diagnosis.

HC is the most variable TAC in terms of frequency and duration. The superimposed attacks may last from seconds to 2 weeks and the frequency ranges widely from one attack every 4 months to 20 attacks in a day [7].

One characteristic symptom that may help with diagnosis is a foreign body sensation in the ipsilateral eye. This symptom in a patient with persistent side-locked headache is suggestive of HC.

Similar to CH, agitation or restlessness can replace autonomic symptoms to make a diagnosis; moreover, they are very helpful in differentiating HC from migraine.

Therefore, patients with chronic side-locked headaches who seem to have chronic migraine at the first look should be asked for the presence of prominent autonomic features, agitation during the pain, foreign body sensation in the ipsilateral eye, and lack of response to triptan if used. The presence of one or more of these features should prompt a trial of indomethacin, which provides a dramatic response in HC. As in other TACs, photophobia and phonophobia are unilateral in HC compared to bilateral presentation in migraine.

ICHD-3 classifies HC into nonremitting (persistent pain lasting more than a year without even 1 day of remission) and remitting (a remission period of at least 1 day). Interestingly, the nonremitting type is much more common (more than 80%).

The treatment of HC is similar to what described for PH. Once a diagnosis of HC is made, a trial of indomethacin should be considered. Indomethacin is started at a dose of 25 mg TDS and increased gradually to 300 mg per day as tolerated. Response to indomethacin may be observed at higher doses with a longer delay compared to patients with PH because of pain chronicity. Other NSAIDs including COX-2 inhibitors may also be used.

In patients not responding to or tolerating NSAIDs, drugs like topiramate, verapamil, and/or melatonin may be added to the regimen as described for PH. There are promising reports about other agents like lamotrigine and lithium.

GON block is recommended as in PH and can be repeated every 3 months. Botulinum toxin is reported to be effective in almost half of the patients.

Finally, neuromodulation or radiofrequency ablation of the C2 root may be helpful in some medically refractory cases.

Short-lasting unilateral neuralgiform headache

Short-lasting neuralgiform headaches with conjunctival injection and tearing (SUNCT) and short-lasting unilateral headaches with autonomic symptoms (SUNA) only differ in the type of autonomic symptoms. They are the least common of all TACs (Table 4.5).

This headache is characterized by short attacks of severe unilateral stabbing pain mostly in the V1 territory although any part of the head may be involved. The episodes last from 1 to 600 s and are severe and disturbing with a sharp and stabbing quality. Pain episodes could be triggered by cutaneous stimuli over the face, talking, and chewing. The main differential diagnosis is trigeminal neuralgia (TN). Features to differentiate SUNA/SUNCT from TN are as follows:

1. The V1 territory is mainly involved in SUNA/SUNCT, while it is involved in less than 5% of the cases suffering from TN. V2 and V3 territories are involved in more than 95% of the TN cases.
2. The presence of a refractory period (lack or delayed onset of pain after physical stimuli) is a distinguishing feature in TN, while it is absent in patients with SUNA/SUNCT. Therefore, in patients with SUNA/SUNCT, repeated cutaneous and physical stimuli provoke the pain indefinitely.
3. Autonomic symptoms are more prominent in patients with SUNA/SUNCT.

Table 4.5 ICHD3 criteria for short-lasting unilateral neuralgiform headache attacks.

- **A.** At least 20 attacks fulfilling criteria B–D
- **B.** Moderate or severe unilateral head pain, with orbital, supraorbital, temporal, and/or other trigeminal distribution, lasting for 1–600 s and occurring as single stabs, series of stabs, or in a saw-tooth pattern
- **C.** At least one of the following five cranial autonomic symptoms or signs, ipsilateral to the pain:
  - **1.** Conjunctival injection and/or lacrimation
  - **2.** Nasal congestion and/or rhinorrhea
  - **3.** Eyelid edema
  - **4.** Forehead and facial sweating
  - **5.** Miosis and/or ptosis
- **D.** Occurring with a frequency of at least one a day
- **E.** Not better accounted for by another ICHD-3 diagnosis.

A brain MRI is mandatory as in all TACs. Underlying pathologies such as pituitary disorders, posterior fossa lesions, and multiple sclerosis may be more common in SUNA/SUNCT compared to other TACs. There is emerging evidence that neurovascular compression of the trigeminal nerve akin to TN is responsible in some cases. This may explain the possible concurrence of SUNA/SUNCT and TN.

The treatment is unique. In very disabling cases where the disease interferes with speaking and/or eating, an infusion of lidocaine (1.3—3.6 mg/kg/h) in an inpatient setting may be administered to provide a more rapid relief. Alternatively, a short-term steroid course or GON block may be used followed by standard prophylactic treatment. The drug of choice for prophylactic treatment is lamotrigine starting at a dose of 25 mg per day and increasing gradually to 400 mg per day. In patients that do not tolerate or respond adequately to lamotrigine, other agents such as topiramate, gabapentin, carbamazepine, oxcarbazepine, or duloxetine may be added. Finally, in medically refractory patients, invasive approaches such as microvascular decompression of the trigeminal nerve, occipital nerve stimulation, or deep brain stimulation may be considered [5,8].

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CHAPTER FIVE

Other primary headaches

Samaneh Haghighi[1], **Somayeh Nasergivehchi**[2]
[1]Neurology Department, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran
[2]Neurology, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Primary stabbing headache, primary exercise headache, primary cough headache, and primary headache associated with sexual activity are less common primary headache disorders compared to the headaches described before. They are short lasting headaches without autonomic features. These relatively uncommon headache syndromes can be secondary to more serious causes [1]. Assessment for underlying causes is often recommended before a diagnosis of primary type is made.

Primary stabbing headache

- Previously known as "ice pick headache" or "jabs and jolts syndrome" [2]
- This headache often occurs in association with other primary headaches such as migraine, hemicrania continua, or cluster headache.
- Quality of pain: sharp, jabbing
- Location: often in extratrigeminal areas but any other location may be affected. It may change from one side to another.
- Duration: stabs of irregular pain that last for seconds (usually less than 1 min)
- Frequency: usually low with one or a few episodes in a day
- No associated cranial autonomic symptoms in contrast to SUNCT/SUNA [3–5]
- No cutaneous triggering of attacks in contrast to trigeminal neuralgia, SUNCT/SUNA [6]
- Patients with stabbing pain episodes localized to a particular site or side should be evaluated with appropriate imaging to exclude structural causes. However, patients with stabs of pain that change location and respond expectedly to treatment may not need imaging.

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Treatment

It is considered an indomethacin-responsive headache and therefore a trial of indomethacin is recommended whenever a diagnosis is suspected. Indomethacin is started at a dose of 25 mg TDS and titrated to 50 mg TDS over 1–2 weeks [7,8].

There are promising results that melatonin may improve the symptoms. The suggested dose is 3–12 mg/day [9].

There are reports of cases who responded to celecoxib (100 mg BD), paracetamol, gabapentin (400 mg BD), and slow release nifedipine (90 mg/day) [10,11,12].

These alternative agents can be used alone or added to indomethacin in patients who do not respond adequately or do not tolerate indomethacin.

Primary exercise headache

The episodes of pain occur only during or after vigorous exercise, especially in hot weather or at high altitude [13].

- Quality and location of pain: bilateral and pulsatile
- Duration: 5 min to 48 h
- It can be secondary to different causes such as cerebral structural lesions or nonneurologic etiologies such as pheochromocytoma or cardiac disorders [14].
- A brain MRI with and without contrast is recommended in all cases before a diagnosis of primary type is made.
- Neurovascular evaluation is recommended in the first episode or in patients suspected of having aneurysm or dissection.
- Treatment: indomethacin 25–150 mg 30–60 min before exercise [15]
- Propranolol, naproxen, phenelzine, and ergotamine may be effective in some patients.

Primary cough headache

- Primary cough headache is defined as a sudden onset headache provoked only by cough or other Valsalva maneuvers in the absence of any underlying secondary causes.
- Age: usually above 40 years
- Location: bilateral and posterior
- Duration: seconds to minutes, may occasionally last for 2 h with less severity [16]

- No autonomic features
- Secondary causes are present in almost 50% of the patients. Secondary causes should be suspected in those with posterior fossa symptoms, atypical response to indomethacin, and longer attack durations (lasting for even days).
- Secondary causes: Arnold–Chiari malformation (most common), other structural lesions, posterior fossa tumors, vascular disorders, low intracranial pressure [17,18,19,20]
- Notice: cough headache in children should be considered a secondary headache until proven otherwise [21,22]

Treatment

- Treat chronic cough.
- Drug of choice → indomethacin (150–250 mg/D) [23,24]
- Acetazolamide, propranolol, naproxen, intravenous dihydroergotamine, and phenelzine may be effective according to some reports [25].
- Some authors have reported the effectiveness of CSF drainage [26].

Headache associated with sexual activity

- Headache provoked by sexual activity in the absence of detectable causes
- Onset: variable (sudden or gradual)
- Pain location and quality: bioccipital or diffuse in most cases, initiates as a dull pain, and intensifies to a severe explosive pain around orgasm
- Duration: variable (minutes to hours)
- No autonomic features [27]
- Many patients also suffer from migraine-type headache; therefore, it is not reasonable to consider sex-related headache only as a migraine headache episode without proper evaluation
- All neurological and nonneurological secondary causes should be excluded in the first presentation [28]
- Secondary causes: vascular abnormalities, posterior fossa pathology, SIH, cardiac ischemia, drugs, pheochromocytoma, hypoglycemia, and glaucoma [29,30]
- Essential workup: brain MRI ± contrast and neurovascular evaluation.

Treatment

- Acute treatment → intranasal triptans [31]
- Prophylactic treatment → Indomethacin starting at 25 mg 30–60 min before sexual activity
- Propranolol (40–240 mg/D) and other beta-blockers as well as various triptans and calcium channel blockers have been reported to be effective [32,33].

Cold stimulus headache

- Primary headache
- External cold stimuli, inhalation, or ingestion of cold material may induce headache
- Pain quality and location: stabbing, midfrontal in most cases
- Duration: sudden onset, starts immediately after exposure to stimulus and lasts for less than 30 min after external cold stimulus removal or 10 min after cold material inhalation and ingestion
- Triggers: inhalation or ingestion of cold foods and beverages (more common in migraineurs)
- Treatment: Stimulus avoidance and warming [3,34]

External pressure headache

Headache occurs within an hour or during sustained subtle external compression or traction of the scalp; therefore, people who have to use tight hats, headbands, or helmets are likely to develop this type of headache.

- Location: generalized, maximal at the site of compression
- Duration: headache resolves within an hour after external compression is removed [3].

Nummular headache

- Persistent or intermittent, unifocal coin-shaped head pain in a small restricted area with a diameter of 2–6 cm usually in the parietal region.
- Short-lasting lancinating pain may deteriorate the background pain.
- Allodynia, paresthesia, and hyperesthesia of the affected area are reported.
- Not associated with any autonomic symptoms [35,36].
- Can be primary or secondary.
- Secondary causes: structural or dermatological pathologies including cranial bone metastasis, multiple myeloma, Paget disease, osteomyelitis [37,38].

Treatment

Gabapentin (900–1800 mg daily) may be effective; one case series found that amitriptyline was a good treatment option.

Botulinum toxin injection is also reported to be effective and well tolerated in some patients. Overall, this headache is often refractory to different treatments [39,40].

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Hypnic headache

Hypnic headache (HH) is a rare primary headache characterized by frequently recurring headache attacks only during the sleep that wakes the sufferer. It was first described by Raskin in 1988 and was included in ICHD-2 in 2004 [1].

Epidemiology

The prevalence of HH is unclear, but it seems to be about 1% [2]. It is more common in women with a female to male ratio of 5 to 1 [3]. It usually begins after age 50 (mean age of onset: 60 years, range: 36–83 years) [1].

Clinical manifestations

HH is also known as alarm clock headache. A pathognomonic characteristic of HH is a clear association between headache attacks and sleep. Most of the patients suffer from headache attacks usually at the same time, between 2 and 4 a.m., every night. The patients usually experience 1–2 attacks a night although there are reports of up to 6 attacks. The attacks occur 10 nights or more per month [4]. Contrary to cluster headache, the patients are not restless when they wake up with a headache, and almost all of them undertake a motor activity like watching TV, making a drink, taking a shower, reading, etc. [5]. The headache is often bilateral (55.5%) although unilateral headaches have been also reported (30.3%), affecting the frontotemporal region. It is usually moderate in intensity and described as a sharp, stabbing, burning, throbbing, pulsating, or dull pain. The headache duration varies, but it usually lasts for about an hour (range: 15–180 min). Associated symptoms like nausea, photophobia, and autonomic manifestations may be very mild. The disease course is unclear, but most of the studies have reported a relapsing-remitting episodic course [6].

Pathophysiology

The pathophysiology of HH is unclear. The circadian rhythmicity of the headache attacks is pathognomonic for HH, suggesting the possible involvement of the hypothalamus. This hypothesis was further confirmed with demonstrating a marked gray matter volume reduction in the posterior hypothalamus in 14 HH patients compared to 14 healthy controls using voxel-based morphometric MRI [7]. Recent studies found that the majority of the attacks occurred in the non-REM stage, mostly in N2 [2].

Diagnosis

HH is diagnosed based on the history and ruling out other night attacks caused by primary and secondary headaches. Neuroimaging should be done in patients presenting with night headaches for evaluation of structural causes and ruling out other secondary diagnoses [1].

ICHD-3B diagnostic criteria

A. Recurrent headache attacks fulfilling criteria
B. EB. Developing only during sleep and causing wakening
C. Occurring on $\geq$10 days per month for >3 months
D. Lasting $\geq$15 min and for up to 4 h after waking
E. No cranial autonomic symptoms or restlessness
F. Not better accounted for by another ICHD-3

Differential diagnosis

Secondary forms of HH are rare; however, this headache may be associated with posterior fossa lesions, pituitary tumors, hypertension, and hypoglycemic sleep apnea [5].

A diagnosis of HH is suggested only when other primary headaches with sleep-related attacks have been ruled out. Both sleep-related and nonsleep-related headache attacks are seen in cluster headache, which helps

to distinguish this type of headache from HH [6]. Moreover, pronounced headache-associated trigemino-autonomic manifestations and restlessness are characteristics of cluster headache that are absent in HH [1]. Migraine frequently wakes the patients from sleep but its manifestations are very different.

In exploding headache syndrome, the patient wakes from sleep complaining about an explosive noise in their head, but these attacks do not cause a headache [6].

Points to remember in nocturnal headaches:

- Brain MRI with contrast enhancement should be done to rule out cerebral lesions, especially in the pituitary and brain stem [5].
- Nocturnal hypertension should be evaluated, and a Holter monitoring should be performed in suspicious cases [4].
- Polysomnography (PSG) should be done, especially for HH patients with additional manifestations like excessive daytime sleepiness, unintentional sleep episodes, and fatigue during wakefulness to rule out obstructive sleep apnea syndrome (OSAS). Although OSAS is frequently seen in HH patients, HH attacks are not associated with the oxygen desaturation observed in PSG [7].

Treatment

Available treatments are limited and based on anecdotes and case series studies [8,9].

Acute treatment [3,9]:

1 Strong coffee
2 Caffeine containing analgesics

Treatment with analgesics increases the risk of medication overuse headache (MOH); therefore, it is not recommended routinely [8].

Preventive treatment

Preventive treatment includes regular medication before sleep. In elderly patients, drug tolerance is as important as its effectiveness [9].

1 The first line of treatment is caffeine as a strong cup of coffee before sleep (100–200 mg) [2].
2 Daily indomethacin administration (25–150 mg) is an alternative for caffeine; however, about half of the patients respond to indomethacin, especially patients with unilateral headaches or mild autonomic manifestations [5,6].
3 The second line of treatment is lithium administered at a dose of 300–600 mg every day. It is effective in two-thirds of the patients but is not prescribed for the elderly patients due to its side effects.

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New daily persistent headache

New Daily Persistent Headache (NDPH) is a subgroup of chronic daily headache (CDH) that includes chronic tension-type headache (CTTH), chronic migraine (CH), and hemicranias continua [1]. Primary CDH is seen in 4% of the general population [2] and 80% of the headache patients attending headache centers [3].

Epidemiology

NDPH is a rare headache that has been addressed in few epidemiological studies. According to community-based studies, its annual prevalence is 0.1% in people above 14 years of age in Spain and 0.03% in the 30–44-year-old Norwegian population [4]. NDPH is more common in women and children [5]. It has a wide range of age of onset (6–76 years) with an earlier peak in women compared to men (women = 10–35 years, men = 30–50) [6].

Pathophysiology

The pathophysiology of NDPH is not clear, but some studies have suggested triggers for the onset of headache, including EBV infection, upper respiratory tract infections (flulike illness), stressful life events, extracranial surgery, physical characteristics like cervical spine joint hypermobility, and systemic infections [1,7]. NDPH is diagnosed based on its pathognomonic initiation since there is no laboratory or imaging test for diagnosis [8].

Clinical manifestations

A unique characteristic of NDPH is its definite time of onset that becomes persistent consequently [9]. Most patients can recall the exact date or even the moment as well as what they were doing when the headache started [10]. Inability to recall the date or certain conditions of the headache onset may suggest worsening of an infrequent underlying headache rather than NDPH [3]. The headache is commonly felt in the occipital and temporal region with a moderate to severe intensity. It may be bilateral in 64%–86% of the patients [11].

NDPH has a pressing quality and is generally associated with nausea, phonophobia, and photophobia [5]. Prior headaches like migraine and

TTH are common in patients suffering from NDPH. None of the clinical manifestations are exclusive to NDPH and the patients may manifest the characteristics of CM and CTTH [10].

Diagnosis

A diagnosis of NDPH is made based on fulfilling the diagnostic criteria and ruling out the secondary causes [12]. According to the ICHD-3, NDPH is described as a persistent headache whose onset is clearly remembered [10]. It may be migraine-like or tension-type like, or have elements of both.

ICHD-3 Diagnostic Criteria:

(A) Persistent headache fulfilling criteria B and C

(B) Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 h

(C) Present for >3 months

(D) Not better accounted for by another ICHD-3 diagnosis [5].

Patients with migraine and tension-type headache are not excluded from this diagnosis. The patients with NDPH may also suffer from other headaches such as TTH and migraine (7%–38%) [8]. A diagnosis of NDPH should be made with caution if prior headaches had a high frequency or their frequency was increasing prior to the onset of NDPH. The presence of daily headaches should also raise suspicion for MOH. Hemicrania continua should also be considered in unilateral headaches associated with autonomic symptoms, which are also relatively common in NDPH (16.9%–27.5%), and indomethacin 300 mg should be prescribed for 2 weeks [3].

Evaluation

All patients with acute NPDH should be investigated for secondary causes of headache [5]. Therefore, neuroimaging as MRI with or without enhancement is recommended in all patients. If MRI cannot be done or is contraindicated, a brain CT scan with contrast is advised [3]. Temporal arteritis should be on the list of differential diagnosis in patients above 50 years [13]. Some secondary causes of headaches that can mimic NPDH are as follows [5]:

- Venous sinus thrombosis
- Headache attributed to spontaneous cerebrospinal fluid leak
- Idiopathic intracranial hypertension
- Giant cell arteritis

Treatment

There are no randomized, placebo-controlled medication trials for treatment of NDPH, and abortive (NSAID and acetaminophen) and preventive (TAC, flunarizine, antiepileptics like topiramate) drugs used for treatment of TTH and migraine are used to treat the patients [11]. Other treatment options include the following:

- Muscle relaxants—based therapy
- Haloperidol
- Dihydroergotamine
- GON block
- Pulse methylprednisolone therapy [8].

Amitriptyline, sodium valproate, gabapentin, and topiramate are used for treatment of NDPH in children, but there is no information about response to treatment [8]. Although there is no evidence-based protocol, treatment can be started according to the headache characteristics [3,5]; for example, abortive and preventive drugs can be used to treat NDPH with migraine elements [11].

MOH has a high prevalence (34.8%—75%) in patients with NDPH; therefore, simultaneous treatment of both conditions seems logical. MOH can be treated via abrupt discontinuation or tapered withdrawal of current painkillers with or without concurrent use of preventive drugs [3].

As mentioned earlier, NDPH may be associated with cervical hypermobility, neck stiffness, or cervical tenderness [7]. Studies have shown that more than 50% of the patients respond to peripheral nerve block; however, the response lasts for a short time and the pain returns to the baseline level in less than 24 h [7,10].

Prognosis

The prognosis of NDPH is poor, and headache continues despite different treatments [11].

NDPH is divided to two groups:

- Remitting NDPH that resolves within several months with or without relapse in the future
- Persistent NDPH which may resolve in certain conditions despite its poor prognosis, as in patients with a shorter duration of the disease and those that have TTH elements [3,4].

The rate of comorbidities, including anxiety and depression, is higher in patients with NDPH that has features of migraine. Different studies suggest that the rate of improvement is lower in patients with NDPH that shares migraine features [1,3].

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CHAPTER SIX(A)

Headache attributed to trauma

Samaneh Haghighi
Neurology Department, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran

Introduction

Traumatic brain injury (TBI) is not uncommon and headache is the most common presenting symptom. It is frequently associated with other symptoms of postconcussion syndrome. Paradoxically, posttraumatic headache (PTH) is more common after a mild TBI [1–9].

Criteria

According to the diagnostic criteria of ICHD3, headache is attributed to trauma or injury to the head provided that it develops **within 7 days after trauma** or injury to the head. In patients with a decreased level of consciousness or in patients who take medicines impairing the ability to sense or report pain, headache should develop within 7 days after regaining of consciousness following the injury to the head or discontinuation of culprit medicines. Acute PTH resolves within 3 months, while chronic PTH lasts for more than 3 months [1–10].

Pathophysiology of posttraumatic headache

The pathophysiology of such headaches is not fully understood. Changes in the metabolism or hemodynamics of the brain, cellular edema, cellular ionic fluxes, axonal damage, and increased blood–brain barrier permeability, increased or decreased cerebral blood flow [11], and increased intracranial pressure [12] have been noted in the literature [9,13–26].

Mediator release has been also mentioned as a mechanism of PTH. Among neurotransmitters, glutamate has the highest evidence as a possible etiology of posttraumatic headache, specifically PTH with a migraine phenotype. Several studies have shown the release of glutamate and alteration of glutamate receptors in migraine [1–10,27].

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Moreover, genetics, psychological comorbidities, and patient's expectation to have a headache following head injury, female sex, history of headache, and less severe brain injury are the reported risk factors.

For example, it has been shown that patients with a family history of migraine are significantly more likely to suffer from posttraumatic headache with a migraine phenotype [28].

One of the most important risk factors contributing to the transformation of an acute posttraumatic headache to a persistent form is overusing abortive medications following the head trauma. Medication overuse headache should be suspected whenever acute posttraumatic headache becomes chronic [29] (Fig. 6a.1).

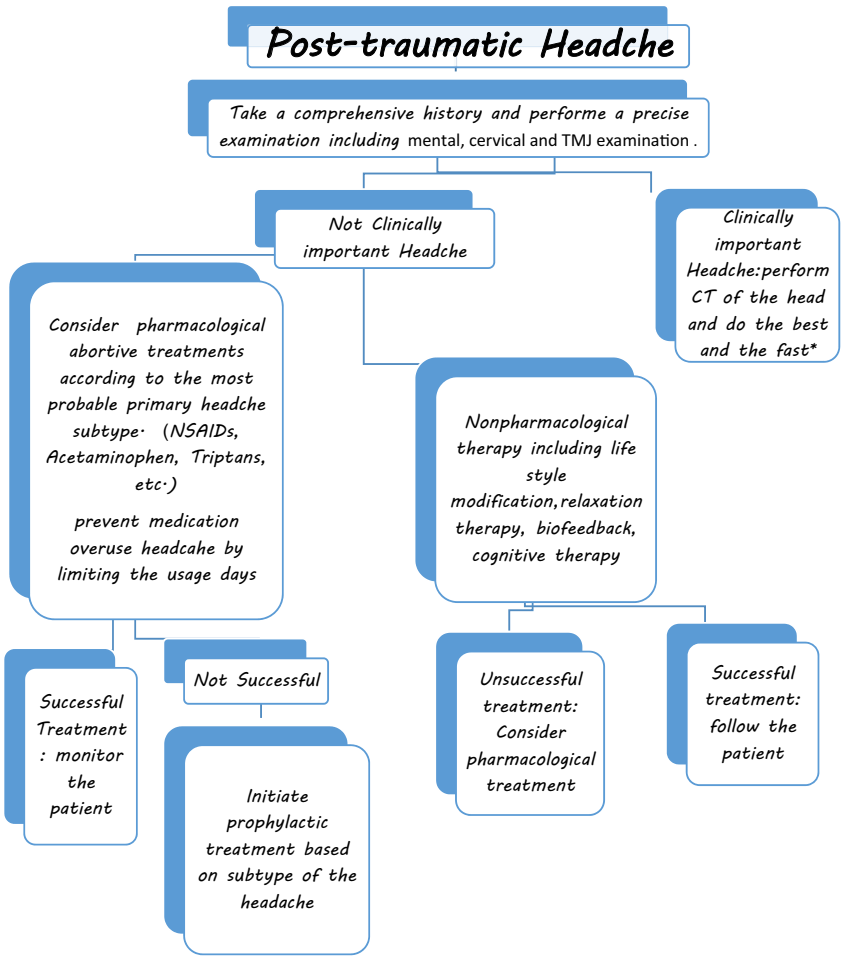

Figure 6a.1 Approach to posttraumatic headache.

CT scan is necessary in:

- Major head injury
- Minor head trauma, and any of the following findings:
  1. GCS score <15
  2. Suspected open or depressed skull fracture (scalp laceration or hematoma or bony step-off of the skull)
  3. Any sign of basal skull fracture (hemotympanum, periorbital bruising, retroauricular bruising, otorrhea, rhinorrhea)
  4. Vomiting ≥2 episodes
  5. Age ≥60 years
  6. Seizure
  7. New neurologic deficit
  8. Bleeding diathesis or use of anticoagulant drugs
  9. Retrograde amnesia before impact ≥30 min
  10. Potentially high impact head injury
  11. Intoxication, headache, or abnormal behavior [32–34].

Posttraumatic headache can mimic different primary headaches, frequently resembling tension-type headache or migraine.

When a preexisting primary headache becomes chronic or worsens significantly (usually a twofold or greater increase in the frequency and/or severity) in close temporal relation to such injury, both the initial primary headache diagnosis and a diagnosis of PTH should be given [1–10,13–27,30,31] (Table 6a.1).

Table 6a.1 More common types of posttraumatic headache [1–10,13–27,30,31].

Tension-type headache:
Most common reported PTH
Migraine-type headache:
Second most common type especially in military service
Trigeminal autonomic cephalgia:
Rare, cluster type is the most common
Low cerebrospinal fluid pressure headache:
• Even after a mild trauma
• Associated features: Positional headache, nausea and vomiting, meningeal signs and symptom
• Onset of headache can be thunderclap or slowly progressive, less or more orthostatic during the time, may be nonpositional or become worse when lying down after a while.

Continued

Table 6a.1 More common types of posttraumatic headache [1–10,13–27,30,31].—cont'd

Painful posttraumatic trigeminal neuropathy:
- Unilateral facial pain in the distribution of the same trigeminal nerve within 3–6 months of a trigeminal nerve trauma with signs of the nerve damage

Supraorbital and infraorbital neuralgia:
- Continuous or intermittent pain with or without sensory dysfunction and neuralgia

Whiplash and cervicogenic headache:
- The triad of neck pain, decreased neck range of motion, and headache
- Frequently occurs following whiplash injuries
- Unilateral occipital pain migrating to frontal regions as a usual complaint

Occipital neuralgia:

Frequent recurrent occipital nonthrobbing or stabbing pain

"Third occipital nerve" headache:

A unilateral pain in occipital region
- **Temporomandibular joint injury**
- **Dysesthesia at the site of scalp injury**

Treatment

Acute headaches should be treated sufficiently to prevent chronicity. No definite and strong treatment guidelines exist for the treatment of PTH. Many studies have recommended posttraumatic headache management according to the primary headache categories although treatment of PTH is usually more difficult and unsatisfactory. A multidisciplinary approach should be considered as follows:

- Avoiding headache triggers, such as certain foods or other environmental triggers
- Corrective exercise
- Psychiatric assessment for anxiety and depression and appropriate therapies such as biofeedback, relaxation therapy, and cognitive behavioral therapy
- Medical treatment
- Intervention (e.g., botulinum toxin, nerve block with anesthetic/steroid combination)
- For acute attacks and deteriorations, NSAIDs or other simple pain killers and triptans are usual first-line treatments based on the headache type.
- Prophylactic treatments include β-blockers, antidepressants, or antiepileptic drugs. A greater occipital nerve block can also be used in patients with occipital neuralgia.

- Associated features such as sleep disorders and psychiatric comorbidities should be considered in drug selection.

Treatment failure might be due to medication abuse causing medication overuse headache or psychiatric comorbidities (e.g., depression, posttraumatic stress disorder, or anxiety) [32–38].

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CHAPTER SIX(B)

Headache attributed to cranial and/or cervical vascular disorder

Elham Jafari
Tehran University of Medical Sciences, Iranian Headache Association, Sina Hospital, Tehran, Iran

Introduction

Headache is commonly a presenting or accompanying symptom of cerebrovascular disorders. When a new headache occurs for the first time in close temporal relation to a cranial or cervical vascular disorder, it is coded as a secondary headache attributed to that disorder. If a preexisting primary headache becomes chronic or it worsens significantly in close temporal relation to a cranial or cervical vascular disorder, both the initial headache diagnosis and a diagnosis of headache attributed to cranial and/or cervical vascular disorder should be made [1].

Headache attributed to cerebral ischemia

Stroke is the most common neurologic disease causing morbidity and mortality.

- Prevalence of headache: 25%–40% [2].
- Headache characteristics: It has a gradual or abrupt onset and is more commonly continuous similar to tension-type headache but may be throbbing. Its intensity decreases within days to weeks concurrent with the decrease in infarction size. Worsening of headache should raise suspicion of cerebral edema or intrainfarction hemorrhage [2].
- Headache Location: It is usually bilateral but may be ipsilateral to ischemia, especially in MCA occlusion. It is felt above the eyebrow ipsilateral to ischemia in ICA embolism or thrombosis, and retro orbital in PCA stenosis.
- Headache is more prevalent in posterior circulation strokes, larger strokes with more deficits; in cerebellar and right hemisphere strokes, especially with cortical involvement; and in patients with a history of migraine

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headache, younger patients, and women [2,3]. It is very rarely associated with lacunar infarcts [1].

- Headache may be overshadowed by the focal neurologic deficits (FNDs) of an acute stroke [2].
- Acute headache attributed to stroke significantly improves in parallel with stabilization or improvement of other symptoms or clinical or radiological signs of ischemic stroke and resolves within 3 months from stabilization spontaneously or through treatment. It is classified as persistent if headaches persist for >3 months after stabilization of the ischemic stroke [1].

Patients with TIA may experience headache during attacks, which is of no prognostic or localizing value. According to ICHD3, any new headache that has developed simultaneously with other symptoms and/or clinical signs of TIA and resolves within 24 h can be attributed to TIA [1,4].

Migraine aura could be a mimicker of TIA; however, it is typically perceived as a positive phenomenon while TIA is usually a negative phenomenon.

Note: Retinal artery embolism and calcarine ischemia may present as positive phenomena, but the visual disorder is usually of abrupt onset and fixed in stroke and TIA while it moves across the visual field for a few minutes in migraine.

- Certain medications should be avoided in migrainous patients with a history of stroke or TIA, including vasoconstrictors, triptans, serotonin antagonists (pizotifen), and ergots.
- Beta-blockers may be associated with a higher rate of stroke in migraine patients who are over 60 years and smoker.

Headache attributed to nontraumatic subarachnoid hemorrhage

An unruptured cerebral aneurysm can cause a headache if it develops in proximal cerebral arteries where pain fibers are present [5]. Pain from supratentorial structures is felt in the orbitofrontal area, while pain from infratentorial structures is felt in the posterior neck [5]. Most people with saccular aneurysms at distal arteries are asymptomatic unless they grow large enough to apply pressure to pain-sensitive structures or rupture. The prevalence of migraine and TTH has been reported to be higher in patients with unruptured aneurysms than in the general population, but their relationship with aneurysm is usually unclear [6].

SAH is a life-threatening neurological emergency with a prehospital mortality rate of 50% and is divided into aneurysmal and nonaneurysmal [7]. The incidence of SAH ranges from 2 to 16 in 100,000 with a higher incidence in women than in men, and also in blacks and Hispanics. The risk factors include hypertension, smoking, alcohol abuse, and use of certain drugs like cocaine. The risk of SAH is also higher in the presence of ruptured intracranial aneurysm, a family history of SAH, and some genetic syndromes such as autosomal dominant polycystic kidney disease and type IV Ehlers–Danlos syndrome [8].

About half of the patients with SAH present with a thunderclap headache (TCH).

- Headache is explosive and of abrupt onset (onset to peak <1 min) [7]. It becomes generalized very rapidly and worsens with head movement.
- It is usually associated with photophobia, phonophobia, vomiting, neck and back pain, and possibly decreased level of consciousness.
- Triggering factors include vigorous physical activity, straining, sexual activity, use of caffeine, transient hypertension, and sudden emotional events.
- About 10%–45% of the patients experience a sentinel headache within hours, days, or even weeks before SAH [2]. It is experienced as a transient TCH in the frontal or occipital region following activity that lasts for hours to days. It might be associated with nausea, vomiting, and interscapular pain [8].
- Other associated symptoms include photophobia, nausea, vomiting, loss of consciousness, neck stiffness, focal neurological signs, and ocular hemorrhage [8].
- It seems that occipital location, stabbing quality, presence of meningism, and onset of headache during exertion are characteristics in the clinical history that can distinguish headache due to SAH from other causes [9].

According to the Ottawa headache rule, patients presenting to the emergency department with acute nontraumatic headache that meet any one of the following six criteria should be investigated to rule out subarachnoid hemorrhage: onset ≥40 years, presence of neck pain or stiffness, witnessed loss of consciousness, onset during exertion, thunder clap headache, and limited neck flexion on examination [10].

An initial aneurysmal bleeding carries a risk of rebleeding that peaks within the first 24 h and is associated with a high rate of mortality and morbidity [2].

Diagnosis

A combination of CT scan without contrast and CSF assessment 12 h after the onset of pain is 100% sensitive for detecting SAH [7]. The sensitivity of CT in the first 3 days is very high but decreases after 5–7 days [8].

MRI, particularly FLAIR, PD, DWI, and GRE sequences, can be useful in the diagnosis of SAH in patients with negative CT scan findings and clinical suspicion of SAH [8] (Fig. 6b.1).

If brain imaging fails to demonstrate SAH, LP is indicated in highly suspicious cases to assess xanthochromia, which appears 12 h after SAH and persists for weeks [2].

The differential diagnoses of TCH include cerebral venous thrombosis (CVT), cervicocephalic arterial dissection, pituitary apoplexy, acute hypertensive crisis, spontaneous intracranial hypotension, meningitis, embolic cerebellar infarction, and reversible cerebral vasoconstriction.

Prognosis

Patients who initially have moderate to severe headache experience significant headache improvement at discharge that continues over 12 months. Headaches of mild to moderate intensity usually improve by discharge [11].

Endovascular treatment of aneurysms and arteriovenous malformations (AVMs) generally improves the headache after treatment. If headache

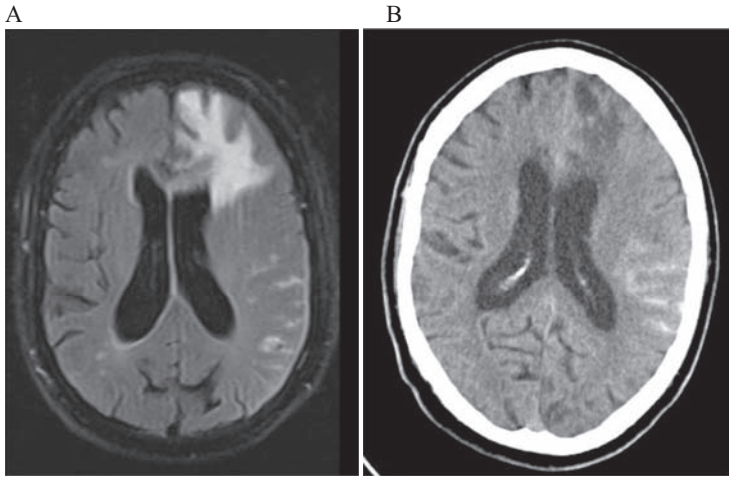

Figure 6b.1 A) Axial FLAIR MRI. Abnormal signal intensity in the left frontoparietal sulci of a patient with left ACA aneurysm and acute SAH; (B) axial noncontrast brain CT scan of the same patient.

exacerbates, it is typically reported to be temporary and resolves within days or months [6]. Surgical clipping of a ruptured intracranial aneurysm may be associated with an increased risk of headache compared to coil embolization because of the postcraniotomy headache [12].

The drug of choice for treatment of headache after SAH is acetaminophen or nonsteroidal antiinflammatory drugs, but the effect is limited in many cases. Pregabalin and gabapentin have been reported to reduce postoperative pain scores. Opioids may be used in some cases but they can induce sedation and respiratory depression. Low-dose intravenous fentanyl has been used for postoperative pain with fewer adverse effects [12].

Headache attributed to arteriovenous malformation

AVMs of the brain are relatively rare congenital developmental vascular lesions occurring in 0.1% of the population [13]. They may cause hemorrhagic stroke, epilepsy, chronic headache, or FNDs. The most common age of onset of symptoms is the third or fourth decade of life, but AVMs may become symptomatic at any age.

- Classic triad of symptoms: migraine, seizures, and FNDs
- Headache is a presenting symptom in 16% of the cases.
- Headache characteristics:
  - Nonspecific recurrent headaches, migraine, or trigeminal autonomic cephalgia (TAC) type [14].
  - Classic migraine with or without neurologic signs (10% of the cases, mostly in unilateral parieto-occipital AVM).
  - Headache is almost always ipsilateral to AVM; aura is usually on the contralateral side [14].
  - Photophobia and phonophobia are less frequent compared to primary migraine.
- Headache mechanism: increased intracranial pressure, steal phenomenon, and cortical spreading depression [13].

AVMs are observed if the patient is older in age, asymptomatic, low risk for hemorrhage or high risk for treatment, and also when the AVM is large and is in an eloquent location with a diffuse nidus. Follow-up imaging is usually performed every 1–2 years [14].

Interventions like surgery, embolization, and stereotactic radiosurgery may provide symptomatic relief in patients suffering from severe headaches [13].

Developmental venous anomaly

- It is the most common cerebral vascular malformation (60%).
- Noncomplicated cases do not cause a headache. Complications like hemorrhage, hydrocephalus, and thrombosis may result in secondary headaches [14].

Headache attributed to intracranial endovascular procedures

Headache occurs in 19%–55% of the patients undergoing endovascular procedures including therapeutic embolization and diagnostic angiography [6,8].

- The headaches are usually of abrupt onset and start within seconds of the procedure.
- Headaches are unilateral and ipsilateral to the procedure.
- It is typically characterized by severe stabbing, nonpulsatile, or pressure-like pain that lasts for a short time and resolves within 24 h after the end of the procedure.
- Risk factors include female sex, therapeutic interventions, psychiatric comorbidities, tobacco use, and previous headache frequency of more than four attacks per month [6,8].
- Some patients respond to steroid therapy, a feature that supports an inflammatory etiology [6].

Headache attributed to subdural hemorrhage

Subdural hematoma (SDH) refers to bleeding between the dura mater and arachnoid membrane. It occurs in patients with severe traumatic brain injury and in patients with less severe injuries, particularly in the elderly or those receiving anticoagulants. It may also be caused by certain procedures, such as a lumbar puncture, or may occur spontaneously.

- Headache is the most common symptom.
- It is usually severe and bitemporal and is more prevalent in young individuals with or without focal neurologic signs.
- The onset may be acute, subacute, or chronic. Associated signs and symptoms include changes in personality or cognitive function, dizziness and drowsiness, focal seizures, weakness, or sensory changes.
- There may be fluctuations in neurological symptoms like TIA.

- SDH, particularly the chronic subtype, should be considered as a differential diagnosis in the evaluation of any elderly person with recent onset headaches, especially with a positive history of trauma (even mild).

Headache attributed to intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is defined as bleeding in the brain parenchyma. It is twice as common as aneurysmal subarachnoid hemorrhage. Hypertension is the most common attributable risk factor in nontraumatic cases. Other risk factors include cerebral amyloid angiopathy, advanced age, anticoagulation, hematologic abnormalities, chronic kidney disease, alcohol and drug abuse (amphetamine, cocaine, heroin, and ecstasy), and possibly low cholesterol [15].

ICH occurs in the basal ganglia, thalamus and internal capsule (35%–70%), lobar area (15%–30%), brain stem (5%–10%), and cerebellum (5%–10%) [15].

Headache is a presenting symptom in one third of the cases [2]. It has a rapid onset and increases in intensity. Bleeding into the subarachnoid space worsens the headache and causes signs and symptoms of meningeal irritation. A large hematoma with an increased ICP leads to a generalized headache.

- Headache location has no value in localizing the lesion, but it is usually ipsilateral to the hematoma.
- Headache is more prevalent in lobar hemorrhage ICH; however, among nonlobar ICH, it is reported to be more common in putaminal hemorrhage [2].
- Associated symptoms include vomiting, acute hypertension, FND, involvement of cranial nerves, and decreased consciousness.
- A combination of headache and vomiting is at least three times more common in ICH than in ischemic stroke [2].

Headache attributed to cervical carotid or vertebral artery dissection

Intracranial and extracranial cervical artery dissection accounts for 2% of all ischemic stroke cases and 14%–20% of stroke cases below 50 years [16]. The most common age is 35–50 years. It is rare above 65 years and is slightly more prevalent in men. Intracranial dissection is more common in children and in Asian populations [17–19]. Intracranial artery dissections affect the posterior circulation (especially V4 segment) more frequently than

the anterior circulation, whereas cervical artery dissections are more common in the anterior circulation [17–19].

Predisposing factors include head trauma, exercise, Valsalva maneuver, swimming, head rotation while driving, head hyperextension during dental procedures, washing hair, and chiropractic neck manipulation [2]. Only a minority of the patients may have underlying arteriopathies, including fibromuscular dysplasia (most common), Ehlers–Danlos syndrome, Marfan syndrome, and polycystic kidney disease [2].

- Headache characteristics: headache is the first and most common symptom in 60%–80% of the cases. It is usually a severe, throbbing headache ipsilateral to dissection. The highest intensity of the headache is in the eye and face in anterior circulation dissections and in the occipito-nuchal area in vertebral artery dissections [18]. It may present in the form of TCH; however, it commonly has a more gradual onset and occurs several days before TIA or stroke [19].
- Ipsilateral Horner syndrome, pulsatile tinnitus, dysgeusia, or visual scintillations may be present in carotid artery dissections [2].
- In internal carotid artery dissection, Horner syndrome is caused by expansion of the intramural hematoma and compression of the peri-carotid sympathetic plexus, whereas it may result from brainstem ischemia in vertebral artery dissection [16].
- The third most common presentation after headache and Horner syndrome is cerebral ischemia due to TIA or stroke, which occurs in up to two thirds of patients with cervical artery dissections [19].
- Vertigo and nausea are frequently present in posterior circulation dissections [19].
- Intracranial dissections can be complicated by aneurysm formation or SAH more commonly compared to extracranial dissections [19].

Diagnosis

Diagnosis is made by demonstration of an eccentric, smooth, or irregularly tapered stenosis of the dissected artery on imaging [19]. CT angiography (CTA) and MR angiography (MRA), especially using the fat suppression protocol, have a high sensitivity. CTA shows an eccentric arterial lumen with mural thickening [16]. MRI should be done to evaluate the complications of dissections and exclude other possible causes. The most common finding is a crescent-shaped intramural hematoma on axial T1-weighted images [19] (Fig. 6b.2).

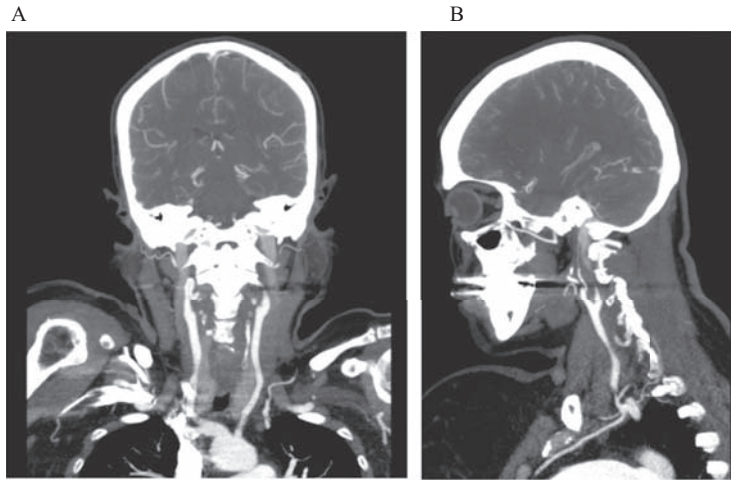

Figure 6b.2 Left ICA dissection: coronal (A) and sagittal (B) reformatted cervical CT angiography: narrowing and then cut off in the proximal part of the left ICA.

The goal of the treatment is to prevent thromboembolism in the site of dissection [19]. Medical treatment includes antiplatelets or anticoagulants for at least 3–6 months; however, anticoagulation has little or no benefit over antiplatelet therapy alone [2]. Anticoagulation is generally avoided in intracranial dissections due to the risk of SAH. Endovascular or surgical treatment of dissection might be an option if additional embolic events occur despite medical treatment or if there is a progressive increase in the aneurysmal size [17].

For patients who present with TIA or stroke within 3 h of onset, intravenous thrombolysis can be recommended. Endovascular interventions including mechanical thrombectomy and intraarterial thrombolysis are also effective up to 24 h after stroke.

Follow-up imaging should be done after 6 months to make sure of dissection improvement using a less invasive imaging method [2].

Prognosis

The risk of recurrence is 1%–2% in 1-year follow-up. The prognosis of the neurological outcomes is good to excellent with low mortality in 75% of the cases. Dissections associated with aneurysms have a worse prognosis [19].

Headache attributed to reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is the most common cause of TCH after aneurysmal SAH. It is the most common cause of recurrent TCH. In fact, recurrent TCH in a short time is a characteristic of RCVS. It may occur at any age, even in children, and is twice as common in women as in men. The age of onset is mid-forties in women, which is a decade later compared to men. RCVS is far more common than expected and many cases remain undetected [20,21] (Table 6b.1).

The main pathophysiology is transient deregulation of the cerebral arterial tone that could be triggered by sympathetic over activity, endothelial dysfunction, mitochondrial dysfunction, and oxidative stress, and leads to vasoconstriction. Hormonal and biochemical factors and genetic predisposition are also proposed. Vasoconstriction of medium- and large-sized arteries could be a reaction to the distal blood flow abnormalities [20,21].

- Headache characteristics: severe, acute TCH in the bilateral occipital region with rapid generalization that resolves within hours, mostly associated with an intense emotional reaction such as screaming, crying, agitation, panic, fear of dying, confusion, or collapse [20,21].
- TCH is the most frequent presenting symptom and the sole manifestation in up to 75% of the cases [20].
- The patients typically experience recurrent TCH attacks for up to 3 weeks, with an average of 4–8 attacks, over 1–4 weeks, which makes

Table 6b.1 ICHD3 diagnostic criteria for reversible cerebral vasoconstriction syndrome.

A. Any new headache satisfying criterion C
B. RCVS has been diagnosed
C. Causation linked with at least one of the following:
  1. Headache, with or without focal deficits and/or seizures, and angiographic findings diagnostic of RCVS
  2. Headache has either or both of these features:
    (a) Thunderclap onset and recurrent during first month
    (b) Triggered by sexual activity, exertion, Valsalva, emotion, and/or bathing
  3. No new significant headache 1 month after onset
D. No other more appropriate ICHD-3 diagnosis and aneurysmal subarachnoid hemorrhage excluded

them agitated and restless. The attacks are often associated with nausea, vomiting, photophobia, and phonophobia. Headache of intermediate intensity is present between attacks [20,21].

- In atypical cases, the headache is nonthunderclap, nonspecific, solitary or recurrent or progressive, and even of mild intensity. A small number of patients do not experience a headache; these patients may suffer from severe RCVS with overt neurologic deficits.
- One-third of patients have associated blood pressure surges [20].
- A specific trigger may be found in 50%–80% of the cases including sexual activity, straining at defecation, stressful or emotional situations, exertion, coughing, sneezing, laughing, singing, contact with water, and bending down suddenly [20].
- At least half of the patients with RCVS have precipitating factors with the most common factor being exposure to vasoactive medications or illicit drugs. The duration between exposure and RCVS varies from days to months, but it may occur with exposure to the first dose, prolonged use, or excess doses [20,21] (Table 6b.2).

RCVS has an association with migraine and cervical artery dissection. About 40% of the RCVS patients have a history of migraine, and migraine is a risk factor for hemorrhagic RCVS too. On the other hand, treatment of migraine with triptans may cause or worsen RCVS. Cervical artery dissection has been detected in 12% of RCVS patients. These patients are usually women with a history of migraine and neck pain [20].

The main differential diagnoses include SAH due to aneurysmal rupture, cervical artery dissection, and primary angiitis of the central nervous system (PACNS) [21].

Some complications of RCVS including hemorrhage (ICH and cortical SAH), seizures, and posterior reversible encephalopathy syndrome (PRES) usually occur in the first week, while ischemic complications develop in the second and third weeks (Table 6b.3).

- RCVS is the most common cause of isolated convexity SAH below 60 years.
- RCVS should be investigated as a differential diagnosis in any patient with convexity SAH or ischemic stroke/ICH in the presence of TCH.

Prognosis: Coma or death secondary to severe vasoconstriction causing massive brain edema, large ischemic stroke, and/or intraparenchymal hemorrhage may develop in less than 5% of the patients [20,21].

Table 6b.2 Precipitating conditions associated with RCVS.

Pregnancy and postpartum

Exposure to licit or illicit drugs: Cannabis/marijuana, cocaine, ecstasy, (meth)-amphetamines, lysergic acid diethylamide (LSD), nicotine patches, alcohol

Exposure to medications:

- Antidepressants: selective serotonin reuptake inhibitors, noradrenaline and serotonin reuptake inhibitors, monoamine oxidase inhibitors
- Alpha sympathomimetics: nasal decongestants (phenylpropanolamine, pseudoephedrine, ephedrine), norepinephrine, amphetamines
- Triptans.
- Ergot alkaloid derivatives: methergine, bromocriptine, lisuride.
- Ginseng, herbal medications.
- Immunosuppressant drugs: tacrolimus, cyclophosphamide, interferon-α.
- Immunomodulator drugs: fingolimod, interferon beta-1a.
- Blood products: intravenous immunoglobulin, red blood cell transfusion.

Vascular associations: cervical artery dissection, fibromuscular dysplasia, unruptured intracranial aneurysm, endovascular procedures, carotid endarterectomy.

Catecholamine-secreting tumors: pheochromocytoma, glomus tumors, bronchial carcinoid tumors.

Extra- or intracranial disorders: head and neck surgery, head trauma, CSF hypotension, spinal subdural hematoma.

Others: hypercalcemia, porphyria, macroangiopathic hemolytic anemia, autonomic dysreflexia, antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura.

Table 6b.3 Complications of RCVS.

Complication	Prevalence	Explanation
Convexity SAH	33%	Usually small, bilateral, or unilateral; most commonly located over the frontal and parietal lobes.
Parenchymal ICH	6%–20%	Usually in the lobar, basal ganglia, or thalamic locations, single or multiple; more than 50% accompanied by other forms of stroke. SDH and IVH may also occur.
PRES	10%–38%	Most patients with PRES also develop vasoconstriction similar to RCVS.
FND	10%–40%	Most commonly visual then sensory, dysphasic, or motor.
Seizure	20%	Rarely recurrent in the absence of ischemic or hemorrhagic brain injury.
Ischemic complications	6%–39%	Usually bilateral, in the anterior and posterior circulation watershed area. Infarction in the areas of major arteries is uncommon and warrant investigation for cervical artery dissection.

Diagnosis

Imaging has a key role in detection of RCVS and may reveal the classic finding of the beading of intermediate to large vessels, associated complications, and differential diagnoses. The findings are usually generalized and bilateral and fluctuate over time. Primary imaging may be normal in one third of the cases since RCVS is a dynamic process that starts in distal small vessels and angiographic changes may be delayed for up to 3 weeks. Hence, imaging should be repeated after 2 weeks in highly suspected cases. The imaging of choice for the diagnosis and monitoring of RCVS is CTA, MRI, and MRA of the brain. MRA has the limitation of evaluating the small distal arteries, while they are better seen on DSA or CTA. The most specific finding is vasoconstriction that is reversible within 12 weeks. Brain imaging reveals cortical SAH, PRES, ICH, subdural hemorrhage, or ischemic stroke in one third to half of the cases. If cervical artery dissection is also suspected, CTA, MRA of the neck with contrast, or cervical MRI with T1 fat suppression can be performed [20,21].

Routine blood tests are generally normal. Vasculitic tests, serum and urine toxicology screens, plasma metanephrines, and urinary catecholamines are tested in specific circumstances. CSF analysis is essential to exclude SAH, infection, and inflammation and is usually normal in RCVS.

Differential diagnoses include aneurysmal SAH, intracranial atherosclerosis, cervical artery dissection, fibromuscular dysplasia, PACNS and primary headache disorders including migraine, primary TCH, and headaches associated with exertion or sexual activity [20,21].

Treatment of RCVS

(1) Identification and prevention of precipitating factors
(2) Symptomatic treatment of headache with simple analgesics including paracetamol or opioids (indomethacin and triptans should be avoided)
(3) Benzodiazepines to decrease anxiety especially after antidepressant withdrawal
(4) Calcium channel blockers, especially nimodipine 30−60 mg oral every 4 h or 1−2 mg/kg/h infusion titrated to blood pressure, in case of severe vasospasm, ischemia, hemorrhage, and PRES.
(5) Milrinone (a phosphodiesterase inhibitor) in refractory cases
(6) Corticosteroids might worsen the clinical course of the disease (differentiation from vasculitis).

(7) Antiepileptic drugs for symptomatic seizures; benzodiazepines may be used to treat seizures, pain, and anxiety.
(8) Hypertension management according to current acute stroke guidelines and avoiding hypotension
(9) Treatment of associated conditions
(10) Avoiding glucocorticoids as they are potentially harmful

Prognosis

RCVS is usually monophasic, benign, and self-limiting. Recurrence has been reported in 5% of the cases, especially in patients with sexual activity as a trigger for TCHs. Although the risk of recurrence with reexposure is unknown, patients are advised to avoid vasoconstrictive medications including serotonin reuptake inhibitors, nasal decongestants, and illicit drugs in the future. One third to half of the patients continue to have chronic headaches of mild to moderate intensity. Permanent severe deficits and death occur in less than 10% and 2% of the cases, respectively [20,21].

Postpartum RCVS comprises 10% of the RCVS cases. It usually occurs within 1 month, mostly within 10 days, of delivery. One-third of the cases are associated with other causes, like the use of vasoconstrictive agents in epidural anesthesia and postpartum bleeding. Half of the patients have a history of proteinuria, suggesting an overlap with preeclampsia. It may also be associated with HELLP and PRES syndrome. Calcium-channel blockers and magnesium sulfate have been used for treatment. Postpartum RCVS is associated with a worse outcome and higher mortality rate [20,21].

Headache attributed to cerebral venous thrombosis

CVT affects approximately five in one million people annually and accounts for less than 1% of all strokes (22). It is caused by different factors (Table 6b.6). CVT is three times as common in women as in men, and has a lower age of onset as compared to arterial stroke (mean age: 37 years). CVT may cause one or more of these syndromes: 1 - increased ICP, 2 - FNDs, and 3 - encephalopathy [23,24] (Table 6b.4).

- Headache is the most common symptom (90%). It may be the only symptom in 10%–25% of women and young patients [2,3]. It is usually unilateral with a gradual progression that eventually becomes generalized and persistent following increased ICP. It may be associated with a transient blurred vision. About 10% of the patients may present with TCH [2,23–25].

Table 6b.4 Conditions associated with cerebral venous thrombosis.

Pregnancy and puerperium
  Oral contraceptives
  Hormone replacement therapy
Genetic prothrombotic states:
• Plasminogen deficiency
• Protein S deficiency
• Protein C deficiency
• Antithrombin III deficiency
• Factor V Leiden mutation
• Prothrombin gene mutation
Inflammatory and autoimmune diseases:
• Nephrotic syndrome
• Behcet's disease
• Wegener's granulomatosis
• Inflammatory bowel disease
• Sarcoidosis
• Antiphospholipid antibodies syndrome
Malignancy intracranial or extracranial
Drugs
• Lithium, androgens
• Sumatriptan
• Intravenous immunoglobulin
• L-asparaginase
• Steroids
• Illicit drugs (such as ecstasy)
• Erythropoietin
Infections
• Meningitis
• Otitis, mastoiditis, sinusitis
• Neck, face, mouth infection
• Systemic infectious diseases
• AIDS
Head injury
  Lumbar puncture
  Neurosurgical procedures
Polycythemia
  Thrombocytopenia
  Sickle cell disease or trait
Dehydration

- Patients presenting with headache are younger than those without headache due to cerebral atrophy in the elderly, which is protective against intracranial hypertension and decreased pain sensitivity [22,24].
- Migraine is the major differential diagnosis of CVT headache as the majority of the patients describe nausea, vomiting, and/or phono/photophobia. CVT headache differs from migraine as it is often exacerbated by the Valsalva maneuver and recumbency, the onset is usually subacute, the pain is more often diffuse rather than unilateral, and a neurological examination is abnormal in 68% of the patients due to neurological deficits and signs of intracranial hypertension [22].
- CVT may cause a chronic headache that is difficult to differentiate from IIH. In these cases, it is not clear whether transverse sinus stenosis is the cause of the disease or results from external pressure due to increased ICP. CVT may rarely cause cluster-like headaches or headaches that respond to indomethacin, like hemicrania continua.
- Pathophysiology of headache: mechanical stretching of nerve fibers in the walls of occluded venous sinuses, compression of the nerve fibers within the veins, cortical irritation and inflammation, and increased intracranial pressure [22].

Associated symptoms

- Seizures: the second most common presentation (40%), usually isolated and transient; lack of aggressive treatment may cause fatal status epilepticus. Seizures and headache are more common presenting features in CVT compared to arterial stroke [22–24].
- Focal neurological symptoms: 20% due to venous ischemia or venous hemorrhage, including motor weakness (40%), visual field loss, sensory symptoms, inattention, or neglect [23,24].

Most common involved sinuses:

- The superior sagittal sinus is involved in more than 60% of the cases, resulting in intracranial hypertension, headache, nausea, papilledema, and signs and symptoms of hemorrhagic infarction.
- The transverse sinus is involved in 40% of the patients. It can be a complication of otitis or sinusitis.
- Deep sinuses are involved in 15% of the cases and are associated with more severe symptoms like decreased consciousness and rapid neurological deterioration [23,24].

Diagnosis

MRI + MRV is the preferred method (Fig. 6b.3) (Table 6b.5).

Attention should be paid to anatomical variations of cerebral veins in any diagnostic procedure. The most common variation is dominance of the lateral sinus on one side and hypoplasia or absence of the lateral sinus on the other side [24].

It is recommended that a follow-up MRV be performed 3–6 months after the diagnosis to evaluate recanalization. If an infective or inflammatory cause is suspected, lumbar puncture should be performed before anticoagulation if there is no contraindication such as a mass lesion [23].

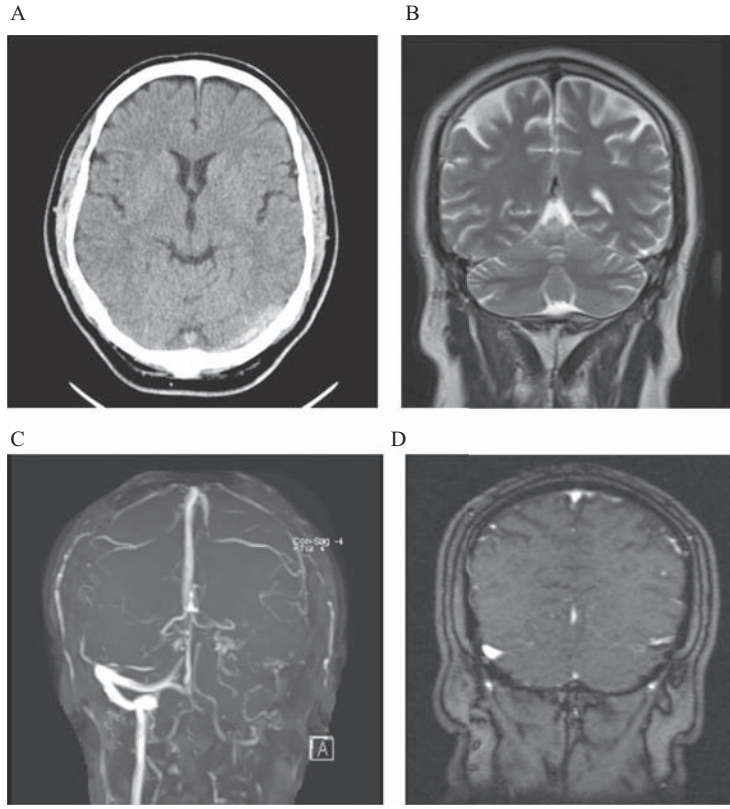

Figure 6b.3 Transverse sinus thrombosis. (A) axial noncontrast brain CT scan. Dense vein sign in the left transverse sinus. (B) coronal T2-weighted images of brain. Abnormal signal intensity and loss of the left transverse sinus signal void. (C and D) 3d and coronal brain MRV. Absence of flow in the left transverse sinus.

Table 6b.5 Diagnostic methods of CVT [23,24].

Diagnostic method	Findings
CT without contrast	Several hemorrhagic infarctions not confined to the territory of a certain artery, bilateral or parasagittal lesions, juxtacortical lesions, and dense cord sign (homogeneous hyperdensity inside a vein or sinus in 33% of the cases).
CT with contrast	Empty delta sign: 30%, filling defect with peripheral enhancement (may not appear in the first few days but continues to exist for weeks).
CT venography	Sensitivity similar to MRV, useful in subacute or chronic stages.
MRI	T_1 and T_2 signal change due to thrombosis depending on elapsed time (since CVT is usually diagnosed 7 days after the onset of symptoms on average, the most frequent signal observed is $\uparrow T_1$ and $\uparrow T_2$).
MRV	Lack of signal and lack of flow void in the involved vein.
Angiography	Gold standard: only when MRV and CVT are inconclusive.
D-dimer	Helpful (normal values do not rule out a diagnosis).

Measuring D-dimer is recommended before neuroimaging in patients with suspected CVT, except in those with isolated headache and in case of prolonged duration of symptoms (>1 week) before the test because of false negative results in these cases [26].

A thromboembolic state should be investigated at least 2 weeks after discontinuation of oral anticoagulants. Screening includes antithrombin, Pr C, Pr S, factor V Leiden, prothrombin G20210A mutation, fibrinogen, MTHFR gene mutation, homocysteine, lupus anticoagulant, anticardiolipin, and antibeta2 glycoprotein-I antibodies. The principles of acute and long-term treatment of CVT are given in Tables 6b.6 and 6b.7.

Severe thrombophilia: antiphospholipid syndrome; deficiency of protein C, protein S, and antithrombin III; homozygous factor V Leiden.

- New oral anticoagulants have been used successfully in case reports [28], including dabigatran and rivaroxaban [29–31], but they are not still approved, especially in the acute phase, and remain a potential treatment option in patients for whom warfarin is not suitable [23,26].
- The annual risk of thrombotic events, including recurrent CVT, DVT, ischemic stroke, PTE, and acute limb ischemia, is 6.5% following a CVT.

Poor predictive factors include large parenchymal lesions, age more than 37 years, Glasgow Coma Score less than 9/15, seizures, posterior fossa lesions, intracranial hemorrhage, and malignancy [23].

Table 6b.6 Acute treatment of CVT [23,24,26,27].

Anticoagulant therapy (even in the presence of hemorrhage)	UFH LMWH is preferred except in patients with a contraindication to LMWH or situations where fast reversal of the anticoagulant effect is required [26]. New oral anticoagulants: not still approved.
Endovascular treatments	Include endovascular thrombolysis or mechanical thrombectomy. Should be applied if the level of consciousness is severely decreased, the symptoms progress despite anticoagulant therapy, or if anticoagulation is contraindicated.
Anticonvulsive treatment	Should start from the first seizure attack.
Steroids	Not recommended as they are linked to a poorer prognosis unless indicated by an underlying condition, such as meningitis, Behcet's disease, or other inflammatory diseases (e.g., SLE) and malignancy [23,26].
Treatment of raised ICP	Pharmacological therapy Lumbar puncture (if there are no parenchymal lesions and prior to considering anticoagulation) Sinus recanalization Ventriculostomy or VP shunt.

Table 6b.7 Long-term management of CVT [23,24,26].

Long-term anticoagulation (INR: 2–3)	• Provoked CVT • Unprovoked CVT • Severe thrombophilia *, recurrent CVT, or venous thromboembolism after CVT	• Warfarin for 3–6 months • Warfarin for 6–12 months • Long-term anticoagulant therapy

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CHAPTER SIX(C)

Thunderclap headache

Ali Asghar Okhovat
Neurology, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Thunderclap headache (TCH) is a very severe headache with a sudden onset that takes about 1 min from onset to reach its maximum intensity. It is described by the patient as an explosive headache or the worst headache of all time. To define this headache, in addition to its intensity, attention should be paid to the time it takes to the peak [1].

The annual incidence of TCH is estimated at 43 cases in 100,000 [2]. The pain location is different, but the most common location is the occipital region along with neck pain.

Causes of thunderclap headache

A TCH is a neurological emergency, and urgent assessments are required to find the cause. Although this headache has several causes (Table 6c.1), subarachnoid hemorrhage (SAH) is the most important differential diagnosis due to its high morbidity and mortality.

In general, TCH is categorized as primary or secondary; therefore, an extensive investigation should be conducted to identify the underlying cause before a diagnosis of primary TCH is made.

Although there are no specific findings to differentiate the etiology of TCH, some findings help to make a diagnosis:

- Recurrent TCH during days to weeks is indicative of reversible cerebral vasoconstriction syndrome (RCVS).
- Decreased level of consciousness (LOC), seizures, or focal neurological deficits on examination suggest SAH, HTN crisis, cerebral artery dissection, ischemic stroke, RCVS, or CVT.
- TCH associated with orthostatic headache and auditory muffling suggests spontaneous intracranial hypotension (SIH) [3].

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Table 6c.1 Causes of thunderclap headache.

Subarachnoid hemorrhage	Pituitary apoplexy
Sentinel bleed related to unruptured aneurysm	Retroclival hematoma
Cerebral arterial dissection	Aqueductal stenosis
Reversible cerebral vasoconstriction syndrome	Colloid cyst of the third ventricle
Cerebral venous sinus thrombosis	Giant cell arteritis
Intracranial hemorrhage	Brain tumor
Ischemic stroke	Cardiac cephalgia
Reversible posterior leukoencephalopathy	Pheochromocytoma
Arterial hypertension	Primary TCH
Spontaneous intracranial hypotension	Primary cough headache, primary exertional headache, and primary sexual headache
Meningitis	Complicated sinusitis

SAH

Subarachnoid hemorrhage

Aneurysmal SAH (aSAH) accounts for 5%–10% of all strokes and it has a higher morbidity and mortality as compared to other types of stroke, and at least one-fourth of the patients hospitalized due to aSAH die and half develop permanent neurological sequelae [4].

The annual incidence of aSAH is different in various parts of the world. Recent studies have shown an annual incidence of 14.5 in 100,000 [5]. Since about 15% of the patients die before arriving at the hospital, the exact incidence of aSAH is probably higher [6,7]. The mean age of the patients is over 50 years [8] and it is 1.2 times more prevalent in women than in men [9].

- SAH is the most common secondary cause of TCH as it is seen in 25% of the patients with TCH [2].
- The possible mechanisms of this headache include vascular wall stretching, increased ICP, or meningeal irritation by blood products.
- About 70% of the patients with SAH have a headache that is in the form of TCH in 50% of the cases. The cause of TCH is SAH in 25% of the patients [10].
- In addition to headache, there may be other associated symptoms and signs like nausea and vomiting, neck stiffness, photophobia, decreased LOC, and focal neurological deficits (cranial nerves palsy).

- In a patient with TCH, the presence of the following signs and symptoms increases the odds of SAH:
  1. Decreased LOC
  2. Neck stiffness
  3. Nausea and vomiting
  4. TCH following the Valsalva maneuver or activity
  5. Occipital headache
  6. History of smoking [11].
- Up to 43% of the patients with aSAH experience a sentinel headache. The patients with this headache may have TCH without meningismus or altered LOC. It is probably due to a small aneurysmal blood leak into the subarachnoid space [12].
- In most cases, a sentinel headache is diagnosed retrospectively. One study found that 75% of the patients with aSAH had sentinel headache within 2 weeks of SAH [13].
- Cerebral vascular aneurysms, especially in the ICA or posterior communicating artery, may be associated with oculomotor nerve palsy. In most cases, because the fibers innervating the pupil are superficial to the oculomotor nerve, the pupil is also involved (mydriasis).
- Even small basilar artery and superior cerebellar artery aneurysms may cause third nerve palsy.
- As mentioned earlier, a brain CT scan should be performed as soon as possible in any patient with TCH. CT scan shows the location and severity of SAH along with its complications like ICH, hydrocephaly, and cerebral edema. Moreover, SAH due to an aneurysm rupture should be differentiated from cortical SAH due to RCVS. SAH often occurs in the Sylvian fissure and basal cistern, while RCVS is seen in the cortex convexity (Fig. 6c.1).
- A lumbar puncture (LP) is indicated if the CT scan is nondiagnostic. About 2%−15% of the patients with TCH and a normal CT scan who are finally diagnosed with aSAH have evidence of SAH in the CSF [3].
- Nonetheless, if a diagnosis of aSAH is made, angiography should be done to determine the location and morphology of the aneurysm. Although Digital Subtraction Angiography (DSA) is the gold standard, MRA or CTA may be used as alternative methods in early stages. Another advantage of DSA is that it shows vasospasm as a consequence of SAH.
- CTA or MRA have a very high sensitivity for detecting aneurysms, especially if they are larger than 3 mm in size. Nevertheless, if an aneurysm is not detected using these methods, DSA should be performed.

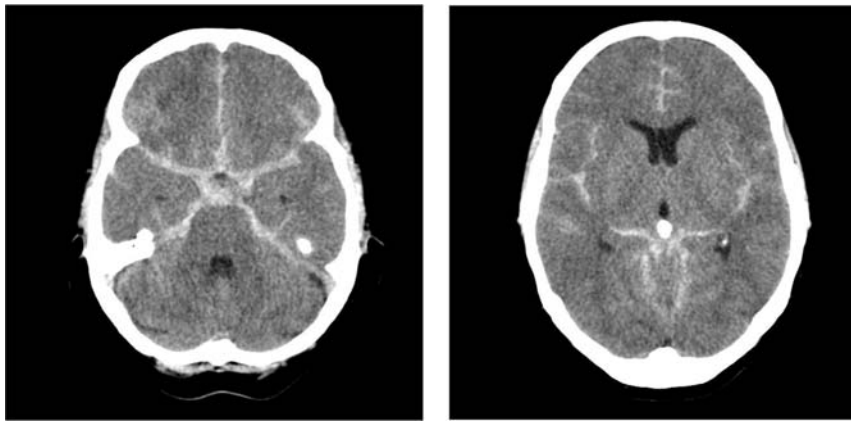


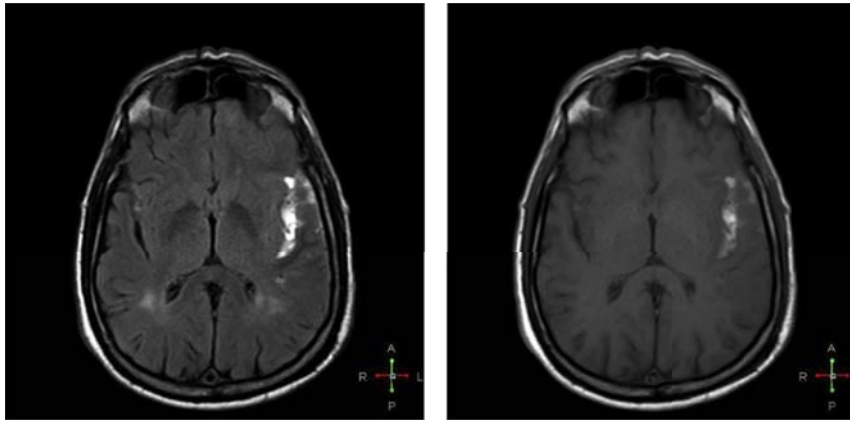
Figure 6c.1 CT image shows diffuse subarachnoid hemorrhage in all basal cisterns, bilateral Sylvian fissures, and interhemispheric fissure.

Studies have shown that the sensitivity of a CT scan to detect SAH is 92%–100% within 6 h of the onset of symptoms, 85%–95% during the second day, 75% on the third day, and 50% on the fifth day [10].

In addition, a CT scan helps to detect other causes of TCH, like ischemic stroke, CVT, colloid cyst of the third ventricle, brain tumors, and complicated sinusitis.

If a CT scan is unremarkable, an LP is the next step. The sensitivity of CSF analysis to detect SAH is increased when an LP is performed 6 h after the onset of symptoms (preferably after 12 h). However, an LP should not be delayed for this purpose to diagnose and manage promptly, because the odds of rebleeding are high in the first 24 h [14].

- In LP, it is important to measure the opening pressure and the protein and glucose levels. Moreover, a red blood cell count is necessary along with its difference between the first and the fourth test tube. If there is a high suspicion of SAH, the necessary investigations should be done.
- Spectrophotometry of the CSF for xanthochromia has a high sensitivity (98%) for detection of SAH if performed within 12 h to 2 weeks of SAH [15].
- Patients with TCH who have a nondiagnostic LP and CT scan should undergo a brain MRI with contrast and noninvasive cerebral vascular imaging modalities like CTA or MRA to rule out other vascular causes such as RCVS and arterial dissection (Fig. 6c.2).
- The sensitivity of MRI for detecting SAH is higher in the acute phase (Fig. 6c.2). In the subacute phase, T2-weighted images show



A B

Figure 6c.2 Hyperintense fluid in FLAIR (A) and T1 (B) sequences filling and expanding the left sylvian fissure and adjacent sulci.

hypointensity in the subarachnoid space, which is the most sensitive test (94% and 100% sensitivity in the acute and subacute phase) [16].

If the first angiography is negative, which occurs in 14%–22% of the cases, it should be repeated within 4–14 days. An aneurysm is detected on the second angiography in up to 24% of the patients [17].

Management of SAH

Once a diagnosis of SAH is made, the patient should be referred to a medical center with experience in SAH and ICU facilities. These hospitals improve the outcome and decrease morbidity and mortality [18].

The first step in the assessment of these patients is the evaluation of the neurological status and severity of aSAH.

Before an aneurysm is treated, the most dreadful complication of aSAH is rebleeding. The risk of rebleeding is the highest 2–12 h after SAH. There are reports of rebleeding within the first 24 h in 4%–13% of the cases. Rebleeding is associated with a high mortality and poor prognosis [19].

Factors associated with a higher risk of rebleeding include a long interval between the onset of symptoms and aneurysm treatment, low LOC on admission, prior sentinel headache, a larger aneurysm, and SBP>160 mmHg [19,20].

Supportive treatments before treatment of aneurysm include blood pressure control (it is reasonable to lower SBP below 160 mmHg), water and electrolyte maintenance, pain control, maintenance of normal defecation, and prevention of secondary complications like bedsores.

Vasospasm is a serious complication of SAH, which results from blood leak and breakage of blood products. It increases the morbidity and mortality of aSAH. It commonly occurs 7–20 days after aSAH and is therefore referred to as delayed cerebral ischemia (DCI). Angiographic vasospasm is seen in up to 70% of aSAH patients but becomes clinically symptomatic in 30% of the patients [21].

Careful clinical monitoring of the patients in the ICU and the use of cerebral imaging techniques play an important role in the diagnosis and treatment of vasospasm. Deterioration of the clinical condition suggests vasospasm in which case Transcranial Doppler can be used on a daily basis at the patient's bedside for detecting vasospasm.

Nimodipine should be administered orally at a dose of 60 mg every 4 h for 21 days to prevent spasm.

Reversible cerebral vasoconstriction syndrome

RCVS, previously known as Call–Fleming syndrome, benign CNS angiopathy, postpartum cerebral angiopathy, drug-induced angiopathy, migraine vasospasm, and TCH with vasospasm, is a group of syndromes with similar characteristics.

RCVS is characterized by TCHs with or without other signs, without aSAH, with a normal or near-normal CSF and multifocal constriction of cerebral arteries that normalize within 12 weeks of onset [22,23] (Table 6c.2).

A brain CT scan and MRI are abnormal in 30%–80% of RCVS patients. These abnormalities include cortical SAH (22%–34% of the patients), ICH (6%–20% of the patients), ischemic stroke (14%–39% of the patients), and cerebral edema (9%–38% of the patients) [23,24] (Fig. 6c.3).

Vertebral and carotid artery dissection

A headache or neck pain is the most common symptom of cervical artery dissection reported in 60%–95% of the cases of carotid artery dissection and 70% of the cases of vertebral artery dissection. The headache may precede focal neurological signs and symptoms by 4 days in carotid artery dissection and 14.5 h in vertebral artery dissection [25].

Table 6c.2 Suggested RCVS criteria.

1	TCH with or without FND or seizures
2	Monophasic course with no new symptoms 1 month after the disease onset
3	Multifocal, multivessel, and segmental constriction of cerebral vessels
4	Absence of aSAH
5	Normal or near-normal CSF analysis (normal glucose level, WBC<15/mm^3, protein<100 mg/dL)
6	Complete or significant normalization of cerebral vessels within 12 weeks of onset of symptoms

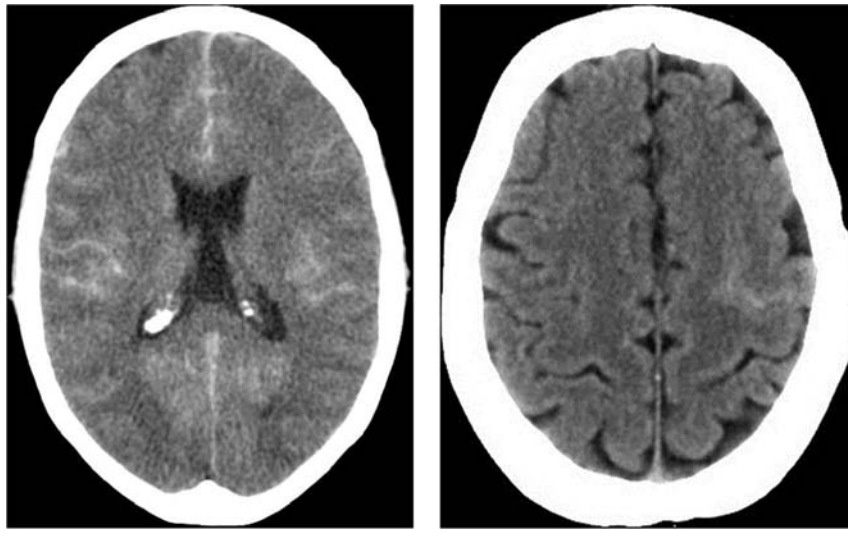


Figure 6c.3 Axial noncontrast CTs showing aneurysmal subarachnoid hemorrhage (left image) and versus cortical subarachnoid hemorrhage (right image) seen in up to one-third of patients with RCVS.

TCH is reported in 9.2% and 3.6% and neck pain is seen in 66% and 33% of the cases of vertebral and carotid artery dissection, respectively [26].

- The associated signs and symptoms of cerebral ischemia are observed in 84%–90% of the cases of vertebral artery and 70%–73% of the cases of ICA dissection [27].
- SAH (6% vs. 0.6%) and ischemic stroke (69.5% vs. 52.2%) are more common in vertebral artery dissection in comparison with ICA dissection [28].

Spontaneous intracranial hypotension

SIH occurs due to a decreased CSF volume secondary to its leak. Most CSF leaks are found at the cervicothoracic junction or in the thoracic spine. In one study, 90% of the patients with SIH were initially diagnosed with tension or migraine headache despite the presence of orthostatic headache. Although orthostatic headache is pathognomonic of SIH, it is seen in 4%–15% of the patients with TCH [29].

Cerebral venous sinus thrombosis

About two-thirds of the patients with cerebral venous sinus thrombosis have subacute or chronic daily headaches and only 5% of them have TCH. A headache is the only sign of the disease in 25% of the patients [30]. If there is a clinical suspicion, MRI and MRV should be done to rule out CVT (Fig. 6c.4).

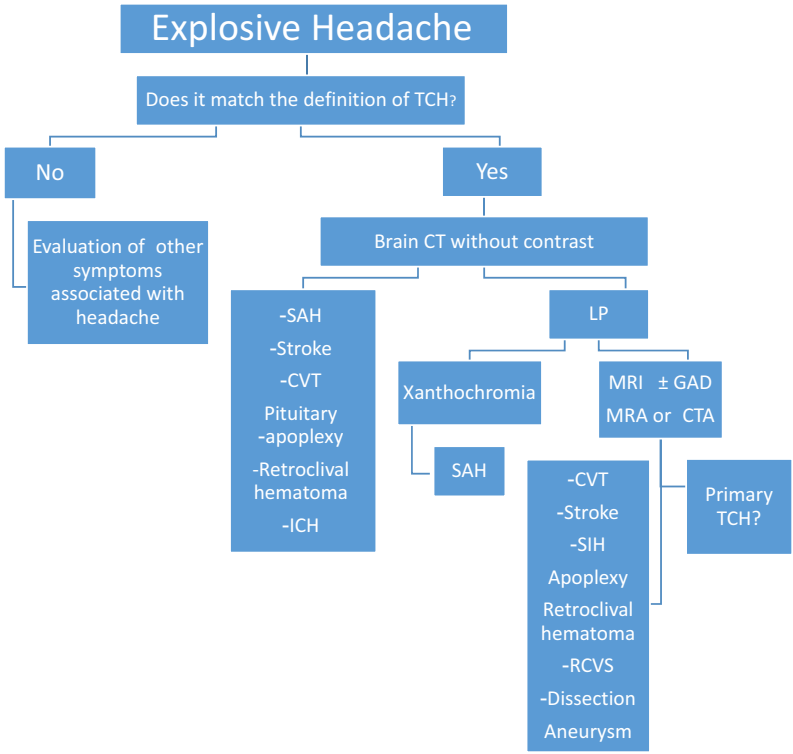


Figure 6c.4 Diagnostic algorithm of TCH.

Primary thunderclap headache

Primary TCH is defined as a high-intensity headache of abrupt onset mimicking that of an aSAH in the absence of any intracranial pathology. Primary TCH should be a diagnosis of exclusion.

The diagnostic criteria of primary TCH according to ICHD-3 beta include the following [31]:

A. Severe head pain fulfilling criteria B and C
B. Abrupt onset, reaching maximum intensity in <1 min
C. Lasting for ≥5 min
D. Not better accounted for by another ICHD-3 diagnosis.

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CHAPTER SIX(D)

Headaches related to alteration in the cerebrospinal fluid pressure

Mahsa Arzani
TUMS, Neurology, Tehran, Iran

Speaking of cerebrospinal fluid (CSF) pressure, one should keep in mind that inside the closed space of the dura, the normal CSF pressure is determined by the balance between the brain parenchyma and CSF producing and draining system. If this balance is lost, the CSF pressure will be affected.

Changes in the CSF pressure stimulate pain-sensitive structures in the CNS, which in turn activate afferent nerve endings, and lead to headache. Headaches attributed to the CSF pressure are usually generalized, retro orbital, or bioccipital. The pain is sometimes referred to the vertex or cervical spine, lacking specific features of migraine or tension-type headaches. Positional dependency at the early stages of the disease and exacerbation with cough and Valsalva maneuver are the most important diagnostic clues.

Headache attributed to idiopathic intracranial hypertension

- Definition: CSF pressure above 25 cmH_2O in adults and 28 cmH_2O in obese children. The intermediate gray zone of 20−25 cmH_2O in adults and 20−28 cmH_2O in children should be individualized with clinical features in a particular patient (and reference values) [1−6].
- Obesity is the main underlying factor predisposing patients to idiopathic intracranial hypertension (IIH) (its prevalence is 20 times higher in obese subjects than normal weight individuals) [7].
- Pathogenesis of IIH is not completely identified, but proposed mechanisms include excess CSF production, reduced CSF absorption, increased abdominal and cerebral venous pressure, and altered vitamin A metabolism [8].

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- Clinical clues:
  1. Alteration in the headache intensity by position change: headache is worsened by lying down and is more intense in the morning.
  2. Transient visual obscuration
  3. Pulsating tinnitus, indicating elevated cerebral vein pressure
  4. Vomiting
  5. Papilledema which is typically bilateral and is the hallmark sign.
  6. Visual field defects
  7. Bilateral or unilateral sixth nerve palsy
  8. Other less prevalent cranial nerve involvements, including olfactory, 3rd, 4th, 5th, 7th, and 8th nerves palsy
  9. Alterations of the consciousness level (Tables 6d.1, 6d.2 and 6d.3).
- Many patients with IIH may mimic the features of migraine or tension-type headaches during the course of the disease; on the other hand, these primary headaches commonly coexist with IIH.
- IIH should be diagnosed with caution in those with altered mental status. Moreover, the presence of either focal neurological defect or seizure is against the diagnosis of IIH.

Investigations

Neuroimaging

The first step to evaluate the patients with headache and papilledema is neuroimaging.

Table 6d.1 Secondary causes of intracranial hypertension.

Space occupying lesions of the parenchyma
Vascular causes: Cerebral venous thrombosis, arteriovenous fistula, arteriovenous malformation
Chronic meningitis
CSF hypersecretion: Choroid plexus papilloma
Aqueductal stenosis
Craniocervical junction malformations such as Arnold–Chiari malformation
Metabolic causes: acute hepatic failure, renal failure, hypercarbia, acute hypertensive crisis, Reye's hepatocerebral syndrome, right heart failure, Addison's disease, hypoparathyroidism, anemia, sleep apnea, systemic lupus erythematosus, Behcet's, polycystic ovary syndrome
Medications: growth hormone, thyroxine replacement, corticosteroid withdrawal, retinoids, tetracyclines, lithium, nalidixic acid, nitrofurantoin
Chromosomal disorders: Turner syndrome, Down syndrome

Table 6d.2 Diagnostic criteria for pseudotumor cerebri syndrome.

1. Required for diagnosis of pseudotumor cerebri syndrome[a]
   - **A.** Papilledema
   - **B.** Normal neurologic examination except for cranial nerve abnormalities
   - **C.** Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
   - **D.** Normal CSF composition
   - **E.** Elevated lumbar puncture opening pressure (250 mm CSF in adults and 280 mm CSF in children [250 mm CSF if the child is not sedated and not obese]) in a properly performed lumbar puncture
2. Diagnosis of pseudotumor cerebri syndrome without papilledema

   In the absence of papilledema, a diagnosis of pseudotumor cerebri syndrome can be made if B–E from above are satisfied, and in addition, the patient has a unilateral or bilateral 6th nerve palsy.

   In the absence of papilledema or 6th nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if B–E from above are satisfied, and in addition, at least three of the following neuroimaging criteria are satisfied:
   - **i.** Empty sella
   - **ii.** Flattening of the posterior aspect of the globe
   - **iii.** Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
   - **iv.** Transverse venous sinus stenosis

a: A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria A–E. The diagnosis is considered probable if criteria A–D are met, but the measured CSF pressure is lower than specified for a definite diagnosis.

Brain MRI with and without contrast is mandatory to rule out secondary causes. Brain MR Venography is suggested for any patient who has an atypical feature.

Slit ventricles, flattening of the posterior aspect of orbital globes, increased perioptic subarachnoid space, protrusion of the optic nerve papillae into the posterior globe, orbital veins tortuosity, empty sella turcica, and cerebral vein stenosis on the brain MRI are in favor of a diagnosis of IIH (Fig. 6d.1).

Table 6d.3 ICHD3 criteria for IIH.

A. New headache, or a significant worsening of a preexisting headache, fulfilling criterion C
B. Both of the following:
  1. idiopathic intracranial hypertension (IIH) has been diagnosed
  2. cerebrospinal fluid (CSF) pressure exceeds 250 mm CSF (or 280 mm CSF in obese children)
C. Either or both of the following:
  1. headache has developed or significantly worsened in temporal relation to the IIH, or led to its discovery
  2. headache is accompanied by either or both of the following:
    (a) pulsatile tinnitus
    (b) papilledema
D. Not better accounted for by another ICHD-3 diagnosis

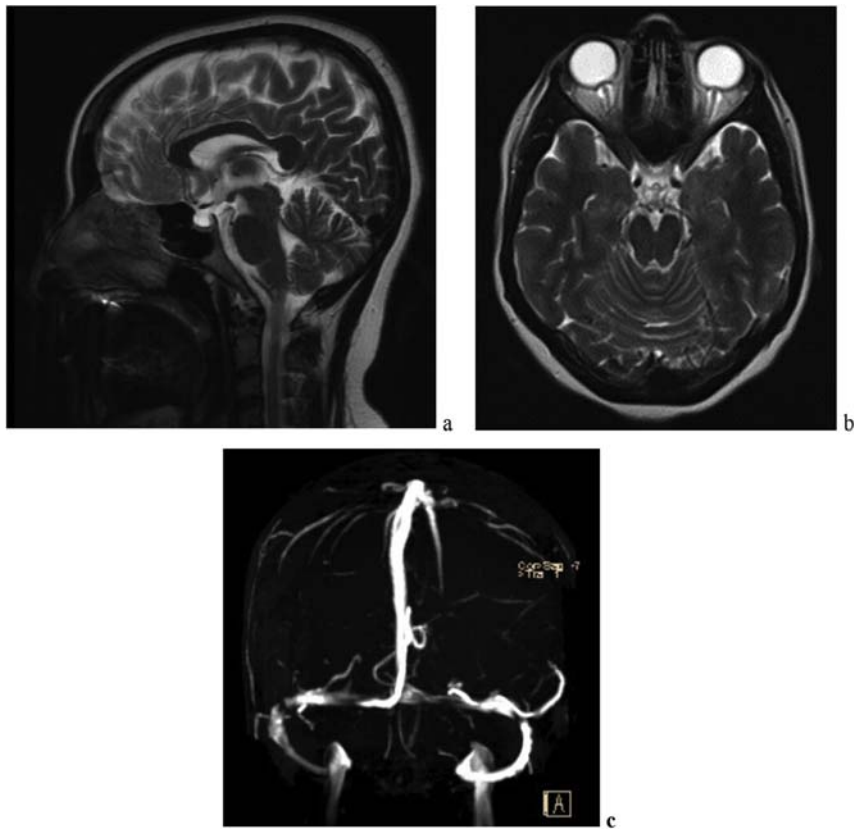

Figure 6d.1 (A) sagittal brain MRI. partial empty sella; (B) axial T2-weighted brain MRI. Increased csf space around optic nerves; (C) brain MRV. Narrowing and stenosis in the lateral aspect of bilateral transverse sinuses.

Lumbar puncture

If imaging studies reveal no identifiable cause, a lumbar puncture (LP) should be performed for measurement of exact CSF pressure and CSF analysis. It is done in the lateral decubitus position with legs extended without sedative medications. In the sitting position, pressure is almost doubled compared with recumbent position.

A single measurement may not be indicative of the average CSF pressure over 24 h because of the CSF pressure alterations during the day. Also, prolonged lumbar or intraventricular pressure monitoring is recommended in these cases.

Treatment

- A significant weight reduction is an essential consideration in obese patients with IIH [9].
- Potential drugs that worsen IIH should be avoided.
- Corticosteroid has a dual effect; it can induce or exacerbate increased intracranial hypertension while it is also considered a temporary treatment in preoperative emergencies in which vision is threatened by increased CSF pressure to save the time for surgery.
- Carbonic anhydrase inhibitors such as acetazolamide are the most effective drugs to reduce intracranial hypertension. These drugs improve headache and perimetric measurements of the visual field. A dose of 2–4 g per day for adults and 25 mg/kg up to 2 g per day for children is permissible. The least recommended dose of acetazolamide to be effective is 1 g per day. Under dosage of acetazolamide is one of the most common mistakes in practice. The patient should be encouraged to titrate the drug slowly to tolerate the higher doses.
- Topiramate is an antiepileptic agent with carbonic anhydrase inhibitor activity that is also effective in weight reduction and treatment of coexistent migraine headache [10].
- Loop diuretics (for example, furosemide 20–40 mg/day) are less effective and may be used as an adjunctive therapy.
- Iron deficiency is mentioned as a risk factor of IIH, so iron supplement must be used for IIH patients with iron deficiency anemia.

Serial lumbar puncture

Serial lumbar puncture for treatment of IIH is no longer recommended, but LP still performs for diagnosis and measurement of CSF pressure to

differentiate coexistent migraine, tension or medication overused headache from exacerbation of intracranial hypertension, and also temporary reduction of CSF pressure in emergent setting and in pregnant women.

Follow-up

A detailed fundoscopic examination and visual acuity testing should be performed in each visit.

Visual field testing is an essential method for the follow-up of patients with IIH. Involvement of inferior nasal visual field in perimetric measurements is the sign of beginning optic nerve damage. The interval of assessment depends on the patient visual course. It can be every 1–2 weeks in patients with visual deterioration or longer intervals in cases that have stable vision.

Surgical treatment

Surgical treatment is a choice of treatment in circumstances that visual acuity is threatened or increased ICP is refractory to medical treatment. The surgical interventions include CSF shunting (lumboperitoneal and ventriculoperitoneal) or optic nerve sheath fenestration (ONSF). Refractory headache in the absence of increased ICP should not be a reason for surgical procedures.

- ONSF mainly prevents damage of visual system without significant effect on headache. Complications of ONSF can be serious and include visual loss as a result of ischemic injury of the optic nerve, traction, and hemorrhage into the optic nerve sheet and compressive hematoma, so requires experienced surgeon.
- Venous sinus stenting is controversial and is not recommended as a routine part of IIH treatment.

Headache attributed to low cerebrospinal fluid pressure

If the closed space of the dura becomes perforated, the result will be dropping of the CSF pressure. Most cases of spontaneous CSF leak occur at the level of thoracic or cervicothoracic junction; however, perforation is often iatrogenic as a result of LP. Other contributing factors may include minor trauma, connective tissue disorder, degenerative disc disease, and csf shunt over drainage. Sagging of the brain in the cranial cavity causes traction on pain-sensitive structures which is exaggerated in the upright position [11].

Female gender, age between 31 and 50 years, a previous history of migraine or postdural puncture headache, and more number of attempts to obtaining sample and orientation of the needle bevel perpendicular to the long axis of the spinal column are risk factors of post-LP headache. An atraumatic 22-gauge needle decreased the risk of post-LP headache.

Clinical findings in favor of intracranial hypotension

1. Headache exacerbated by upright position and reviled by lying down at the beginning but after becoming chronic the changing of position affects less.
2. CSF leakage (rhinorrhea or otorrhea) in the case of traumatic dural fistula
3. Confusion, stupor, and coma as a result of frontal lobe sagging or pressure on the diencephalon or brain stem arousal structures
4. Downward herniation of posterior fossa elements may lead to cerebellar symptoms due to hemorrhage, signs of posterior circulation infarction, quadriparesis, and movement disorders including Parkinsonism, tremor, chorea and dystonia (deep midline structures dysfunction)
5. Downward traction of the cranial nerves results in diplopia due to six nerve palsy, changes in hearing (hyperacusis, echoing, or tinnitus), vertigo or dizziness, anorexia and diaphoresis, visual field defects, hearing loss, photophobia, hiccups, and dysgeusia.
6. Neck pain or stiffness
7. Nausea and vomiting
8. Hyperprolactinemia and galactorrhea due to pressure on the pituitary stalk.

In patients without history of LP within the prior month, ventricular shunting, or dural rupture after traumatic injury, spontaneous intracranial leak must be considered. The reasons of spontaneous intracranial leak are not completely understood. History of vigorous coughing and valsalva maneuver for example in an asthmatic patient hints the diagnosis of spontaneous intracranial hypotension (SIH) [12].

SIH incidence is estimated in about 5 per 100,000 and is more prevalent among women than men and occurs more frequently in the fourth decades of life. The headache may be sudden or gradual in onset (Tables 6d.4 and 6d.5).

Table 6d.4 ICHD-3 criteria for headache attributed to spontaneous intracranial hypotension [6].

A.	Either or both of the following:
	1. low cerebrospinal fluid (CSF) pressure (<60 mm H_2O)
	2. evidence of CSF leakage on imaging
B.	Absence of a procedure or trauma known to be able to cause CSF leakage
C.	Headache has developed in temporal relation to occurrence of low CSF pressure or CSF leakage, or has led to its discovery
D.	Not better accounted for by another ICHD-3 diagnosis.

Table 6d.5 Causes of spontaneous intracranial hypotension.

Rupture of spinal perineural Tarlov cyst
Heritable connective tissue disorders: Marfan syndrome
Epidural venous hypotension
Degenerative disc disease and osseous spore

Investigations

- Neuroimaging studies generally are not necessary in patients with obvious post-LP headache and they will be followed by conservative therapies.
- In the other cases of intracranial hypotension, brain and spinal MRI is mandatory to detect the site of CSF leakage and other brain abnormalities. Brain MRI commonly reveals frontal sagging, venous sinus engorgement, displacement of the pons against the clivus, descent of cerebellar tonsil, flattening and inferior displacement of the optic chiasm and third ventricle, pituitary hyperemia, diffuse pachymeningeal enhancements, subdural effusion or hematomas, and decrease in the size of ventricles.
- Spine MRI shows extradural CSF, engorgement of the epidural spinal vein, meningeal diverticula.
- Radioisotope cisternography is the next step to detect CSF leak in some cases with high clinical suspicion of CSF hypotension in whom MRI is not diagnostic (up to 20% of patients)

- CT myelography is the best method to localize the level of spinal leak before targeted epidural blood patch (EBP).
- A measurement of CSF pressure by dural puncture is not necessary if MRI shows signs of intracranial hypotension.

Treatment

Post-LP headache usually remits spontaneously within 2 weeks. SIH could also improve with conservative treatment. Recommendation for patients with uncomplicated headache attributed to intracranial hypotension is conservative treatment which includes bed rest, IV hydration, and caffeine intake. For intractable or complicated cases blinded autologous lumbar EBP must be done and usually it is repeatable up to two or more times [13]. Trendelenburg position after EBP might improve the result [14]. Patients who have not respond to EBP are considered for spinal CT myelography to detect the exact location of the contrast leak. If the site of the leakage is identified, they will be candidate for targeted EBP at the level of leakage and CSF leak surgery after targeted EBP failed to improve the symptoms and signs [15,16].

In patients with altered level of consciousness (somnolence or stupor) as a consequence of brain sagging, head-down Trendelenburg position and intrathecal injection of normal saline for restoration of CSF pressure and volume is a preferable initial treatment [17] (Fig. 6d.2).

Although the severe side effects of EBP are not common, it may result in rebound IIH, CVT (rarely), and superficial siderosis, so the patients should be under close observation after any intervention.

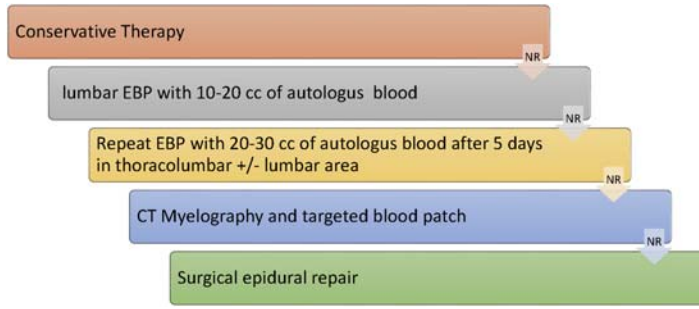

Figure 6d.2 Suggested treatment protocol for SIH.

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CHAPTER SIX(E)

Medication overuse headache

Seyed Ehsan Mohammadianinejad[1], **Behnaz Ansari**[2]
[1]Iranian Center of Neurological Research, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran
[2]Neurology, Isfahan University of Medical Science, Isfahan, Iran

Introduction

Medication overuse headache (MOH) is defined as the occurrence of chronic daily headache (CDH) in patients with preexisting frequent primary headache disorders, who overuse analgesics to 10–15 days per month for more than 3 months.

It is considered as a secondary headache disorder with a median prevalence of about 1%–2% in the general population [1]. Up to 70% of people with chronic migraine have associated MOH [2]. Females are affected more common (about 4 times) and the most common age of onset is in fourth decade [3,4]. Most patients have chronic migraine who overuse analgesics, but a smaller number of patients have tension type headache (TTH) and rarely other primary headache disorders are present.

How it clinically manifests?

MOH usually presents as an increased frequency of preexisting primary headache. In patients with migraine, it is in the form of CDH with migraine features in most of the days. Analgesics may suppress accompanying symptoms of migraine headache, mimicking a TTH. Hence, the pattern of headache may change after MOH develops. In patients with prior TTH, it is mainly in the form of increased frequency of headache episodes.

Therefore, there is not a particular feature of headache, characteristic for MOH, and it is mainly in the form of an increased frequency of preexisting headache with some modification due to analgesic effect [5].

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What is the pathophysiologic process causing MOH?

Almost all patients with MOH have preexisting migraine and a much smaller number have other primary headache disorders. Patients with cluster headache do not develop MOH, unless they also suffer from migraine or have family history of migraine [6]. Patients with migraine who overuse analgesics due to musculoskeletal comorbidities can experience exacerbation of headache but not musculoskeletal symptoms. All these data suggest that it is the migraine brain or migraine gene that makes the patient prone to MOH, after an exposure to a psychosocial stressor. The dopaminergic gene system involved in pain modulation seems to have the main role [7].

Are acute symptomatic medications the same in producing MOH?

Any analgesic can cause MOH, but it is shown that triptans and opioids have the most risk, and do it in a shorter period compared with other ones. This study also showed that triptan-induced MOH presents more with migraine like headaches, while other analgesics mainly cause a TTH like presentation [8]. In practice, many patients use multiple medication and these differentiating features may not be so clear.

Who is at more risk for MOH?

Among many patients with migraine or TTHs, those who have psychiatric comorbidities including depression and anxiety and/or frequent use of tranquilizers are at higher risk of MOH. Other risk factors that are associated with increased risk of MOH are shown in Table 6e.1 [5].

Patients who are of lower educational level are prone, due to their increased risk of psychiatric comorbidity, less availability to appropriate treatment, and also less education about the disadvantage of analgesic overuse. Patients with migraine who have musculoskeletal or gastrointestinal comorbidities and overuse analgesics for other pain syndromes are also a higher risk group. Sedentary life and some habits such as smoking and high caffeine use are among other factors associated with more risk of MOH [9].

Table 6e.1 Risk factors for MOH.

Demographic features
Age<50
Female sex
Low educational level
Comorbidities
Anxiety or depression
Musculoskeletal disorders
Gastrointestinal disorders
Lifestyle and habits
Smoking
Physical inactivity
Metabolic syndrome
High daily caffeine intake

These factors should be addressed in patients with primary headache disorders who have frequent episodes to prevent the development of MOH. Once MOH develops, the headache becomes more disabling and the management more difficult.

How to diagnose a patient with MOH?

ICHD-3 proposes the following criteria for the diagnosis of MOH [10]:

1. There should be recent onset of CDH (headache on $\geq$ 15 days/month) in a patient with preexisting primary headache disorder.
2. There is regular overuse of analgesics for >3 months. This is $\geq$ 15 days for simple analgesics (acetaminophen, NSAIDs) and $\geq$10 days for triptans, ergots, opioids, or combination analgesics.
3. There should not be a better explanation.

In practice, a patient with frequent episodic migraine or less commonly TTH transforms to CDH, while she/he overuses analgesics. The question arises here that if the patient is suffering from a chronic migraine or TTH or from MOH. The diagnosis of MOH could be definite on a retrospective view, if the patient improves after stopping analgesics. This improvement within 2 months of withdrawing medications proposed by ICHD-2 is not a requirement in current criteria because of producing challenges in earlier

diagnosis and treatment. MOH is a secondary headache disorder superimposed on a primary one. The additional diagnosis of primary headache type and the substance abused should also be reported in the diagnosis [10].

What differentials should be considered before the diagnosis of MOH?

Most patients with CDH overuse analgesics, but not all suffer from MOH. Actually, one should differentiate between medication overuse and MOH. MOH is a secondary headache disorder that should be considered in every patient with CDH. However, it is important to exclude alternative secondary causes of CDH, before the diagnosis of CDH [11].

1. Focus on the onset of symptoms. The acutely remembered onset of headache that has become continuous in less than 24 h in a patient with CDH points to the diagnosis of new daily persistent headache, which has a distinct approach. Onset of headache with orthostatic pattern points to the diagnosis of spontaneous intracranial hypotension. Many patients with SIH will transform to CDH without orthostatic pattern over time and it is the quality of pain at onset that discloses the diagnosis.
2. Ask for symptoms of sleep apnea if present. This may be an underscored cause of CDH in clinical practice.
3. Examine the patient for evidence of increased ICP, which may manifest as a nonspecific CDH. Of course, any abnormal systemic or neurologic finding mandates an appropriate related workup.

Hence, MOH is a secondary headache disorder that should also be made after a targeted history and physical examination does not show evidence of alternative secondary causes. Laboratory tests, imaging, and CSF analysis are helpful on an individualized basis.

How to manage MOH?

Management of MOH includes consultation and advice about the disease and what the patient can do for better management, nonpharmacologic treatments, withdrawing analgesics and managing this period, prophylactic treatment, and management of psychiatric comorbidity if present. All these steps are better to be started simultaneously and at the beginning of treatment. The patient should be explained that she/he is prone to recurrence of MOH if restarting frequent use of analgesics.

1. The first step is to give advice and education about the challenges and how the patient can help. The patient should believe that she/he is

Table 6e.2 Essential advice for management of MOH.

1.	It is stopping the analgesics that finally improves the condition.
2.	Be patient. It may take weeks or even few months to get good results.
3.	You should stick on withdrawing medication and withdrawal symptoms are transient.
4.	Maintain or improve your daily exercise.
5.	Do not overuse caffeine, alcohol, or smoking.

directly responsible for management. Some advice that are of significance are shown in Table 6e.2.

2. Nonpharmacologic measures are of great significance and should be encouraged during the course of treatment and in each visit. Regular moderate exercise, modifying caffeine and alcohol consumption and smoking, stress management, and biofeedback are helpful. Cognitive behavior therapy (CBT) can be beneficial in patients who have psychiatric comorbidity or have difficulty in coping with the psychosocial stressors and the disease.

3. The patient should be emphasized to stop taking analgesics. A Danish study showed that complete withdrawal and detoxification of analgesics will have better result compared with allowing the patient to take analgesics as needed for a maximum of 2 days per week [12].

Patients who abuse opioids, barbiturates, or benzodiazepines, those with severe depression, epilepsy, or major medical problem may be considered for inpatient management [13]. Other patients can be managed in an outpatient setting.

The patient may experience withdrawal symptoms such as exacerbating headache, nausea, vomiting, insomnia, and agitation for 1–3 weeks depending on the type and amount of overused medication [11].

Bridge therapy with short-term IV or oral steroids to manage withdrawal period has given paradoxical results in different studies [14–16]. In a comparative trial, patients with MOH were randomized to two groups of oral treatment with celecoxib and prednisone for 10 days. The celecoxib group experienced lower headache intensity during the first 3 weeks after withdrawal than those treated with prednisone, but headache frequency and the need for rescue medication were not significantly different [17].

Overall, steroids, NSAIDs, antiemetics, and triptans could be used in patients not overusing them, and seems to have some effect in managing withdrawal period, but does not have the support of strong placebo controlled studies [13]. This intermittent use of acute symptomatic therapies for less than 2 times per week could be particularly useful for patients who cannot tolerate complete withdrawal of analgesics.

4. Prophylactic treatment for migraine headache facilitates withdrawing analgesics and also helps long-term management of headache [13]. Since it takes time for prophylactic treatment to be effective, it is better to start treatment at the beginning.

   The choices are topiramate and botulinum toxin injection in a patient with chronic migraine. Topiramate is useful for chronic migraine but is not often tolerated in higher doses in patients with migraine. It is started with a dose of 25 mg and titrated 25 mg every 2 weeks to a dose of 50 mg BID, but may be titrated up to 400 mg/day in particular cases. Adverse effects are common especially in higher doses and are often troublesome. Impairment of cognition and concentration, problems with speech, irritability and depression, and disturbing paresthesia may limit its use. It should be used with caution in patients with significant psychiatric comorbidity.

   Botulinum toxin is an effective and well-tolerated treatment for chronic migraine and may let us to use lower tolerable doses of topiramate. Monoclonal antibodies targeting CGRP are other well-tolerated new options for prophylactic treatment. Fremanezumab and erenumab have shown promising results even in patients who are not able or do not stop analgesics [13].

5. Treatment of psychiatric comorbidity has been shown to be beneficial in withdrawing medication overuse. CBT along with drug treatment can be used. Tricyclic antidepressants and SNRIs such as venlafaxine may be used according to headache and psychiatric profile [18].

In conclusion, the treatment of MOH and associated primary headache disorder may be performed better in a multidisciplinary approach including pharmacologic and nonpharmacologic treatments. An algorithm is shown for practical steps in diagnosis and management of MOH (Fig. 6e.1).

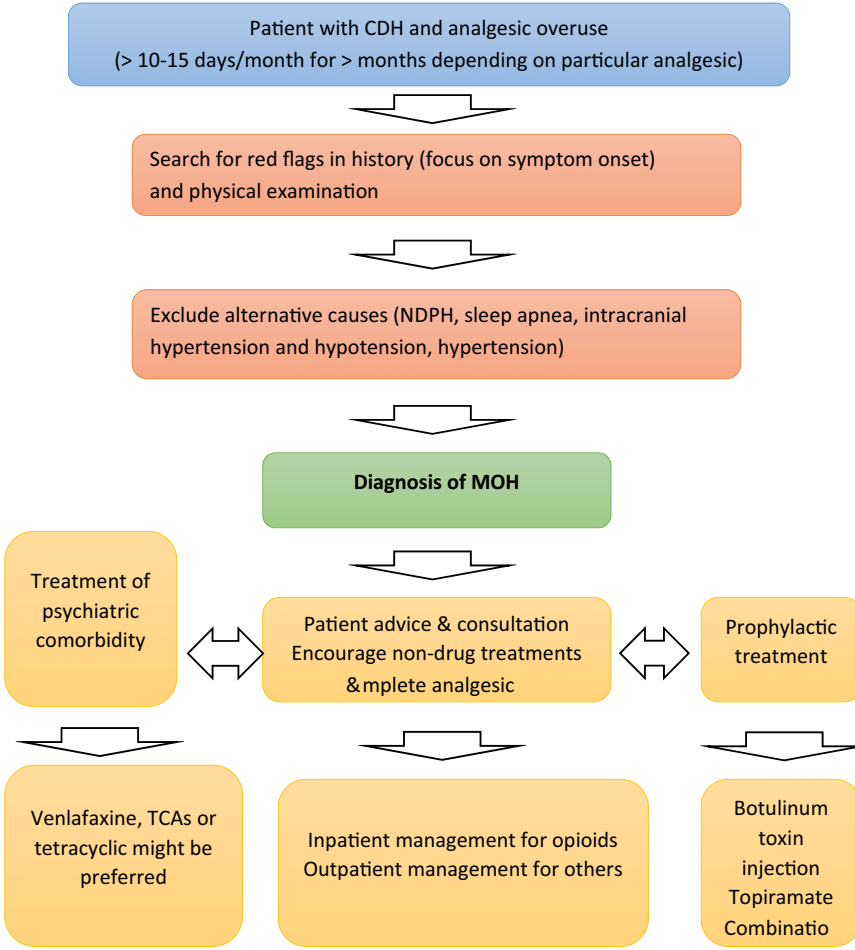

Figure 6e.1 Algorithmic approach to diagnosis and management of MOH.

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CHAPTER SIX(F)

Headache attributed to infection

Samaneh Haghighi
Neurology Department, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran

Introduction

Headache is common in systemic and intracranial infections. A new headache may have the features of any of the primary headache disorders.

When a previous primary headache worsens with infection (usually meaning at least a two-fold increase in frequency and/or severity), both the primary headache diagnosis and a diagnosis of headache attributed to infection are given [1–3] (Fig. 6f.1) (Table 6f.1).

Systemic infections, meningitis, encephalitis, brain abscess, sinusitis, mastoiditis, epidural, subdural or intraparenchymal abscess formation, and osteomyelitis of the skull can all cause either focal or generalized headache. The diagnosis is usually considered when other associated symptoms and signs are present [4].

Pathophysiology of headache

There are a number of possible mechanisms [1,3,5–7], including

(1) Direct stimulation of intracranial pain-sensitive structures as in the case of brain abscesses.
(2) Irritation of the meninges as in cases of bacterial or viral meningitis
(3) Intracranial hypertension as seen in obstructive hydrocephalus secondary to TB meningitis
(4) Bacterial toxins and inflammatory mediators as in bacterial meningitis. Inflammatory mediators may play a role in postinfectious headache.

Headache attributed to intracranial infection

- In acute meningitis or meningoencephalitis, headache is the most common and may be the earliest presenting feature. Headache is usually acute, severe, and generalized, and may be one of the flu-like symptoms

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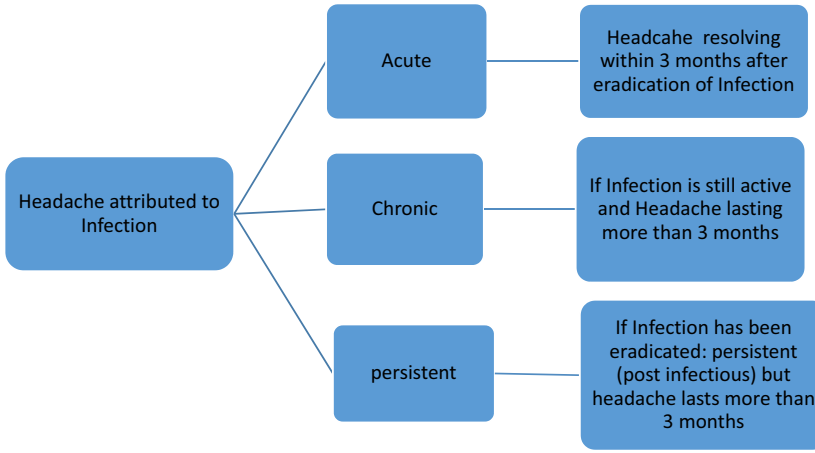

Figure 6f.1 Headache attributed to infection.

Table 6f.1 International Classification of Headache Disorders (International Headache Society Classification ICHD-3) criteria for headache attributed to infection [4].

A. Headache fulfilling criterion C
B. An infection, or sequela of an infection, known to be able to cause headache has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
  1. Headache has developed in temporal relation to the onset of the infection
  2. Either or both of the following:
    (a) Headache has significantly worsened in parallel with worsening of the infection
    (b) Headache has significantly improved or resolved in parallel with improvement in or resolution of the infection
  3. Headache has characteristics typical for the infection
D. Not better accounted for by another ICHD-3 diagnosis.

preceding meningoencephalitis. Neck stiffness, fever, and confusion are three cardinal associated features of acute meningitis. Patients with encephalitis usually present with a decreased level of consciousness, seizures, and focal neurologic deficits. In most cases of full-developed meningitis and encephalitis, features of the involvement of both the meninges and brain parenchyma coexist. Headache is usually due to a combination of intracranial hypertension, meningeal irritation, and hyperthermia. The most common microorganisms causing meningitis are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Listeria*

monocytogenes. Herpes encephalitis is the most frequent type of sporadic encephalitis [1,3,5–7].

- Enteroviruses are the most common culprit organism in headache attributed to viral meningitis or encephalitis; Herpes simplex, adenovirus, mumps, and other viral agents may also be responsible.
- Whenever a headache is associated with fever, ongoing several focal neurological deficits and progressive mental regression, subacute to chronic meningitis or meningoencephalitis should be considered.
- Headache due to brain abscess is usually accompanied by fever, focal neurological deficits, or confusion. Direct stimulation, pressure on the intracranial pain sensitive structures, and elevated intracranial pressure are the mechanisms noted in this type of headache.
- The clinical features of subdural empyema, which is often secondary to sinusitis, otitis media, or meningitis, include headache, fever, and meningeal or raised intracranial pressure signs. Like other types of infection-related headache, the diagnosis is determined based on the presence of other associated symptoms [1,3,5–7].

Headache attributed to systemic infection

According to ICHD-3 criteria, headache attributed to systemic infection is caused by an infection in the absence of meningitis or meningoencephalitis. In this type of headache, headache occurs during the systemic infection and remits in parallel with improving the infection. Headache itself is not a diagnostic feature but can be the cardinal or may be the only feature as in influenza in which the headache is a predominant symptom. Differences in the tendency of the microorganisms to cause headache demonstrated that headache attributed to systemic infection is not simply a febrile-induced headache [1,3,5–7].

Postinfectious headache

Persistent headache attributed to infection is defined as a headache that does not remit after successful treatment of the infection daily headache lasting for more than 3 months with an exactly mentioned onset is the characteristic of the NDPH (New daily persistent headache).

Several studies have shown an association between NDPH and infection. About 30%–43% of the patients with NDPH report that their headache starts after an established infection; thus, infection should be suspected in

the etiology of NDPH. Serological tests for different viruses have shown that Epstein–Barr virus (EBV) is the most common microorganism in NDPH. However, a number of other viral infections such as HSV, CMV, etc., have also been noted in patients with NDPH.

Although infection is reported as the etiology of NDPH, a positive EBV titer in patients with NDPH can be an epiphenomenon due to EBV reactivation as a result of the stress of long-lasting headaches [7–11].

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CHAPTER SIX(G)

Headache attributed to disorders of homoeostasis

Majid Ghafarpour
Tehran University of Medical Sciences, Neurology, Imam Khomeini Hospital, Tehran, Iran

Metabolic (systemic) headaches

According to the new classification of headaches (ICHD-3, 2018), when a new headache occurs for the first time in close temporal relation to a disorder of homoeostasis, it is coded as a secondary headache attributed to disorder of homeostasis. In other words, "headache attributed to disorder of homeostasis" is now used instead of "metabolic or systemic headaches," which includes the following entities:

- Headache attributed to hypoxia and/or hypercapnia (high-altitude headache, airplane travel, diving, sleep apnea).
- Headache attributed to arterial hypertension (pheochromocytoma, hypertensive crisis with or without encephalopathy, preeclampsia or eclampsia, metabolic syndrome).
- Erythrocyanotic headache
- Cardiac cephalgia
- Autonomic dysreflexia
- Hypothyroidism
- Fasting
- Dialysis
- Other conditions such as hypercalcemia, drug use, and withdrawals

Although homeostatic or metabolic disorders cause headache via different mechanisms, the majority of them share the following criteria (Table 6g.1):

Headache attributed to hypoxia and/or hypercapnia/ hypercapnia

Headache attributed to hypoxia/hypercapnia occurs in conditions of exposure to hypoxia and/or hypercapnia. It is established within 24 h of

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Table 6g.1 ICHD3 criteria for headache attributed to disorder of homeostasis.

A.	Headache fulfilling criterion C
B.	A disorder of homoeostasis known to be able to cause headache has been diagnosed
C.	Evidence of causation demonstrated by at least two of the following:
	1. headache has developed in temporal relation to the onset of the disorder of homoeostasis
	2. either or both of the following:
	(a) headache has significantly worsened in parallel with worsening of the disorder of homoeostasis
	(b) headache has significantly improved after resolution of the disorder of homoeostasis
	3. Headache has characteristics typical for the disorder of homoeostasis
D.	Not better accounted for by another ICHD-3 diagnosis.

exposure to acute hypoxia with PaO2 below 70 mmHg or chronic hypoxia with PaO2 $\geq$ 70 mmHg. It occurs in pulmonary diseases (asthma, COPD), congestive heart failure, and hematological disorders associated with anemia. In ICHD-3, this entity includes headache attributed to high-altitude, diving, airplane travel, and sleep apnea.

High-altitude headache

This headache is caused by ascending to 2500 m above sea level, worsens by further ascent, and resolves within 24 h after descent. It is mild to moderate in intensity and worsens with movement, exertion, coughing, and bending. Although it is bilateral according to the diagnostic criteria (Table 6g.2), it may be unilateral, usually in migraine patients.

This headache is the most frequent complication of ascent to high-altitude places with an incidence of 73.3%–88% [1,2]. High-altitude headache is usually associated with nausea, photophobia, dizziness, concentration and judgment disturbances, and possibly the signs of cerebral edema in severe cases. The risk factors include a history of migraine, low arterial oxygen saturation, high degree of exertion, low fluid intake (<2 L in 24 h), insomnia, a high heart rate, and a high self-rating anxiety scale score [3].

Although its pathophysiology is not clear, some researchers believe that hypoxia increases the hydrostatic pressure and capillary leakage through neurohormonal and hemodynamic changes of the cerebral microvascular bed, resulting in cerebral edema. Imaging studies have confirmed the

Table 6g.2 ICHD3 criteria for high-altitude headache.

A. Headache fulfilling criterion C
B. Ascent to altitude above 2500 m has occurred
C. Evidence of causation demonstrated by at least two of the following:
  1. headache has developed in temporal relation to the ascent
  2. either or both of the following:
    (a) headache has significantly worsened in parallel with continuing ascent
    (b) headache has resolved within 24 h after descent to below 2500 m
  3. headache has at least two of the following three characteristics:
    (a) bilateral location
    (b) mild or moderate intensity
    (c) aggravated by exertion, movement, straining, coughing, and/or bending
D. Not better accounted for by another ICHD-3 diagnosis

presence of cerebral edema. A lower prevalence of this headache in the elderly population, possibly due to brain atrophy, corroborates this hypothesis.

A recent study found that water shifts toward the intracellular space in the white matter in acute hypoxia, which is related to the severity of headache while there is no sign of brain swelling.

Most cases respond to treatment with paracetamol (acetaminophen) or ibuprofen, antiemetics, acetazolamide (125—250 mg BD), and steroids. It has been shown that administration of 350 mg acetylsalicylic acid (aspirin) three times, 4 h apart, 1 hour before ascent, or 600 mg ibuprofen TDS starting from a few hours before ascending to 3480—4920 m reduces the probability of the headache. Liberal fluid intake, slow ascent to the altitude, avoidance of alcohol and sedatives, and acclimatization before ascending to higher altitudes may also decrease the occurrence of this headache. It has been reported that acclimatization in intermediate altitudes is the most effective preventive measure.

Ascent to altitude is associated with acute and chronic complications:

1. Acute high-altitude sickness

This condition occurs in people dwelling at the sea level that ascent to high altitudes very fast. It manifests with headache, loss of appetite, nausea and vomiting, weakness, and insomnia and occurs following ascent above 8000 feet (2438 m). Ataxia, tremor, sleepiness, slight confusion, and delusion may be seen at higher altitudes. Staying at higher altitudes for a longer time may cause decreased level of consciousness eventually leading to coma.

2. Chronic high-altitude sickness (Monge's disease)
   This condition is seen in people who live at high altitudes for a long time. The main manifestations of this disease are pulmonary hypertension, polycythemia, and cor pulmonale. Hypercapnia is usually present, resulting in confusion, nighttime headache, papilledema, and burning hand-foot syndrome.

Airplane travel headache

Headache attributed to airplane travel is usually a severe, unilateral, and periorbital headache without autonomic symptoms, occurring only during airplane travel. Headaches are stereotypic, more frequent in males, and last for less than 30 min in more than 85% of the cases (Table 6g.3).

The pathophysiology of airplane travel headache is not yet clear. It is believed that this headache is caused by increased intrasinus pressure in frontal sinuses, compression of the sinus wall, and production of a negative pressure, resulting in sinus mucosal swelling and transudation during airplane landing. Some researchers have attributed this headache to local inflammation due to hypoxia or sinus barotrauma.

Application of local pressure on pain points, Valsalva maneuver, chewing, and pulling the ears relieve the headache in 25% of the cases. Analgesics

Table 6g.3 ICHD3 criteria for headache attributed to airplane travel.

A. At least two episodes of headache fulfilling criterion C
B. The patient is traveling by airplane
C. Evidence of causation demonstrated by at least two of the following:
   1. headache has developed during the airplane flight
   2. either or both of the following:
      (a) headache has worsened in temporal relation to ascent following take-off and/or descent prior to landing of the airplane
      (b) headache has spontaneously improved within 30 min after the ascent or descent of the airplane is completed
   3. headache is severe, with at least two of the following three characteristics:
      (a) unilateral location
      (b) orbitofrontal location
      (c) jabbing or stabbing quality
D. Not better accounted for by another ICHD-3 diagnosis.

like naproxen 550 mg and antihistamines such as pseudoephedrine and nasal decongestants administered 30–60 min before flight may have a preventive effect [4].

Diving headache

Diving headache is caused by diving to a depth greater than 10 m and is the best clinical example of headache attributed to hypercapnia. It is usually accompanied by symptoms of CO_2 intoxication (confusion, orthostatic headache, difficulty breathing, and flushing). It remits within 1 hour with oxygen and spontaneously (with no oxygen) within 3 days after the diving has ended. Evidence suggests that hypercapnia ($PCO2 > 50$ mmHg) causes relaxation of cerebrovascular smooth muscle, resulting in intracranial vasodilation, and elevated intracranial pressure.

During diving, CO_2 may accumulate as a result of intentional hypoventilation such as skipping breathing to conserve air or due to taking shallow breaths in the narrow passages of a wreck or cave. Hypoventilation may be unintentional (a tight wetsuit). Strenuous exercise during diving may increase the rate of CO_2 production by more than 10-fold, resulting in CO_2 levels above 60 mmHg. This headache usually worsens upon surfacing (decompression).

A cross-sectional study in men showed Scuba diving, an intense physical activity characterized by cerebral microvascular distress, was not associated with cephalalgia in general or migraine, tension headache, or migraine with aura more commonly than in a matched, nondiving population [5].

Although this headache is not prevalent in divers (4.5%–23%) and is relatively benign, it may be accompanied by serious complications like arterial gas embolism, decompression illness, and barotrauma of the ear and paranasal sinuses. Therefore, when assessing a patient whose headache is not benign, it is necessary to consider further workup to rule out ear barotrauma and barosinusitis, gas embolism, decompression illness, CO_2 retention, CO intoxication, hyperbaric-induced migraine, supraorbital neuralgia, carotid artery dissection, neck and TMJ trauma, and cold or exercise-induced headaches. If neurological symptoms are present (even in people with a history of migraine headache), 100% oxygen should be administered immediately and the patient should be transferred to centers equipped with hyperbaric chamber facilities. Moreover, since the association of migraine and a patent foramen oval (PFO) was first described in divers, it is recommended that the patient be evaluated for PFO before attributing the headache to diving.

Sleep apnea headache

Sleep apnea headache is a morning headache that is bilateral, recurrent, and pressing without nausea, photophobia, and phonophobia. This headache usually resolves within 4 h (Table 6g.4).

In addition to a positive history of OSA, female sex, a history of migraine, psychologic distresses, and obesity are other predictors of sleep apnea headache.

The pathophysiology of sleep apnea headache is not yet clear, and different mechanisms including hypoxia, hypercapnia, short REM, and increased ICP have been proposed.

Sleep apnea headache is diagnosed by polysomnography and determining the Apnea–Hypopnea Index (AHI). AHI is calculated by dividing the number of apneic events by the number of hours of sleep, and AHI≥5 is in favor of sleep apnea headache.

There is a complex relationship between sleep and headache, because sleep disorders can provoke headache. On the other hand, snoring and other sleep disorders are risk factors of migraine progression and cluster headache. Moreover, although morning headache is more common in patients with sleep apnea than in the general population, headache upon awakening is a

Table 6g.4 ICHD3 criteria for sleep apnea headache.

A. Headache present on awakening after sleep and fulfilling criterion C
B. Sleep apnea with apnea–hypopnea index ≥5 has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
  1. headache has developed in temporal relation to the onset of sleep apnea
  2. either or both of the following:
    (a) headache has worsened in parallel with worsening of sleep apnea
    (b) headache has significantly improved or remitted in parallel with improvement in or resolution of sleep apnea
  3. headache has at least one of the following three characteristics:
    (a) recurring on ≥15 days/month
    (b) all of the following:
      i. bilateral location
      ii. pressing quality
      iii. not accompanied by nausea, photophobia, or phonophobia
    (c) resolving within 4 hours
D. Not better accounted for by another ICHD-3 diagnosis.

nonspecific finding in a variety of primary and secondary headache disorders as well as other sleep-related disorders like COPD, periodic leg movements, and Pickwickian syndrome.

Dialysis headache

Headache is the most common side effect of dialysis occurring in 30%–70% of the patients undergoing hemodialysis. Irritability, toxic encephalopathy, sleepiness, nausea, vomiting, and muscle cramps are seen in 5%–10% of the cases. It is more common in children and in hemodialysis than in peritoneal dialysis. It was first believed that reverse urea syndrome was the cause, but it is now attributed to water toxicity (intracellular edema) secondary to SIADH. The latter syndrome is diagnosed with hyponatremia, a hypoosmolar serum, and a hyperosmolar and hypertonic urine.

Although dialysis headache has no specific characteristics, it usually occurs 3–4 h after hemodialysis and resolves spontaneously within 72 h after the hemodialysis session has ended. However, there are also reports of the headache starting 8–48 h after a hemodialysis session. In a retrospective study, one third of the patients who had typical dialysis headache had similar headache episodes between dialysis sessions as well, and most of the headaches (86%) occurred in the second half of dialysis (Table 6g.5).

The exact pathophysiology of dialysis headache is not yet understood, but it is commonly associated with hypertension and dialysis disequilibrium syndrome. In the severe forms of this syndrome, it may begin as a headache and then progress to coma, with or without seizures.

Table 6g.5 ICHD3 criteria for dialysis headache.

A. At least three episodes of acute headache fulfilling criterion C
B. The patient is on hemodialysis
C. Evidence of causation demonstrated by at least two of the following:
  1. each headache has developed during a session of hemodialysis
  2. either or both of the following:
    (a) each headache has worsened during the dialysis session
    (b) each headache has resolved within 72 h after the end of the dialysis session
  3. headache episodes cease altogether after successful kidney transplantation and termination of hemodialysis
D. Not better accounted for by another ICHD-3 diagnosis

Variations in arterial pressure and body weight during dialysis may provoke headache. Changing dialysis parameters may prevent this disorder. There is no specific treatment in the literature but analgesics and NSAIDs are used during dialysis. There is a report of the beneficial effects of ACE inhibitors like Lisinopril for the management of this type of headache.

Headache attributed to arterial hypertension

This headache is often bilateral and pulsating, and is caused by arterial hypertension, usually during an acute rise in systolic (to ≥180 mm Hg) and/or diastolic (to ≥120 mm Hg) blood pressure. It worsens in parallel with increasing hypertension and remits after normalization of blood pressure. Most of the patients wake up with an occipital headache [6]. Mild (140–159/90–99 mm Hg) or moderate (160–179/100–109 mm Hg) chronic arterial hypertension does not appear to cause headache; however, there is evidence that moderate hypertension predisposes the patients to this headache disorder [7]. Glomerulonephritis, pheochromocytoma, hypertensive encephalopathy, eclampsia/preeclampsia, and autonomic dysreflexia may be associated with headache attributed to arterial hypertension [8]. Disturbances in baroreceptor reflexes have been proposed as the mechanism of this headache [9].

- Headache attributed to hypertensive crisis without encephalopathy is defined as a bilateral and pulsating headache due to a paroxysmal rise in the arterial blood pressure (SBP≥180 mmHg and DBP≥120 mmHg) that remits after normalization of blood pressure. The mechanism is believed to be the failure of baroreceptor reflexes (following carotid endarterectomy or neck radiotherapy) or enterochromaffin cell tumors.
- About 75% of the patients with pheochromocytoma experience short-term paroxysmal headaches associated with nausea, pallor, sweating, anxiety, palpitation, abdominal or chest pain, tremor, and paresthesia during the hypertensive crisis and catecholamine release. The headache usually affects the frontal or occipital regions. An important feature of the paroxysmal headache is its short duration (less than 15 min in 50% of the cases and less than 1 hour in 70% of the patients) [10]. Measurement of VMA in a 24-hour urine sample is used for diagnosis.
- Patients with pheochromocytoma, mastocytosis (in which serotonin, heparin, and histamine are released), carcinoid syndrome, serotonin secreting tumors, and some pancreatic tumors may experience an intense, generalized, and pulsating headache with flushing of the face and

hands and numbness of fingers (erythromelalgia) known as erythrocyanotic headache. The symptoms tend to occur on awakening from sleep.

- Patients with hypertensive encephalopathy may complain about a bilateral and pulsating headache caused by persistent elevation of blood pressure accompanied by symptoms of encephalopathy (confusion, seizures, and lethargy). It improves after normalization of blood pressure. From a pathophysiological point of view, hypertension impairs cerebral autoregulation and increases endothelial permeability, resulting in cerebral edema, especially in the parieto-occipital white matter. Although hypertensive encephalopathy occurs in patients with chronic arterial hypertension (a diastolic blood pressure of >120 mm Hg) and grade III or IV hypertensive retinopathy, previously normotensive individuals may develop signs of encephalopathy with blood pressures as low as 160/100 mm Hg.
- Metabolic syndrome refers to a cluster of clinical, metabolic, and biochemical abnormalities like central obesity, insulin resistance, and dyslipidemia, which increases the risk of type 2 diabetes, coronary artery disease, stroke, and headache [11]. It also has been shown that metabolic syndrome is associated with an increased risk of hepatic steatosis, nonalcoholic fatty liver disease, gonadal dysfunction, polycystic ovary syndrome, vascular dementia, hypercoagulable state, Alzheimer's disease, obstructive sleep apnea, and carcinoma, especially pancreatic and colorectal cancer [12].
- Hypertension, obstructive sleep apnea, and complications related to hypercoagulability can cause headache. On the other hand, this syndrome is more common in patients with migraine and the prevalence of migraine is also higher in patients suffering from metabolic syndrome; however, the mechanism of the relationship between metabolic syndrome and migraine is not still clear [13].

Headache attributed to preeclampsia and eclampsia

The diagnosis of preeclampsia and eclampsia requires hypertension (>140/90 mm Hg) documented on two blood pressure recordings at least 4 hours apart, or a rise in diastolic pressure of ≥15 mm Hg or in systolic pressure of ≥30 mm Hg, coupled with urinary protein excretion >0.3 g/24 h. In addition, tissue edema, thrombocytopenia, and liver function abnormalities may also occur. Headache is usually bilateral and pulsating and worsens with physical activity. It occurs during pregnancy or in the immediate puerperium (up to 4 weeks postpartum).

Headache attributed to autonomic dysreflexia

Autonomic dysreflexia occurs in patients with spinal cord injury (SCI). The time to onset of autonomic dysreflexia after SCI is variable and ranges from 4 days to 15 years [14]. The location and severity of the lesion are important predictors of dysreflexia, with complete SCI being the most important one.

Autonomic dysreflexia is often triggered by painful or painless stimuli, often of the visceral origin (bladder distension, urinary tract infections, bowel distension or constipation, urological procedures, gastric ulcer) but sometimes of somatic origin as well (pressure ulcers, ingrown toenail, burns, trauma, surgical, or invasive diagnostic procedures).

From a clinical point of view, this disorder is characterized by paroxysmal hypertension, headache, palpitation, and sweating above the level of injury. Intense pulsating headaches are present in 56%—85% of the cases. There is limited information about the mechanism of headache in these patients. It is suggested that these headaches have a vasomotor origin (passive dilatation of cerebral vessels or increased prostaglandin E2 levels).

Autonomic dysreflexia is a life-threatening condition and therefore early diagnosis and proper management of the acute phase is of extreme importance, including (1) sitting the patient up, (2) removing or loosening tight clothing, (3) identifying the triggering stimuli, and (4) administering rapidly acting antihypertensive drugs like nifedipine and nitrates.

Headache attributed to hypothyroidism

One-third of the patients with hypothyroidism develop headache. Headache occurs about 2 months after the onset of hypothyroidism and resolves within 3 months of treatment. There is a female preponderance, and the patients often report a history of migraine in childhood. The headache is usually bilateral, persistent, and nonpulsating. In migraineurs with subclinical hypothyroidism, treatment of hypothyroidism may have a significant effect on headache management. The mechanism of the headache is not yet clear, but it has been shown that hypothyroidism is an important risk factor for new daily persistent headache [15]. In the presence of hypothyroidism, headache can also be a manifestation of pituitary adenoma.

Cardiac cephalgia

Cardiac cephalgia is a migraine-like headache of moderate to severe intensity that usually worsens by exercise. It occurs during cardiac ischemia

and improves by nitroglycerine. According to Lipton, this headache disorder is a treatable form of exertional headache.

Diagnosis must include careful documentation of headache and simultaneous cardiac ischemia during treadmill or nuclear cardiac stress testing; however, there are also reports of cardiac cephalgia occurring at rest [16]. Failure to correctly diagnose cardiac cephalgia may have serious consequences because it may be the only manifestation of myocardial ischemia. On the other hand, both migraine and cardiac cephalgia are triggered by exercise and both can produce severe head pain accompanied by nausea. Furthermore, the antimigraine drugs with vasoconstriction properties (e.g., ergots and triptans) are contraindicated in ischemic heart disease. Therefore, it is very important to distinguish cardiac cephalgia from migraine.

Although the mechanism of cardiac cephalgia is not clear, neuronal convergence, including accumulation of somatic and sympathetic impulses in the posterior gray column, transient elevation in the intracardiac pressure resulting in increased intracranial pressure, and functioning ventricular pacemaker have been proposed.

Headache attributed to fasting

Headache attributed to fasting is a diffuse nonmigraine headache that starts after at least 3 hours of fasting and improves after eating. This headache is more prevalent in people who have a prior history of headache, but prolonged fasting may also cause headache in people with no previous history of a primary headache disorder; the latter occurs during religious fasting, especially in the first days of Ramadan. Therefore, it is known as Yom Kippur headache or First-of-Ramadan headache. Mild to moderate headache may also be seen following fasting in patients with a prior history of migraine; therefore, headache attributed to fasting may resemble migraine without aura.

Hypoglycemia is a triggering factor for migraine headache. Headache attributed to fasting also occurs in the absence of hypoglycemia; therefore, other reasons like caffeine withdrawal, sleep pattern changes, and circadian factors have been proposed as well.

New studies suggest that preventive use of COX-2 inhibitors like Rofecoxib 50 mg immediately before the onset of fasting is effective in decreasing this type of headache [17]. Long-acting NSAIDs or triptans may also be a proper treatment.

Headache and hypercalcemia

Hypercalcemia is defined as a serum calcium level above 10.5 mg/dL. If serum proteins are within the normal limits, neurological manifestations occur at serum calcium levels higher than 12 mg/dL; however, these manifestations may appear at lower calcium levels (even below 10 mg/dL) if there is hypoproteinemia.

Headache, loss of appetite, nausea, and vomiting are initial symptoms, which may be followed by confusion and rarely delirium. Coma may occur if there is persistent severe hypercalcemia. Seizures are not common, but there are rare reports of generalized myoclonus and rigidity.

Hyperparathyroidism is the most common cause of hypercalcemia in young people, while multiple myeloma and osteolytic tumors are usually responsible for this condition in older patients. Decreased urinary excretion of calcium (renal failure), carbon monoxide intoxication, prolonged inactivity, hyperthyroidism, and sarcoidosis are less common causes of hypercalcemia.

Drug-induced headaches

Although headache is among the common side effects of a large number of drugs, it is more expected with some drugs like hydralazine, captopril, prazosin, calcium channel blockers, nitroglycerine, dipyridamole, minoxidil, and SSRIs. Headache is a common side effect of cocaine use that usually occurs at the time of taking the drug. Cocaine withdrawal headache is also described in cocaine addicts.

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CHAPTER SIX(H)

Headache or facial pain attributed to disorder of the cranium, eyes, ears, nose, sinuses, teeth, mouth, or other facial structure

Hossein Ansari[1], **Samaneh Haghighi**[2]
[1]Headache and Facial Pain Clinic, Kaizen Brain Center, San Diego, CA, United States
[2]Neurology Department, Tehran University of Medical Sciences, Sina Hospital, Tehran, Iran

Introduction

Convergence of the nociceptive pathways of the ears, eyes, nose, neck, and head leads to headache following any painful disorders of these structures. Therefore, the occurrence of a new headache or deterioration of the previous one, in close temporal relation to disorders of the mentioned structures, can be referred to as secondary headache attributed to these disorders, provided the disorders are able to cause headache. One important feature of the pain attributed to disorders of these structure(s) is that the pain is nociceptive rather than neuropathic in nature.

Headache attributed to disorders of cranial bone

According to the ICHD3, headache attributed to disorders of the cranial bone is a type of headache occurring in close temporal relation to nontraumatic cranial bone diseases. Headache could be the earliest symptom in multiple myeloma, cranial osteomyelitis, and Paget disease; however, headache is not a usual manifestation of nontraumatic cranial bone disorders, including congenital cranial bone defect, tumors, or metastases [1].

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Headache related to ophthalmologic disorder

Eye pain can be the cause or result of headache. It is also divided in groups, one of which is primary, the other secondary:

1. Corneal and optic nerve disorders, severe refractive errors, uveitis, scleritis, conjunctivitis, angle closure glaucoma, trochleitis, orbital pseudotumor, and Tolosa–Hunt syndrome (THS) can cause headache.
2. On the other hand, eye pain can be a manifestation of some primary headache disorders such as migraine.

Here we discuss the primary ophthalmologic disorders that can cause headache:

- Corneal disorders: can be due to foreign body, corneal abrasion, or infection, deficiency or abnormality of tear, infrequent blinking, corneal epithelial disease, using contact lenses, some drugs, or may be a symptom of a rheumatologic disease.
- Glaucoma: chronic open angled glaucoma, the most common type of glaucoma, is not generally associated with headache and eye pain. Acute angle closure glaucoma presents with red eye, severe eye pain, and vomiting. It can be an idiosyncratic reaction to some drugs such as topiramate and acetazolamide.
- Refractive errors: can cause headache especially in children, but the prevalence is much less than what is believed to occur within the general population.
- Trochlear headache: trochlear headache should be considered in approaching unilateral periorbital pain. Patients with trochleitis and trochlear headache present with unilateral local pain and tenderness in the superomedial orbit, and trochlear inflammation or dysfunction, which is clinically evident or documented by imaging modalities (see Fig. 6h.1). The pain is ipsilateral to the culprit trochlea, worsened by eye movement, and markedly improves by local injection of anesthetic or steroid agent into the peri-trochlear region. Despite the inflammatory nature of this condition, patients do not typically exhibit eyelid edema or erythema. Besides trochleitis, trochlear headache can be due to previous trauma to head and face. Most patients may not even recall the childhood trauma that caused the anatomical changes in the trochlear area, which can go on to present with headache in adulthood.

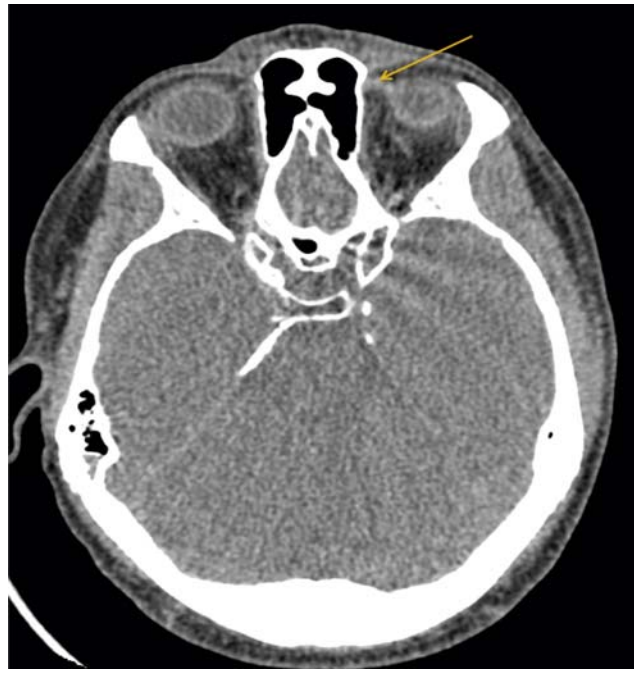

Figure 6h.1 Coronal CT showing soft tissue enhancement of left trochlea (*yellow arrow*) in patient with trochlear headache.

- Painful ophthalmoplegia should always be considered in the differential diagnosis of headache in association with visual symptoms. The differential for painful ophthalmoplegia includes:

A. Vascular: microvascular cranial neuropathy, aneurysm, cavernous-carotid fistula, and cavernous sinus thrombosis

- Microvascular cranial nerve palsy: Acute diplopia with findings to suggest isolated involvement of the third, fourth, or sixth cranial nerve is one of the more frequent acute neuro-ophthalmic conditions. Pain is often present. The pain may predate the onset of diplopia by several days or more. Pain was present in 62% of patients in a clinical series of 89 patients with microvascular third, fourth, and sixth nerve palsies. Microvascular cranial nerve palsy is typically seen in patients older than 60 years of age, and in those with atherosclerotic risk factors, including diabetes, hypertension, hyperlipidemia, and smoking. Diabetes appears to be the most common denominator. The prognosis for these patients is excellent, with nearly 90% having full recovery.

- Patients with cavernous sinus thrombosis most commonly complain of fever, headache (50%–90%), periorbital swelling and pain, vision changes, such as photophobia, diplopia, and loss of vision. Eye findings are nearly universal (90%). These include periorbital edema (initially unilateral but typically bilateral), lid erythema, chemosis, ptosis, and proptosis (due to impaired venous drainage of orbit), restricted, or painful eye movement. Less common findings include papilledema, retinal hemorrhages, decreased visual acuity (7%–22%), photophobia, diminished pupillary reflex, and pulsating conjunctiva. Blindness can result in 8%–15% of cases. Individually, a sixth cranial neuropathy is the most common neuropathy, resulting in partial ophthalmoplegia with limited eye abduction. Most cases, however, progress rapidly to complete external ophthalmoplegia from third, fourth, and sixth cranial neuropathy.

B. Mass lesions: pituitary apoplexy, orbital mass, intracranial mass, meningeal carcinomatosis:

- Pituitary apoplexy: is a rare and life-threatening condition and is typically associated with acute severe headache with nausea and vomiting. Clinical symptoms also include diplopia, visual loss, epistaxis, and, in some cases, alteration of consciousness. The sudden increase in pressure compromises the vascular supply, as well as causing compression of the vital structures within the Sella. Common predisposing factors for apoplexy include closed head trauma, blood pressure alterations, a history of pituitary irradiation, cardiac surgery, anticoagulation, and treatment with dopamine agonists, pituitary stimulation testing, and pregnancy. Pituitary apoplexy is often associated with acute pituitary insufficiency, making this a life-threatening condition.

C. Infection: orbital cellulitis, contiguous sinus disease, fungal disease:

- Fungal infection of the orbital region is a serious and life-threatening condition that requires timely diagnosis and aggressive treatment. Rhino–cerebral–orbital mucormycosis (zygomycoses) and aspergillus infections are aggressive fungal infections with a high mortality rate. Orbital invasive fungal infections usually start in the paranasal sinuses. These infections have a higher incidence in patients with diabetes, renal failure, and those who are

immunosuppressed secondary to immunosuppressive therapies, hematologic malignancy, intravenous drug use, and bone marrow transplant or HIV infection. The agents of mucormycosis rarely cause disease as a result of their low virulence potential. Undefined defects of macrophages and neutrophils present in diabetics, steroid-treated patients, and with deferoxamine treatment allow replication of this mold. A combination of urgent surgery and early administration of an antifungal drug is crucial for cure; therefore, delayed diagnosis may result in death. The first symptoms are the acute onset of orbital pain, orbital congestion, and vision loss secondary to central retinal artery occlusion. Ophthalmic signs and symptoms include proptosis, severe chemosis, external and internal ophthalmoplegia, ptosis, and corneal anesthesia. When untreated, patients quickly develop cerebral involvement with meningitis and cavernous sinus thrombosis. Once the CNS is affected, the mortality rate is greater than 50%.

D. Inflammatory processes: antineutrophil cytoplasmic autoantibody-associated vasculitis (Wegener granulomatosis), sarcoidosis, giant cell arteritis, IgG4-related disease, thyroid eye disease (Graves'), THS and idiopathic inflammatory orbital syndrome:

- Idiopathic inflammatory orbital syndrome: this condition, which is sometimes referred to as "orbital pseudotumor," is a noninfective inflammatory condition of the orbit without any identifiable local or systemic cause. It can be present as an acute, subacute, or chronic headache or eye pain and can affect any part of orbital structure (anterior, diffuse, apical, intraocular muscles, dacryoadenitis). In evaluating the headache related to eye problems, examining the eye movement is a paramount. Detecting any abnormality requires careful assessment. Imaging modality may show the inflamed structure (Fig. 6h.2). This syndrome, which shares lots of clinical features with THS, is typically treated with high-dose oral corticosteroids. There is usually a dramatic response to treatment in 24 h. Immunosuppressive drugs and radiotherapy are beneficial in refractory cases. Recurrence is very common, and many of these patients require long-term steroids [2,3].

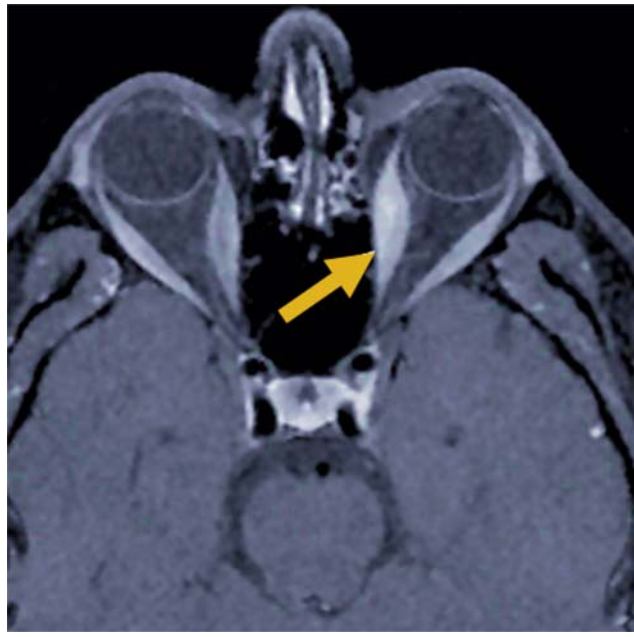

Figure 6h.2 Coronal CT showing enlargement of left medical rectus muscle (*yellow arrow*) in patient with recurrent unilateral orbital pain diagnosed with idiopathic inflammatory orbital syndrome.

Headache attributed to disorder of the ears

If headache appears in close temporal relation to the infectious, neoplastic, or other disorders of the ear, and the severity of headache is in parallel with the ear pain, the headache can be considered secondary to the ear disorders. Inflammation of the petrous apex can cause headache, which is oftentimes secondary to chronic otitis media. Gradenigo's syndrome is a rare syndrome of constant otorrhea, headache, and diplopia, which is attributed to inflammation of the petrous apex.

Headache attributed to temporomandibular joint disorders

Temporomandibular joint disorder (TMD) is the second most common cause of facial pain after toothache. Clinical features of TMD include the following:

- Headache, ear pain, and facial pain aggravating by jaw movement
- Impaired function of the masticatory muscles

- Tenderness of temporomandibular joint
- Cervical muscle spasm or pain

Pain in TMD is usually unilateral and located in the periauricular region or ear. Using the affected masticatory muscles typically worsens pain. Predisposing factors of TMD can be bruxism or clenching of the teeth, and morning headaches are commonly seen with TMD. TMD can be primary, for which there is no identifiable etiology, or secondary whereby an identified disorder (trauma, infection, autoimmune disorder, or crystal deposition) is causing the pain.

ICHD3 diagnostic criteria of headache attributed to TMD are as follows:

A. Any headache fulfilling criterion C

B. Clinical evidence of a painful pathological process affecting elements of the temporomandibular joint(s), muscles of mastication, and/or associated structures on one or both sides

C. Evidence of causation demonstrated by at least two of the following:
   1. The headache has developed in temporal relation to the onset of the temporomandibular disorder, or led to its discovery
   2. The headache is aggravated by jaw motion, jaw function (e.g., chewing), and/or jaw parafunction (e.g., bruxism)
   3. The headache is provoked on physical examination by temporalis muscle palpation and/or passive movement of the jaw

D. Not better accounted for by another ICHD-3 diagnosis

In evaluating the patient with a complaint of periauricular pain, other important disorders like trigeminal and glossopharyngeal neuralgia, disorder of parotid gland, malignancies of the neck, acute otitis media, migraine, cluster, middle ear disorders, and carotidynia should also be considered. It is noteworthy that masticatory muscles may generate nociceptive impulses in the CNS and therefore be a source of peripheral sensitization.

Treatment of TMD

Treatment of TMD, based on potential etiology, can vary and includes both pharmacologic and nonpharmacologic modalities as shown in Table 6h.1. Surgery is rarely recommended as treatment.

Table 6h.1 Treatment of TMD.

Pharmacological treatment	Nonpharmacological treatment
NSAIDs (brief course)	Patient education
TCA	Physical therapy
Muscle relaxants	Occlusal splints (occlusal modification)
Long-acting benzodiazepines (short course for acute phase treatment)	Behavioral therapy

Various injection procedures, including trigger point injection with local anesthetic, intraarticular dextrose injection (phototherapy), intramuscular botulinum toxin A, and liquid platelet–rich fibrin (PRF) dry needling, have been shown to be effective in different studies [4–7].

In summary, treatment in TMD is challenging and controversial, and unless splints are effective, combined therapies are performed. A conservative treatment approach that is reliable, cost-effective, and accessible to primary care practitioners or dentists is needed [8–13], [2,3,8,10,11].

Headache attributed to disorder of the nose or paranasal sinuses

The maxillary (V2) and ophthalmic (V1) divisions of the trigeminal nerve provide sensation to the nose and paranasal sinuses. These afferents project via the trigeminal ganglion to the trigeminal brainstem sensory nuclear complex (VBSNC).

Autonomic innervation of the nose is provided by:

- sympathetic nerve fibers: originating at the superior cervical ganglion, to the deep petrosal nerve, to the vidian nerve, then through the sphenopalatine ganglion
- parasympathetic fibers: from the superior salivatory nucleus of VII, then to the greater superficial petrosal nerve, vidian nerve and synapsing, and then in the sphenopalatine ganglion.

The trigeminal fibers in the nose terminate as bare nerve terminal endings, along with the parasympathetic nerves near the basal cells of the nasal epithelium. Therefore, it would not be considered unusual that some pathology of the paranasal sinus or nose, including infection (e.g., sinusitis) cause headache and face pain.

Nasal pain is mediated by Aδ fibers (fast responding, primarily mechanoreceptive pain fibers) and C fibers (slower, unmyelinated fibers associated with a duller pain from mechanothermal and chemosensory stimulation). Activation of the pain fibers is typified by the release of tachykinins family of neuropeptides (substance P, neurokinin A, neuropeptide K) and other neuropeptides, particularly calcitonin gene–related peptide (CGRP).

Sympathetic neurons are associated with neuropeptide Y in addition to norepinephrine, and the parasympathetic fibers release acetylcholine and vasoactive intestinal peptides. These neuropeptides and neurotransmitters are nonspecific markers of nerve activation and are associated with primary headache phenomena like migraine and seemingly unrelated diseases such as allergic rhinitis as well as rhinogenic pain.

Rhinosinusitis is generally divided into four groups: acute, recurrent acute, subacute, and chronic. Sinus inflammation or infection leads to the activation of the trigeminal vascular complex. This activation process causes headache and sometimes the relevant migrainous features such as photophobia, phonophobia, or nausea and vomiting, which can mimic migraine. On the other hand, initiation of migraine could result in activation of the trigeminal autonomic system and its subsequent clinical features such as facial pain, rhinorrhea, lacrimation, and conjunctival injection, fullness of the face, and periorbital edema, which can mimic sinusitis.

More importantly, rhinosinusitis can be a trigger of migraine attacks, and this can complicate and confuse the picture. When patients with underlying migraine develop sinusitis (with infection or allergic), they usually experience a flare up in their migraine attacks. Therefore, they may interpret the migraine attack as sinusitis or sinus-related pain.

Due to the above reasons, there has always been challenge in differentiating between sinus inflammation and migraine.

Although common features in these two groups may make the precise diagnosis difficult, acute rhinosinusitis is not usually mistaken as migraine or tension-type headache, since purulent nasal discharge or other accompanying features of acute rhinosinusitis can help to differentiate these conditions.

On the other hand, migraine is often misdiagnosed as sinusitis, which is commonly referred to as "sinus headache." However, in practice, the majority of patients who are labeled as having "sinus headache" actually suffer from migraine [14,15]. An appropriate recognition of migraine in patients who complain about "sinus headaches" may help to minimize the suffering and unnecessary interventions [16] in addition to beginning appropriate treatment for migraine sooner.

According to the ICHD3, in section "headache attributed to acute or chronic rhinosinusitis," the evidence of rhinosinusitis should be documented clinically, endoscopically, or via imaging. Rhinosinusitis is considered as a cause of headache if at least two of the following are present:

1. Headache has developed in temporal relation to the onset of rhinosinusitis
2. Either or both of the following:
   - **(a)** Headache has significantly worsened in parallel with worsening of the rhinosinusitis
   - **(b)** Headache has significantly improved or resolved in parallel with improvement in or resolution of the rhinosinusitis

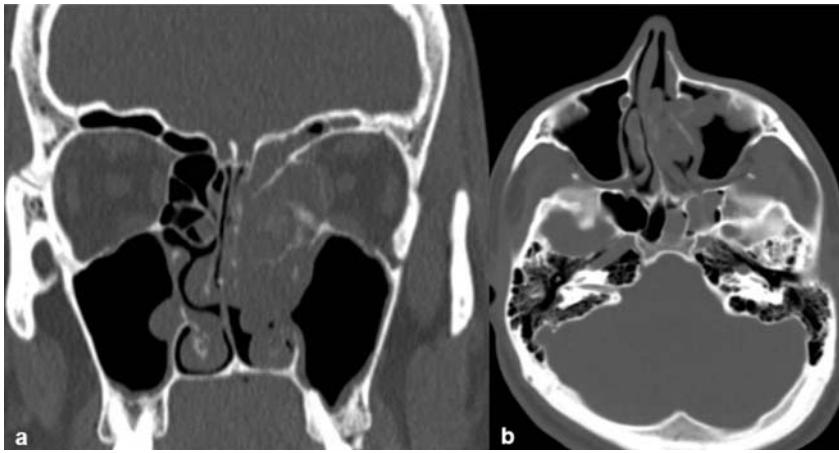

Figure 6h.3 Coronal (A) and axial (B) CT of a 22 years old male. Multiple rounded soft tissue opacities in the left nasal cavity, right greater than left frontal sinuses, filling the left anterior and posterior ethmoid air cells, in the right anterior ethmoid air cells, and in the left sphenoid sinus. Surgical pathology confirmed the diagnosis of aspergillus infection.

3. Headache is exacerbated by pressure applied over the paranasal sinuses
4. In the case of a unilateral rhinosinusitis, headache is localized and ipsilateral to it

Certain types of chronic sinusitis might cause more headache or facial pain, particularly fungal infection. Fungal sinusitis is divided into two types, including invasive and noninvasive. Invasive fungal sinusitis represents acute, chronic, and granulomatous forms of infection, and is more likely to be associated with headache (Fig. 6h.3).

Nasal pain is mediated by Aδ fibers (fast responding, primarily mechanoreceptive pain fibers) and C fibers (slower, unmyelinated fibers associated with a duller pain from mechanothermal and chemosensory stimulation). Activation of the pain fibers is typified by the release of tachykinins (substance P, neurokinin A, neuropeptide K) and neuropeptides such as the CGRP. Sympathetic neurons are associated with neuropeptide Y, in addition to norepinephrine, and the parasympathetic fibers release acetylcholine and vasoactive intestinal peptides. These neurotransmitters and neurochemicals are nonspecific markers of nerve activation and are associated with primary headache phenomena like migraine and seemingly unrelated diseases such as allergic rhinitis, as well as rhinogenic pain. Thus, earlier reports citing the presence of these chemicals (e.g., substance P) as evidence for contact point headache validity were poorly founded.

Neuroplasticity is also a phenomenon of unclear cause, in which acute pain may become chronic or more easily triggered (hyperalgesia) or is temporarily reduced, with a temporary reduction of headache pain mediated by the VBSNC after induction of surgical pain in the same distribution. This area of the brainstem (including the trigeminal nucleus caudalis) is critically important in the pathophysiology of migraine, as is covered elsewhere in this issue [17,18].

Headache attributed to dental or other mouth disorders

Dull, poorly localized, and often severe pain of teeth disorders can be referred to head. There is often local tenderness to heat, cold, and pressure at the offending tooth.

On the other hand, the pain of some primary headaches such as migraine, cluster, hemicrania continua, and trigeminal neuralgia and radiates to gum or teeth and might be mistaken as a toothache. While toothache and other pain originating from dental structures (e.g., gum) can always be considered as differential diagnosis of facial pain, if the initial dental work up is negative and pain is resistant to routine interventions, other etiologies should be considered before continuing with antibiotic treatment or repeated surgical interventions. Dental cavities, a cracked tooth, pulpitis, and dental abscess are other etiologies that can present as facial pain.

Persistent idiopathic facial pain

Constant facial pain, often unilateral, in the nasolabial fold or chin, in the absence of any neurological abnormality is the manifestation of persistent idiopathic facial pain (PIFP). PIFP was previously known as atypical facial pain and in some literature it has been called atypical odontalgia. It is more prevalent in females. Minor surgery, tooth extraction, or periodontal injury are mentioned as index events, but the pain persists after the procedure or injury. PIFP may be the result of hyperactivity of central neurons secondary to damage of primary afferent neurons [19]; on the other hand, it has been suggested that PIFP is likely a combination of both biological and psychosocial elements [20].

Diagnostic criteria for PIFP, according to (ICHD-3), require all of the following:

1. Facial and/or oral recurring pain daily for more than 2 h per day for more than 3 months

2. Pain has both of the following characteristics:
   - Poorly localized, and not following the distribution of a peripheral nerve
   - Dull, aching, or nagging quality
3. Clinical neurological examination is normal
4. A dental cause has been excluded by appropriate investigations

PIFP is a diagnosis of exclusion. Some malignant or infectious structural lesions should be excluded. Although psychiatric problems may be present, it seems to be a central pain syndrome.

Treatment: Tricyclic antidepressants are the first choice. Gabapentin or pregabalin are mentioned in the literature [21,23]. In one case report, topiramate was also mentioned as an effective drug.

Burning mouth syndrome

Burning mouth syndrome (BMS) is an intraoral burning sensation without any obvious medical or dental cause, recurring on a daily basis for more than 2 h in a day over more than 3 months. It is usually accompanied by xerostomia and dysgeusia. BMS has negative impact on quality of life [24–26].

It is a rare condition that predominantly affects elderly women. Although no definite etiology can be detected, neuropathy of small fibers of the trigeminal nerve is suggested. Also, subclinical inflammation suggested as potential etiopathogenesis of BMS considering different cytokine expression levels [27,28]. However, it is not clear whether disrupted cytokine levels are a cause or an effect of the disease process in BMS. Psychiatric comorbidity is mentioned in literature.

Differential diagnosis of BMS

- Oral disorders like herpes simplex and aphthous stomatitis
- Xerostomia
- Deficiency of vitamin B6, B12, iron, folate, and zinc
- Allergic contact stomatitis
- Idiopathic burning syndrome is a diagnosis of exclusion and if there are not any underlying causes, the condition is termed idiopathic BMS.

Treatment of BMS

Tricyclic antidepressants, clonazepam, and gabapentin may be beneficial.

Topical treatment with 0.15% benzydamine hydrochloride, antifungals, capsaicin (0.025% cream), or rinsing with Tabasco sauce and water

(1:2–4 solution) has been shown to be effective in some patients. Also sucking benzodiazepine for 3 min and then expectorate has been reported to help some patients [29].

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CHAPTER SIX(I)

Cervicogenic headache

Hossein Ansari
Headache and Facial Pain Clinic, Kaizen Brain Center, San Diego, CA, United States

Introduction

Cervicogenic headache (CeH) is a secondary headache disorder, which presents with unilateral pain, predominantly on the occipital and upper cervical regions, and is worsened by neck movement, sustained awkward head position, or external pressure over the symptomatic side.

Epidemiology

- Due to diagnostic uncertainties, the epidemiology of CeH is not very clear.
- Based on available data, its prevalence among the general population is estimated to be between 0.4% and 4% [1–3]. Prevalence will vary depending on which criterion is used (*see diagnosis*).
- Cooccurrence of migraine and/or tension-type headache further complicates the diagnostics and subsequently, prevalence of CeH.
- The prevalence of CeH in a population with chronic headache is increased to 15%–20%.
- CeH affects women more often than men.

Pathophysiology

- The anatomic locus for CeH is the trigeminocervical nucleus in the upper cervical spinal cord.
- Trigeminocervical nucleus is the essential structure for migraine headache as well [4]. This can explain the overlap between CeH and migraine symptomatology.

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- Trigeminal afferents overlap with the afferents of upper three cervical segments (C1—C3) at the lower end of the trigeminocervical nucleus [5]. This anatomical connection between the cervical and trigeminal innervation systems would explain the frontal or retro-orbital pain in patients with CeH. This could be another reason why CeH is commonly mistaken as migraine or even tension-type headache.
- CeH usually happens without any demonstrable abnormality in cervical or brain imaging.
- Only the pain stemming from the articulations between the first 3 cervical spines (atlanto-occipital, C1—2, and C2—3 facet joints) can lead to CeH (Fig. 6i.1):

A. The C1 spinal nerve (suboccipital nerve) innervates the atlanto-occipital joint. Pathology or injury affecting this joint is a potential source for pain that is referred to the occipital region of the head.

B. The C2 spinal nerve and its dorsal root ganglion have a close proximity to the lateral capsule of the atlanto-axial (C1—2) zygapophyseal (facet) joint, and innervate the atlanto-axial and C2—3 zygapophyseal joints. Trauma to, or pathologic changes around, these joints can be a source of referred head pain.

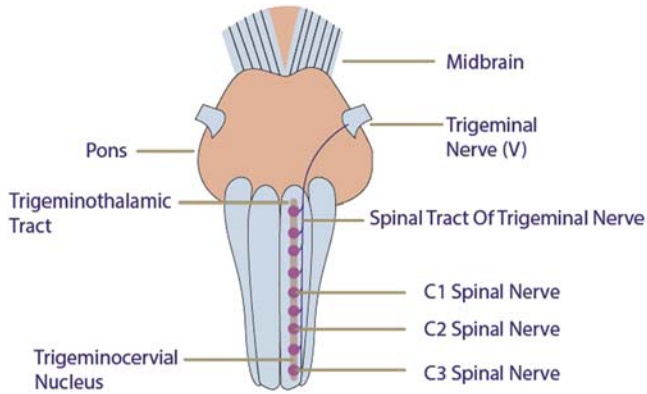

Figure 6i.1 Mechanism of pain referral from the cervical spine to the head: Nociceptive afferents of the trigeminal and upper three cervical spinal nerves converge onto "second-order" neurons in the trigeminocervical nucleus in the upper cervical spinal cord. *From Nikolai B., Jayantilal G. Cervicogenic headache: an assessment of the evidence on clinical diagnosis, invasive tests, and treatment. null. Lancet Neurol 2009;8(10): 959—968.*

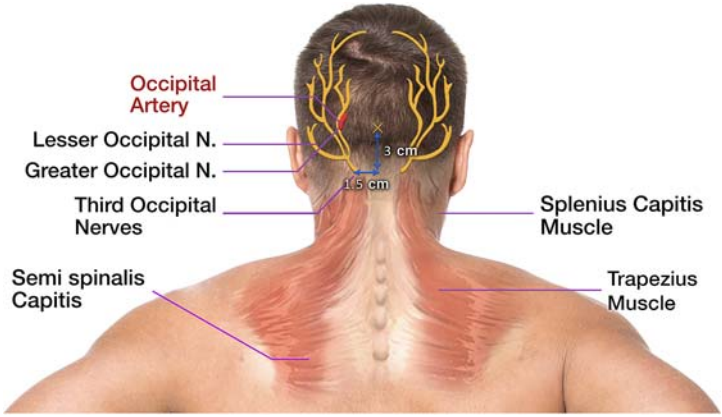

Figure 6i.2 Close anatomic relation of third occipital nerve with great occipital and lesser occipital and nerve. These three nerves are responsible for the cervicogenic headache.

C. The third occipital nerve (TON) (dorsal ramus C3) has a close anatomic proximity to, and innervates, the C2–3 zygapophyseal (facet) joint. Pain from the C2–3 zygapophyseal joint is referred to the occipital, frontotemporal, and periorbital regions of the head.

TON supplies sensation for scalp below the superior nuchal line and to the C2–C3 facet joint which has overlap with both greater and lesser occipital nerve sensory supply and sometime it is difficult to distinguish their supply (Fig. 6i.2).

- The other theory in the pathogenesis of CeH is an inflammatory response, since patients with CeH have a higher serum concentration of IL-1β and TNF-α [6].
- Marked activation of the nitric oxide (NO) pathway, even more so than migraine and cluster headache, has been reported in CeH [7].
- In summary, it seems that the primary causes of CeH are either external compression or inflammation of the nerve(s) mainly from C_2–C_3 zygapophysial and atlantoaxial joints. It seems the C2 nerve may be more susceptible to injury by inflammation or compression than the other structure.

Diagnosis

- There is a lack of an easily applied "*gold standard*" for CeH diagnosis. There are 2 different sets of diagnostic criteria for CeH:
  - **I.** International Headache Society criteria (ICHD-3)
  - **II.** Cervicogenic Headache International Study Group (CHISG)

This explains the variations in CeH diagnosis and the difference in reported epidemiology of this headache. Both of these classifications have their own strengths and weaknesses, a discussion of which follows below:

International Headache Society criteria

Diagnostic criteria for CeH based on ICHD-3 are as follows [8]:

A. Any headache fulfilling criterion C

B. Clinical and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache

C. Evidence of causation demonstrated by at least two of the following:
  1. headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
  2. headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
  3. cervical range of motion (ROM) is reduced and headache is made significantly worse by provocative maneuvers
  4. headache is abolished following diagnostic blockade of a cervical structure or its nerve supply

D. Not better accounted for by another ICHD-3 diagnosis

Imaging abnormalities on the upper cervical spine is a common finding among the general population. Therefore, not every finding in patients with headache can be counted at a causative etiology for headache. Findings such as fractures, tumors, infections, and rheumatoid arthritis of the upper cervical spine are more likely to be a causative etiology for CeH. A majority of patients have a history of prominent whiplash-type injury. In one study, the prevalence of CeH reported is as high as 53% in patients with headache after whiplash [9].

Cervicogenic Headache International Study Group

This classification characterizes CeH based on following criteria [10]:

- Major criteria:
  1. Symptoms and sign of neck involvement:
     a. Precipitation of head pain, similar to the usually occurring one:
        - a1) by neck movement and/or sustained awkward head positioning and/or
        - a2) by external pressure over the upper cervical or occipital region (symptomatic side)
     b. Restriction of ROM in the neck.
     c. Ipsilateral neck, shoulder, or arm pain of a rather vague, nonradicular nature, or occasionally arm pain of the radicular nature
  2. Confirmatory evidence by diagnostic anesthetic blockades.
  3. Unilaterality of pain, without side shift.
- Head pain characteristics:
  4. Moderate to severe, nonthrobbing pain, usually starting in the neck. Episodes of varying duration or fluctuating, continuous pain.
- Other characteristics of some importance:
  5. Only marginal effect or lack of effect of indomethacin
  6. Only marginal effect or lack of effect of ergotamine and sumatriptan
  7. Female sex
  8. Not infrequent occurrence of head or indirect neck trauma by history, usually of more than only medium severity.

Due to this controversy and the different criteria for CeH, the prevalence of this secondary headache will differ. Some clinicians have attempted to establish their own criteria for CeH. In 2001, Antonaci et al. [11] proposed a criterion for CeH based on their own clinical experience. In this proposal, any patient with unilateral headache and pain that starts in the neck qualifies for the diagnosis of "possible" CeH.

If three additional criteria of the five following criteria were fulfilled, their diagnosis advances to "probable" CeH. Their proposed criteria have five characters:

1. Symptoms and signs of neck involvement: pain triggered by neck movement or sustained awkward posture and/or external pressure of the posterior neck or occipital region; ipsilateral neck, shoulder, and arm pain; reduced ROM
2. Pain episodes of varying duration or fluctuating continuous pain
3. Moderate, nonexcruciating pain, usually of a nonthrobbing nature
4. Anesthetic blockades abolish the pain transiently provided; complete anesthesia is obtained, or occurrence of sustained neck trauma shortly before onset

5. Various attack-related events: autonomic symptoms and signs, nausea, vomiting, ipsilateral edema, and flushing in the periocular area, dizziness, photophobia, phonophobia, or blurred vision in the ipsilateral eye

Differential diagnosis of cervicogenic headache

Differential diagnosis of CeH is broad. Basically any headache disorder, particularly headache that can present with occipital pain, can be in differential (Fig. 6i.3).

Most common differential diagnosis include the following:

1. Migraine: Migraine is the most common headache disorder in differential diagnosis. Considering the trigeminocervical complex has a major role in both migraine and CeH (see pathophysiology section), this is not unexpected. Therefore, a detail history and exam are needed in order to differentiate CeH from migraine headache. Some key points in history and exam that can help are
   - Quality of pain, which is usually throbbing (pulsating) in migraine, while in CeH the pain is nonthrobbing.
   - Associated symptoms: Photophobia and sometimes phonophobia can be seen in CeH, but the presence of both photophobia and photophobia is almost always suggestive of migraine.

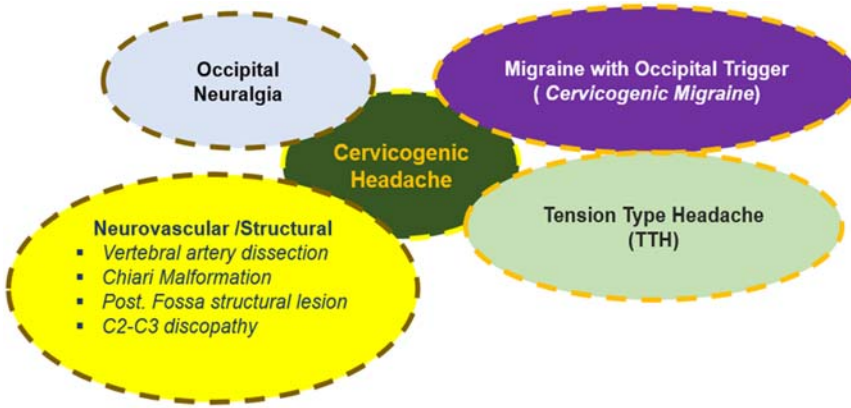

Figure 6i.3 Main differential diagnosis of cervicogenic headache. Sometimes there is overlap between cervicogenic headache and other headache disorder, particularly migraine.

- Laterality: CeH is usually side-locked without side shift. In migraine, despite the fact that unilaterality is one of diagnostic criteria, side-lock appearance is less common.
- In CeH, digital pressure over the triggering area at the upper nuchal region produces the spontaneous pain pattern. Since cervical trigger(s) are also common in migraine patients, this could further confuse the picture.
- Occipital nerve block is more helpful for migraine, since in CeH the facet injection is considered the most helpful intervention (see *treatment*).
- Based on Cervicogenic Headache International Study Group (CHISG), one of the features distinguishing CeH from migraine is side-locked pain in CeH. However, in practice, this cannot be a reliable picture, since CeH can be bilateral (although it is usually one side predominant). On the other hand, migraine could present as side-lock pain. Therefore, despite all of the above features, sometimes differentiating these two headache conditions is difficult.
- Cooccurrence of migraine and CeH is reported in up to 42% of patients [12], which makes this more complicated. Patients with migraine, whose headaches are predominantly located on occipital and neck region, are sometimes classifies as "Cervicogenic migraine."

2. Occipital Neuralgia (ON): The second most common differential diagnosis for CeH is ON. In theory, the "*Neuralgia*" which is defined as "*paroxysmal jabbing pain*" or "*lancinating pain*" has a unique pattern, and should not be mistaken with any other type of pain. However, in practice, many patients with CeH are diagnosed with occipital neuralgia. Part of this could be a general unfamiliarity of some medical providers with the CeH entity. Both occipital neuralgia and CeH may respond to local anesthetic block.
3. Tension-type headache: Muscle tenderness in the posterior head and upper neck is common in tension-type headache. Pericranial muscle tenderness also presents in almost on all patients with CeH, which can be mistaken as TTH. However, TTH is bilateral, while CeH in mostly unilateral. Additionally, CeH pain is generally more intense pain compared to TTH. Pericranial muscle tenderness in CeH is significantly more pronounced on the pain side when compared to nonpain side.
4. Dissection: Vertebral artery and occasionally carotid artery dissection can present with neck pain and headache [13–15]. Dissection could

be traumatic, spontaneous, or secondary to aneurysm. The vertebral arteries and upper cervical dura are innervated by the first three cervical nerves (C1−3); therefore, pain of dissection could be similar to CeH. Key features that can be very helpful for differentiation are the "acute" onset of intense pain in dissection in addition to the possibility of abnormal neurological finding in exam, particularly cranial nerve(s) abnormality. If this differential diagnosis is not considered, there is a risk of patients being treated with cervical manipulation, which can have serious, potentially fatal, consequences. Since a delay in diagnosis of dissection can be life threatening, we usually have low threshold for imaging of vessels in patients with acute onset unilateral neck or occipital pain.

5. Posterior cranial fossa pathology: Since upper cervical nerves innervate dura matter and vessels of the posterior fossa, any pathology in this area can be mistaken with CeH. The onset of neurological features or systemic illness in these etiologies can be distinguishing factors. For example, meningitis of the upper cervical spine can be distinguished from CeH by the presence of systemic illness and neck rigidity. Eruption of vesicles distinguishes herpes zoster of upper cervical from CeH. The C2 spinal nerve can be compromised by a tumor like meningioma, or even by vascular anomaly of vertebral arteries and in turn mimic CeH [16,17], although other neurological symptoms usually accompany the pain.

- Other less common differential diagnoses of CeH include

6. Herniated intervertebral disc
7. Cervical spondylosis or arthropathy
8. Arnold−Chiari malformation,
9. Spinal nerve compression or tumor
10. Arteriovenous malformation
11. Intramedullary or extramedullary spinal tumor

Treatment of cervicogenic headache

There are different treatment modalities for CeH, which we discuss here. Among multiple treatment modalities suggested in the literature, few have been tested and even fewer have been proven successful.

In general, treatment choice may differ based on pain intensity and duration, patient age and comorbidities, and patient preference. Therefore, after

establishing a CeH diagnosis, the treating physician should have a detailed discussion with the patient in order to explain potential treatment options.

Conservative management

Manual therapy, usually in the form of physical therapy (PT), is the referred initial treatment in CeH, since it is noninvasive and may provide long-term improvement [18,19]. PT is better tolerated when initiated with gentle muscle stretching and manual cervical traction. Therapy can be slowly advanced as tolerated to include strengthening and aerobic conditioning. The mobilization of the upper cervical joint using different techniques seems to be relatively safe and helpful. "High-velocity" manipulation therapy should be avoided, and it is critical that therapists treating this type of headache are familiar with the proper ROM.

Lifestyle modifications are of great importance. The patient should stand straight up so that a hypothetical vertical line drawn from the auricle crossed the midclavicle. The patient's sleep posture is also very important. Attention should be paid to correct use of the cell phone and computer and ergonomic factors at the workplace. Stretching exercises should be started for short muscles like the SCM, upper trapezius muscle fibers, and pectoralis major and minor, and weak muscles like the deltoid muscle, rhomboids, and lower trapezius muscle fibers should be strengthened. Use of relaxation and stress management techniques is also beneficial.

Pharmacologic treatment

Four different classes of medication can be used in the management of CeH:

I. Muscle relaxants: Tizanidine and cyclobenzaprine in particular are commonly used muscle relaxants for CeH. The side effect of drowsiness makes the use of this class limited.

II. Tricyclic antidepressants (TCAs): Nortriptyline and amitriptyline are the most commonly used TCAs. Since this class is also used for migraine, it might be the preferred option in patients whose diagnosis is doubtful or in patients with concurrent migraine and CeH. Dosage should be gradually titrated based on the patient's response and potential side effect(s).

III. Calcium channel blockers: Voltage-gated calcium channel blockers have been used for different types of pain for decades. Gabapentin and pregabalin are class prototypes that can be used in CeH. Since pain control with these medications is usually achieved in higher doses, side

effect(s) may be a limiting factor here as well. Within the last few years, extended release forms of gabapentin have been introduced, which have a lower side effect profile. In addition, since it is taken once a day as opposed to 3 to 4 times a day, this may make this a better.

IV. Miscellaneous: Monoclonal antibody againts TNF-α (Infliximab) has been studies in small open label trial [20].

In the acute phase of CeH or in patients who need analgesic for breakthrough pain, a nonSteroidal antiinflammatory medication or acetaminophen/paracetamol component can be used. Avoid use of opioid medication due to the high possibility of dependence and/or the development of medication overuse headache.

Interventional treatment

Different interventional modalities have been used for CeH with varying success rates.

I. Occipital Nerve Block (ONB): Has been studied as a treatment for CeH [21]. It can be used for acute headache relief and to break an intractable headache cycle when medications have failed or are contraindicated due to comorbid medical conditions.
- Patients who experience short-lived relief with ONBs should be considered good candidates for radiofrequency ablation of the occipital nerve(s).
- Although the greater occipital nerve is the commonly used target for ON, a TON could be a potential target for injection (see Section II.b).

II. Zygapophyseal (facet) injection: a local anesthetic injection of the upper cervical facet joint can be done under fluoroscope or with ultrasound guide [22]. It can be done with steroid [23]. In most headache and pain centers, this is the gold standard procedure:

II.a the lateral atlanto-axial joint (C1—C2), which is innervated by the C2 ventral ramus, may account for 16% of patients with CeH. Clinical presentations suggestive of pain originating from the lateral atlanto-axial joint include
- occipital or suboccipital pain
- focal tenderness over the suboccipital area or over the transverse process of C1
- restricted painful rotation of C1 on C2
- pain provocation by passive rotation of C1

Since the C2 nerve seems to be the more common etiology for CeH, targeted blockage of this nerve is the most commonly used procedure.

II.b The C2–3 zygapophyseal (facet) joint is innervated by the TON, which is the superficial medial branch of the dorsal ramus of C3. Pain stemming from this joint is seen in 27% of patients presenting with CeH following whiplash injury. Tenderness over the C2–3 joint is the only suggestive exam finding and a diagnostic TON block is mandatory to confirm the diagnosis. TON block can lead to significant pain relief in >90% of patients. If the diagnostic TON blockade is temporarily successful in providing complete pain relief, more invasive procedures, such as radiofrequency neurotomy (RFA), of the TON can be used in appropriate patients.

- "Intraarticular steroid" injection was effective only in one study.
- TON block is preferred over an intraarticular injection at C2–C3: It is not always technically possible to position a needle into the facet joint, and even a small injected volume can stretch and tear the joint capsule.

II.c Atlanto-Occipital joint (C0–C1 facet) injection is rarely needed. This is a high-risk injection requiring an experienced physician for injection. Symptoms of CeH from this facet include pain with head nodding, more diffused unilateral suboccipital, and occipital pain. In exam, there is not much tenderness on palpation due to the fact that it is difficult to palpate given its depth beneath the dorsal skin of the neck.

III. Percutaneous Radiofrequency Neurotomy: This is probably the most extensively studied procedure for CeH with different outcomes. Some studies reported that radiofrequency neurotomy is not effective [24–26]. Other studies, on the other hand, reported the effectiveness of this procedure specifically when diagnosis was carefully established with controlled diagnostic blocks [27,28]. The results of a randomized, placebo-controlled trial indicate that responses to radiofrequency neurotomy are not due to placebo effects [29].

IV. Onabotulinum toxin A injection (BT-A)

- There is one randomized, double-blind, placebo-controlled crossover study that has been done to evaluate the effectiveness of BT-A on CeH [30]. This study used CHISG criteria for CeH, and included fixed-site and dose injections across six specific muscle areas performed using 30-gauge needle:
  - 20 U in the occipital muscle
  - 20 U in the upper trapezius

- 20 in the splenius Capitis
- 20 U in the SCM
- 20 U in the levator scapulae

Results of this study did not show any significant difference between onabotulinum toxin A and placebo. Therefore, the conclusion of this study was BT-A does not seem to be beneficial in CeH.

V. Transcutaneous Electrical Nerve Stimulation: This has been studied in a noncontrolled study, and showed 80% of patients obtained at least a 60% decrease in their headache index only at 1 month after treatment [31].

VI. Surgery: There are limited available data on the indications and efficacy of surgical interventions in CeH (SS) [32].

In general, surgery is suggested for the following:

(A) C2 spinal nerve compression by vascular/ligamentous structures

(B) Osteoarthritis of the lateral atlanto-axial joint.

(C) Upper cervical intervertebral disc pathology

Considering advancements in intervention and the use of less aggressive modalities, including ultrasound for diagnoses and treatment of CeH, surgical treatment gets less yield in this type of headache.

VII. Radiofrequency ablation (RFA)

High-frequency electrical current to produce controlled thermocoagulation: This is a minimally invasive lesioning procedure, selectively destroying A delta and C fibers which probably produce Wallerian degeneration of the afferent nerve fibers.

- Using radiofrequency energy to disrupt nerve function to a cervical medial branch nerve (like third occipital nerve) prevents pain transmission pain from an injured facet joint.

RFA versus pulsed radiofrequency

- Pulsed radiofrequency (PRF) therapy exposes the nerve to high-voltage radiofrequency pulses, which is hypothesized to induce an inhibitory electrical field around the nociceptive afferents, disrupting pain transmission and potentiation.
- A systematic review analyzed the data for PRF in CeH and found very limited benefit for PRF. Although several case reports suggest benefit, no high-quality randomized controlled trials or strong nonrandomized trials have been conducted to support the use of this intervention [33–35].

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CHAPTER SEVEN

Headache attributed to psychiatric disorder

Farnaz Etesam
Psychosomatic Medicine, Psychiatry, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Psychiatric symptoms, especially anxiety and depression, are well-known comorbidities associated with headache. The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) considers the headache as a symptom of depression and anxiety [1]. Studies have consistently confirmed an association between mental disorders and migraine, especially in women. The rate of psychiatric disorders in tension headache is comparable to or even more than migraine headache; moreover, these disorders are more frequent in chronic headaches than episodic headaches. Therefore, it seems that what causes this association is the intensity and frequency of the headache and its disability rather than the type of headache [2].

In many cases, especially in chronic headaches, timely diagnosis of comorbid mental disorders and appropriate treatment plays an important role in decreasing the intensity and frequency of the headache. Psychotropic medications are routinely used besides common headache treatments. In fact, some psychotropics, including tricyclic antidepressants (TCAs), have analgesic properties and can relieve headache even if no comorbid mental disorders are present [3].

Bidirectional relationship of headache and mental disorders

Studies have consistently shown the effect of chronic pain on the nervous systems associated with mood and cognition. The relationship between headache and mental disorders is usually discussed in three forms:

1. Headaches cause or lead to psychiatric disorders.
2. Psychiatric disorders cause or worsen headaches.

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3. Headaches and psychiatric disorders have a reciprocal association or common mechanisms.

Different mechanisms including causal unidirectional or bidirectional relationship, common genetic or environmental factors, and neurobiological models have been proposed to explain the relationship [4].

Studies suggest that depression is an important factor in the initiation or chronicity of headaches [5]. Some key signs of depression, i.e., anhedonia, decreased concentration, low libido, loss of energy, and sleep problems, are among the most common comorbid symptoms of chronic daily headache. On the other hand, migraine with aura is a strong predictor of mood disorders [6]. According to the results of some longitudinal studies, depression and anxiety are risk factors for migraine, and chronic stress is a risk factor for migraine and depression. Nonetheless, longitudinal studies have failed to show anxiety and depression as the risk factors of nonmigraine headaches [7–10].

Neurobiological mechanisms

Interestingly, studies have shown that similar brain regions (anterior cingulate cortex, amygdala, orbitofrontal cortex, and temporal lobe) are activated in physical pain as well as psychological pain. This finding suggests that even in the biological level, physical and mental pain have a common basis. Studies have shown increased activation of the limbic and serotonergic system in major depressive disorder, chronic pain, and migraine, which explains the high comorbidity of these disorders [11–13].

Psychopathologic studies, also, have shown common genetic and environmental mechanisms between mood disorders and migraine. Even in the structural level, MRI studies have shown white matter lesions in similar brain regions in mood disorders and migraine headache.

Traumatic life experiences, especially during childhood, are one of the contributing factors in the development of migraine and chronic pain. During critical periods in human growth, these experiences can affect the cerebral development and cause disorders in the monoaminergic system and hypothalamic–pituitary–adrenal axis [14]. Central sensitizations are believed to be a contextual contributing process in this association. Physiological and cellular neural activity is increased, leading to sensitization of central nervous system. In central sensitization, negative interpretation of the stimulus to which a person is sensitive and enhanced arousal can result in automatic reactions in the nervous system. For example, this stimulus

may be the light and sound in migraine. Anxiety and chronic psychosocial stressors may increase the headache frequency through enhanced central sensitization. In migraine patients, high levels of constant stress together with anxiety and depression can lead to burn out and exhaustion syndrome [15–17].

The relation between common types of headache and psychological factors

Migraine

The most common comorbid mental disorders with migraine include depression, anxiety disorders, especially generalized anxiety disorder, somatic symptom disorder, and bipolar disorder. Moreover, there is an established relationship between migraine and personality disorders, posttraumatic stress disorder (PTSD), and substance abuse [18,19].

A review of the studies investigating the relationship between depression and migraine shows that odds of depression are twice as high in migraine patients as in individuals with no headaches. This comorbidity is bidirectional. Depression is associated with increased headache attacks, decreased pain threshold, increased use of analgesics, increased disability, and decreased quality of life of the patients [20,21].

Anxiety disorders, including generalized anxiety disorder, panic disorder, phobias, and also obsessive-compulsive and related disorders, are more common in migraine patients than in the general population. These disorders are sometimes considered as risk factors for chronic migraine [22,23].

Anxiety disorders and migraine have many common clinical features; for example, their episodic nature and recurring attacks associated with autonomic dysregulation and hypersensitivity to internal neural environment are seen in both panic disorder and migraine [17,24]. Panic disorder is related to increased risk of migraine chronification and medication overuse and also higher rates of disability and migraine frequency [19].

Bipolar disorder and migraine also have common features; both are episodic, worsen with stress, and are associated with a family history of mood disorders. Dysfunction of calcium channels is suggested as a common pathophysiology for both disorders [19].

The risk of bipolar disorder is three times higher in patients suffering from migraine with aura than in the general population [25]. The patients are more likely to be women, have a rapid cycling course, suffer from comorbid panic disorder, and experience the disease at a lower age [26].

Moreover, in patients suffering from migraine with comorbid bipolar disorder, irritability, seasonal pattern of mood symptoms, cyclothymic temperament, type II bipolar disorder, and mixed bipolar disorder symptoms are more frequent. The frequency of depressive episodes is also higher in these patients [27].

Tension headache

Most mental disorders with an established relationship with tension headache, especially the chronic type, are depressive and anxiety disorders. It seems that tension headache sufferers are more likely to use maladaptive coping strategies like avoidance and catastrophizing, resulting in increased emotional distress in these patients. Emotional problems in patients with tension-type headache increase disability, reduce adherence to treatment, and increase the likelihood of progression to exacerbation and chronicity [28].

One of the mechanisms suggested for tension headache chronicity is central sensitization which has an established relationship with depression and anxiety. A common pathophysiology has also been reported for fibromyalgia, depression, and tension headache [29].

Chronic daily headache

Chronic headaches impose a heavy burden on the society through worsening behavioral and mood problems and absence from work and school [30]. It is estimated that episodic migraine progresses to chronic migraine at a rate of 2.5% per year and is related to other conditions such as depression, anxiety, insomnia, chronic fatigue, and fibromyalgia. Psychiatric disorders that are commonly associated with chronic daily headache include generalized anxiety disorder, followed by major depressive disorder and dysthymia. Women suffering from chronic migraine are more likely to experience the signs and symptoms of moderate to severe depression [4].

The presence of depression may affect the prognosis and treatment of the headache, decrease the patients' compliance, cause chronicity, and result in medication overuse headache (MOH) which is one of the most important and common causes of chronic daily headache [5].

Personal and family history of substance abuse, male sex, sedentary lifestyle, certain personality characteristics like borderline personality disorder, and type of analgesics used (especially barbiturates and opioid analgesics) are among other factors that increase the risk of MOH [31,32]. A high

percentage of recurrence after withdrawal in these patients, lack of control over the use of analgesics despite their harmful effects, resistance against stopping these drugs even when they are ineffective in pain management, and the disturbed function of these patients have led to hypotheses regarding the similarity of MOH to addiction. In fact, according to DSM-5, about two-thirds of these patients fulfill the criteria of substance use disorders. However, some authors believe that analgesic overuse in these patients is related to the availability of these drugs and has no relationship with dependency-related behaviors [33,34]. Some other authors have suggested fear of pain, anticipatory anxiety, and obsessional drug-taking behaviors as the reasons and have pointed to the higher rate of clinical and subclinical obsessive-compulsive disorder in migraine and MOH patients to support their hypothesis [35].

Headache in children and adolescents

Headaches in children and adolescents have important impacts on the quality of life, school performance, daily activities, social interactions, and cognitive conditions, and may lead to depression, hopelessness, and social isolation. On the other hand, the presence of behavioral problems and psychological distress in these ages may serve as a predictor of headache later in life [36].

Children and adolescents are vulnerable groups because of the psychophysical changes in puberty and challenges in social relationships. Headache is one of the most common somatic complaints in this age group and is frequently seen as a comorbid condition with other disorders like seizures, asthma, obesity, and neuromuscular pain. In many cases, signs and symptoms of psychiatric disorders and psychological problems like anxiety and panic attack, sleep problems, school phobia, and educational problems are seen [37].

Losses, physical injuries, lack of family and social support, and low economic level are associated with increased complaints of headache. Exposure to interpersonal violence can trigger the onset of headache, and unpleasant events together with genetic susceptibility result in hyperalgesia and headache persistence. Childhood maltreatment or severe psychological traumas during childhood are reported to be responsible for 30%–70% of the mental symptoms and disorders associated with headaches, including major depressive disorder, anxiety disorders, substance abuse, and PTSD [38].

Boys and girls are more or less equally affected until puberty, but the prevalence of headache is higher in adolescent girls. Different factors like physiological changes, hormonal profile, and psychosocial stressors may contribute to this difference. Adolescents have more contacts with family boundaries and it seems that psychosocial expectations, limitations, and lifestyle are more intense for girls [39].

Personality and headache

Studies suggest that abnormal personality traits can predict the headache onset and severity and affect its chronicity. In fact, a headache is a complaint of more than half of the patients with personality disorders. It seems that patients suffering from tension headaches have more temperamental, behavioral, and emotional problems than migraine patients [40]. Also, the prevalence of personality disorders, particularly obsessive compulsive, dependent, avoidant, and passive-aggressive personality disorder, is shown to be higher in patients with chronic daily headache [41].

According to longitudinal studies, ambitiousness, neuroticism, vulnerability to frustration, competitiveness, perfectionism, and rigidity are other common psychological characteristics of many headache sufferers [42].

Suicide and headache

Chronic daily headache is a major source of severe distress which impairs the ability to enjoy normally pleasurable experiences and functional activities. This decrement in the quality of life can result in despair, hopelessness, and eventually suicidal thoughts. In fact, the headache severity is a risk factor for suicide attempts, especially in individuals with chronic headaches or those who suffer from pain in other body parts. Suicidal ideation is also reported in patients with tension-type headache associated with other risk factors, including mood disorders [13].

In patients with major depressive disorder, the rate of suicidal ideation and suicidal attempts increases in the presence of migraine. The results of different studies suggest that migraine with aura could be an independent risk factor for suicidal attempts [43].

Use of antidepressants for the management of headache in patients with bipolar spectrum disorders, especially type II which is more difficult to diagnose, cyclothymic temperament, and irritability may increase the odds of suicidal ideation and attempts through worsening mood symptoms and agitation [27].

In 2008, the FDA issued an alert for the relationship between the use of anticonvulsants and increased suicidal ideation. Although subsequent research faded the importance of this alert, it is better to follow-up the patients for suicidal thoughts since these drugs are frequently used for headache treatment and prophylaxis [44].

Diagnostic approaches and treatment strategies

Screening of patients for psychiatric signs and symptoms can be part of the treatment process of headache patients. Self-report tools may be used for primary evaluation. The most appropriate recommended tools are the Patient Health Questionnaire (PHQ-9) and Beck Depression Inventory-II (BDI-II) [45].Since most patients suffering from headache with comorbid depression have signs and symptoms of anxiety disorders, anxiety screening is also equally important. GAD-7 and Hospital Anxiety Depressive Scale (HADS) are the other recommended tools for screening mood symptoms in the patients with headache syndromes [46,47]. These patients should be also followed up for suicidal thoughts.

It is particularly important to detect what kind of mental disorders, including mood and anxiety disorders, have led to headache chronicity [42]. If there is a comorbid mental disorder, treatment should be started according to the diagnosis.

Treatment of headache in the presence of depressive and anxiety disorders

Though there is no definite evidence that depression management helps with controlling migraine or changing chronic migraine to episodic migraine, but migraine patients suffering from depression are more likely to develop resistance to antimigraine drugs, which may lead to drug overuse and disability. There is no doubt that treatment of depression is very important due to its impacts on different functional and emotional areas [4].

Treatment of depression includes acute, continuation, and maintenance treatment. The acute phase lasts for 6–10 weeks until complete remission of signs and symptoms is achieved. Treatment then continues for 4–9 months. Long-term maintenance therapy is advised in patients who have a high likelihood of recurrence [3].

Selective serotonin reuptake inhibitors (SSRIs) are the first choice of treatment for depression due to their treatment response and fewer side effects. However, they may be associated with worsening of headache in some

patients because of the vasodilating effect of serotonin. On the other hand, concomitant use of these drugs with triptans increases the risk of serotonergic syndrome and should be used cautiously [3].

Serotonin–Norepinephrine Reuptake Inhibitors are also effective for depression and anxiety, but according to the last Cochrane review, there is not enough evidence for their efficacy for prevention of tension-type headache [48].

The efficacy of TCAs is similar to newer classes of antidepressant drugs in the management of depression. In addition, these drugs can decrease or prevent migraine headaches. Among TCAs, amitriptyline has been widely studied and is used at low doses of 10–25 mg for prevention of migraine attacks [49].

Polypharmacy should be preferably avoided in the management of depression and migraine, but low doses of TCAs, despite controlling the headache, do not usually improve depression. On the other hand, high doses of these drugs are associated with side effects like sedation, weight gain, and anticholinergic complications like constipation and dry mouth, which are hard to tolerate by patients. Therefore, a combination of SSRIs and low-dose TCA is sometimes used, but no study has been conducted in this regard.

Mirtazapine is another drug that is as effective as amitriptyline at daily doses of 10–30 mg in the management of chronic tension headache [50,51]. Weight gain and sedation might occur as troubling side effects.

Benzodiazepines are also used for management of anxiety symptoms associated with headache. These drugs affect GABA receptors and noradrenergic/serotonergic activity and endorphins and increase the pain threshold; however, long-term use of BZDs is not recommended due to the development of tolerance and risk of dependence [52].

Comorbidity of headache with bipolar disorders

Mood stabilizers are the mainstay of bipolar disorder treatment. The main mood stabilizers are lithium, sodium valproate, and carbamazepine. Lamotrigine is used as maintenance therapy in patients with bipolar depressive disorder. Topiramate, gabapentin, and pregabalin are administered as an adjunct to the main medication. Almost all the above drugs, except for lithium, are used for management of chronic pain.

Sodium valproate is an effective drug in migraine prevention. Considering the effect of this drug in reducing the relapse of manic episodes, it is

a good choice in patients suffering from bipolar disorder with comorbid migraine. Moreover, it has been shown effective in migraine headache and panic disorder comorbidity. However, attention should be paid to its side effects like weight gain and metabolic problems [53,54].

Topiramate is very effective in chronic and relapsing headaches. It is also used as an adjunct to control bipolar patients' mood and behavior and is administered for reciprocation of the weight gain, associated with use of psychotropic agents. Therefore, patients suffering from headache comorbid with bipolar disorder may benefit from its favorable effects [22,55].

Lithium is one of the most widely used medications for treatment of bipolar disorder. Among different types of headaches, more evidence supports the use of lithium in cluster headache. A limited number of studies have assessed its use in the treatment of nocturnal migraine, and some authors have reported worsening of migraine following lithium therapy. On the other hand, in lithium-treated patients, use of NSAIDs for pain control may lead to lithium intoxication due to decreased renal excretion of lithium. Therefore, its administration is associated with some limitations in practice [22,56].

Treatment of bipolar depressive disorder with antidepressants is controversial. Some researchers believe that treatment with antidepressants is not associated with response to treatment in these patients. On the other hand, use of antidepressants may increase the risk of manic and hypomanic attacks and switching the disease course to rapid cycling bipolar disorder [22].

There is still no valid method to detect whether the first depressive episode is part of bipolar disorder, but it is very important to consider this possibility in the treatment of depressive disorder because in this condition, treatment with antidepressants may cause a switch to mania. Table 7.1 shows some suggested clinical features as predicative factors for diagnosis of bipolar disorder [57,58].

Treatment strategies of headache in children and adolescents

In early-onset severe or refractory cases comorbid with psychiatric problems, evaluation of the medical history may be the main way to identify the potential interfering factors in initiation or chronification of headache. The patient's family members should be also visited, and factors such as the headache type, frequency, and consistency should be evaluated comprehensively. The dynamics of the family, the relationship of family members with

Table 7.1 Clinical predictors of bipolar disorder.

≥4 previous depressive episodes
Cyclothymic or hyperthymic temperament
Suicidal acts
Family history of bipolar disorder
Substance abuse
Onset age <25
Hypomania following the use of antidepressants
Seasonal depression
Psychotic depression at younger age or after pregnancy
Short-term, recurrent, and refractory episodes of depression
Atypical depression
Resistance to antidepressants

each other and their relationship with the patient, and the patient's interpersonal relationships at school should also be assessed. Evaluation of the parents' response to stress, coping strategies, and knowledge and perception toward pain can provide information on the genetic, educational, and developmental backgrounds of the patients, which will be effective in designing personal and family interventions [38].

Psychological treatments

Psychological treatments include education regarding lifestyle modification (staying hydrated, avoiding hunger, regular sleep, and exercise, etc.) and different types of psychotherapy including behavioral therapy, meditation, and yoga. Treatment methods are not effective unless a therapeutic alliance is established (Table 7.2) [59].

These treatments may be combined with antidepressants to decrease the relapse rate and improve response to treatment and compliance. It is very important to benefit from behavioral methods in the treatment of chronic headaches, especially MOH (Table 7.2). On the other hand, these treatments are sometimes used as the main treatment according to recommendations of the American Neurological Association (Table 7.3) [59].

Among psychological treatments, cognitive behavioral therapy has received considerable attention for control and prevention of chronic pains, especially headache in recent years. In this treatment method, patients learn about the effect of negative automatic thoughts on the mood and feelings as well as triggers that start or worsen a headache, and try to gain more control over their life through having a daily schedule and engaging in joyful activities [60].

Table 7.2 Psychological and behavioral interventions in chronic headache.

Education
Adherence enhancement strategies
Motivational interviewing techniques
Progressive muscle relaxation
Stress management's training
Cognitive behavioral therapy
Insight-oriented therapies
Biofeedback
Hypnosis

Table 7.3 Indications for preference of behavioral methods over pharmacological treatments in headache.

Patient's preference
No response to pharmacological treatment
Drug side effects or intolerance
Pregnancy
History of overusing prescribed drugs
Severe stress or inability to cope with pain or stress

Summary

Headache is a multifactorial disease and interventions should consider all established factors. The complex association of psychological factors and mental disorders with headache impedes headache treatment and prevention. Therefore, concurrent psychiatric and neurological treatment and integrity of the approaches are essential to achieve and maintain the best treatment response.

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CHAPTER EIGHT

Painful lesions of the cranial nerves and other facial pain

Fereshteh Naderi Behdani
Department of Neurology, Ziaeeyan Hospital, Tehran, Iran

Neuralgia is an electric shock-like pain that is short in duration. It is usually unilateral with a sudden onset and termination. The pain is in the distribution of a cranial nerve. The most common neuralgias include (1) trigeminal neuralgia (TN), (2) glossopharyngeal neuralgia, (3) trigeminal neuropathy, (4) occipital neuralgia, and (5) nervus intermedius neuralgia [1].

Trigeminal neuralgia

TN is the most common neuralgia worldwide. It was formerly known as tic douloureux because the facial expression of the patients during pain resembles a tic [1,2]. According to ICHD-3, TN is divided into classic and secondary forms. There is nerve/root compression by a vascular loop causing atrophy and/or displacement in the classic form [1].

Idiopathic trigeminal neuralgia

Idiopathic TN is suspected when there is no imaging or electrophysiological abnormality. The mean age of the patients is about 53 years old and its prevalence increases with age. Women are affected 1.7 times more than men [2].

Pain can be electric shock-like, stabbing, or shooting, lasting from a few seconds to 2 min. Pain is unpredictable and usually involves the maxillary and mandibular nerves although it might affect the ophthalmic branch in about 5% of the cases [1]. Nonpainful stimulants in certain areas known as the trigger zone may induce pain. These areas are on the same side of the face where pain is felt [3]. These triggers are usually daily activities like speaking, chewing, tooth brushing, or even air currents on the face [2].

The trigger zones include the nasolabial fold, lip, gum, and tongue. These areas are innervated by the ipsilateral trigeminal nerve. Some patients lose weight as a result of fear of chewing [1,2]. There is usually a refractory

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period after each individual attack during which the pain is not triggered [4]. Attacks rarely occur during sleep [1].

The number of attacks varies from 4 to 5 to more than 100 episodes per day. Most of the patients experience remission after some months. About 50% of the patients report a vague chronic pain problem on the same side [5]. TN may be bilateral in 5% of the classic cases [6].

- Sensory and motor examination of the fifth cranial nerve is intact in the idiopathic form.

Secondary trigeminal neuralgia

TN is usually idiopathic but about 20% of the cases are secondary. The most important causes are presented in the following table [1] (Table 8.1).

- Characteristics leading the physician to secondary causes:
  1. sensory and motor abnormalities of the fifth nerve on examination
  2. bilateral involvement
  3. disturbances in trigeminal reflexes
  4. young age of onset
  5. lack of response to medical treatment
  6. lack of a trigger point for pain and lack of a refractory period after pain suggest symptomatic causes [4,7].

The prevalence of TN is about 20 times higher in MS patients compared to the normal population (about 1%–6.3%). These patients suffer from episodic pain in addition to the underlying pain in the face. Pain is bilateral in only 30% of the patients [2,6].

Classic trigeminal neuralgia

Classic TN usually results from vascular compression. All patients with TN should first undergo a brain MRI with and without contrast. The most common vascular compression is caused by superior cerebellar artery that applies pressure to the root of the trigeminal nerve, causing demyelination in the root entry zone. This phenomenon is not seen in routine MRI and is discovered by CISS/FIESTA imaging; therefore, it is suggested for all patients with

Table 8.1 Secondary causes of trigeminal neuralgia.

1. Multiple sclerosis (MS)
2. Space-occupying lesion (SOL): SCC of the face, CP angle lesions, skull base tumors, Arnold Chiari malformation
3. Other disorders

TN [3]. Among neurophysiological tests, trigeminal reflexes, including the blink reflex for V1, reflexes caused by stimulation of infraorbital and mentalis branches (V2,V3), and record from masseter muscle have a role in the diagnosis of classic TN [3].

Medical treatment

Medical treatment is the first step in the idiopathic and secondary forms. Antiepileptics are the drugs of choice.

Carbamazepine is the first line of treatment and is a level A drug. Response to treatment with carbamazepine within few days is a diagnostic characteristic of TN [2]. The drug is initiated at a dose of 200 mg and, if needed, its dose can be increased to 1300 mg. Response to treatment is expected in 75% of the patients. The dose may be tapered to the lowest maintenance dose once response to treatment is seen. Drug side effects, including drowsiness, loss of balance, rash, and leukopenia, are possible in the elderly or if the dose is increased rapidly. CBC, LFT, and serum Na should be checked a few weeks after the start of carbamazepine [7,8]. It is recommended to evaluate the Asian patients for HLA-B*15:02 that predisposes the patients to Stevens–Johnson and toxic epidermal necrolysis before prescribing carbamazepine [8].

Oxcarbazepine is a keto-analog of carbamazepine that is converted to an active metabolite very rapidly. The active metabolite does not cross the liver; therefore, oxcarbazepine has fewer side effects and drug interactions compared to carbamazepine. It is started at a dose of 300 mg and, if needed, the dose can be increased to 1800 mg depending on the patient's tolerance and response [7,8].

Few studies have assessed second-line drugs, including baclofen, tizanidine, lamotrigine, phenytoin, fosphenytoin, pregabalin, gabapentin, and pimozide. These drugs are usually used as an adjunct to carbamazepine to decrease its dose and prevent side effects [6,7].

Baclofen is a GABA agonist that is usually added to carbamazepine to reduce its dose. It is very helpful in MS patients because it serves as a muscle relaxant in addition to relieving pain. Sudden withdrawal of the drug at high doses may be associated with serious side effects like hallucination and convulsion. It is started at a dose of 10 mg/day and the dose can be increased to 80 mg/day [7,8].

Gabapentin is a GABA agonist that may be effective in persistent pain and in MS patients. Its benefits include rapid titration in comparison with

carbamazepine and lamotrigine, little interaction with other drugs, and lack of known skin reactions. Hyperlipidemia is an important side effect of gabapentin [8].

Pregabalin is structurally similar to gabapentin. It is started at a dose of 150–600 mg, which usually improves pain in 50%–74% of the patients [8].

Lamotrigine has been assessed in few studies. It is started at a dose of 25–50 mg and titrated to 400 mg. Its side effects include tremor, insomnia, and headache. The prevalence of Stevens–Johnson syndrome due to lamotrigine is about 1 in 100,000 patients [8]. Its combination with carbamazepine has been reported to be more effective, but should attention should be paid to the complications [6].

Topiramate has different analgesic mechanisms. It is initiated at a dose of 25–50 mg and the dose may be increased to 400 mg/d. Its side effects include drowsiness, weight loss, mental disorders, and nephrolithiasis. Its effectiveness was similar to carbamazepine in a study by Khalid W. Al-Quliti [8].

Pimozide is a dopamine antagonist that is reported to be effective in refractory TN. It is administered at a dose of 2–12 mg/day. Its side effects include drowsiness, EKG abnormalities, and extrapyramidal symptoms. Monitoring the patient for QT prolongation is recommended [8].

Levetiracetam lacks a well-understood mechanism of action. It is usually administered at a dose of 1000–4000 mg/day. It does not require routine lab tests and has little interaction with other drugs. Common side effects include drowsiness, headache, restlessness, and muscle weakness [8].

Other drugs that may be helpful are sodium valproate, clonazepam, local capsaicin cream, intranasal lidocaine gel, sumatriptan [9], and amitriptyline [6]. Some studies have reported that IV fosphenytoin (15–20 gr/kg) or other IV antiepileptics are useful in acute exacerbations (2). Ropivacaine can be injected into triggering points to block acute crises [6].

Botulinum Toxin A may be injected subcutaneously or intramucosally in refractory patients. It should be injected into the trigger zones, if there are any. The regular dose is 20–50 U (Botox) in each trigger zone. The frequency of the attacks is reported to decrease 4 weeks after injection [9].

Surgical treatments

Surgery is suggested as the first treatment in classic TN. It can also be considered in idiopathic TN that is refractory to treatment or if drug side effects develop. At least three drugs should be tried before proceeding to surgery. The patient's age, concurrent diseases, and his/her opinion should be used for selecting the most appropriate treatment method [2,7,10].

1. **Microvascular decompression** is the method of choice in classic TN and idiopathic TN, especially in young patients with no comorbidities or those who experience relapse after other methods. In classic TN, the patients become pain free immediately and the risk of relapse is lower than other methods. More than 90% of the patients are pain free after surgery, more than 80% are pain free after 1 year, and about 73% are pain free after 5 years. This technique is associated with few complications. The most important complication is aseptic meningitis. Other complications include CSF leak, cerebral hematoma, cerebral infarction, diplopia, decreased facial sensation, and Bell's palsy. Unilateral hearing loss is the most important long-term complication [2,8,10].
2. **Gamma knife surgery** is a noninvasive method in which radiation beams are focused at the trigeminal root at a dose of 70–95 GY. It may take about 1 month for pain to go away, so this method is not appropriate when an immediate response is desired (7). The relapse rate is very high, and about 69% and 52% of the patients are pain free after 1 and 3 years, respectively. Complications include decreased sensation in the face, dysesthesia, or paresthesia [7,8].
3. **Percutaneous procedures**: In this method, a cannula is inserted into the foramen ovale to destroy the Gasserian ganglion or trigeminal sensory root via different methods including thermal (radiofrequency thermocoagulation: RFT), chemical (glycerol injection), and mechanical (balloon compression of Meckel's cave) techniques (Fig. 8.1). Initial pain relief is seen in 90% of the cases, but the relapse rate is high and only 50% of the patients are pain free after 5 years. This procedure can be repeated if there is a relapse. The most important complication is decreased sensation in the trigeminal nerve distribution (50%). Other complications include decreased sensation in V1 resulting in keratitis, facial dysesthesia, anesthesia dolorosa, and aseptic meningitis [7,8].
4. **Peripheral Techniques**: These techniques are performed to destroy or block the distal portion of the trigeminal nerve distal to the Gasserian ganglion through injecting streptomycin, lidocaine, alcohol, or phenol. Other methods like cryotherapy, thermoregulation, or acupuncture have also been tried but they are not used due to their ineffectiveness or high relapse rate [7,8].
    - All drugs should be examined in MS patients with TN before using surgical interventions. Surgery is less beneficial in MS patients compared to classic patients. Regarding nonmedical treatments, one study compared gamma knife with percutaneous balloon

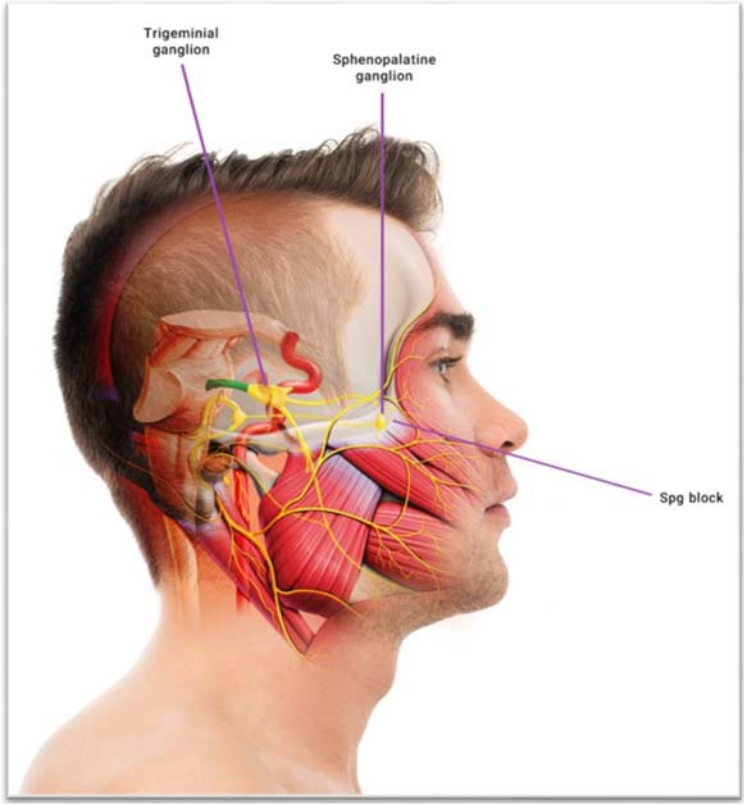

Figure 8.1 Trigeminal ganglion.

compression (PBC) in MS patients suffering from TN. The results showed that gamma knife was associated with a lower rate of relapse and complications. However, PBC is preferred when immediate pain relief is desired because the effects of gamma knife start with a delay and pain relief is achieved after 1–2 months [11,12]. There are reports of the beneficial effects of Nabiximols, a cannabinoid derivative used for treatment of MS spasticity, in refractory TN [13].

Glossopharyngeal neuralgia

The quality of pain is similar to TN although it is of less intensity. It is caused by compression of the glossopharyngeal nerve or auricular or pharyngeal branches of the vagus nerve [2], and is responsible for 0.2%–1.3% of facial pains [14]. It is more prevalent on the left side than the right side

[14]. The pain is usually felt in the pharynx, tonsils, posterior tongue, ear, or mandible angle and is usually unilateral. It may be mistaken for TN [2]. An atypical presentation is pain paroxysms that may be associated with dysrhythmia, reflex bradycardia, or syncope during or after the pain. These signs are more common in vagoglossopharyngeal neuralgia [14]. The reason may be innervation of the carotid body and carotid sinus by branches of the glossopharyngeal and vagus nerves. These symptoms usually respond to medical or surgical treatment of glossopharyngeal neuralgia (GFN). Some patients present with cough, hoarseness, or dysphagia [2]. The most important cause of pain is swallowing, especially drinking cold liquids, resulting in fear of eating. Other causes include chewing, speaking, touching the gum, and sneezing. Some patients experience pain upon sudden head movement or raising the hand on the affected side. Some patients complain about tinnitus, vertigo, vomiting, and a feeling of swelling on the affected side [1].

GFN is divided to classic and symptomatic forms. The classic form may result from vessels compressing the nerve. The causes of the symptomatic form are presented in the following table [14].

Secondary causes of GFN

1. Tumors: skull base, CP angle, oropharyngeal
2. Infections: tonsillitis, pharyngitis, para pharyngeal abscess, TB
3. Trauma: skull base trauma, postradiation
4. Surgery: posttonsillectomy, postcraniotomy
5. MS
6. Vascular malformations: AVM, fusiform aneurysm
7. Eagle syndrome: elongation of the styloid process

GFN may occur concurrently with TN and Chiari type 1 malformation. An important differential diagnosis is nervus intermedius neuralgia. Temporal arteritis may present with similar pain characteristics.

Diagnosis is clinical but there is a need for imaging modalities like MRA and brain MRI + CISS picture (with emphasis on PICA and AICA) and neck evaluation to rule out tumors in these regions, X-ray to assess the styloid process, and ESR and EKG during pain episodes.

Treatment is similar to TN. Surgical techniques like microvascular decompression (MVD) may be used in refractory cases. The risk of surgery is much higher in these patients compared to TN patients; therefore, it is advisable to consider surgery for patients with an underlying cancer [14]. Pacemaker replacement is required in patients with refractory syncope [2].

Postherpetic neuralgia

VZV virus remains inactive in the DRE of the trigeminal ganglion. About 95% of young people have varicella zoster antibody. However, the virus may reactivate. The symptoms of herpes zoster include pain and vesicles in the affected dermatome. The prevalence of herpes zoster is about 3–4 in 1000 patients, which increases to 11 in 1000 people after 50 years of age [2].

1. Acute: Pain is present for 2–4 weeks. Skin rashes usually appear 7–10 days after the onset of pain, which become vesicular and recover within 2–4 weeks. Pain is usually unilateral and felt in the affected dermatome. The ophthalmic branch of the trigeminal nerve is affected in 80% of the cases. Ophthalmic herpes is sometimes associated with oculomotor, trochlear, or abducens nerves palsy. Zoster vesicles may be absent, which is known as zoster sine herpete. PCR of the CSF samples helps to diagnose herpes zoster in these cases. Pain usually lasts for less than 3 months [1].
2. Postherpetic trigeminal neuropathy (PHN) is defined as the persistence or relapse of unilateral neuralgiform facial pain beyond 3 months after herpes zoster. About 10% of herpes zoster patients develop PHN. Pain is felt in the previously affected dermatome and may be persistent, deep, burning, or neuralgiform in quality. Allodynia may be present in the dermatome [15,16].

Available treatments include nortriptyline, amitriptyline, gabapentin, pregabalin, lidocaine 5% patch, opioids (hydrocodone, oxycodone, morphine, hydromorphone, methadone, and fentanyl), tramadol, capsaicin 8% patch, and carbamazepine (15). A study in rats revealed that melatonin could effectively decrease PHN pain [17].

Occipital neuralgia

Occipital neuralgia is a primary headache with a very challenging diagnosis. Pain may be felt along the GON (90%), lesser occipital nerve (10%), or third occipital nerve. GON is a C2 branch that is responsible for exteroception of the posterior part of the scalp from the external occipital protuberance to the vertex. Neuralgiform pains along the GON may be felt from the occipital protuberance to the vertex. Light tapping (percussing) the nerve may cause paresthesia or tingling along the GON, known as the

Tinel's sign. Lying the head on the pillow and hyperextending or turning the head may also cause pain (pillow sign) [15].

The cause of occipital neuralgia is not clear. Head trauma or whiplash injury has been proposed as one of the mechanisms in some studies. Other mechanisms include neurological diseases like schwannoma in the craniocervical junction, myelitis, and MS. Vascular causes like cervical dural AVF and bone causes like cervical osteochondroma are also suggested. Head and neck MRI and neck X-ray are used to evaluate structural causes [18].

Characteristics of Occipital Neuralgia According to the International Headache Society:

1. Pain is felt along the greater or lesser occipital nerve.
2. Pain may be unilateral or bilateral.
3. Pain bouts may last seconds to minutes.
4. Pain is of high intensity.
5. Pain is commonly described as sharp, shooting, or stabbing.
6. Painless stimulation of the scalp or hair results in dysesthesia or allodynia.
7. There is tenderness along the nerve.
8. There is a trigger point where the GON pierces the semispinalis capitis or along the distribution of C2.
9. Nerve block reduces pain [18,19].

Migraine headache is the most important differential diagnosis of occipital neuralgia:

1. Migraine pain is severe and persistent, and may be superimposed by episodes of pulsatile pain.
2. Occipital tenderness and allodynia are common in migraine.
3. Occipital nerve block reduces pain in migraine [15,18,19].

Other differential diagnoses include temporal arteritis involving the occipital artery, cervicogenic headache, and postherpetic neuralgia involving the GON [15].

Treatment includes resting, massage, hot or cold compress, NSAIDs, and muscle relaxants and AEDs like pregabalin, gabapentin, CBZ, TCA, and baclofen [8].

Some authors recommend an occipital nerve block with lidocaine and bupivacaine [8,15]. There are reports of the use of triamcinolone and methylprednisolone although they have not proved effective [15]. Other treatment options include botulinum toxin A, occipital nerve stimulation, and pulsed radiofrequency [15].

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CHAPTER NINE

Pediatric headache

Doga Vuralli[1,2,3], Aynur Ozge[4], Hayrunnisa Bolay[1,2,3]
[1]Faculty of Medicine, Department of Neurology and Algology, Gazi University, Ankara, Turkey
[2]Neuropsychiatry Center, Gazi University, Ankara, Turkey
[3]Neuroscience and Neurotechnology Center of Excellence (NÖROM), Ankara, Turkey
[4]Faculty of Medicine, Department of Neurology and Algology, Mersin University, Mersin, Turkey

Introduction

Headache is the most common complaint in pediatric neurology outpatient clinics in children and adolescents and migraine is among the top five diseases of the childhood [1]. The World Health Organization ranks headache disorders among 10 most disabling disorders in both genders and among 5 most disabling disorders for females [2]. In children, the types and clinical features of headache are different than adults which is first described by Vahlquist in 1949 [3]. The incidence of migraine and headache in children increased over the last decades probably as a result of lifestyle changes and stressors. Headache in children and adolescents is mostly neglected by the parents and teachers which results in school absenteeism and social impairment.

Epidemiology

Headache can affect up to 88% of children and adolescents [4,5]. Headache is rare before the age of 4 years, with a prevalence of 3%–8% [6,7] but its prevalence increases throughout childhood and about 75% of children report headache by the age of 15 [8]. Headache begins at a median age of 7.5 years in children [9]. In another study, median age at onset for migraine is 7.2 years in males and 10.9 years in females [10]. 33%–40% of school children describe at least one headache attack per week [9]. Headache in children peaks at 11–13 years of age in both sexes. There is no gender difference until puberty; however, after puberty, headache increases in girls and a female predominance is observed with a 2.5:1 ratio [11]. Like adults, the majority of headaches is primary in children with migraine and tension-type headache (TTH) as the most common ones. Migraine prevalence in children varies between 3.2% and 14.5% [12–18] in different

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studies. According to two systematic reviews published in the last decade, its prevalence among children and adolescents ranges between 7.7% and 9.1% [19,20]. Stewart et al. [10] assessed the prevalence of migraine according to age and found that it was 3% in children between 3 and 7 years of age, 4%−11% in children between 7 and 11 years of age, and 8%−23% in those between 11 and 15 years of age. TTH prevalence is 10%−24% in children and adolescents [21]. Onset of cluster headache (CH) in childhood is very rare [22], with a reported prevalence of 0.1% [23]. One infant was reported to have cluster symptoms in 1980 [24]. 5%−10% of CH patients have their first attacks in adolescence.

Frequent headaches may cause significant disability and decrease the quality of life. Early and right diagnosis and treatment is required to alter the disease progression. The impact of headache on child's life is comparable with cancer, heart disease, and rheumatic disease [25]. The greatest negative impact on a child will be from migraine. Children with frequent headache attacks and headache onset early in life, girls, and the patients in whom therapy is delayed have a poorer prognosis.

Diagnosis of primary and secondary headaches

A comprehensive headache history and complete physical and neurological examinations are the fundamentals of the headache diagnosis (Fig. 9.1). The diagnosis is based on the criteria established by the International Classification of Headache Disorders, third edition (ICHD-3) [26]. In the history, the questions must include the number of headache types, the onset and the progress of headache, the frequency and the duration of the headache attacks, the triggers, the warning symptoms, the location and quality of the headache, the associated symptoms, and pain-relieving or worsening factors. Child's personal medical history including the birth history, developmental history, any chronic diseases, operations, early childhood and current dietary habits, history of substance abuse, and the family history especially for headaches should be obtained. Family relationships, socioeconomic, and psychosocial status of the child and the parents should be evaluated. Sufficient time should be given for history taking and terminology which is age appropriate should be used. Studies show that parents may be unaware of the children's headache and its frequency; therefore, it would be more helpful in the diagnosis and the treatment to also use child-completed diaries and teacher observation forms [27,28]. Some symptoms of the children may be inferred from their behavior. The child may

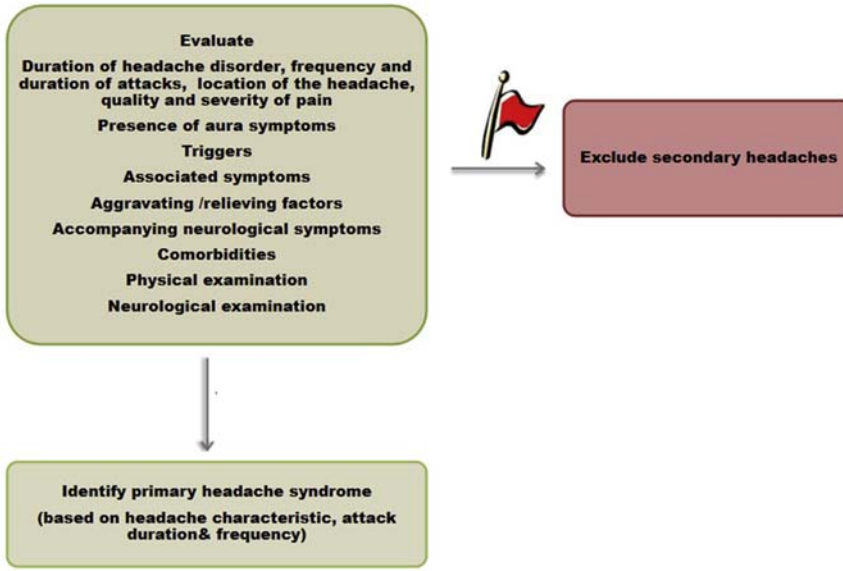

Figure 9.1 The evaluation of a child with headache.

stop playing or watching TV and may want to go to a quiet, dark room and sleep. The younger children may be asked to draw their headache since they communicate better through pictures.

The headache severity should be quantified using a pain rating scale such as visual analogue scale, numeric rating scale, or other equivalents according to the children's age. The children should be examined physically, neurologically, and psychologically. In the primary headache disorders, the physical and neurological examinations are expected to be normal [12,29]. Frequent headache may cause negative effects on daily activities such as playing, going to school, eating, and sleeping. Pediatric patients with headache should be evaluated especially for signs and symptoms of depression and anxiety. Children with TTH have a higher rate of divorced parents and less peer relations [30]. Children with frequent headache have an increased risk of headache, multiple physical problems, and psychiatric morbidity such as anxiety and depression in adulthood [31,32]. There is an association between headache in childhood and maternal depression, and depression in childhood [6]. Headache in children and adolescents can interfere with the patients' family life, leisure time activities, and school performance. Headaches rank third among medical reasons of school absenteeism [33]. Transition from migraine to other headaches or vice versa may occur and

the clinical picture of migraine may change with age in some patients. In one study when the headache patients were evaluated 3 years later, 30%–50% of patients with a prior migraine diagnosis received the same diagnosis [34].

The clinical signs and symptoms of headaches are different in children. The duration of migraine attacks is shorter, usually lasts less than 12–24 h and can be less than 2 h. It is harder to distinguish between migraine and TTH. If the pain is severe and pulsatile, it suggests migraine. The headaches are usually bilateral and associated symptoms such as nausea and vomiting decrease with age. Improvement after sleep, nausea, vomiting, worsening with physical activity, photophobia, phonophobia, and osmophobia may separate migraine from TTH. Osmophobia shows more specificity than photophobia and phonophobia to migraine and may help differentiate migraine from TTH [35,36]. There are also childhood periodic syndromes that may be related to migraine such as cyclic vomiting, abdominal migraine, benign paroxysmal vertigo of childhood, and benign paroxysmal torticollis [37]. Detailed laboratory and imaging investigations are required in patients with these episodic syndromes that may be related to migraine [37].

In a primary headache disorder, such as migraine, TTH, CH, and other trigeminal autonomic cephalalgias, the headache is not attributed to another disorder; the headache is the disease itself. However, in a secondary headache disorder, headache is the symptom of a structural, metabolic, or systemic disorder. Primary headaches usually follow an acute recurrent course, whereas secondary headaches usually follow a progressive course. Space-occupying lesions develop over time and follow a chronic progressive course over weeks to months. Infections usually occur more quickly and follow an acute–subacute course. It is important to keep in mind the red flags to distinguish primary headaches from secondary headaches based on ICHD-3 (Fig. 9.1). Red flags are the first or worst headache ever, fever, weight loss, rash, neck stiffness, abnormal neurological examination findings, orthostatic headache, morning headaches with severe vomiting, waking up from sleep with headache, headache always on the same side or persistent location on occipito-cervical junction, increase in headache severity or frequency and headache worsening with straining, coughing, or physical activity, and no family history of headaches (Table 9.1). Secondary headaches may be acute as in subarachnoid hemorrhage, arterial dissection, subacute as in meningitis, brain abscess or chronic as in brain tumors, and posttraumatic headaches. Patients with focal or progressive neurological deficits should be investigated by imaging modalities such as cranial computed

Table 9.1 Red flags to differentiate primary headaches from secondary headaches.

• The first or worst headache ever
• Recurrent headache waking the child at night
• Morning headaches with severe vomiting
• Worsening with straining, coughing, or physical activity
• Sudden change in behavior, decrease in school success
• No family history of headaches
• Age less than 10 years old
• Persistent location of headache on the same side or occipito-cervical junction
• Signs of systemic illnesses (fever, rash, neck stiffness)
• Recent history of cranial or cervical trauma
• Focal neurological deficits, altered consciousness, meningeal irritation signs, papilledema, visual disturbances, disorders of coordination, gait and speech

tomography (CT) or magnetic resonance imaging (MRI). EEG may be used in migraine-triggered seizures or in the differential diagnosis with developmental disorders [38,39]. Lumbar puncture is helpful in the diagnosis of meningitis, subarachnoid hemorrhage, or intracranial pressure changes.

Primary headaches

Migraine

Migraine and TTH are the most common causes of headache in children. Migraine has a prevalence of 3.2%–14.5%. It is diagnosed according to ICHD-3 [26] diagnostic criteria for migraine. The pain is moderate to severe in intensity with pressing or pulsating quality and is aggravated by routine physical activity such as walking or climbing stairs. Nausea and/or vomiting and/or photophobia and phonophobia accompany the headache attacks.

Premonitory symptoms such as tiredness, mood swings, food cravings, and yawning can occur early in a migraine attack (as well as in abdominal migraine and cyclic vomiting syndrome) and they are commonly overlooked in routine practice [40]. Aura is an important but rarely seen phenomenon especially in younger ages. Migraine headache attacks may last shorter and the attack duration ranges from 2 to 72 h, but in younger children, attacks may last less than 1 h. The headache is usually bilateral and the unilateral pain usually begins in late adolescence or early adulthood. Frontotemporal location is typical, whereas occipital headache is rare. Positive family history is reported in 60%–77.5% of the cases. In children

and adolescents, less typical visual symptoms may be present as an aura. Allodynia is present in more than one third of children with migraine during their headache attack. The symptoms of allodynia mostly consist of sensitivity to touch and difficulty brushing hair [41]. Key points for migraine in children and adolescents are summarized in Table 9.2.

Chronic migraine (CM) is less common when compared to episodic migraine (EM). Lipton et al. found that the prevalence of CM between the ages of 12 and 17 years was 0.79% when medication overuse headache is excluded [42]. When CM patients with medication overuse are included, the prevalence is still less than 2%. Most migraine headaches in the pediatric population are without aura. Migraine with aura (MWA) is less common than migraine without aura (MWOA). MWA was reported in 26.2% of the patients in a retrospective study conducted by Genizi et al. in 260 children with migraine [43] and 65% had visual aura. MWA was found to be more common in females, older children, and patients with a family history of migraine.

It can be hard to differentiate migraine from TTH in children because of overlapping of some symptoms. If the headache has a pressing character and is mild to moderate with no associated symptoms or one out of phonophobia or photophobia is present, TTH must be considered. In chronic TTH, one out of nausea, phonophobia, or photophobia may be present. Osmophobia is more specific to migraine. Positive family history for migraine and osmophobia are useful in the differentiation of migraine and TTH. Vomiting may point to migraine in young children with a positive family history of migraine. Dizziness which is more common in children >11 years old can be helpful to diagnose migraine.

Syndromes that may be related to migraine

Several episodic syndromes are associated with migraine and they are called syndromes that may be related to migraine according to ICHD-3. They are seen in 3%–5% of migraine patients and mostly in children and adolescents [40,44]. Recurrent gastrointestinal disturbance is described as recurrent episodic attacks of abdominal pain and/or discomfort, nausea, and/or vomiting which may be associated with migraine. The gastrointestinal examination and evaluation must be normal. Cyclic vomiting is defined by recurrent stereotypic attacks with nausea, vomiting, and need for rest. Pallor and lethargy may accompany the attacks. Nausea and vomiting occur at least four times per hour and the duration of the attacks ranges from 1 h to 10 days. At least 1 week of complete resolution period between the attacks must be present. This syndrome has a cyclic nature with predictable

Table 9.2 Key points for migraine in children and adolescents.

- Attacks may last 2—72 h (even as short as 1 h)
- Migraine is generally bilateral *(unilateral pain usually emerges in late adolescence)*.
- Migraine headache is often frontotemporal
- Occipital headache in children is rare; exclude secondary causes
- Osmophobia shows more specificity than photophobia and phonophobia to migraine
- 30% cannot describe the quality of pain
- 16% cannot define photophobia and phonophobia in the terms required by ICHD-3 criteria *(photophobia and phonophobia may be inferred from the behavior in young children)*
- Aggravation by physical activity is more prominent than adults.
- Vomiting, photophobia, phonophobia are more prominent after age 8.
- Migraine attacks can be associated with cranial autonomic symptoms and cutaneous allodynia.
- Aura is rare and commonly cannot be described properly.
- Nonheadache presentations of migraine need to be considered.
- Syndromes that may be related to migraine are seen in pediatric outpatient clinics especially in patients with positive family history of migraine.

episodes. Abdominal migraine is encountered in approximately 20% of children with migraine, usually between the ages of 5 and 9 [45]. It is characterized by recurrent episodes of moderate to severe midline abdominal pain associated with loss of appetite, pallor, `nausea, and vomiting, lasting 2—72 h. Headache does not accompany these attacks. In one study, 4.4% of children referred to the pediatric gastroenterology clinic for recurrent abdominal pain were diagnosed with abdominal migraine [44]. Benign paroxysmal vertigo of childhood consists of recurrent attacks of vertigo, occurring without any warning, accompanied by at least one of the following: nystagmus, ataxia, vomiting, pallor, or fearfulness. The vertigo attacks resolve spontaneously and the neurological examination, audiometric, and vestibular functions are normal between the attacks. Exclusion of other causes of vertigo such as posterior fossa tumors, seizures, and vestibular disorders is required. Benign paroxysmal torticollis is a rare disorder characterized by attacks of torticollis lasting less than 1 week and recurring from every few days to every few months. The attacks consist of head tilt to one side, with or without slight rotation which resolves spontaneously after

minutes to days. Pallor, irritability, malaise, vomiting, and ataxia may accompany the attacks. These attacks begin within the first year of life, improve by the age of 2 years, and end by the age of 3 years. The differential diagnosis consist of gastroesophageal reflux (Sandifer syndrome), idiopathic torsional dystonia, complex partial seizure, posterior fossa, and cranio-cervical junction lesions [40].

Migraine is a biopsychosocial disorder presenting with epigenetic factors

In addition to its biological pathogenesis, migraine follows the biopsychosocial model in its presentation, in its trigger and relieving factors, and also in its response to pharmacological and nonpharmacological therapies. The relationship between primary headache disorders and psychological comorbidities is likely to be bidirectional. Early life events, illnesses, and behavioral characteristics can predict the likelihood of headache in childhood. The results of a longitudinal study conducted in children under the age of 6 years suggested that poor health and feeding problems at 9 months of age and sleeping difficulties at 3 years of age could predict the development of headache at 6 years of age [46]. At the age of 5 years, travel sickness, nocturnal enuresis, and the existence of a long-term disease were strong predictors of later headache [46]. At the same age group, poor concentration, behavioral problems, unusual tiredness, and, conversely, high sociability were also predictors of headache [46]. In school-age children, a history of migraine and other forms of pain in first-degree relatives were associated with an increased risk of migraine [45,47].

Migraine variants

Familial hemiplegic migraine Familial hemiplegic migraine (FHM) is a rare autosomal dominant migraine subtype which is MWA in which the aura includes fully reversible motor weakness (lasting <72 h). Aura consist of both motor weakness and visual, sensory, and/or speech symptoms. The patient with FHM has at least one first- or second-degree relative with migraine aura including motor weakness. It is genetically heterogeneous with three specific subtypes described: FHM1, FHM2, and FHM3. Mutations in the CACNA1A gene (encoding a calcium channel) on chromosome 19 are responsible for FHM1; mutations in the ATP1A2 gene (encoding a K/Na-ATPase) on chromosome 1, are responsible for FHM2; and mutations in the SCN1A gene (encoding a sodium channel) on chromosome 2 are responsible for FHM3 [48].

Migraine with brainstem aura Migraine with brainstem aura is an MWA subtype in which aura symptoms originate from the brainstem, but there is no motor weakness. Aura consists of fully reversible visual, sensory, and/or speech symptoms and at least two brainstem symptoms, such as dysarthria, vertigo, tinnitus, hypoacusis, diplopia, ataxia, and decreased level of consciousness, must be present. Transient ischemic attack has to be excluded.

Retinal migraine Retinal migraine is described as repeated attacks of monocular visual disturbance such as scintillations, scotomata, or blindness which are associated with migraine headache. Aura consists of fully reversible monocular positive and/or negative visual phenomena which is confirmed during an attack by visual field examination and/or the patient's drawing of a monocular field defect. Other causes of amaurosis fugax have to be excluded in the differential diagnosis.

Alice in wonderland syndrome Alice in Wonderland syndrome is a rare migraine variant, The children may define perceptual distortions such as micropsia (object is perceived to be smaller than its actual size), macropsia (object is perceived to be larger than its actual size), metamorphopsia (object appears distorted or misshapen in form), teleopsia (object looks further away than it actually is), Lilliputianism (people appear very small), palinopsia (persistence of an image after the removal of a stimulus), cerebral polyopia (simultaneous two or more copies of a single object are seen), zoopsia (visual hallucination of animals), achromatopsia (color blindness), prosopagnosia (impairment in recognition of familiar faces), visual agnosia (impairment in recognition of visual objects), and akinetopsia (motion blindness), before, during, or after the headache. In 1952, for the first time, Lippman [49] described seven migraine patients with body image distortions, before, during, or after the headache, and in 1955, the syndrome was named by Todd [50].

Acute confusional migraine Acute confusional migraine (ACM) is an uncommon type of migraine defined as acute confusional state, agitation, and aphasia lasting 4–24 h which is usually seen in juvenile migraine patients. ACM may be seen in CADASIL; therefore, in adult patients with ACM, brain MRI and testing for Notch3 mutation should be performed.

Tension-type headache

TTH is the most common headache type in children aged 8–12 years and its prevalence increases with age in adolescence [14,51,52]. In contrast to migraine, not much is known about TTH in children and most of our knowledge comes from adult studies.

TTH is characterized by mild to moderate pain which is typically pressing or tightening in quality. The pain is not aggravated by routine physical activity. The diagnosis of TTH is based on the absence of associated symptoms diagnostic of migraine. There are no associated symptoms or no more than one out of photophobia and phonophobia in episodic TTH and one out of mild nausea, photophobia, and phonophobia in chronic TTH [26]. Infrequent episodic TTH is defined as headache occurring less than once a month. In frequent episodic TTH, headache occurs 1−14 days per month, and in chronic TTH, headache occurs at least on 15 days per month or 180 days per year.

TTH is usually accompanied by anxiety and psychological stress factors [53] which should be evaluated. A higher rate of divorced parents and less peer relations are observed in TTH patients [30]. More than 50% of children with chronic TTH have predisposing physical or psychological stress factors.

After the exclusion of secondary headaches which is required in the diagnosis of TTH, a headache diary would be useful for the differentiation of TTH from other headache types. The phenotype of MWOA in childhood may not be fully developed in children and migraine may present as bilateral, short-lasting headache with different levels of associated symptoms and may resemble TTH. There are a substantial number of patients who remain unclassifiable or are diagnosed as probable migraine or probable TTH [54].

Cluster headache and other trigeminal autonomic cephalalgias

CH onset is usually between 20 and 40 years and childhood onset is very rare, though CH in children as young as 3 years of age and one infant were reported in the literature [24]. During the adolescence period, 5%−10% of CH patients experience their first attacks. Males are affected more often than females with a male to female ratio of 3.2:1. In CH, the pain is severe, strictly unilateral, and located in the orbital, supraorbital, and temporal regions. It lasts 15−180 min and occurs from once every other day to eight times a day. Children with CH more often have throbbing pain rather than stabbing. Like all other trigeminal autonomic cephalalgias, CH is accompanied by autonomic symptoms such as conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead and facial sweating, forehead and facial flushing, sensation of fullness in the ear, miosis, and ptosis. Trigger factors for CH in children are warm weather and second hand smoke exposure. It has been recently suggested that the attacks can be shorter and less frequent in children than in adults and restlessness can be more difficult to demonstrate [48].

Paroxysmal hemicrania (PH) is a rare headache disorder with a prevalence of 0.02%, and contrary to CH, there is no male predominance. The onset of PH is usually in the adulthood, after the third decade of life; however, also some childhood cases even as young as 3 years old have been reported [55–57]. It is characterized by brief, severe, unilateral attacks lasting 2–30 min located in the supraorbital and temporal region. The patients may have 5–30 attacks per day and the attacks may be prevented by indomethacin [48].

Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) is defined by repetitive short lasting, moderate to severe attacks with orbital, supraorbital, and temporal distribution which are associated with ipsilateral autonomic phenomena [26]. SUNCT is a very rare condition with only few pediatric case reports described [58]. The pain attacks last for 1–600 s and have a frequency of at least one a day for more than half of the time in the active phase of the disorder [26]. SUNCT is unresponsive to indomethacin, oxygen, or other nonsteroidal antiinflammatory drugs (NSAIDs), however often responds to lamotrigine [48].

Headache and comorbid disorders in children

Children with headache have tendency to have other somatic complaints such as abdominal pain and other psychiatric disorders such as anxiety and depression. Primary headaches, especially migraine, are associated with a variety of comorbid disorders. Depression, anxiety, epilepsy, sleep disorders, attention deficit and hyperactivity disorder, atopy, cardiovascular disease, ischemic stroke, and patent foramen ovale are some of the conditions associated with migraine [59–62].

The frequency of some comorbid disorders in primary headaches is studied by Pavone et al. in 280 children and it is shown that anxiety and depression are significantly associated with the primary headaches [63]. It is also a well-known fact that the risk of migraine is higher in patients with anxiety and depression [64]. Long-term migraine persistence and disability is shown to be predicted by anxiety [32,65,66]. Phobic disorder is associated with frequent and longer migraine attacks [66].

Atopic disorders including asthma are very frequent in children and adolescents, far from being a coincidence. Another aspect is that it is a frequent reason of the misdiagnosis of migraine as headache is attributed to chronic rhinosinusitis. Associated asthma also restricts the use of beta blockers which are well-known migraine preventive medicines [67,68].

Chronic daily headache (CDH), 15 or more headache days per month, is also associated with functional disability and impairment in the quality of life [69]. Disability related to recurrent headaches is also associated with psychiatric disorders such as depression [70]. When comorbid psychiatric disorders in young CDH patients are evaluated, 29.6% of the patients are shown to have at least one current psychiatric disorder [69]. Anxiety disorders, such as specific phobia, generalized anxiety disorder, obsessive compulsive disorder, are the most common ones as they are seen in 16.6% of the patients. Mood disorders are seen in 9.5%.

Sleep may be both a trigger and a remedy for headache. Sleep deprivation or oversleeping may trigger a headache attack particularly migraine. Sleep, spontaneous or induced by hypnotics, relieves a migraine attack especially in children. Melatonin also reduces the headache frequency, intensity, and duration in children, but the mechanism remains unclarified. Migraine attacks may emerge during sleep, mostly early in the morning. Migraine is both associated with rapid eye movement (REM) and slow-wave sleep, whereas CH attacks are only associated with REM sleep and usually occurs during the first REM period [71].

Pediatric headache patients usually have a high rate of sleep problems, such as difficulty falling asleep, night waking, insufficient sleep, restless sleep, and fatigue during daytime [72]. Parasomnias such as sleepwalking, night terror, and bedwetting are seen higher in migraine patients compared to controls [73,74]. The prevalence of sleepwalking in migraine patients is 30%–55% [75]. Sleep disturbances such as obstructive sleep apnea syndrome may also cause headache.

Medication overuse headache

Medication overuse is not uncommon in children and adolescents. Medication overuse varies between 21% and 60% of pediatric patients with chronic primary headache disorders [42,76–80]. Medication overuse is more common among girls (48%) than boys (28%) with chronic headache [79]. Most of the pediatric patients with medication overuse have CM. In one study, 77.5% of the medication overuse headache patients had CM [81].

The most common overused medications in children are nonspecific analgesics. In a study of 42 pediatric headache patients with medication overuse, >50% overused NSAIDs, about 25% overused acetaminophen, and 12% overused prescription medications [79]. When the overused medications are withdrawn, not all of the patients with medication overuse improve [76,77]. In one study, after the withdrawal of the overused medications, headache frequency reduced in only 40% of pediatric patients [76].

Barbiturate-containing compounds and opioids are the most problematic medications to overuse; they should be tapered slowly to prevent withdrawal symptoms and their further use must be discouraged. Opioid and barbiturate-containing medication use for headache is rare in children when compared to adults. Combined analgesics are not used so much in the Middle East and Eastern countries as in Western countries. For acute headache treatment, NSAIDs and triptans with antiemetics may be used in these patients with barbiturate and opioid overuse; however, their use should also be limited. Dopamine receptor antagonists, such as chlorpromazine or prochlorperazine, are other alternatives. During the withdrawal period of the overused medication, greater occipital nerve injections may be beneficial. In a pediatric study, the benefit of the injections started with a mean latency of 4.7 ± 2.3 days [82]. The likelihood of developing triptan overuse headache may be decreased by combining a triptan with naproxen. An effective preventive therapy may be required to reduce the need to use acute medications so frequently.

Management of headache

Once the diagnosis of headache is established, accompanying somatic and psychiatric diseases, trigger factors, and the disability of the patient should be assessed. Proper and realistic therapeutic goals have to be set and the child and the family have to be educated about the headache disorder. Regular meals, adequate fluid intake, exercise, and good sleep habits must be advised. The child must be educated to cope with trigger factors. Behavioral interventions, such as, relaxation, biofeedback, and cognitive-behavioral therapy may be used in headache in children and adolescents. They are shown to decrease the frequency and severity of the headache [33].

Pharmacological treatment of migraine

The benefits and risks must be weighed carefully before starting a pharmacological treatment in pediatric headache patients since there are a limited data on efficacy and safety of medications in children. Few randomized placebo-controlled clinical trials are present in children for acute and preventive treatment in headache. In children, the placebo response rate is high, up to 55% for preventive medications and 69% for symptomatic medications which makes it difficult to find effective agents statistically significantly superior to placebo [83].

The symptomatic treatment consists of medications used in the relief of an acute headache attack, whereas prophylactic treatment requires the daily use of a medication for a certain period of time in order to decrease the frequency and the severity of headache attacks.

Symptomatic treatment

Abortive medications are the drugs taken during an attack to relieve pain. The goal is to provide quick relief from headache. Limited use of abortive medications should be advised in order to avoid medication overuse headache. For an optimized effect, the symptomatic medications should be used shortly after the headache onset, before the intensification of headache and in the appropriate dose.

Commonly used symptomatic drugs in children are acetaminophen and ibuprofen in children (Fig. 9.2). The effectiveness of ibuprofen, acetaminophen, and placebo was compared in children with migraine [84] and both ibuprofen and acetaminophen caused a greater decrease in the headache intensity at 2 h posttreatment when compared to placebo. Ibuprofen was superior to acetaminophen in aborting migraine within 2 h. Other NSAIDs may also relieve migraine headache. Naproxen is an NSAID which may also be used in pediatric migraine patients. Triptans are the most extensively studied group among the abortive medications. They reverse the blood vessel dilation that occurs during a migraine attack and are most effective when given early during the headache attack. They have oral formulations, but sumatriptan and zolmitriptan are also available as nasal sprays

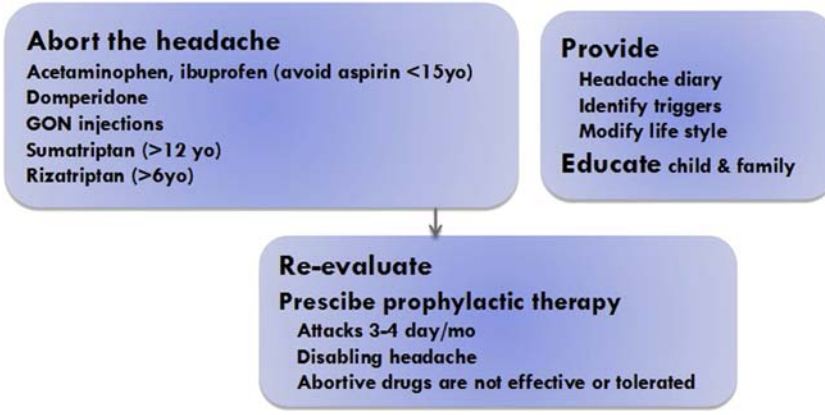

Figure 9.2 The management of migraine.

which may be preferred in patients with severe vomiting. Injectable preparation of sumatriptan is hard to use in pediatric patients due to compliance problems. Almotriptan, rizatriptan, and sumatriptan/naproxen sodium combination is FDA approved for the treatment of migraine attacks in adolescents between the ages 12 and 17. Rizatriptan has been also approved for the treatment of acute migraine in children between the ages 6 and 11. Even though sumatriptan is the most widely used triptan in adults, in children, there are conflicting results in different studies. In a randomized, double-blind, placebo-controlled study, there was no statistically significant difference in pain relief at 2 h between oral sumatriptan and placebo [85]. In another study, sumatriptan nasal spray (20 mg) was superior to placebo in pain relief at 30 min and 2 h [86]. Oral zolmitriptan and ibuprofen were shown to provide similar rates of pain relief at 2 h when compared to placebo [87]. Eletriptan and placebo caused a similar headache improvement at 2 h; however, eletriptan reduces the headache recurrence within the 24-h [88] more when compared to placebo. Rizatriptan is effective in children as young as 6 years of age [89]. Children with EM benefit more from triptan than CM patients [90]. The patients and the families should be aware of the side effects such as drowsiness, dizziness, tingling, chest tightness, and the rare risk of serotonin syndrome. In children taking other serotonergic medications such as SSRIs or SNRIs, there is no sufficient data to avoid or limit triptans [91]. Even though triptans were thought to be contraindicated in migraine with brainstem aura, hemiplegic migraine, or migraine with prolonged aura, there are some smaller studies suggesting that triptans can be used safely in these types of migraine without a significant increased risk for vascular events [92,93].

Prophylactic treatment

In the therapeutic management, if lifestyle changes, avoidance of triggers, and nonpharmacological interventions are not effective, pharmacological treatment must be considered. Preventive treatment (Fig. 9.2) is recommended only when migraine occurs at a frequency of $\geq 3-4$ attacks per month (or one or more headache per week) and the headache severity affects the patient's daily life or quality of life (e.g., missing school). The purpose of the preventive treatment must be explained to the patients and the families to avoid improper dosing just on headache days. In the preventive treatment, the medications are taken on daily basis to reduce the headache frequency, duration, and severity. The patient and the families must not

expect to have a positive response quickly; it may take weeks. Realistic goals must be set in the response to treatment such as a 50% reduction in the headache frequency and severity.

Few prophylactic medications have been studied in controlled trials. The prophylactic medications are started at the lowest dose and titrated upward as required to minimize the side effects. The medications are continued for at least 4–6 months; therefore, before the onset of preventive treatment, comorbidities of the patients and the side effects of the drug should be considered.

The most common medications used for migraine prevention are the anticonvulsants such as valproate, topiramate, and gabapentin, the tricyclic antidepressant amitriptyline, and beta blockers such as propranolol. The pediatric studies in migraine prophylaxis are few and relatively small. In pediatric patients, topiramate is the best studied medication used in the migraine prophylaxis. Topiramate is associated with a greater reduction in headache frequency, school absenteeism, and headache-related disability when compared to placebo [94]. It is also shown to be more effective than propranolol at reducing headache frequency, severity, duration, and disability [95]. Cognitive slowing and paresthesias are the most common side effects. Topiramate results in decreased appetite and weight loss which may be favorable in overweight patients.

Valproate and propranolol are found to be effective in decreasing monthly headache frequency by 50% or more, they also reduce the headache severity, and improve the response to acute attack treatment [96,97]. Valproate should not be used in young women in childbearing age since it increases the risk of teratogenicity especially neural tube defects. Valproate also causes weight gain. Propranolol should not be used in patients with asthma since it is a beta blocker and may result in exacerbation of this condition. Additionally, it may result in bradycardia and hypotension.

The effectiveness of antidepressants for migraine prophylaxis in children is not extensively studied; however, low doses of amitriptyline are used in pediatric migraineurs. The common side effect is drowsiness; thus, it is better to advise the patients to take amitriptyline at night and can be preferred in patients with poor sleep quality. QT prolongation is another side effect to keep in mind. Cyproheptadine, an antihistaminic, may also be used in children with migraine. Most patients benefit from cyproheptadine within a few weeks. Its side effects are weight gain and drowsiness. Flunarizine is an effective drug especially in children; however, daytime sedation and weight gain limit its use. Daytime sedation is observed in 10% of the patients

and weight gain in more than 20% of the patients. There is a probable D2 receptor interaction with flunarizine; therefore, it should not be given for a long time and it should be administered in the early evening to avoid daytime sleepiness. There are limited data about levetiracetam, gabapentin, and zonisamide. Childhood and Adolescent Migraine Prevention Study (CHAMP) was the largest enrolling study of migraine prevention in children and adolescents [98]. It looked at the efficacy of amitriptyline and topiramate as the two most commonly used prophylactic treatment. It failed to show any significant differences with regard to the primary outcome, although it might be prematurely discontinued [99]. Also a few small case series reported the positive effect of onabotulinum toxin A in the treatment of migraine in pediatric and adolescence [100–102]. Szperka et al. published recommendations on the use of anti-CGRP monoclonal antibodies (anti-CGRP mAb) in children and adolescents who failed two or more preventive treatments and experienced frequent migraine attacks ($\geq$8 headache days per month) and had moderate to severe migraine-related disability (PedMIDAS score $\geq$30), with careful monitoring in especially younger children [103]. Greene et al. reported a significant benefit in 29.5% of patients at first follow-up visit and 30.1% at second follow-up visit in 112 adolescents (94 patients with CM, 12 patients with new daily persistent headache, and 6 patients with persistent posttraumatic headache) who received at least one dose of an anti-CGRP mAb [104]. Five patients discontinued the anti-CGRP mAb treatment because of side effects [104] and the most common reported side effects were injection site reactions (17.0% patients) and constipation (8.0% of patients).

Pharmacological treatment of TTH

In TTH, acute attack treatment and preventive treatment may be required according to frequency of headache and impact on daily life. Medication overuse is a problem when the headache attacks are frequent. Behavioral treatment, avoidance of triggers, and lifestyle modifications are needed for both episodic and chronic TTH. They minimize the need for pharmacological therapy and their potential side effects. Preventive pharmacological therapy may be needed if lifestyle modification and nonpharmacological treatments are not effective. There are a few studies on the efficacy of medication in children with TTH. For acute treatment, paracetamol, aspirin, combination analgesics, and NSAIDs are effective medications; however, because of the risk of Reye's syndrome, aspirin is not recommended under the age of 15 years. There is limited evidence for the efficacy of

prophylactic treatment in TTH in children. Amitriptyline is usually used when there are frequent headache attacks; however, more randomized controlled trials are required.

Treatment of cluster headache

The symptomatic treatments include oxygen, nasal, or subcutaneous sumatriptan and nasal zolmitriptan. If oxygen is given at a high flow rate (12−15 L/min) at the onset of an attack, pain relief may be established within 15 min in most of the patients. Additionally, sumatriptan nasal spray or subcutaneous sumatriptan may be required during an attack. When oxygen is discontinued, headache may return; therefore, concurrent use of triptan should be considered. Children between the ages of 6 and 10 years should start with 5 mg sumatriptan nasal spray, and children over the age of 10 years and 50 kg may use sumatriptan 20 mg nasal spray. Ergotamine is not recommended for acute treatment in children, but may be used to prevent night-time attacks. Lidocaine spray may be applied to the nostril ipsilateral to pain as an adjunctive therapy.

There are no placebo-controlled studies regarding prophylactic treatments in CH. Steroids are used as a bridge therapy to cease the attacks and help to prevent further attacks in adults; however, it is less attractive in children. Steroids should be tapered and ceased within 10 days to avoid rebound headache. For prophylactic treatment, the first choice is verapamil 3−10 mg/kg/d. It is usually well tolerated and can be used with corticosteroids and sumatriptan. Even though verapamil is a calcium antagonist, it has minimal effect on vascular structures and probably it shows its efficacy on CH through acting on the opioid system. Verapamil modulates the inhibitory activity of hypothalamic peptides on morphine analgesia and restores the function of the analgesic system in the presence of excess hypothalamic peptides [105]. Possible side effects with verapamil are constipation and dizziness and patients need to be followed with ECG for AV block at high doses. Other preventive agents are melatonin 0.1−0.2 mg/kg/d and topiramate 1−2 mg/kg/d in children. Melatonin may cause sleepiness and topiramate is associated with cognitive slowing, paresthesias, weight loss, renal stones, and decreased sweating.

Quality of life

In children and adolescents, headache disorders have an important impact on quality of life [106]. Recurrent headache attacks are associated with school

absences, poor school performance, and impaired physical and social functioning and worsening family interactions [107]. Hershey et al. showed that Pediatric Migraine Disability Assessment (PedMIDAS) questionnaire was a reliable assessment for migraine associated disability in children and adolescents and showed that due to their headaches, children and adolescents suffered from impaired school performance and home and play activities [108]. Children with headache were shown to experience more somatic symptoms and more anxiety with lower levels of well-being [109]. Adolescents with headache showed worse psychological functioning, increased physical complaints, and they were less satisfied with health and life than healthy adolescents [110]. Increased stress, fatigue, depression, and somatic symptoms were more common in children and adolescents with headache compared to the headache-free controls [30]. Most of the studies on pediatric headache point out the impact of psychological factors and comorbid conditions for headache. Comorbidities such as depression, somatization, and anxiety also impair the quality of life. Early diagnosis and treatment of headache would ameliorate both physical and psychological well-being of the child and provide improvement in academic and social areas. Effective coping strategies with stress and known comorbidities are an essential step in the management of headache in children.

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CHAPTER TEN

Headache in women

Elham Jafari
Tehran University of Medical Sciences, Iranian Headache Association, Sina Hospital, Tehran, Iran

Introduction

Headache is a common problem in women of reproductive age. Tension-type headache (TTH) and migraine headache are the most common types of headache in this age group, while cluster headache (CH) has a much lower prevalence.

- TTH is 1.5 times more frequent in women than in men [1]. Menstruation, pregnancy, and menopause can worsen headaches in some patients [1,2]. The prevalence of TTH is reported to be higher in postmenopausal women than in premenopausal women [1]. Current evidence suggests that TTH is not influenced by hormonal contraception [3].
- Migraine headaches are three times more prevalent in women than in men at the age of 30 years with 25%–30% of the female population being affected in comparison to only 8% of the male population [1,4]. Hormonal changes during a woman's life including menarche, oral contraceptive pills (OCPs) use, pregnancy, menopause, and hormone replacement therapy (HRT) may all have a profound effect on the course of migraine. Perimenopausal and peripubertal periods are associated with increased risk of migraine headaches [5], most probably due to female sex hormones and estrogen level fluctuations. The burden of the disease and use of analgesics are also greater in female migraine patients compared to men [1]. Photophobia, phonophobia, nausea and vomiting, and skin allodynia are more frequent complaints in women than in men [6].
- Sex hormones appear to modulate hypothalamic activity in CH [7]. The majority of female patients experience their first attack of CH during menopause. Reduced levels of estrogen are assumed to provoke CH, while higher estrogen levels can have a protective effect [1].

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Migraine and menstruation

- Migraine headaches affect both sexes equally until puberty, while they are more prevalent in women after puberty and the frequency, duration, and intensity of the attacks are increased [5].
- Headaches usually start around menarche with the beginning of cyclic hormonal changes although ovulation occurs 1 or 2 years later. Migraine with aura has a peak incidence between ages 12–13, while migraine without aura typically presents a few years later [1]. Thus, migraine without aura may be associated with the establishment of a regular ovulatory menstrual cycle.
- About 20%–60% of the women with migraine headaches mention an association with menstruation [8].
- Menstruation is an important risk factor for migraine without aura as the incidence of migraine is increased from 2 days before until the first 3 days of menstruation [5].
- The attacks are usually longer, more severe, and more debilitating in menstrually related migraine and respond less favorably to painkillers.

Note: A diagnosis of menstrual migraine (MM) should not be made in women with frequent migraine attacks because they might coincide with menstruation (Table 10.1).

- It is reported that only 7%–35% of women experience PMM; however, MRM occurs in up to 60% of the patients [4].
- Some women experience an exacerbation in migraines following ovulation but there is no strong evidence in favor of this association. Moreover, premenstrual headaches can be part of premenstrual syndrome together with depression, irritability, fatigue, change of appetite, bloating, back pain, breast tenderness, and nausea [8]. It is important to note that premenstrual headache typically improves with the onset of menstruation [10].

Table 10.1 ICHD3 criteria for menstrual migraine [9].

ICHD 3 criteria for menstrually related migraine (MRM)	ICHD3 criteria for pure menstrual migraine (PMM)
Attacks of migraine in a menstruating woman, occurring on day 1 ± 2 (i.e., days −2 to +3) of menstruation in at least two out of three menstrual cycles, and additionally at other times of the cycle	Attacks, in a menstruating woman occurring exclusively on day 1 ± 2 (i.e., days −2 to +3) of menstruation in at least two out of three menstrual cycles and at no other times of the cycle

Pathophysiology

- The timing of MM attacks corresponds to falling estrogen levels in the late luteal phase, which is supposed to be the most potent trigger of migraine [11]. Estrogen drop can trigger migraine, especially if it is preceded by a phase of high estrogen levels, as in the luteal phase, and if the decrease is greater than 10 μg by discontinuation of contraceptive pills [1].
- Steady or rising concentrations of estrogen do not precipitate migraine; however, high estrogen levels can trigger migraine aura [12,13].
- Estrogen withdrawal causes an oxidative stress, reduced production of serotonin, increased sensitivity to prostaglandins, and a release of neuropeptides such as calcitonin gene-related peptide (CGRP), substance P, and neurokinins, which could result in alterations in the microvasculature of the dura mater, changes in calcium and magnesium concentrations, and an imbalance in serotonin and dopamine concentrations [11,14,15,100–102]. Endogenous opioid activity also decreases at low estrogen levels [11].
- The levels of CGRP are reported to be higher in women of reproductive age than in men and cyclic hormonal fluctuations influence CGRP release [1,14].
- Various studies have confirmed the role of prostaglandins and melatonin, as important pain mediators in the CNS, in the pathogenesis of migraines. Prostaglandin levels are elevated threefold in the luteal phase with a further increase during menstruation [4]. These findings have led to the clinical use of NSAIDs and melatonin for prophylaxis of MMs [8].
- It seems that migraine with aura occurs more frequently with high estrogen levels. Estrogen seems to change cortical susceptibility and contributes to the development of cortical spreading depression (CSD) [16].

Treatment

- Women who have known stimuli for their headaches should avoid them during menstruation and have enough sleep, regular meals, and good hydration [8] (Table 10.2).
- Acute MM attacks are treated like other acute migraine attacks. Acute migraine treatments are less effective in menstrual attacks than in nonmenstrual attacks [17]. Rizatriptan 10 mg has the best evidence for pain relief at 2 h, followed by naratriptan. Rizatriptan is the best for sustained pain freedom [15].

Table 10.2 Treatment of hormonally influenced migraine.

Acute treatment	Acetaminophen, caffeine, triptan, mefenamic acid
Short-term prophylaxis	Naproxen, frovatriptan, naratriptan, zolmitriptan, estradiol, magnesium
Long-term prevention	Standard prophylactic drugs Hormonal treatment

- Preventive treatment depends on the effectiveness of acute treatments, menstrual regularity, need for contraception, and the presence of menstrual disorders [5].
- Women who suffer from frequent MRM benefit from standard migraine prophylaxis [5]. If standard prophylaxis reduces the frequency and intensity of the nonmenstrual attacks but does not affect the attacks during menstruation, it can be combined with perimenstrual prophylaxis or the dose of prophylactic drugs can be increased around menstruation [5].

Perimenstrual prophylaxis

- If migraines occur 3–4 times per month or the attack is unresponsive to acute therapy, preventative options must be considered [4].
- Women with regular menstrual cycles and PMM may benefit from short-term perimenstrual prophylaxis. Periodic prophylaxis or mini-prophylaxis includes the use of common acute phase drugs like NSAIDs or triptan starting from 2 to 3 days before until the end of the menstrual period [5] (Table 10.3).

Table 10.3 Short-term prophylaxis for menstrual migraine.

Drug		Dose
NSAIDS	Naproxen	550 mg bid for 7–14 days
	Mefenamic acid	500 mg tid on days −4 to +3
Triptans	Frovatriptan (level A)	5 mg bid on day −2 2.5 mg bid on days −1 to +4
	Naratriptan (level B)	1 mg bid on days −3 to +3
	Zolmitriptan	2.5 mg bid on days −2 to +5
Estradiol (level C)		1.5 mg transdermal starting between days −5 and −2 for 7 days
Magnesium		120 mg tid begin on the 15th day until the next menses

- The first line of treatment in women with dysmenorrhea is different types of NSAIDs. Although there is a potential risk of MOH development, it seems that NSAIDs prevent the chronicity of migraines [5].
- Perimenstrual prophylaxis with triptans is effective and well-tolerated. There is level A evidence for the use of frovatriptan for short-term prevention of MMs [18]. Level B evidence supports the use of naratriptan and zolmitriptan [5,8,18].
- Magnesium can also be used for acute and prophylactic treatment of menstrual headache.
- Standard migraine prophylactic drugs may be used for 5–7 days before the onset of menstruation to the end of the vulnerable time period for migraine [4] (Fig. 10.1).

Hormonal therapy

In women with PMM, the attacks can be prevented through stabilization of the estrogen level in the late luteal phase with the use of subcutaneous or transdermal estradiol or combined oral contraceptive pills around the menstrual period. There is currently no evidence that hormonal therapy is more

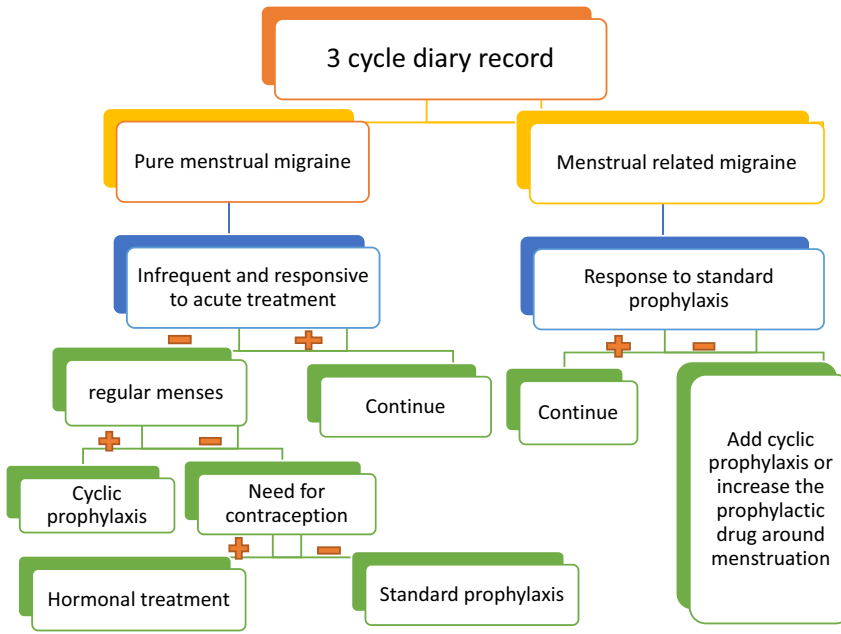


Figure 10.1 Treatment algorithm for PMM/MRM.

effective than nonhormonal treatment strategies; therefore, hormonal prophylaxis at the lowest effective dose may be considered for refractory cases who have no contraindications to estrogen therapy and no vascular risk factors [4]. It is particularly recommended if there are other indications like acne or hirsutism or there is a need for contraception [1].

- If the patient needs contraception, low-dose OCPs may be prescribed in the absence of aura. The conventional method of prescription can aggravate headaches due to estrogen withdrawal in the no-pill period. However, estrogen supplements, like oral ethinyl estradiol (EE) 10 mcg, oral conjugated estrogen 0.9 mg, estradiol dermal patch 100 mcg, or estradiol gel 2 gr, can be used in these no-pill periods to prevent this condition [11]. Low-dose contraceptives containing 20 mcg EE can be given continuously for 12 weeks, followed by 7 days of 10 mcg EE [11]. This method may lead to irregular bleeding in the first treatment cycles, which usually resolves spontaneously. It is important to evaluate cardiovascular risk factors before the start of contraceptive pills [5].
- There is little information about the effect of progesterone-only pills on worsening of migraines [19]. In general, progesterone alone is not effective in the treatment of MMs.
- Methods that induce amenorrhea may be effective in migraine headaches. GnRH analogues, synthetic androgens, tamoxifen, and bromocriptine can be considered in refractory MM [4]. Phytoestrogens like soy isoflavone, dong quai, or black cohosh may have a beneficial effect on migraine [1].
- Surgery is not usually recommended for the treatment of MM, because hysterectomy with or without oophorectomy has been associated with worsening of migraines Fig. 10.1 [5].

Headache and contraception

- Headache is one of the most common side effects of hormonal therapies [20]. The IHS identifies two headache entities related to the use of hormonal contraceptives: exogenous hormone—induced headache and estrogen-withdrawal headache. The onset of headache is usually within the first months of use [1,21].
- OCPs, when used for the first time, have different effects on migraine headaches. The frequency or intensity of the headache may increase or its characteristics may change. However, the pattern of migraine

headaches does not change significantly if low doses of estrogen and progestin are used. The use of OCP aggravates headaches in 18%–50%, improves migraine in 30%–35%, and causes no change in 40%–65% of the women suffering migraine headaches. The odds of migraine aggravation are higher in migraine with aura and lower in MM. Headaches most frequently occur in the "pill-free" week [1].

- The existing evidence is in favor of an almost twofold increase in the risk of ischemic stroke in women suffering from migraines as compared to their age-matched nonmigraine counterparts, especially in case of OCP use, heavy smoking, or migraine with frequent aura [22]. However, the risk is still low and there is no evidence that very low doses of estrogen (<20 mcg EE) increase the risk of stroke in nonsmokers with a normal blood pressure and migraine without aura [13]. It is noted that active migraine with more than 12 attacks per year is associated with an increased risk of ischemic stroke [23] (Table 10.4).
- It is not advised to perform thrombophilia screening, patent foramen oval evaluation, or neuroimaging to decide about OCP prescription, unless they are indicated by the patient's specific history [24].
- Current evidence is against the use of combined hormonal contraceptives in women with migraine with aura and in women with migraine without aura who have additional cardiovascular risk factors, like smoking, arterial hypertension, and a previous history of a thromboembolic event [25]. Women with migraine with aura may have a high prevalence of other vasculopathies such as antiphospholipid syndrome, systemic lupus erythematosus, vascular risk factors, and patent foramen oval, which place them at higher risk of stroke [4].
- In women with migraine without aura who have no additional risk factors, monophasic OCPs containing <20 mcg EE can be used as contraception along with monitoring of migraine frequency and characteristics [4,23]. Biphasic and triphasic pills are not a good choice in migraineurs because of the fluctuating levels of EE [4] (Table 10.5).

Table 10.4 Absolute risk of ischemic stroke in women aged 20–44 years in relation to hormonal contraception and migraine status [23].

	No migraine	Migraine without aura	Migraine with aura
Without hormonal contraception	2.5/100,000	4.0/100,000	5.9/100,000
With hormonal contraception	6.3/100,000	10.0/100,000	14.5/100,000

Table 10.5 Recommendations for prescribing OCPs in women with migraine.

1. Identification and evaluation of vascular risk factors and hypercoagulability states.
2. Identification of the type of migraine, especially the presence of aura
3. Cessation of smoking before starting these compounds
4. Treatment of other conditions like hypertension and hyperlipidemia
5. Use of methods other than EE, like progesterone compounds, in high risk women
6. Use of ultralow-dose combined oral contraceptives containing 10−15 μg of EE [13] or new generation hormones like estradiol valerate/dienogest [15,28]
7. Eliminating the pill-free week for women with estrogen withdrawal headache [22,29]

- The type of progestin does not seem to affect arterial risks such as stroke and myocardial infarction.
- Migraine signs that warrant further evaluation or require OCP discontinuation include new-onset persistent headache, new-onset migraine headache with aura, increased frequency or severity of the headache, or unusual aura symptoms particularly prolonged aura.
- In women with migraine who require hormonal treatment for a medical condition, there is a different risk and benefit profile and the choice of hormonal treatment should be selected based on the clinical grounds [26].
- Levonorgestrel 1.5 mg orally, ulipristal acetate 30 mg orally, or copper-bearing intrauterine device is suggested for emergency contraception in migrainous women [27].

The use of the progesterone-only pill is popular with women with migraine because it can be used continuously with no effect on CSD threshold and does not increase the risk of vascular events or migraine [30].

Headache is a common complaint at the beginning of progestin-only methods, but it classically improves after a few months [1].

Progestin-only pills have a shorter half-life and should be taken consistently and on time to offer effective contraception with minimal abnormal bleeding. In addition, progestin-only pills may not reduce the episodes of migraine because they prevent ovulation only about half of the time. Progestin-only arm implants can prevent ovulation more reliably and may reduce MM and aura.

Headache and pregnancy

According to a study investigating acute headache diagnosis in pregnancy, primary and secondary headache was diagnosed in 65% and 35% of the patients, respectively. The most common diagnosis was migraine followed by hypertensive disorders of pregnancy [31]. Evaluation of the patient's history, headache features, drug history, and a complete examination are important to rule out secondary headaches. In patients with a previous history of primary headache, a history of new symptoms is important; longer attacks are the most common feature suggesting a secondary cause [24].

- **Secondary headaches**

When a headache occurs for the first time during pregnancy or in the postpartum period, diagnostic evaluations are warranted considering pregnancy complications, including severe preeclampsia, cerebral thrombosis, posterior reversible encephalopathy syndrome (PRES), stroke, and pituitary apoplexy. Hypercoagulable state of pregnancy increases the risk of secondary headaches. Furthermore, migraine is an independent risk factor for the development of secondary headaches including gestational hypertension and preeclampsia [32].

Diagnostic tests are not necessary when the patient has a long history of headache with no change in signs and symptoms (Table 10.6).

Table 10.6 Warning signs of secondary headaches in pregnancy.

Signs and symptoms	Possible diagnosis
Thunderclap headache	SAH Postpartum angiopathy Pituitary apoplexy
Headache with atypical aura (aura >1 h or including motor weakness)	TIA Ischemic stroke
Postural headache	SAH, CVT, intracranial hypotension
Fever	Meningitis
Elevated blood pressure	Preeclampsia, PRES, RCVS
History of cancer	Secondary brain metastases
History of thrombophilia	Stroke, CVT
History of HIV or active infections	Meningoencephalitis
Progressive headache, cognitive change, symptoms of raised ICP, new-onset seizure, progressive neurologic deficit	Intracranial SOL, IIH, CVT, eclampsia, RCVS
Visual disturbance	Preeclampsia, IIH, PRES, pituitary apoplexy, CVT

The blood pressure should be measured if there is a new-onset headache after 20 weeks' gestation. In case of hypertension, urinary protein should be analyzed and laboratory tests for preeclampsia should be considered.

The indications for imaging and LP in pregnancy are similar to other people. MRI is not associated with side effects for the fetus, although cataract has been reported in animal studies if it is used in the first trimester. Therefore, it is recommended that MRI be postponed if possible. The use of gadolinium is usually avoided in pregnancy because there is little experience about its use although no adverse effects have been reported [33]. MRA without intravenous contrast may be used to detect arterial lesions. MRV is the best modality for detecting cerebral venous thrombosis (CVT) that can be done without contrast injection. CT scan exposes the fetus to ionizing radiation. However, it can be performed using abdominal lead shielding if necessary [33,34]. Iodinated contrast media cross the placenta and have transient effects on the fetus's thyroid gland [34]. A lumbar puncture is not contraindicated in pregnancy and should be done after brain imaging if necessary.

Important secondary headaches in pregnancy

Stroke

Although stroke may occur during pregnancy, its odds are higher during the 3rd trimester to the first 6 weeks postpartum. The risk factors of pregnancy-related stroke include older maternal age, migraine with aura, cesarean delivery, gestational hypertension, sickle cell anemia, connective tissue disorders, severe postpartum hemorrhage, sepsis, structural heart disease, and thrombophilia [35]. A headache may be present in up to one third of the stroke cases, which is usually moderate and self-limited. Its quality is nonspecific and can be bilateral or ipsilateral to the stroke [32].

MRI is the preferred choice of neuroimaging in pregnant women with suspected stroke. CT can be done when MRI is not available [36]. The treatment of acute ischemic stroke in pregnancy follows the same principles as in the general population. According to the recent guidelines, intravenous alteplase may be considered in pregnancy when the benefits of treating moderate to severe stroke outweigh the increased risk of uterine hemorrhage. Prepregnancy or early pregnancy weight is used for dose calculations [37]. The safety and efficacy of IV alteplase in the early postpartum period (<14 d after delivery) have not been well established [38]. Endovascular

treatments may be preferable in women with high risk of bleeding, such as women with a placenta previa or a history of obstetric hemorrhage [39]. Primary mechanical thrombectomy may be considered in pregnant women with occlusion of a proximal intracranial artery [36]. Low-dose aspirin can be used safely in pregnancy for secondary prevention of stroke. It should be stopped within one or 2 weeks of a planned delivery.

Although the risk of recurrent ischemic stroke during a subsequent pregnancy is low, it depends on the underlying disease or cause of stroke and the risk is higher in the postpartum period. Future pregnancies should not be discouraged in women after a stroke, but adequate counseling is advised [36].

Subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) usually manifests with a sudden severe headache peaking in seconds that is mostly unilateral and is associated with nausea, vomiting, neck rigidity, and decreased level of consciousness. In 50% of the cases, sentinel or warning headaches with a sudden onset and moderate intensity are reported within 2 weeks before aneurysmal rupture. SAH is caused by rupture of an aneurysm or vascular malformations. The risk factors of pregnancy-related SAH include preexisting and gestational hypertension, aging, CVT, coagulopathy, black race, alcohol consumption, and tobacco use [35]. The risk of SAH increases in the first few days after delivery [40]. It is not clear whether pregnancy increases the risk of hemorrhage from an AVM. Pregnancy is not discouraged in women with intracranial AVM [41]. Hemodynamic changes in pregnant women may increase the risk of aneurysm formation, progression, and rupture, especially in the third trimester [42]. Pregnancy may cause an increase in size and risk of bleeding of a cavernoma [39].

In general, treatment of ruptured intracranial aneurysms and symptomatic vascular malformations in pregnancy is similar to nonpregnant patients. Endovascular coiling is preferred to surgical clipping for appropriately shaped aneurysms. In near-term patients, child delivery prior to treatment may improve child outcomes and facilitate the management of patients during surgery [42]. Asymptomatic lesions can be observed without intervention during pregnancy.

Women with definitively treated aneurysms or malformations can undergo labor and delivery. Otherwise, they can undergo prophylactic cesarean delivery or regional anesthesia with instrumental delivery. Analysis of

the current literature shows a clear preference for cesarean delivery in pregnant women with intracranial aneurysms. Lumbar puncture for spinal and epidural anesthesia has been reported to increase the risk of aneurysm rupture [42].

Cerebral venous thrombosis

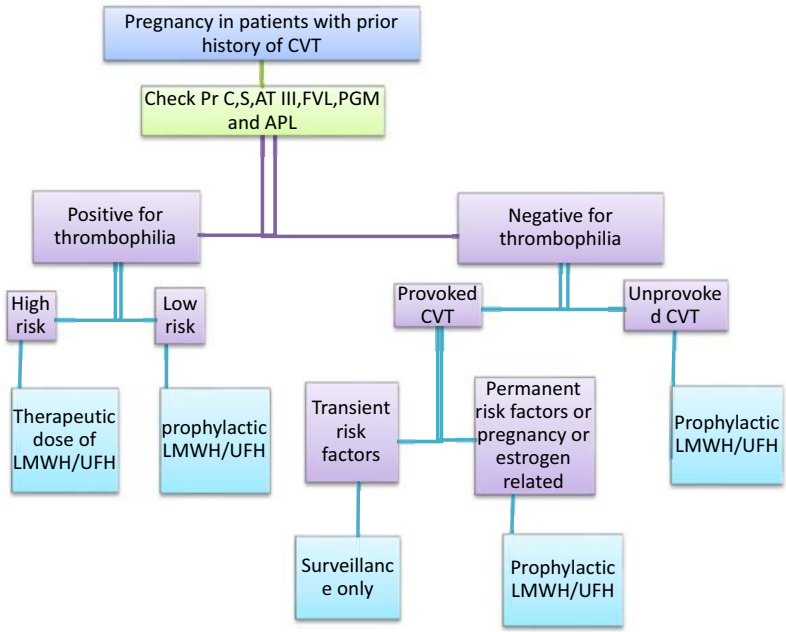
Pregnancy and postpartum are associated with an increased risk of cerebrovascular complications. CVT occurs in 1 in 2500 to 10,000 pregnancies, usually during the third trimester and postpartum period. The overall proportion of pregnancy-related CVT is 25% in women [43]. It is more likely in women with a prothrombotic state, hypertension, cesarean delivery, advanced age, infections, and excessive vomiting. Headache is present in most of the cases and is often severe, diffuse, and progressive, but it can also be unilateral, mild, or even thunderclap type [44]. It is usually associated with seizure, focal neurological signs, intracranial hypertension, or subacute encephalopathy [45]. The mortality rate of CVT is 2%–10%, but it is lower in pregnancy-associated cases [40].

Warfarin crosses the placenta and may cause teratogenicity as well as miscarriage, fetal bleeding, and neurodevelopmental deficits; therefore, it is generally avoided during pregnancy [43]. Although it has been used in the second trimester, the risk of fetal bleeding exists. Oral direct thrombin and factor Xa inhibitors may also cross the placenta and should be avoided in pregnancy and breast feeding, since data on their use are limited [43].

Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) do not cross the placenta and are considered safe in pregnancy [43]. LMWH is commonly preferred for treatment of pregnancy associated CVT in all but the final weeks of pregnancy due to its favorable safety and efficacy and low incidence of bleeding.

LMWH is replaced with UFH at 36 weeks' gestation until a scheduled labor at 39 weeks. UFH is usually discontinued with the beginning of spontaneous labor or 6–12 h before a planned labor or cesarean delivery. Epidural or spinal anesthesia can be done 12 h after a prophylactic dose and 24 h after a therapeutic dose of LMWH. It is also done once PTT is normalized following discontinuation of UFH. Anticoagulation in the postpartum period with UFH or LMWH can be resumed 4–6 h after vaginal delivery or 6–12 h after cesarean delivery, unless there is significant postpartum bleeding. Warfarin can also be started immediately after delivery.

Women with prior history of CVT should be advised against the use of combined hormonal contraceptives to reduce the probability of venous thrombosis recurrence [43]. Future pregnancies should not be contraindicated based only on a history of CVT, but the patient should be informed about the relative risk of venous thrombotic events and abortion [43]. Prophylaxis with LMWH during pregnancy and puerperium is recommended for pregnant women with a history of CVT [43]. Anticoagulation is usually started when the pregnancy is established and continued throughout the postpartum period, at least for 6 weeks, because of the increased risk of CVT following delivery [37]. LMWH, UFH, and warfarin are all tolerated during the postpartum period and breast feeding (Fig. 10.2).



Pr C, S: protein C and S; AT III: Antithrombin III; FVL: factor V leiden; PGM: Prothrombin gene mutation; APL: antiphospholipid

High risk thrombophilias: AT deficiency, homozygotes for FVL or PGM, double heterozygotes for FVL and PGM

Low risk thrombophilias: protein C, S deficiencies, heterozygotes for FVL or PGM

Figure 10.2 Thromboprophylaxis during pregnancy in patients with prior CVT. *APL*, antiphospholipid; *AT III*, Antithrombin III; *FVL*, factor V leiden; *PGM*, Prothrombin gene mutation; *Pr C, S*, protein C and S. High risk thrombophilias: AT deficiency, homozygotes for FVL or PGM, double heterozygotes for FVL and PGM. Low risk thrombophilias: protein C, S deficiencies, heterozygotes for FVL or PGM.

Idiopathic intracranial hypertension

Pregnancy is not considered to be a risk factor for idiopathic intracranial hypertension (IIH), but IIH affects women of child-bearing age [46]. It may occur at any time during pregnancy but it is more common in the first half of pregnancy [35]. It usually manifests with a progressive daily headache that worsens with position and strain. The headache is described as frontal, retro-orbital, pressure like, and less commonly migraine-like pain [34]. Transient visual obscurations may be precipitated by a change in posture. On examination, papilledema, an enlarged blind spot, visual field deficits, and sixth nerve palsy are observed.

Women who develop IIH during pregnancy are diagnosed and treated like nonpregnant women. The frequency of reevaluation depends on the severity of visual loss and disc swelling [46]. Visual outcomes in pregnancy are similar to nonpregnant cases [46]. The major differential diagnosis of IIH in this setting is CVT. Close follow-up control should be carried out to avoid excessive weight gain. A moderate weight loss is recommended.

Limb malformations due to acetazolamide use have been associated with its administration at high doses during early gestation in some animals. There is no convincing evidence to limit the usual dose of acetazolamide throughout pregnancy, even when it is started during the first trimester, other than a unique case report of sacrococcygeal teratoma. However, it should be started if the risk of progressive visual loss is sufficiently high to warrant its use and appropriate counseling should be considered regarding the risk—benefit ratio of treatment [47]. Acetazolamide is started at 0.5—1 g/d in divided doses and can be gradually increased to a maximum of 2 g/d [46].

Use of other diuretics is controversial because of a potential decrease in the placental blood flow. Furosemide is FDA category C in pregnancy and thiazides should be avoided [46]. Lumboperitoneal shunts can be performed during pregnancy; however, they may become occluded, infected, or displaced, requiring reoperation in more than 50% of the cases and therefore it is best to avoid them [46].

The presence of IIH in pregnancy does not increase the risk of IIH relapse, does not worsen the prognosis, and has no effects on the maternal, fetal, or neonatal mortality or morbidity. There is no indication to terminate a pregnancy in a woman diagnosed with IIH; moreover, a women with a history of IIH can become pregnant [34,46].

Cesarean delivery is not necessarily indicated in women with IIH, and regional anesthesia with slow injection is a better choice as general anesthesia

may be associated with a rise in the CSF pressure. If vaginal delivery is planned, adequate labor analgesia is recommended because uterine contractions are associated with a transient increase in the CSF pressure. The second stage of labor can be shortened by instrumental delivery [48]. There is no limitation for spinal anesthesia in pregnant patients [49,50].

Pituitary tumors

There is a gradual increase in the maternal pituitary volume in pregnancy, but the rate of pituitary tumor formation, specifically prolactinoma, does not usually increase. Use of dopamine agonists, cabergoline and bromocriptine, during the period of conception and in early pregnancy does not carry a significant risk to the mother or child, but they should be discontinued as soon as the pregnancy has been confirmed. In women with macroprolactinoma who become pregnant under therapy, dopamine agonist therapy can be continued throughout the pregnancy, especially if the initial tumor was invasive or close to the optic chiasm [51]. Microprolactinomas and small macroprolactinomas limited to the sella turcica rarely increase significantly in size during pregnancy and no special treatment is required. However, symptomatic tumor growth occurs in 20%–30% of macroprolactinomas and if the patient develops symptoms such as headache or impaired vision, reinitiating or increasing the dose of dopamine agonists can be done. Transsphenoidal surgery is indicated if treatment failure or pituitary apoplexy occurs [52].

A pregnant woman with microprolactinoma must be examined every 3 months for the presence of symptoms of tumor growth such as progressive headache or visual field defects [40]. The recommendation for macroprolactinoma includes clinical examination every month and visual field testing every 3 months [52]. Regular monitoring of the prolactin level is not needed for asymptomatic patients and may be only useful for patients with macroprolactinoma as an indicator of tumor growth; however, regular clinical examinations and visual field testing are more important. MRI without gadolinium is indicated in cases with a significant prolactin rise or symptoms such as persistent headache or visual impairment. Asymptomatic prolactinoma is not a contraindication to breastfeeding [52].

Pituitary apoplexy results from acute bleeding into the anterior pituitary or hemorrhagic infarction of a preexisting adenoma [35,53]. A macroadenoma is present in more than 80% of the cases [52]. The median gestational age reported at the beginning of symptoms is 24 weeks [51]. It is a rare but life-threatening complication that manifests with a sudden-onset headache that may be felt behind the eyes or in the frontal region or may be diffuse

and is associated with nausea, vomiting, decreased level of consciousness, ophthalmoplegia, visual loss, and hypopituitarism [54]. An emergency CT scan is indicated if MRI is not available. The recommended treatment for patients with headache and/or hormonal deficiency is usually conservative with adequate substitution of the deficient hormones and administration of a dopamine agonist in cases with prolactinoma. Surgery should be reserved for patients with neuro-ophthalmological symptoms [52].

Brain tumors

Pregnancy does not increase the risk of brain tumors, but hormonal changes associated with pregnancy may accelerate the growth of preexisting tumors, especially pituitary adenoma and meningioma. Pregnancy is not a contraindication to surgical resection or brain tumor biopsy. Steroid therapy in symptomatic brain tumors can delay specific treatments until the baby is safely delivered. If the patient is in her first trimester, any delay in treatment may be unsafe for the mother and therapeutic abortion may be offered. Because of a potential increase in the intracranial pressure during the Valsalva maneuver in a patient with a brain tumor, scheduled cesarean delivery under general anesthesia is usually preferred to vaginal delivery [55].

Preeclampsia

Preeclampsia complicates 5% of pregnancies [45]. A coincidence of headache with hypertension and proteinuria after 20 weeks of pregnancy or in the puerperium suggests preeclampsia, prompting a need for urgent treatments to lower blood pressure and prevent eclampsia [35,40]. Headache is present in about 2/3 of all patients with preeclampsia or eclampsia. A new onset, severe, progressive, or persistent headache is considered a severe feature of preeclampsia, a premonitory symptom of eclampsia, an indication for delivery, and an indication for postpartum magnesium sulfate prophylaxis when the patient is hypertensive [56]. It should have at least two of the following three characteristics: a) bilateral location, b) pulsating quality, and c) aggravation by physical activity [9] and must resolve within a week after blood pressure adjustment [57]. Eclamptic headache can be associated with visual changes that may mimic a typical visual aura [40]. Preeclampsia/eclampsia increases the risk of hemorrhagic stroke during pregnancy and childbirth.

The definitive treatment is delivery to prevent disease progression. Antihypertensive drugs are used to lower the blood pressure and prevent stroke.

Treatment with magnesium sulfate reduces the risk of seizure and should be administered in all women with severe preeclampsia and eclampsia. Magnesium is generally given as a loading dose followed by a continuous intravenous infusion. It is more effective than phenytoin and nimodipine in preventing eclampsia [58]. Eclamptic patients with contraindications to magnesium should receive antiepileptic drugs.

Reversible cerebral vasoconstriction syndrome

Reversible cerebral vasoconstriction syndrome (RCVS) is characterized by recurrent thunderclap headaches over few weeks with or without associated neurological symptoms and neuroimaging findings of reversible constriction of cerebral arteries [59]. About 7%–9% of all RCVS cases are reported to occur in the postpartum setting [60]. The main risk factors are high concentrations of vasoconstrictor substances in a pregnant woman, hormonal fluctuations due to sudden drop of estrogen and progesterone after delivery, and the use of ergometrine maleate in postpartum hemorrhage. It may develop following a normal pregnancy or in the context of proteinuria or HELLP. Up to one third of the cases have predisposing factors like postpartum hemorrhage, lactation suppression, depression, or use of vasoconstrictors with epidural anesthesia. A thunderclap headache may occur in a proportion of women in the first postpartum month although it is of benign course in a vast majority of cases [59,61]. RCVS may mimic the signs of SAH with stroke being one of its complications. A "string of beads" appearance is seen on angiography [40,62]. Transcranial Doppler may be helpful in identifying associated vasospasm, but intracranial flow velocities may be high in the first postpartum days or weeks for reasons other than focal vasoconstriction and the use of Lindegaard Index is recommended instead of velocimetry [59].

All patients should be advised to rest and avoid possible triggers of severe headaches. Patients who show no signs of clinical progression are only observed with attention to recurring symptoms and complications. In cases with consistent clinical and brain imaging features and visible vasoconstriction, symptomatic treatment is indicated, which includes the avoidance of vasoconstrictive substances, headache relief, blood pressure control, and treatment of associated conditions such as stroke, seizure, and cerebral edema. Calcium channel blockers and magnesium sulfate have been used to alleviate vascular abnormalities [63].

RCVS typically has a self-limiting course with full recovery and few if any sequelae and there is no evidence to discourage future pregnancies [63].

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is characterized by vasogenic cerebral edema that causes focal neurological symptoms [58]. PRES is often associated with hypertensive encephalopathy, preeclampsia, eclampsia, and RCVS [64]. The clinical syndrome typically includes headache, encephalopathy, visual symptoms, and seizures. Headache is the most common symptom that is usually dull and bilateral and is predominantly felt in the occipital area. Typical findings are bilateral and symmetrical white matter vasogenic edema most commonly in the parieto-occipital regions, but also the frontal lobes, temporal lobes, cerebellum, and brain stem. The condition is usually reversible when appropriate treatment is started and the symptoms generally resolve within days or weeks [40]. There may be clinical differences between PRES associated with preeclampsia/eclampsia and PRES from other causes and the preeclampsia/eclampsia patients are younger and have a less severe disease.

The goal of treatment is to control elevated blood pressure and seizures and to minimize vasospasm and risk of secondary infarct or hemorrhage. Magnesium sulfate is the treatment of choice for PRES as it improves both seizures and hypertension. Other antiepileptic agents, alone or together with $MgSO_4$, such as diazepam, phenytoin, and valproic acid, have been used for seizure control [65].

Symptoms generally resolve in about 3–8 days and the prognosis is good with early diagnosis and prompt treatment [65]. A negative course with persistent severe neurologic deficits or death may occur in 5%–12% of cases [65].

Primary headaches

Most of the headaches during pregnancy are primary headaches [8]. In most cases, a diagnosis of primary headache is already made before pregnancy. However, a headache may occur or may be diagnosed during pregnancy for the first time in 10% of the patients. In pregnant women with a new-onset or atypical headache, the reason may be migraine in 1/3, preeclampsia or eclampsia in 1/3, and other causes in 1/3 of the cases [34].

- **Effect of pregnancy on migraine:**

About 50%–70% of the women with a history of migraines experience an improvement during pregnancy, 5% complain about worsening of the symptoms, and 5%–30% report no changes [8,34,40]. The odds of

improvement are higher in women with MM, migraine without aura, and in the second and third trimester [66,67]. Migraine may worsen at the end of the first trimester, possibly due to the rapid fall in human chorionic gonadotropins, but it remits during the second and third trimester with an increase in the estrogen concentration [11]. Lack of improvement during pregnancy has been shown to be correlated with an abnormal course of the pregnancy, persistence of hyperemesis gravidarum during the second trimester, and multiparity [40,68]. Patients with severe migraine may not experience any improvement or their headaches may worsen during pregnancy [35]. About 2% of women experience their first migraine attack during pregnancy, usually in the first trimester; these patients are more likely to have aura [34].

Headaches relapse in the postpartum period in 30%–40% of women, especially in those with a history of MM [67]. In lactating women, regular secretion of prolactin can inhibit ovulation, plasma fluctuation of estrogen levels, menstruation, and vasopressin and oxytocin levels, which have antinociceptive properties, increase [69]. Therefore, it seems that breastfeeding may have a protective effect against migraine [70].

In women undergoing in vitro fertilization and embryo transfer treatment, headache occurs most frequently at the first stage of the procedure with GnRh analogue administration [71].

- **Effect of migraine on pregnancy:**

Migraine with or without aura does not seem to affect the occurrence of congenital anomalies but increases the risk of preeclampsia, gestational hypertension, and low birth weight [32,34,40]. The risk of preeclampsia is 12 times higher in obese women with migraine compared to their healthy nonobese nonmigrainous counterparts, especially in women whose migraine worsens during pregnancy [32]. The risk of dyslipidemia is also higher in pregnant women with migraine compared to pregnant women without migraine headaches [34]. Active migraine in pregnancy is associated with an increased risk of venous and arterial thrombosis, stroke, and myocardial infarction [32,40].

Disorders like thrombocytopenia, CVT, and eclampsia may mimic aura and should be considered in women who experience migraine with aura for the first time during pregnancy.

- **Postpartum Headache**

Women whose migraine has relieved during pregnancy may experience a relapse in migraine after delivery, most commonly on postpartum days 3–6, due to a sudden drop in the estrogen level [11]. In addition, sleep

irregularity and emotional stress increase the odds of migraine [34,40]. Primary headaches may start in the postpartum period for the first time [35].

Secondary headaches like preeclampsia, postpartum stroke, RCVS, CVT, subdural hematoma, meningitis, and pituitary tumors should be considered when a diagnosis of postpartum headache is made [40].

Post dural puncture headache

Postdural puncture headache is a debilitating complication of spinal anesthesia occurring in 2%–5% of the cases. Following accidental dural puncture, which complicates between 0.5% and 2.5% of epidural anesthesias, 80%–86% of the obstetric patients will develop postdural puncture headache [72].

This headache occurs 1–7 days after the procedure. It is position dependent, worsens when the patient stands up, and improves upon resuming the recumbent position. Associated symptoms include neck rigidity, photophobia, nausea, and hearing symptoms. Supportive treatment includes hydration, caffeine use, and adequate bed rest. An epidural blood patch should be considered for post-LP headache refractory to supportive treatment after a week [35]. Moderate use of caffeine is harmless during lactation.

Treatment of migraine in pregnancy

Pregestational planning is a very important step in migraine patients to stabilize nonmedical treatments before pregnancy and to determine a safe strategy for the use of drugs during pregnancy [34]. If a pregnancy is planned, preventive drugs should be gradually discontinued and the use of high-risk analgesics should be reduced.

Treatment decisions during pregnancy are similar to recommendations in nonpregnant patients with the only difference that the safest drugs for the fetus and the lowest dose of the drugs are selected to control the symptoms [8]. The first step in the treatment of migraine and tension headaches is nonmedical measures, while nonmedical treatments are not effective in CH (Table 10.7).

Nonmedical treatments

These treatments are the first line of therapy in all women suffering from migraine headaches during pregnancy, especially those with low frequency headaches. Further treatments are required in patients with frequent headache episodes.

Table 10.7 Treatment options for migraine during pregnancy and lactation [34].

Treatment options	
Nonpharmacological options	Good nutrition, trigger avoidance
Healthy lifestyle	Relaxation, cognitive behavioral therapy, biofeedback, stress management
Behavioral treatments	Meditation, yoga
Mind-body treatments	
Pharmacological options	Acute medications
	Preventive drugs
Dietary supplements	CoQ10, magnesium, vit B_2, vit D
Procedure-based interventions	Physical therapy
	Acupuncture
	Nerve blocks

The patients are advised to avoid migraine triggers during pregnancy, including mental or physical stress, irregular or improper eating patterns, sleep irregularity, caffeine withdrawal or overconsumption, decreased or excessive physical activity, etc. [73] Psychiatric comorbidities and persistent nausea are treatable factors that may worsen migraine.

Behavioral therapy techniques like relaxation, cognitive behavioral treatment, biofeedback, and emotional control have an important role in migraine prevention [34]. Many of the above improve depression and anxiety and reduce the need for drugs [74]. Behavioral therapy causes a marked decrease in the frequency of migraine episodes during and after pregnancy. In the absence of obstetric or medical complications, at least 30 min of moderate exercise is recommended on all or most days of the week. Mind-body therapies like yoga and meditation are effective for the treatment of migraine [34].

Medical treatment

Severe chronic pain can lead to stress, sleep disturbance, depression, and poor nutritional intake, which may have adverse effects on pregnancy health and require intervention [40]. If nonpharmacological interventions are inadequate, medical treatment should be considered for women who have severe or prolonged migraine accompanied by nausea, vomiting, and dehydration [4]. Since many women experience an improvement in migraine during the second and third trimester, these treatments can be postponed to the end of the first trimester, considering their risk in the first 3 months of pregnancy [34].

Supplements

Coenzyme Q10, 100 mg three times a day, has level C evidence for migraine prophylaxis. In addition, the use of CoQ10 after 20 weeks gestation markedly reduces the risk of preeclampsia [8].

Magnesium can be used during pregnancy and lactation at a maximum dose of 350 mg per day [8]. However, transient neurological symptoms in newborns and hypotonia have been reported [75]. Prolonged IV injection of magnesium sulfate may be associated with fetal bone demineralization [73]. Magnesium supplements that are used for migraine prophylaxis reduce the risk of eclampsia, as well.

Vitamin B_2 at a dose of 400 mg per day has level B evidence for migraine prophylaxis in adults with minimal side effects. It may cause diarrhea, polyuria, and light yellow urine discoloration. Vitamin B_2 has no beneficial or harmful effects on the pregnancy outcome [34,35].

Vitamin D deficiency is associated with increased risk of migraine headache. Vitamin D 10 mcg a day is now recommended for all pregnant and lactating women [35]. Feverfew (*Tanacetum parthenium*) should be avoided during pregnancy due to concerns of uterine contraction [34].

Acute medications

Acetaminophen is the analgesic of choice for mild to moderate headache in pregnancy. Acetaminophen at doses less than 4 g a day for a few weeks is safe during pregnancy and lactation [35]. Recent studies suggest a possible association between the use of acetaminophen by mothers and ADHD, wheeze, and asthma in children. The risk is highest in mothers who use acetaminophen for more than 20 weeks during pregnancy [34,76]. Combination products with butalbital are not recommended due to withdrawal symptoms in the baby, risk of neonatal vitamin K deficiency, and abuse potential [34] (Table 10.8).

There has been no report of increased risk of fetal malformations and poor pregnancy outcomes in codeine-exposed mothers; however, its use in the third trimester increases the risk of acute caesarian section delivery and postpartum hemorrhage [4].

The use of acetylsalicylic acid at low doses (<150 mg/day) is safe in pregnancy [73]. Low-dose caffeine is assumed to be safe in pregnancy; moderate to high daily doses may be associated with miscarriage, low birth weight, and preterm delivery. Combinations of paracetamol, aspirin, and caffeine should be avoided [54,76,77].

Table 10.8 Treatment of acute migraine during pregnancy.

Drug	Pregnancy category	Notes
Acetaminophen	B	First line; association with ADHD and asthma
Ibuprofen	B–C	Second line; use in T1 and T2 only; avoid in T3: Premature closure of DA and oligohydramnios
Aspirin	C–D	Use in T1 and T2 only; avoid near term: risk of prolonged labor, postpartum and neonatal bleeding, premature closure of the DA, and oligohydramnios Caution while breastfeeding: Risk of Reye's syndrome.
Indomethacin	C–D	Use in T1 and T2 only; avoid near term
Diclofenac	B–C	Second line; use in T1 and T2 only; avoid near term
Naproxen	B–C	Use in T1 and T2 only; avoid near term
Ketorolac	C	Avoid immediately postpartum
Metoclopramide	B	10 mg IM, IV
Chlorpromazine	C	25–50 mg IM
Prochlorperazine	C	10 mg IM
Promethazine	C	25–50 mg IM
Triptans	C	Third line, consider for severe unresponsive attacks
Ergots	X	Absolutely contraindicated

The NSAIDs of choice in the second trimester are nonselective COX inhibitors like ibuprofen, naproxen, and diclofenac [8,40]. Recent data suggests that NSAIDs should be avoided during the first trimester due to increased risk of miscarriage and probable risk of congenital malformations [40]. If indicated, ibuprofen seems to be safer. Chronic or high-dose use of NSAIDs after 30 weeks' gestation increases the risk of premature closure of the ductus arteriosus (DA), oligohydramnios, cerebral palsy, and neonatal intraventricular hemorrhage [35,40,76,77]. Selective COX2 inhibitors are contraindicated in pregnancy based on the few available data [78].

Although opioids can be safely used for treatment of moderate to severe pain during pregnancy, they are not a proper choice in migraine because they worsen nausea and reduce gastric movements. Chronic use of opioids during pregnancy may cause withdrawal symptoms in the baby, growth retardation, and even respiratory depression and arrest at high doses [34,35]. If an opioid drug is necessary as a rescue therapy, oxycodone may be the safest one [73].

Among antiemetics, metoclopramide, prochlorperazine, and promethazine are safe during pregnancy and lactation. Ondansetron is not approved by the FDA for nausea and vomiting in migraine or pregnancy [8]. Recently, there are concerns about the development of serotonin syndrome and serious dysrhythmias, especially in patients with a positive history. Furthermore, there is contradictory information on the teratogenic effects of this drug. Some studies have shown an increased risk of cleft palate and cardiac anomalies following the use of ondansetron [34].

Sumatriptan can pass the placenta, but only about 15% of the maternal dose reaches the fetus after 4 h [79]. There is no evidence for increased risk of congenital malformations associated with the use of triptans in pregnancy; however, their use during pregnancy is not recommended unless other treatments are not effective [35,80]. An increased risk has been reported for postpartum bleeding, atonic uterus, and spontaneous abortion [34,81]. There is a risk of behavioral problems like attention deficit and aggression disorders after prenatal exposure to triptans, particularly in the first trimester [82]. Sumatriptan, which is the most studied triptan, appears to be an acceptable option in pregnancy, but data on eletriptan and frovatriptan are still insufficient [80].

Ergotamine and dihydroergotamine are absolutely contraindicated in pregnancy because they increase the uterine tonus and result in vascular disorders, increasing the risk of abortion [35] (Table 10.9).

Preventive treatments

Prophylaxis is indicated if attacks occur frequently or do not respond to symptomatic treatment. There are more restrictions on prophylactic drugs compared to acute phase medications during pregnancy and lactation, but a number of options are available (Table 10.10).

Table 10.9 Treatment of acute refractory headache in pregnancy [40,83–85].

Tramadol 50 mg
Intravenous hydration
Metoclopramide 10 mg or chlorpromazine 25–50 mg IM ± diphenhydramine 12.5 mg
Combination of a triptan and droperidol (2.5 mg IV every 30 min up to 3 doses)
Decremental doses of prednisolone (60 mg for 2 days, 40 mg for 2 days, 20 mg for 2 days) or methylprednisolone (4 mg, 21 tablets) for 6 days
Magnesium sulfate 1–2 g over 15 min
Peripheral nerve blocks

Table 10.10 Prophylactic treatment of migraine during pregnancy.

Drug group	Drug name	FDA pregnancy category	
• Beta blockers			Discontinue 2–3 days before delivery
	Atenolol	D	
	Metoprolol	C	Second choice
	Propranolol	C	Beta blocker of choice
	Nadolol-Timolol	C	
• Tricyclics	Amitriptyline	C	10–50 mg/d, taper, and discontinue 3–4*w* before delivery
	Nortriptyline	C	10–50 mg/d, taper, and discontinue 3–4*w* before delivery
• Antiepileptics	Gabapentin	C	Third line
	Topiramate	D	Associated with oral clefts
	Valproic acid	X	Contraindicated
• SSRI/SNRIs	Citalopram	C	Conflicting data
	Fluoxetine	C	
	Sertraline	C	
	Venlafaxine	C	
• CCBs	Nifedipine	C	
	Verapamil	C	Tocolytic effects on uterus
• ACE inhs	Lisinopril	D	Category C in first trimester
• ARBS	Candesartan	D	Category C in first trimester

- Beta blockers

The lowest effective doses of propranolol or metoprolol are the first line options if prophylaxis is indicated during pregnancy. Long-term administration of beta blockers may result in mild fetal growth retardation (especially with atenolol), mild transient neonatal bradycardia, preterm birth, respiratory suppression, hyperbilirubinemia, and hypoglycemia. Beta blockers should be gradually tapered 4 weeks before delivery and stopped 2–3 days before childbirth to lower the risk of fetal bradycardia and decrease uterine contractions. The neonate should be also monitored for bradycardia, hypotension, and hypoglycemia [35,40].

- Antidepressants

Low doses of amitriptyline 10–25 mg per day are a good second choice in pregnancy. Although there is contradictory information about cardiovascular and limb abnormalities with high doses of amitriptyline, no association has been reported with low doses (10–50 mg per day) [34,76,85]. It is advised that the drug be tapered and discontinued 3–4 weeks before delivery; otherwise, the baby should be carefully monitored for side effects like drowsiness, irritability, and sucking problems [8,75].

The results of the studies investigating congenital malformations following the use of SSRIs during pregnancy are contradictory. A large study suggested an increased risk of cardiovascular malformations, although the overall risk was low. The use of SSRIs at the end of pregnancy may lead to transient withdrawal syndrome in the neonate manifested by persistent crying, irritability, chills, fever, hypertonia or rigidity, tachypnea or respiratory distress, hypoglycemia, and seizures. Use of SSRIs after 20 weeks' gestation could be associated with persistent pulmonary hypertension.

Venlafaxine, a serotonin norepinephrine reuptake inhibitor (SNRI), should be avoided during pregnancy. There is no evidence for the teratogenic effects of duloxetine [54,76,78].

- Calcium channel blockers

There are no reports of congenital anomalies in humans although there is limited information in this regard. Verapamil is the drug of choice in this group because it is safe and well tolerated. Verapamil has tocolytic effects on the uterus; therefore, its use should be avoided at the end of pregnancy [8].

- Drugs affecting renin–angiotensin system

There are reports of congenital anomalies, fetal renal injury, oligohydramnios, skull defects, and neonatal death following exposure to angiotensin receptor blockers in the uterus. Lisinopril poses no significant risks in the first trimester but is reported to be teratogenic in the second and third trimesters. Drugs like lisinopril and candesartan are contraindicated at any stage of pregnancy [35,40].

- Anticonvulsants

Sodium valproate is contraindicated in nonseizure patients. It has been associated with neural tube defects, oral clefts, developmental delay, and cardiac and genitourinary defects [40,73].

Topiramate has been associated with oral cleft, hypospadias, and low birth weight, especially if used during the first trimester, and should be avoided in pregnancy [34,40,73].

Gabapentin has been linked with osteological deformities. Therefore, its use is not recommended during pregnancy [40,78].

- Other drugs

Cyproheptadine is a pregnancy category B drug and is possibly effective in migraine headaches (level C evidence). Memantine is a pregnancy category B drug and may be used for migraine prevention; however, more studies are required to evaluate its effectiveness. Administration of melatonin in pregnancy can interfere with the development of the postnatal circadian rhythm [86]. Lithium has toxic and teratogenic effects on the fetus.

Procedure-based interventions

Considering the risks of different drugs, many procedure-based interventions may be useful, especially in combination with other nonmedical treatments.

There are no reports on the safety of chiropractic interventions in pregnancy, and this form of alternative medicine should be avoided during pregnancy with regards to the grave risks of spinal manipulation [34].

The most recent studies on acupuncture indicate that its benefits in migraine prevention may be equal to prophylactic drugs with fewer side effects. Acupuncture may relieve nausea and vomiting associated with headache. It seems to be a safe procedure during pregnancy and its most common side effect is pain at the site of needle insertion. Abortion is a rare complication [34].

Peripheral nerve blocks, due to lack of central effects, are a safe procedure in pregnancy. Lidocaine and ropivacaine are preferred for nerve blocks, since bupivacaine may be associated with fetal cardiotoxicity [34,40,87]. Steroids should be avoided because of the risk of accelerated fetal lung maturity.

Botulinum toxin is a category C drug and is not recommended in pregnancy, although human studies, mainly on cosmetic treatment, have not shown its teratogenicity during pregnancy [87].

Treatment of migraine during lactation

Nonmedical treatments during pregnancy should be continued during lactation. A drug is considered safe during breastfeeding if the relative infant dose is $<10\%$ of the maternal dose [40]. Some measures may be taken to reduce complications in the neonate when acute treatments are used, including taking medication directly after breastfeeding, replacing breast milk with formula milk, and pumping the breast and discarding the milk for at least 4 h after drug use [34].

Acute treatment

Acetaminophen and ibuprofen are the drugs of choice for acute migraine attacks during lactation. Their concentration is low in the breast milk and there is no need for breastfeeding restriction. NSAIDs can exacerbate jaundice in newborns [78,88]. Caution should be exercised when using aspirin due to the risk of Reye's syndrome [35].

Only small amounts of sumatriptan are secreted into human milk, indicating its safety in lactation. The baby is exposed to lower concentrations when the oral form of the drug is used compared to injection [35]. Eletriptan may also be used during lactation with lower infant doses [85]. Sufficient data is lacking on other triptans [40].

Ergotamine derivatives have antiprolactin effects and reduce milk production. Ergotamine may cause nausea, vomiting, diarrhea, and weakness in the baby.

Opioids may be used for a short time during lactation because they cause respiratory depression and apnea in the neonate. Some women metabolize opioids slowly, leading to higher concentrations in the breast milk and drowsiness in the neonate.

Moderate use of caffeine is harmless during lactation.

Oral forms of prednisone and prednisolone are compatible with lactation, but breastfeeding should be delayed until 2–8 h after IV administration [40,89].

Preventive treatment

The minimum effective dose of preventive drugs should be administered. The dose should be increased gradually and the baby should be carefully monitored for side effects.

B-blockers are excreted in the breast milk at very low doses and are safe. Metoprolol is preferred to propranolol in nursing women. Possible side effects include drowsiness, neonatal hypoglycemia, hypotension, weakness, and bradycardia [34]. They should be used with caution in mothers of infants with asthma [88].

Small amounts of amitriptyline and nortriptyline are secreted into the human milk (1%–2% of maternal dose), so they can be safely used by lactating mothers. However, drowsiness and anticholinergic symptoms may occur in the infant [34,78].

No adverse effects have been reported in nursing infants of mothers using the SNRIs, but data are not sufficient [88].

Verapamil is secreted into the breast milk and may cause adverse effects in the baby.

Although small amounts of valproate are secreted in the breast milk and it seems to be safe during breastfeeding, it should be avoided in women of childbearing age [40,73]. The topiramate level reaches up to 25% of the maternal levels in the newborns and may cause sedation, irritability, poor sucking, weight loss, and diarrhea [87,88,90].

Melatonin at low doses seems to be safe during breastfeeding [88].

Although botulinum toxin transfer to breast milk is not probable due to its high molecular weight, it should be avoided during lactation due to lack of adequate evidence and should only be reserved for refractory patients with chronic migraine [34,87]. Nerve blocks are an effective treatment option in lactating women. Lidocaine and bupivacaine are secreted in the human milk in small amounts and seem to be safe during lactation. Triamcinolone should be avoided because it may decrease milk production.

Tension-type headache during pregnancy and lactation

In comparison to migraine, the frequency of tension headache does not usually change during pregnancy because it is not affected by hormones [91]. Symptomatic treatment with nonopioid analgesics is appropriate when the frequency of the attacks is less than 2 days a week. Prophylactic treatment of chronic tension headache is necessary when the frequency of the attacks is more than 2−3 days a week. The drug of choice for prophylaxis during pregnancy and lactation is amitriptyline [35].

Cluster headache during pregnancy and lactation

CH is not affected by pregnancy. The treatment during pregnancy and lactation is similar to nonpregnant cases [92]. Subcutaneous or intranasal administration of sumatriptan, inhalation of normobaric 100% oxygen, and intranasal administration of 0.5 cc lidocaine 4% is used for the treatment of acute attacks [35]. Ergotamine is absolutely contraindicated in pregnancy. The preferred drugs for prophylaxis of CH during pregnancy and lactation are verapamil and prednisolone. Cardiac conduction disorders may develop in 20% of the patients receiving verapamil, which is not related to the dose or duration of drug use. EKG should be done at baseline, before any dose increment, and then every 6 months in long-term treatments. Gabapentin is the second drug of choice [35]. Screening for sleep apnea is useful since its prevalence seems to be higher in cluster patients and in pregnancy [93].

Migraine and menopause

Perimenopause is a 2–8-year phase ending 12 months after the last menstrual period and onset of menopause. There is no significant difference in age at menopause between women with and without migraine [8]. The perimenopause period is associated with increased risk of migraine headaches and medication overuse [5]. The hormonal alterations during perimenopause [94], iron deficiency caused by increased menstrual bleeding [95], and depression and sleep disturbances [96] in this period can increase migraine headaches. The women with a previous history of MMs or hormonal headaches have a higher chance of worsening around menopause [97]. The headache is not affected by menopause in 50% of the patients. Physiologic menopause has been associated with a lower incidence of migraine compared to surgical menopause [98,99].

Hormone replacement therapy

Early perimenopause is an important time when estrogen replacement therapy may have beneficial effects on cognition and neuroprotection. There is not enough evidence in favor of an increased risk of stroke in women with migraine headaches above 45 years of age. Therefore, HRT should be administered according to its common indications and contraindications, even with migraine with aura [99]. The risk of stroke is not increased in women who receive low-dose transdermal HRT (less than 50 mcg). In addition, transdermal combinations provide more stable serum levels [8]. The presence of aura does not contraindicate the use of physiological doses of transdermal estrogen although elevated doses can induce new migraine with aura or exacerbate the frequency and intensity of attacks [12].

The old form of cyclic HRT is not currently recommended. Continuous HRT with estrogen with or without progesterone is more standard in women with a healthy uterus [5,8].

If headaches worsen following HRT, the dose of estrogen may be lowered, the form of estrogen may be changed, or the cyclic form may be switched to the sustained form. HRT should be stopped if the headache continues to worsen after HRT or there are contraindications to HRT, including a positive history of thromboembolism, cancer, or hypercoagulable states.

Other drugs

- If estrogen is contraindicated, paroxetine 7.5 mg every night is a nonhormonal treatment approved by the FDA for vasomotor signs and symptoms and may reduce headaches [5].
- Some evidence supports the efficacy of escitalopram and venlafaxine for controlling vasomotor symptoms and for migraine prophylaxis.
- Clonidine (50–75 μg bid.) is approved for menopausal hot flushes and could be effective for migraine prophylaxis [12].
- Level A evidence supports the effect of gabapentin on controlling vasomotor symptoms [5].
- If migraine continues in the early years after menopause, prophylaxis with anticonvulsants is recommended [8].

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CHAPTER ELEVEN

Headache in the elderly

Zahra Vahabi[1,2]
[1]Geriatric Department, Tehran University of Medical Sciences, Tehran, Iran
[2]Psychiatry Department, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Headache is one of the most common problems in older people (above 65 years). About 50% of this population experiences different types of headaches [1]. The proportion of primary headaches decreases markedly from 90% in young individuals to 66% in the elderly; therefore, secondary causes should be investigated and careful diagnostic assessments should be conducted [2–4]. The following secondary causes should be considered:

- Obstructive sleep apnea
- Cerebrovascular disease
- Temporal arteritis
- Medication-related headache
- Brain tumor
- Cardiac cephalgia
- Subacute glaucoma

Sleep apnea headache

Sleep apnea headache is a morning headache that is usually bilateral, lasts less than 4 hours, and improves after diagnosis and treatment of sleep apnea. Sleep apnea is defined as an apnea/hypopnea index of above 5 [5]. The incidence of sleep apnea increases with age, and about 11.8% of the patients suffering from obstructive sleep apnea experience headache. The cause of headache may be multifactorial, including hypercapnia, vasodilation, increased intracranial pressure, and impaired sleep quality [6,7].

The first step in treating sleep apnea is lifestyle modification, including weight loss, regular exercise, and correction of sleeping posture. Exclusive treatment includes correction of airway obstruction (if there is a structural disorder) and sleep apnea using the CPAP. If sleep apnea is corrected but the headache does not resolve, other causes of nocturnal and morning

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headaches like hypnic headache, cluster headache, and caffeine withdrawal headache should be considered. Moreover, attention should be paid to the possibility of increased intracranial pressure in the supine position [3].

Giant cell arteritis

Giant cell arteritis (GCA) is a systemic arteritis of medium and large vessels. It occurs in susceptible individuals after initial events involving immune responses that lead to progression of inflammatory infiltrates through the artery wall. The prevalence of GCA increases with age. Any delay in the diagnosis may result in complete or partial blindness in 50% of the patients due to the involvement of the posterior ciliary artery. Other complications of GCA include external carotid artery stenosis, aortic aneurysm or dissection, and rarely internal carotid artery stenosis and stroke [8,9].

Neurologic manifestations

- Headache is reported in 60%–90% of the patients with GCA [8,10]. The headache is usually pulsatile, although other qualities like dull, sharp, and lancinating headaches have also been reported. The headache is usually refractory and more severe than other headaches. The patients usually complain about pain that worsens by resting the head on a pillow, combing the hair, and washing the face. In 50% of the patients, there is focal tenderness or decreased pulse rate on direct palpation of the temporal artery. The headache is bilateral in 50% of the patients and is felt in the frontotemporal region in 60% of the patients. However, the headache in GCA may be unilateral or felt in the occipital area [11]. Although the pain usually has an acute onset, a diagnosis is usually made after 2–3 months.
- The prevalence of neurological signs and symptoms associated with the headache varies in different studies. In one study, the prevalence of neurological findings was 31%, of which 20% was related to ocular findings [12].
- Paresis of the third, fourth, and sixth cranial nerves results in ophthalmoplegia in 3%–4% of the patients [13].

Ocular findings

- Vision loss due to anterior and posterior ischemic optic neuropathy (AION and PION), central and branch retinal artery occlusion,

anterior segment ischemia, and prechiasmal, peri-chiasmal, and postchiasmal field defects (about 10%) [13].
- AION is the most common cause of permanent visual loss.
- Diplopia, which may be due to cranial nerve paresis or extraocular muscle involvement
- Amaurosis fugax, which might be the first manifestation of the disease [13].

Systemic features

- Systemic signs and symptoms include anemia, fever, fatigue, weakness, anorexia, weight loss, cough, depressed mood, and generalized muscle pain.
- Polymyalgia rheumatica is seen in 50% of the cases as morning stiffness and pain extending to the back and neck.
- Jaw claudication is seen in almost 50% of the patients, and is highly associated with positive arterial biopsy [8].

Diagnosis of GCA

- The diagnostic criteria of GCA are based on the American College of Rheumatology Criteria for classification of GCA (Table 11.1).
- According to ICHD3 criteria, headache should significantly improve or resolve within 3 days of high-dose steroid treatment. The headache is associated with scalp tenderness and/or jaw claudication [5].
- Temporal artery biopsy remains the gold standard test for diagnosis of GCA. Biopsy of the superficial temporal artery shows necrotizing arteritis with infiltration of mononuclear cells or granulomatous changes together with giant cell infiltration. The rate of false-negative reports varies from 5% to 44% in different studies. The causes of false-negative results may be indeterminate pathologic findings, skip lesions, inadequate length of biopsy specimens, small number of sections, and initiation of

Table 11.1 America Collage of the Rheumatology criteria for the diagnosis of temporal arteritis.

Three out of the following five criteria should be satisfied:
1. Age at least 50 years
2. New onset of localized headache
3. Temporal artery tenderness and decreased pulse
4. ESR of at least 50 mm/h
5. Positive histology

corticosteroid therapy. If biopsy of the involved side is negative, biopsy of the contralateral side increases the odds of positive results by 5%–15%. Pathological evidence of GCA remains positive for 4–5 days after the start of corticosteroid therapy.

- Color Doppler ultrasonography can detect GCA with a specificity of 91%. Visualization of perivascular hypoechoic abnormality (halo sign) in the large vessels and temporal artery is diagnostic with a sensitivity of about 68% [14].
- A contrast-enhanced MRI may reveal mural enhancement in the temporal artery. Contrast-enhanced MRI has a sensitivity of 78.4% and a specificity of 90.4%, which begin to decrease about 5 days after treatment with corticosteroids [15].
- ESR is elevated in almost all of GCA patients. However, it increases with age and is not specific for GCA as it also increases in inflammatory, rheumatologic, and infectious diseases. ESR may not be elevated in the beginning of the disease in 10%–35% of the cases and therefore should be repeated. CRP is an acute phase protein that is not affected by hematologic factors and is more sensitive than ESR. Simultaneous measurement of ESR and CRP is up to 97% specific for diagnosis of GCA [8].
- Elevated liver enzymes, normochromic normocytic anemia, and decreased $\alpha 2$ globulin are less frequent.

Treatment

- Prednisone should be administered at a dose of 1 mg/kg/day. The headache improves within 24–48 h after the initiation of steroid therapy. The starting dose should be continued for up to 4 weeks and then the dose should be reduced by 10% every 1 or 2 weeks, considering the results of periodic ESR and CRP tests, clinical findings, and response to treatment. GCA remains active for at least 1 year; therefore, long-term corticosteroid therapy is required. Attention should be paid to the complications of corticosteroid therapy such as diabetes and osteoporosis.
- It is not helpful to add cytotoxic agents like methotrexate.
- Infliximab may be beneficial in severe cases, if there is no response to treatment, or if the patient is intolerant to corticosteroid therapy.
- Tocilizumab is a new drug with promising effects according to some studies. It should be started at a dose of 162 mg subcutaneous weekly and can be tapered according to the clinical response [8,9].

Cardiac cephalgia

This headache resembles a migraine attack that usually worsens with physical activity and follows an episode of cardiac ischemia. Headache is reported as the first symptom of cardiac ischemia in up to one third of the patients. The prevalence of cardiac cephalgia increases with age. Men aged over 60 with risk factors of vascular disease are at the greatest risk. The location of pain is different and it may be unilateral or bilateral. Headache has at least two of the following four characteristics: moderate to severe intensity, accompanied by nausea, not accompanied by photophobia or phonophobia, and aggravated by exertion. It usually develops during physical activity but may also occur at rest. Possible mechanisms include referred cardiac pain, a transient rise in the intracranial pressure secondary to decreased cerebral venous drainage as a consequence of reduced cardiac output, and vasodilation of cerebral vessels caused by the release of proinflammatory mediators [5].

This type of headache usually responds well to nitrate derivatives. It improves after revascularization or treatment of myocardial ischemia; therefore, cardiac ischemia should be ruled out in older patients who develop a headache during physical activity [3,16].

Subacute glaucoma

Acute angle-closure glaucoma occurs when the intraocular pressure elevates following the obstruction of aqueous outflow at the trabecular meshwork. It usually manifests as an acute one-sided eye pain, red eye, blurred vision, and a mid-dilated unreactive pupil; however, the patients sometimes present with a unilateral acute headache [17].

Subacute angle-closure glaucoma is associated with mild to moderate ocular pain and blurred vision, especially in low light conditions, and headache. The headache is usually felt in the frontal region and is usually one-sided and nonpulsatile. It usually lasts for less than 4 h and may occur several times a month or even every day. The headache worsens upon entering a low light place [3,18,19]. The increase in the IOP may result in damage to the optic nerve if not diagnosed.

Cervicogenic headache

Any lesion or disease in the neck, including cervical spondylosis and muscle spasm, can cause a cervicogenic headache, which usually resolves with treating the disorder. It is usually unilateral and felt in the occipital region but may be sensed in the parietal or frontal regions too. Diagnostic maneuvers and digital pressure on the suboccipital region initiate a headache.

There should be evidence of structural involvement such as tenderness on some elements or limitation of cervical movements. The pain may result from occipital neuralgia, myofascial pain associated with trigger points, or referred pains from cervical vertebrae like upper facet joints.

Cranial/cervical vascular disorders and nonvascular intracranial disorders

These disorders include subarachnoid hemorrhage, intracerebral hematoma, subdural hematoma, ischemic stroke, infection, and intracranial neoplasm [5]. Considering the increase in the prevalence of these disorders in the elderly population and their chief clinical manifestation as a headache, it is very important to consider these conditions in the differential diagnosis [3,20].

Tumors

The prevalence of headache in the setting of primary tumors or cerebral metastasis varies from 50% to 70%. The headache is proportionate to the tumor size, location, and type; patient's age; and previous history of headaches. Headaches are more commonly seen in infratentorial and intraventricular tumors [20].

Trigeminal neuralgia

The mean age of onset of trigeminal neuralgia is the 6th and 7th decades of life and 90% of the patients suffering from TN or facial pain are above the age of 40 years. The patients describe the pain as severe and complain about mild constant pain between attacks [3,21].

Postherpetic neuralgia

Herpes zoster and postherpetic neuralgia (PHN) increase with age. The prevalence of this neuralgia ranges from 8% in the age group 50–54 years to 21% in the age group 80–84 years old. The risk factors of PHN are advanced age, severe prodromal signs, rashes, and pain in the acute phase of herpes zoster. Its incidence increases in the context of chronic diseases like diabetes, chronic pulmonary diseases, and immune deficiency conditions [22].

Treatment: Gabapentin and pregabalin are the first line of treatment in the elderly. Gabapentin is started at a dose of 100 mg per night and is gradually increased to 300 mg, reaching a maximum dose of 1200 mg every 8 hours. Pregabalin is initiated at a dose of 75 mg and increased to

300 mg/day. Adverse effects like dizziness and fatigue may occur in some patients. Peripheral edema is another adverse effect that should receive further attention in patients with cardiac or renal failure.

Carbamazepine, oxcarbazepine, lamotrigine, and valproate might be effective in PHN, but potential side effects limit their use in the elderly population.

TCAs are the next line of treatment. Amitriptyline, which is the most effective TCA, is used cautiously in the elderly. Nortriptyline and desipramine are less effective.

Opioids like extended release oxycodone, morphine, and methadone may be effective in refractory cases. Tramadol is tolerated better but is less effective than other opioids.

Local treatment with a 5% lidocaine patch or capsaicin may be effective.

If pain control is not achieved through medical management, a number of interventions can be tried. Botulinum toxin injection reduces pain. Epidural injection of steroids has a moderate short-term effect on pain management and so does percutaneous peripheral nerve block or stimulation.

Drugs causing headache

Medical history is of paramount importance in headache sufferers. Older people use several drugs for different diseases and conditions, which may cause headache. Table 11.2 presents a list of medicines that can cause or worsen a headache.

Parkinson's-related headache

In Parkinson's patients, headache is mainly caused by the rigidity of the neck muscles, which improves with treatment of Parkinson's disease. On the other hand, some drugs used for the treatment of Parkinson's disease like amantadine and levodopa also cause headache [8].

Primary headaches

Migraine headache

Migraine is the second cause of primary headaches in the elderly. The prevalence of migraine decreases with age and the largest decrease is seen in the 5th and 6th decades of life; however, it is not uncommon for migraine headaches to start in the 5th decade. The annual prevalence of migraine headaches in individuals above 65 years is about 10% and is higher in women [23–27].

Table 11.2 List of medicines that can cause or worsen a headache.

(A) Medication- overuse:
1. Opiate-containing medication
2. Triptans: almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan
3. Ergotamine
4. NSAIDS (ibuprofen, aspirin, naproxen, diclofenac)

(B) Other mechanism:
- SSRI: Paroxetine
- OCP: Progesterones, estrogens,
- Nitrates
- Sildenafil
- Ca-antagonists
- Omeprazole (PPI), ranitidine, cimetidine
- Morphine, morphine derivatives
- Interferon, immunoglobulin
- Isoniazid, rifampin
- Theophylline, pentoxifylline
- Nitrofurantoin
- Antihistamine
- Vitamin A
- Ondansetron
- Octreotide
- Dipyridamole
- Bromocriptine
- Amantadine
- Acetazolamide
- Clofibrate
- Chloroquine

The manifestations of migraine are different in the elderly. Associated symptoms like photophobia, phonophobia, nausea, vomiting, and pulsatility are less frequent. The headache is usually bilateral or generalized although it is often felt in the occipital region and neck. Some patients may also suffer from other symptoms like rhinorrhea and epiphora. Moreover, premonitory symptoms are common in the elderly, including anorexia, paleness, dry mouth, etc. Migraine headaches are less intense in older people and they can undertake their daily activities during migraine attacks. However, the headache worsens during menopause or years preceding it when there are hormonal changes. Young people suffering from migraine with aura may experience migraine without aura in advanced ages [28] although migraine

Table 11.3 Migraine aura without a headache.

(1)	Visual symptoms (blindness) homonymous hemianopia, blurred vision, difficulty focusing
(2)	Visual symptoms and paresthesia
(3)	Visual symptoms and speech disturbances (aphasia and/or dysarthria)
(4)	Visual and brainstem symptoms
(5)	Visual symptoms, paresthesia, and speech disturbances
(6)	Visual symptoms, paresthesia, speech disturbances and paresis
(7)	Only nonvisual accompaniments (paresthesia, speech disturbances, etc.)
(8)	Recurrence of old stroke deficits
(9)	Miscellaneous

aura without a headache is also common. Visual aura is the most common migraine aura without headache, and sensory and aphasic auras are less frequent. Motor auras are very rare and vascular events should be investigated if they develop. Migraine aura without headache is divided to nine groups in the elderly (Table 11.3). The main characteristics for detection of these auras include a short duration of 15–25 min and a benign course without leaving sequelae. Moreover, gradual worsening of neurological symptoms, a positive history of these symptoms together with severe headaches, and a history of attacks in the past assist in diagnosis. Angiography may be normal, and other causes like polycythemia, venous sinus thrombosis, embolism, seizures, hyper viscosity syndrome, subclavian steal syndrome, and arterial dissection should be ruled out.

Differential diagnosis of migraine aura in the elderly: Table 11.4

- TIA, seizures: the most important [4,24,29–32] (Table 11.5).
- Cortical SAH: This nontraumatic and nonaneurysmal SAH produces transient clinical presentations in the elderly. A collection of these signs is known as a transient focal neurological episode, including positive ocular signs, sensory symptoms, stereotyped limb weakness, and speech disorders. CAA is the most common cause of cortical SAH in patients above 60 years. SWI and T2 MRI reveal hemorrhages resulting from CAA [4,33–36].

Migraine comorbidities

- Although no causal relationship has been found between migraine headache and vascular events, the incidence of cardiovascular events is higher in migraine patients [25,37–39].

Table 11.4 Migraine aura/TIA.

Migraine aura	TIA
- Visual - Positive visual phenomena - Involvement of both visual fields - Slowly moving from visual field - Average duration 15–60 min	- Negative symptoms (loss of vision) - Unilateral - Static - Average duration 3–10 min
- Sensory - Positive symptoms (paresthesia) - Cheiro-oral distribution (hand and face) - Sequential progression from one body part to another - Area involved first clears last - Repetitive attacks of identical nature - Average duration 20–30 min - Sequential progression from one modality to another (visual, sensory, speech)	- Negative symptoms (numbness) - Abrupt onset - Average duration 5–10 min - Unilateral paresis - Variable attacks - Symptoms appear and disappear simultaneously (sensory, motor) - Simultaneous appearance of symptom modalities and body parts - Involvement of oral and tongue is rare

Table 11.5 Migraine aura/seizure.

	Migraine aura	Seizure
Onset	Gradual build-up	Abrupt onset
Duration	5–30 min	1–3 min
Frequency	Rarely daily	Daily or frequent
Visual phenomena	Zig zag/fortification spectra	Small circular spot pattern (circle balls) Brightly colored (multicolored, mono chromatic, dichromatic)
Location	Starts near fovea and spreads peripherally	Starts in temporal hemifield and moves to central
Spreading	Slowly moves across visual field	Rapid movement to contralateral side
Scotoma	Common	Rare
Colored	Sometimes	Common

- A positive history of major depressive disorder at any age affects the occurrence of migraine headaches in advanced ages [25].
- Prospective studies have shown a significant association between vascular dementia and some types of migraine and nonmigraine headaches. Although there are white matter changes in migraine patients, there is

not enough evidence regarding the relationship between cognitive disorders and migraine [40,41].

- Although vestibular symptoms like dizziness, vertigo, and unsteadiness are more common in migraineurs, especially in advanced ages, assessment of the otovestibular system, vertebrobasilar circulation, and drug history is recommended in the elderly [42].

Diagnostic interventions

Since the prevalence of secondary headaches is higher in the elderly population, all elderly patients should undergo contrast-enhanced MRI (considering renal function).

Appropriate imaging techniques, including diffuse-weighted MRI, GRE T2-weighted MRI, and SWI, are necessary for evaluation of secondary causes like TIA, dissection, stroke, SAH, neoplasm, vascular malformations, seizure, etc.

Numerous studies have shown white matter changes in migraine patients. These changes are mostly seen in the frontal, limbic, and parietal lobe. White matter changes are also seen in 10%–15% of normal people and increase with age [43,44]. The odds of vascular risk factors like diabetes, hypertension, and hyperlipidemia are higher in elderly people, which may result in white matter changes in the form of small vessel disease.

MRA and Doppler sonography of the carotid artery are helpful for assessment of carotid and vertebral arteries (stenosis and dissection) when evaluating TIA. An EEG helps to diagnose or rule out seizures [45,46].

Treatment

Due to senile physiological and pathological changes, the metabolism and effects of the medicines change in the elderly population. The physiological changes in the digestive system include decreased acid production, delayed stomach emptying, decreased peristalsis, and metabolic changes in the intestinal wall. The hepatic blood flow reduces by about 40% and its volume and metabolism decrease. Some changes also occur in the renal system, including a 25% decrease in the GFR. Pathological processes like diabetes and hypertension are also common. These risk factors, in addition to their role in myocardial infarction and stroke, affect the hepatic and renal function as well.

Analgesics with fewer adverse effects, like acetaminophen, can be used in the acute phase. Acetaminophen has no drug interactions. Aspirin interacts with MTX, lithium, SSRI, and anticoagulants and should be administered with an antacid or PPI. It is better to stop MTX if aspirin is administered at doses exceeding 300 mg/day.

Triptans can be used in the step; however, ergotamine and triptans are not recommended in people with a history of cardiovascular problems. Attention should be paid that triptans interact with ergotamine, lithium, MAOIs, SSRIs, and propranolol. Medicines known to interact with ergotamine include triptans and beta-blockers (increased vasoconstriction).

NSAIDs should be avoided. Opioids are not advised in the elderly because of inducing drowsiness and cognitive impairment. Propoxyphene may cause ataxia and vertigo and tramadol may induce nausea, vomiting, and seizures.

Metoclopramide is contraindicated in patients suffering from Parkinson's disease or parkinsonism. It is not generally recommended due to causing restlessness and extrapyramidal symptoms. Domperidone, as a replacement for metoclopramide, has no effect on migraine pain control in the elderly.

Intravenous magnesium at a dose of 2 g given over 2 h is effective in controlling acute migraine attacks in the elderly. Inhaled metoprolol is also effective in controlling migraine with aura. The bioavailability of beta-blockers is higher in the elderly and therefore dose adjustment is required. Considering the effect of beta-blockers on diseases such as congestive heart failure, asthma, conductive disorders, and depression, they should be administered with caution.

Drugs known to interact with propranolol include verapamil, rizatriptan, diltiazem, theophylline, and diabetes medicines.

TCAs, especially amitriptyline, are effective in migraine prevention, but their adverse effects have restricted their use in the elderly. TCAs are contraindicated in cardiac arrhythmias, angle-closure glaucoma, and urinary retention. Nortriptyline is used in the elderly due to its fewer side effects although amitriptyline is a more effective analgesic.

The clearance of calcium channel blockers is lower in older people; as a result, they are susceptible to hypotension and bradycardia. Therefore, their dose should be adjusted in the elderly. Caution should be also exercised when using these drugs in patients suffering from congestive heart failure. Attention should be paid that concomitant use of verapamil and antiplatelets increases the risk of GI bleeding.

One study showed the effectiveness of Ginkgolide B in treating headache. Ginkgolide B is extracted from the leaves of Ginkgo biloba and acts as a modulator of NMDA receptors and inhibitor of PAF matrix metalloproteinases, which are involved in the progression of migraine headache.

Sodium valproate has more adverse effects in elderly people due to decreased hepatic blood flow, including impaired renal function, bone marrow suppression, decreased bone density, delirium, tremor, ataxia, extrapyramidal symptoms, and hair loss.

Topiramate is mainly used for maintenance therapy. The risk of adverse effects, including increased IOP, renal stones, weight loss, agitation, drowsiness, dizziness, etc., is higher in the elderly.

In general, acute migraine in the elderly is treated with acetaminophen in the first step and triptans in the next step. NSAIDs and ASA are recommended in special cases. Sodium valproate injection may be used to control acute migraine headaches. Lamotrigine is not effective in the treatment of headache but can control aura.

Beta-blockers, topiramate and sodium valproate, are the drugs of choice for maintenance treatment. Calcium channel blockers and nortriptyline are used in the next step. Botulinum toxin can be used for treatment of chronic migraine headache.

Tension headache

Tension headache is the most common type of headache in the elderly. Its prevalence increases with aging. Other causes of headache should be ruled out to make a diagnosis of tension headache.

The pain is mild to moderate in tension headache. It is usually bilateral and is often described as a constant pressure [21,24].

Hypnic headache

Hypnic headache is a rare primary headache that occurs in people aged 60 ± 10 years. According to the ICDH-II, it is a headache occurring after the age of 50 years but the age condition is removed in ICDH-III beta because of its occurrence in younger people and even children. Hypnic headache is three times as common in women as in men. Because it develops only during sleep, it is also known as alarm clock headache.

Hypnic headache usually occurs between 2 and 4 in the morning. It wakes the sufferer from sleep 1–2 times a night but there are reports of

up to six attacks. The second attack occurs after 4 a.m. This headache makes the patient restless, but not as much as cluster headache, while a patient suffering from migraine prefers to stay in bed and rest.

It is usually experienced as a dull pain but sharp, pulsating, stabbing, or even burning headaches may occur. It may be unilateral or bilateral. The pain is usually felt in the frontotemporal region. It lasts a short time, usually up to 1 hour, although there are reports of it lasting about 10 h. Some people experience nausea without vomiting. Hypnic headaches are not associated with symptoms of autonomic trigeminal syndrome. The mechanism of hypnic headache is still unclear, but studies suggest that the hypothalamus plays an important role in the onset of this headache [47].

Many people suffering from hypnic headaches have experienced other types of headaches as well. For example, one third of these patients have had migraine headaches at some point in their lives. There is one case report of hypnic headache comorbid with sexual headache, which both relieved when indomethacin was prescribed for hypnic headache [48].

Differential diagnosis

1. Migraine headache
2. Cluster headache
3. Paroxysmal hemicrania
4. Nocturnal arterial hypertension
5. Brain mass (especially posterior fossa tumors)
6. Drugs (there are reports of hypnic headache relief after discontinuation of ACEI)

Treatment

The headache relives with waking from sleep and standing up, and patients usually start an activity after waking, like reading or watching TV.

Since hypnic headaches are mild to moderate in most cases, they do not interfere with daily activities and resolve on their own; therefore, treatment is not very common in the acute phase. However, caffeine provides a more effective pain control than other drugs.

Since this headache can become chronic, prophylactic treatment seems necessary. Prophylactic treatment results in pain relief in about 50% of the cases (Table 11.6).

Table 11.6 Hypnic headache treatment.

Drug	Dose	Complication	Effectiveness (%)
Caffeine	A cup during headache		54–73
Indomethacin	25–150 mg/day	Due to their adverse effects, their use is restricted in the elderly	70
Melatonin	3–5 mg/day		36
Amitriptyline	10–100 mg/day	Due to their adverse effects, their use is restricted in the elderly	25
Topiramate	25–100 mg/day	- Depression - Cognitive deficit - Paresthesia - Weight less	45

Cough headache

Cough headaches are triggered by coughing and other types of straining—like the Valsalva maneuver. It is divided to two groups: primary cough headache and symptomatic cough headache.

In the **symptomatic** type, which is caused by a structural disorder, Arnold–Chiari malformation accounts for 40% of the cases. Other causes include occipital space occupying lesions, decreased ICP, noncommunicating hydrocephalus, and unilateral carotid artery (unilateral headache) [3,49]. Imaging studies are necessary to make a diagnosis. The age of onset is earlier than the primary type and the attacks last longer.

The prevalence of **primary** cough headache is about 1% and the mean age of the patients is 55 years [3]. It is usually bilateral and is felt in the frontotemporal region. The pain is moderate to severe and lasts for 30 s–2 h. It is more prevalent in men above 40 years and signs like photophobia, phonophobia, and nausea and vomiting are uncommon [49].

History is an important part of cough headache investigation. Drugs, especially those causing dry coughs, can trigger the headache, including goserelin, a GnRH agonist, and ACEIs like ramipril, perindopril, enalapril, lisinopril, and captopril.

Treatment

Primary cough headaches usually continue for 4 years (there are reports of 12 years, as well) and then resolve completely on their own. Treatment of the acute attacks is not recommended due to the short duration of pain. Maintenance treatment is started if attacks are frequent and disabling. Table 11.7 presents the drugs and their adverse effects.

Cluster headache

The age of onset of cluster headaches is not very clear. However, they usually start in the 3rd and 4th decades of life although they may occur at any age. 10% of the patients are above 60 years. It is more frequent in young men and elderly women. It may recur in the elderly after long years of remission.

A new-onset cluster headache in an elderly person should raise the suspicion of intracranial lesions and secondary causes, and imaging studies are necessary in this setting. Attention should be paid to drug adverse effects in the elderly.

Chronic daily headache

About 4% of the elderly population suffers from chronic daily headaches. They are more prevalent in women. Overmedication headache should be considered in these patients.

Table 11.7 Cough headache treatment.

Cough headache treatment		
1. Indomethacin	50–150 mg	Dyspepsia/peptic ulcer peripheral edema/hypernatremia, hyperkalemia, cardiac complication
2. Topiramate	50–100 mg	Cognitive deficit/…../anorexia
3. Methysergide	2 mg	Pleuritis/pericarditis Retroperitoneal fibrosis
4. Acetazolamide	375–2200 mg	Renal stone, dehydration, metabolic acidosis, paresthesia
5. Propranolol	120 mg	Hypotension Bradycardia
6. Naproxen	550-1100 mg	GI complaints
7. Metoclopramide	10 mg	Drowsiness Dizziness Fatigue Focal dystonia

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CHAPTER TWELVE

Headaches attributed to COVID-19 infection

Mansoureh Togha[1,2]
[1]Iranian Center of Neurological Research, Headache Department, Neuroscience Institute, Tehran, Iran, IRN
[2]Tehran University of Medical Sciences, Tehran, Iran, IRN

Introduction

Headache has been identified as a common neurologic manifestation of COVID-19 infection in several studies. The prevalence of headache among COVID-19 cases was found to be 25.2% according to a metaanalysis of 104,751 COVID-19 cases from 78 eligible studies [1].

The exact pathogenic mechanism of headache in COVID-19 infection is not clear. During the course of COVID-19, headaches have usually exhibited benign features and have even been counted as a good prognostic factor [2]. However, in some instances, headache could be the symptom of a serious complication.

Acute headache in patients affected by COVID-19 could be attributed to systemic viral infection, viral meningitis or encephalitis, noninfectious inflammatory intracranial disease, cough headache, hypoxia and/or hypercapnia, and increased cerebrospinal fluid (CSF) pressure. However, most COVID-19 headaches are benign and are not serious.

The worsening of COVID-19-related headaches has been found to be higher in patients with existing primary headache group disorders. High pain intensity more frequently afflicts younger males with moderate COVID-19 infections [3].

Most cases of headache are transient and improve along with the improvement of the systemic manifestations of the disease. However, in a subgroup of patients, the headaches may continue for several weeks. Migraineurs are more susceptible to developing headaches in the acute phase of COVID-19 infection and to experience a continuation of headache afterward. In a minority of patients, de novo headaches will develop after the disease.

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Development of headache has been observed to be significantly higher in dehydrated patients (defined as serum osmolality of more than 294 mOsm/kg) [4]. Therefore, monitoring of fluid requirements is essential. In one study on 172 patients with COVID-19-induced headache, a previous history of primary headache and dehydration was considered as risk factors for a higher frequency of headache. Fever and dehydration have also been associated with increased pain severity [4]. Another study found that headache prevalence was significantly higher in patients with gastrointestinal (GI) symptoms. The authors suggested that these headaches could be caused by fever and electrolyte imbalances in patients with GI manifestations [5].

Anosmia and ageusia have been reported more frequently in headache patients compared to patients without headache [6]. Involvement of the nasal cavity by the virus and irritation of the branches of the trigeminal nerves which innervate it could be responsible for headache in these patients. In one study, MRI showed evidence of transient olfactory bulb injury in patients with fever and headache, which could indicate the cause of anosmia with headache in these patients [7].

Headaches that occur early in the course of COVID-19 infection may be similar to influenza-type headache and usually will respond well to proper hydration, nonsteroid antiinflammatory drugs, or high-dose acetaminophen. However, the treatment should be continued for a few days after relief to prevent headache recurrence. In many patients, anxiety and concerns about the disease can also provoke or worsen a headache. With this in mind, it could be advisable to add an anxiolytic drug to analgesic mediation. As headache could also be a response to a fever from any cause [8], antipyretic therapy could improve headache symptoms.

A few days after the onset of COVID-19, the body's immune response to it and the accompanying cytokine release could lead to headaches that are more severe that those which can accompany the early course of the disease. Cytokines are involved in the modulation of the pain threshold and sensitization of the trigeminal nerve fibers [8–10]. In this scenario, a headache might become severe and may not respond to simple or combined analgesics. However, this type of headache usually ameliorates in line with an improvement of systemic manifestations.

Headache could be a symptom of a more serious problem, such as cerebral venous thrombosis (CVT) or subarachnoid hemorrhage. There is strong evidence of the possibility of hypercoagulability and vascular endothelial damage and serious vascular consequences of COVID-19. A headache could be a presenting or accompanying symptom of a rare manifestation of

meningitis or meningoencephalitis from COVID-19 infection, although other neurologic symptoms and signs should accompany or follow.

Treatment of headaches caused by serious problems should be directed toward the primary condition. Parenteral analgesics could be of help in patients with severe headaches. A headache in a later phase of COVID-19 may fulfill the criteria for intracranial hypertension; thus, corticosteroids could be helpful for a short period where no contraindications exist. Headache sometimes could be a response to the side effects of drugs used to treat COVID-19 patients.

In conclusion, headaches that accompany COVID-19 infection could have different causes. With the use of ICHD3 criteria, these headaches could be classified as "acute headache attributed to systemic viral infection," "headache attributed to viral meningitis or encephalitis," "headache attributed to other noninflammatory intracranial diseases," "secondary cough headache," "headache attributed to hypoxia and/or hypercapnia," "headache attributed to cranial or cervical vascular disorders," and "headache attributed to increased CSF pressure." It is important to differentiate between benign headaches and those from serious causes and manage them accordingly.

Unremitting headache after recovery

Studies have reported headaches enduring more than 1 month after recovery from COVID-19 infection [6,11]. In one cohort study, headache resolved in most patients within 1 month after recovery from COVID-19 and in the rest after 3 months. An increase in the severity of migraines was noticed more among females and those who had experienced more severe migraines before COVID-19 infection. Similarly, an increase in attack frequency was noted in patients who had experienced more frequent migraine attacks before infection [3]. This indicates that incidences of persistent headache for over 1 month after COVID recovery, both as new-onset or aggravation of a preexisting migraine, should not be underestimated [3].

Headache after vaccination for COVID-19

Headache has been reported to be among the most frequent adverse effects following COVID-19 immunization. Its incidence has been reported by approximately half of vaccine recipients both in clinical trials and from real-world data [12,13]. The headache typically presents within the first

72 h postvaccination and may be accompanied by fatigue, fever, myalgia, arthralgia, or diarrhea [12]. Although headache is a common symptom after vaccination, it typically presents and resolves within 1 day or a few days [14].

Headache is the most frequent symptom of CVT and it may be isolated or accompanied by other symptoms [13,15,16]. As in other secondary headache disorders, CVT can be recognized by the presence of red flags [14]. Delayed onset of headache following an adenovirus vector-based COVID-19 vaccine has been associated with CVT. Patients with new-onset headache within 1 week of vaccination with an adenovirus vector-based vaccine should receive a thorough clinical evaluation and CVT must be considered in the diagnostic work-up [14]. Diagnostic delay is common in CVT. Because prompt treatment likely will improve the clinical outcome, every physician must be aware of the potential risk of vaccine-related thrombotic complications [14].

The pathophysiology of thrombosis with thrombocytopenia syndrome has been recently discussed. The role of antiplatelet factor-4 antibodies seems causative and includes inducing platelet activation, aggregation, and thrombosis, leading to severe platelet consumption and thrombocytopenia. Evidence discussed in an interim guideline published by the World Health Organization (WHO) states that the treatment should include that for immune-mediated phenomenon and adequate anticoagulation. For the first, intravenous immunoglobulins are the preferred option, while nonheparin-based anticoagulants must be used. Heparin-based anticoagulants and platelet infusion should be avoided [17].

Headache in COVID-19 era caused by lifestyle changes

Aside from headache that is directly related to COVID-19 infection, during the pandemic and subsequent lockdowns, an increase in the number of patients complaining of headache with or without a previous history of migraine or tension-type headache has been reported.

Cervical muscle spasm as a cause of headache

One common trigger for headache is neck muscle spasm and the consequent cervical pain. This can be attributed to poor posture and increased screen time using electronic devices [4]. One study conducted on the work from home population during the COVID pandemic reported a 23.5% incidence of neck pain [18]. Neck pain is a common symptom of overuse of mobile phones and electronic devices [19]. It has also been shown that neck pain itself could trigger or be an accompanying symptom of primary headaches, including migraine [20].

External compression headache

According to ICHD3 criteria, external compression headache results from sustained compression of the pericranial soft tissues, for example, from use of a tight band around the head. This will occur within 1 hour of sustained external compression with maximum severity located at the site of external compression. It generally will resolve within 1 hour after the source of external compression is removed (ICHD3 [21]).

The mandatory use of masks in many societies can be a cause of headache in susceptible persons. This is especially an issue for health care providers who work in hospitals or clinics. Ong et al. [22] studied 158 workers who wore N95 face masks with or without eye protection in Singapore and reported that this type of headache was a complaint in 81.0% of workers. The location was bilateral in all participants and corresponded to the contact areas of the protection equipment. It manifested mainly as a sensation of heaviness and pressure and was less accompanied by pulsation (11.7%).

Headaches due to eye refractory errors

In persons with refractive error of one or both eyes, prolonged visual tasks may induce or aggravate headache. During the pandemic, many people spend more time using electronic devices in teleworking; thus, this type of headache can occur in individuals with preexisting refractory error [21].

Other causes

Stress and anxiety is caused by isolation or fear of COVID-19 infection, as well as emotional and economic problems secondary to loss of employment or a decrease in income. These, in addition to changes in dietary habits and irregular sleep hours, are the common causes that can aggravate the incidence of previous headache.

Suggestions for headache management

General considerations

Methods of mitigating the occurrence or increase in headache include publicizing information about headache triggers, encouragement of effective means of stress management, and maintaining correct posture when using electronic devices. Additional efforts should be to strive for a regular and sufficient sleep cycle, healthy diet, and regular physical activity. Stretching

exercises focusing on the neck and shoulder muscles as well as eye rest when working on electronic devices could be helpful in headache prevention. Access to physicians and health care providers and to medical and psychological consulting, especially by virtual routes, can be very effective in controlling headaches and preventing episodic headaches from becoming chronic ones.

An issue requiring attention is headache in medical staff. This occurs mainly as a consequence of increased work hours in highly stressful situations with the requirement of wearing personal protection equipment. All of these factors should be considered and addressed by management to maintain the welfare of the medical staff.

Drug therapy

There is no specifically approved drug for treatment during the acute phase of a headache, although one study recommended indomethacin [23]. Common NSAIDs also can be used without causing specific adverse effects for the disease. High-dose acetaminophen also could be effective.

For more serious headaches, symptomatic relief might be achieved by the transient use of opioids by parenteral or oral route; however, their abuse always is a concern and they should be used cautiously. Short-term corticosteroids at the lowest effective dosage in oral or intravenous form might be considered for severe headaches that are unresponsive to the previously mentioned drugs, especially during the cytokine release phase. It is essential to discuss the risks and benefits of any prescribed drug with the patient prior to its use [24].

For headaches that persist for more than a few weeks, prophylactic treatments might be needed for headaches that are frequent or bothersome. Such prophylactic drugs should be selected according to the headache type or by similarity of the headache to migraine, tension, or trigeminal autonomic cephalalgias types.

For those with a previous history of a primary headache and aggravation due to a trigger or stimulating factor, a change in dosage or the use of prophylactic drugs might be needed. In this case, physicians should strive to prevent patients from developing chronic or medication overuse headaches and promptly managing them if or when this occurs.

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CHAPTER THIRTEEN(A)

Approach to cervicogenic headache from the perspective of physical medicine

Mohaddeseh Azadvari
Physical Medicine and Rehabilitation, Sina Hospital, Tehran University of Medical Science, Tehran, Iran

Cervicogenic headache is less known than other types of headache like migraine and tension headache. A certain type of headache is seen in powerlifters and those with a history of whiplash injury that cannot be explained by common types of headache. Cervicogenic headache is a secondary headache caused by disorders in the cervical spine, including the bone, disc, and soft tissue, and is usually accompanied by neck pain [1,2].

It usually starts from the occipital region unilaterally and the pain is then referred to the scalp vertex, anterolateral part of the skull on the same side, forehead, and shoulder [3–5]. The symptoms may also involve the contralateral side [5], but the pain is more intense on the primary side of involvement [3]. The pain may be deep or stabbing. It is continuous or episodic with or without persistent pain.

The pain starts from the neck and migrates toward the head. The neck pain may be more severe initially, but headache will eventually be the chief complaint of the patient, masking the origin of the pain. It may last from hours to weeks. Complaints like photophobia, phonophobia, and nausea are less frequent than migraine attacks but may occur [6,7]. The patients may rarely experience vertigo, lightheadedness, and syncope-like episodes [6].

Cervicogenic pain may be aggravated by postural factors like inappropriate head position on the pillow (prone sleeping) or inappropriate neck position at work, even cold temperature, hormonal changes, nutrition, or mental factors may worsen cervicogenic headache.

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Epidemiology and pathophysiology

The prevalence of cervicogenic headache ranges from 0.4% to 2.5% in the general population and 36.2% in people with primary headaches. Women (79.1%) are affected more than men (20.9%). The mean age of the patients is 42.9 years and the mean duration of the symptoms is 6.8 years [8].

Different cervical structures like nerve roots and cervical nerves, dorsal root ganglions, uncovertebral (Luschka) joints, intervertebral disc, facet joints, ligaments, and muscles may be involved in cervicogenic headache. It may be caused by degenerative changes or direct trauma with or without underlying biomechanical factors. The zygophyseal joints of C2—C3 and cervical intervertebral discs are suggested as the primary causes of cervicogenic headache.

Trigeminal and afferent cervical branches from C2 and C3 converge in the trigeminocervical nucleus. The convergence of cervical afferents causes pain referral to occipital and auricular regions. Convergence with the first branch of the trigeminal afferents results in pain referral to the parietal, frontal, and orbital regions.

History and physical examination

In the patient's history, attention should be paid to previous head and neck traumas like whiplash injury that can cause injury to cervical zygophyseal joints, intervertebral discs, and nerve roots, predisposing to cervicogenic pain even years after the accident [9—11]. Another cause might be upper crossed syndrome, which is due to lack of balance between neck muscles; some muscles are short and tight and some other muscles are weak. Cervical flexors, rhomboid, and lower trapezius fibers are usually weak and SCM, upper trapezius fibers, and pectoralis major and minor are usually short and tight.

On physical examination, decreased ROM is usually seen due to muscle stiffness, osteoarthritic changes, and decreased flexibility of the soft tissue. To assess the weakness of cervical flexors, the patient is asked to assume the supine position and bend the neck forward. Under normal conditions, the patient can do it very easily, and as a result, cervical lordosis is decreased. If cervical flexors are weak, the patient cannot bend the neck, the chin is positioned upward, and the SCM becomes tightly contracted.

Besides examining the neck ROM and the strength of cervical flexors, cervical vertebrae and facet joints should be also assessed. If cervicogenic

headache is caused by pathologies in zygophyseal joints, the patient can usually show the point of maximum pain on one side of the neck with a finger or palm of the hand. The patient should be in the prone position and rest the forehead on the bed. The examination starts with palpation of spinous processes. The first spinous process that can be palpated prominently belongs to C2. The spinous processes of C7 and T1 can also be palpated easily. To differentiate, the patient is asked to turn his/her head sideways; if the spinous process has a palpable movement, it belongs to C7, and if it does not move or has little movement, it belongs to T1. The facet joints of cervical vertebrae are palpated 1.3–2.5 cm (0.5–1 in.) lateral to the spinous process. They will be painful on deep palpation if there is a pathological condition. Moreover, head and neck movements like axial rotation and neck extension will be painful if facet joints are involved.

If headache is caused by the involvement of the intervertebral disc, the pain starts in the midline and refers to the head and neck along the spine. A unilateral headache in the occipital region that is more intense than the concurrent neck pain indicates zygophyseal joint involvement [9,10].

The Spurling's maneuver is positive in disc protrusion causing pressure on nerve roots, but if zygophyseal joints are involved, the maneuver does not cause radicular pain to the upper extremities but worsens axial pain and pain near the zygophyseal joints. This pain is usually induced by deep palpation on the involved joints. Positive test Spurling's maneuver is reproduction of radicular symptoms distant from the neck with passive lateral flexion and compression of the head.

ICHD3 criteria for cervicogenic headache.

A. Any headache fulfilling criterion C
B. Clinical, laboratory, and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache
C. Evidence of causation demonstrated by at least two of the following:
  1. headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
  2. headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
  3. cervical range of motion is reduced and headache is made significantly worse by provocative manœuvres
  4. headache is abolished following diagnostic blockade of a cervical structure or its nerve supply
D. Not better accounted for by another ICHD-3 diagnosis.

Imaging studies

If there is a history of trauma or whiplash injury to the neck, cervical spine X-ray including anterior–posterior, lateral, flexion, and extension views are necessary to find any displacement. Moreover, an open mouth view of the cervical spine is required to see the odontoid process and rule out fractures [12]. If there is any suspicion of fracture, further assessment using multiplanar reformatted CT scan is essential [12]. MRI is better than CT scan in evaluating intervertebral disc injury. However, compared to discography, MRI has a false-positive rate of 51% and a false-negative rate of 27% in finding discography. Any finding during imaging studies should be compared against clinical signs because some findings are asymptomatic and imaging findings causing clinical signs are of importance [13–15].

Differential diagnosis

Different types of headache are on the list of differential diagnosis. Migraine headache usually starts from the frontal region and is associated with nausea and vomiting, while cervicogenic headache starts from behind the head, is rarely associated with nausea, and is not accompanied by vomiting. Tension headache is more diffuse than cervicogenic headache and its intensity is not increased with cervical movements. An important differential diagnosis is fibromyalgia, in which more than 50% of the patients suffer from headache in addition to other findings.

Treatment

Different treatments have been proposed based on the etiology of cervicogenic headache. Successful treatment confirms the diagnosis since clinical signs disappear. Different treatment options may be used:

- Noninvasive methods: medical treatment, physiotherapy modalities
- Invasive methods: greater occipital nerve block, epidural steroid injection, cervical muscle injection, etc.

NSAIDs are the most effective oral drugs in the treatment of cervicogenic headache. Medicines like morphine, ergotamine, sumatriptan, and supplemental oxygen therapy have no effect on this type of headache and lack of response to them is used for differential diagnosis.

Evidence supports the use of physical methods like transcutaneous electrical nerve stimulation, low-level laser, and cryotherapy. Stretching, mobilization, and massage are also effective.

Cervical manipulation by physical medicine and rehabilitation specialists is also a promising physical treatment. If done correctly, it can alleviate pain. Any mistake in this method worsens the patient's symptoms and local disorders and hinders other treatment methods. Therefore, the manipulation must be performed by a well-trained specialist.

If the patient has not improved after using the above drugs and physical methods, invasive procedures like greater occipital nerve block may be applied. A GON block starts with anesthetics (lidocaine, bupivacaine) and if a favorable response is achieved, a combination with corticosteroid is used for the following injections. Cervicogenic pain resulting from the involvement of zygophyseal joints may be confirmed and treated with diagnostic block. First, the C2−C3 joint is assessed with blocking the third occipital nerve; then, C1−C2 and C3−C4 joints are assessed [9]. If the headache is felt in the anterior part of the head or face, C4−C5 block should also be done [16]. Little evidence supports the benefits of botulinum toxin injection in the cervical muscles and occipital region. Recent studies have shown no difference between botulinum toxin and saline injection. If the patient is unresponsive, more invasive treatments like laminectomy, spinal stimulation, GON neurotomy, etc., may be used.

Rehabilitation

Rehabilitation starts along with medical therapy. Lifestyle modifications are of great importance, including corrected posture. The patient should stand straight up so that a hypothetical vertical line drawn from the auricle crossed the midclavicle. Sleep posture is also very important. Attention should be paid to correct use of the cell phone and computer and ergonomic factors at the workplace. Stretching exercises should be started for short muscles like the SCM, upper Trapezius muscle fibers, and pectoralis major and minor. Weak muscles like the deltoid muscle, rhomboids, and lower Trapezius muscle fibers should be strengthened. Use of relaxation and stress management techniques is also beneficial.

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CHAPTER THIRTEEN(B)

Headache and exercise

Maryam Abolhasani
Sports Medicine Department, Tehran University of Medical Sciences, Tehran, Iran

Introduction

Many studies have shown the benefits of nonpharmacological treatments like exercise in the management of headache. It has been reported that regular moderate exercise causes muscle relaxation, improves cardiovascular fitness, and decreases the intensity, duration, and frequency of headache attacks [1].

Exercise is a subset of physical activity that is planned, purposeful, structured, and repetitive with the aim of improving or maintaining physical fitness. Its specific types include aerobic (endurance) exercise, anaerobic (strength) exercise, and flexibility exercise.

Endurance exercise describes activities with longer durations involving large muscle groups with the objective of improving the oxygen transport system in the body, like running, cardio exercises, walking, etc.

Strength exercise involves shorter durations of physical activity with the aim of increasing muscle strength. The exercise usually focuses on a certain muscle or group of muscles. Weightlifting, sprinting, and polymetrics are some examples of strength exercise.

Flexibility exercise improves the flexibility, range of motion of joints, coordination between muscles, and relaxation. Some examples of flexibility exercise include yoga and stretches [2].

On the other hand, some studies have shown that exercise worsens the headache in 22% of migraine patients, which may be the reason why these patients avoid exercise. According to the literature, migraine sufferers have less physical activity than people without headache [3].

Theories explaining the mechanism of the effect of exercise on headache include decreased peripheral sensitivity, activation of descending inhibitory pathways, a stable increase in the serotonin level, and modulation of the response of the sympathetic and parasympathetic systems to stress [3–5].

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According to a systematic review of the effect of exercise on migraine headache, most of the studies did not report a marked reduction of headache attacks or duration and only found a reduction in pain intensity in migraine patients following regular exercise [6].

The literature lacks adequate evidence as to how headache patients should perform structured exercise, especially aerobic exercise, and the parameters of intensity, frequency, and duration are similar in headache patients and healthy people. Regular aerobic exercise has many benefits for migraine patients, including increased production of endorphins or NO level changes during aerobic exercise. However, controlled studies are required to determine the exact intensity and frequency of these exercises [1–9].

According to CDC (Center for Disease Control and Prevention) recommendations, adults should do at least 150 min a week of intermediate-intensity aerobic activity. In addition, adults should do muscle-strengthening activities two or more days a week using weightlifting or using a resistance band. Moreover, flexibility exercises, like yoga, should be added to the exercise program.

Yoga and other stretching exercises can help to reduce tension and spasm in the head, neck, and shoulder muscles. These exercises are very important because increased muscle tension and spasm worsen headache symptoms. Furthermore, yoga reduces stress as well. However, recommendations should be individualized according the capabilities of each person [10].

The recommended level of aerobic activity for migraine prevention is 30–60 min of regular (3–5 days a week) moderate-to-vigorous intensity exercise (50%–80% of maximum heart rate or Borg Perceived Exertion rating (PRE) of 11–14). The duration of each exercise session can be divided to bouts of at least 10 min in duration according the person's conditions [11,12]. The benefits of exercise in headache, in addition to reduced pain intensity, include a physical and mental feeling of well-being, decreased sensitivity to pain due to release of endorphins, and improved sleep pattern [6].

Other helpful exercises to relieve headaches

The following exercises should be added to aerobic activities to achieve further improvement [12,13]:

- Posture correction [14–16].

Postural dysfunction or poor posture can place an additional burden on the head, neck, and shoulder muscles, which may result in migraine or tension headache. Maintenance of a correct posture at rest or during physical activity may reduce the frequency of migraine headaches: the shoulders should be kept back, ears should be aligned with the shoulder, and the highest point of the head (vertex) should have a slope toward the ceiling (Fig. 13b.1).

Poor posture may result in sleep disturbances, fatigue even after a good night's sleep, recurrent headaches, numbness in hands and feet, body stiffness, lethargy, difficulty waking up, irritability, and major depression.

The following are some useful recommendations for the patients to have proper postures (Figs. 13b.4 and 13b.5):

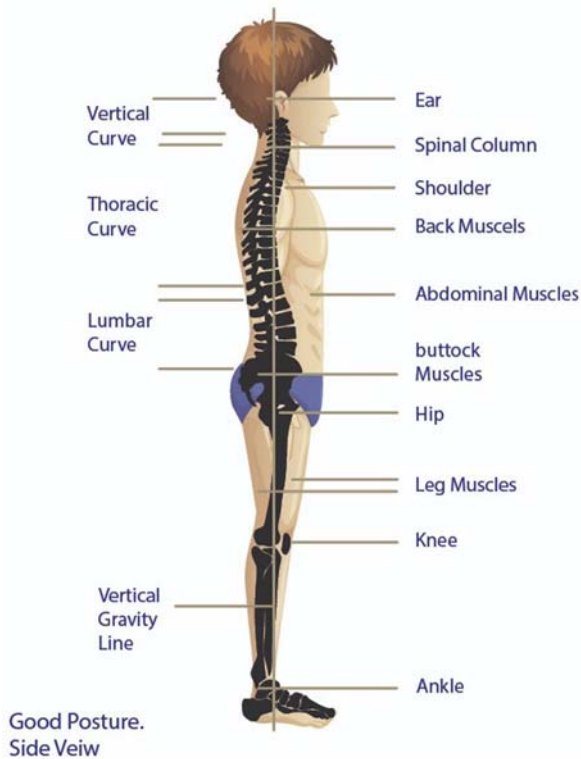


Figure 13b.1 The correct posture.

Wall test

The wall test is the first test to make sure of a correct body posture. This test can be done using any wall in the room. You stand against the wall with your feet about 15 cm away and have your head, shoulders, and buttocks touch the wall. Place your hand between your lower back and the wall and then again between your neck and the wall. If the distance is 2.5–5 cm in the lower back and 5 cm in the neck, you are close to having ideal shape; otherwise, see a specialist.

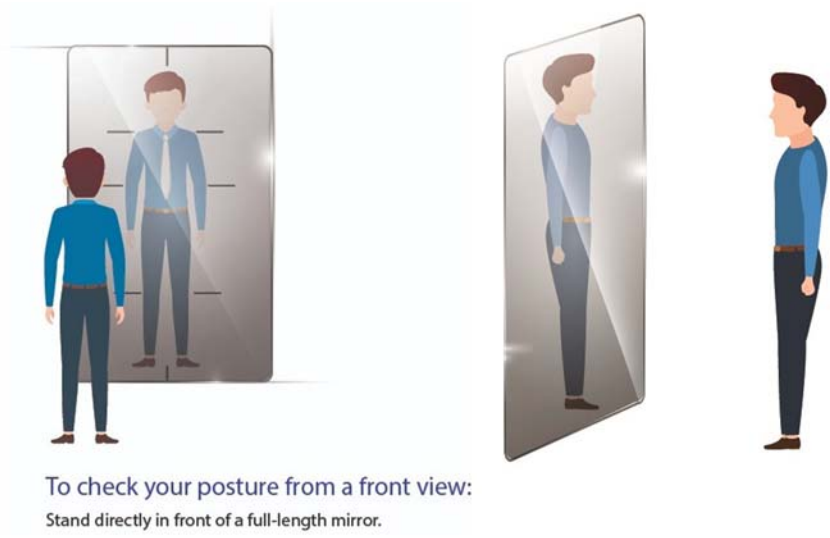
Mirror test

Front view: Stand facing a full-length mirror and check to see if your shoulders are level, your head is straight, your hips are level, your kneecaps face straight ahead, the spaces between your arms and sides seem equal, and your ankles are straight.

Side view: Ask a friend to check if your head is erect, not slumping forward or backwards, you chin is parallel to the floor, not tilting up or down, your stomach is flat, and your knees are straight (Fig. 13b.2).

Correct posture while working on the computer (Fig. 13b.3)

1. Leave the computer desk from time to time, stand up and do some shoulder rolls, neck rolls, or twists. Move and stretch your neck, arms, wrists, and feet slowly.
2. Place your monitor in such a way that the top of your screen is eye level while sitting up straight and the spine is straight.
3. The distance between the monitor and your eyes should not be more than 50–60 cm.
4. Every 30 min, look at an object at least 6 m away for a few minutes.
5. A standard computer desk measures 66–71 cm high.
6. Use an ergonomic footrest to support your feet.
7. The computer desk should be placed between rows of lights. Bright light directly behind the screen can cause eyestrain. When using natural light, the display should be perpendicular to the natural light source.



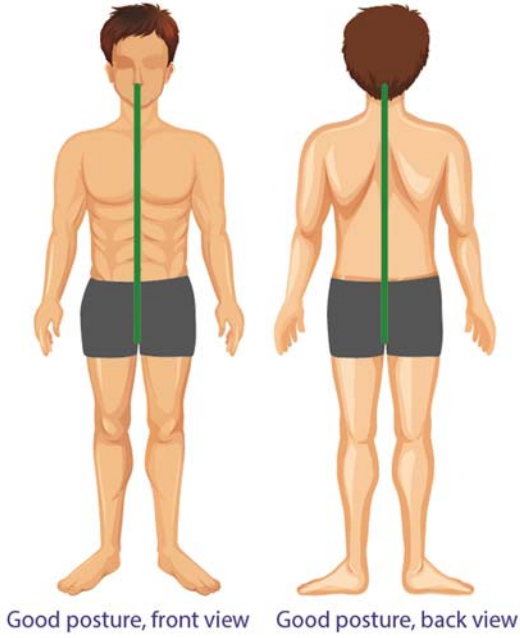


Figure 13b.2 Good posture views.

Figure 13b.3 Good sitting posture.

8. The keyboard and mouse should be placed at elbow height and the wrists should not be bent up or down while typing. The forearms should be roughly parallel to the floor, and the angle between the wrist and forearm should not exceed 5—10 degrees. A footrest provides support for feet.
9. The room should be illuminated with a mixture of yellow and white light at an intensity of 300 lux.

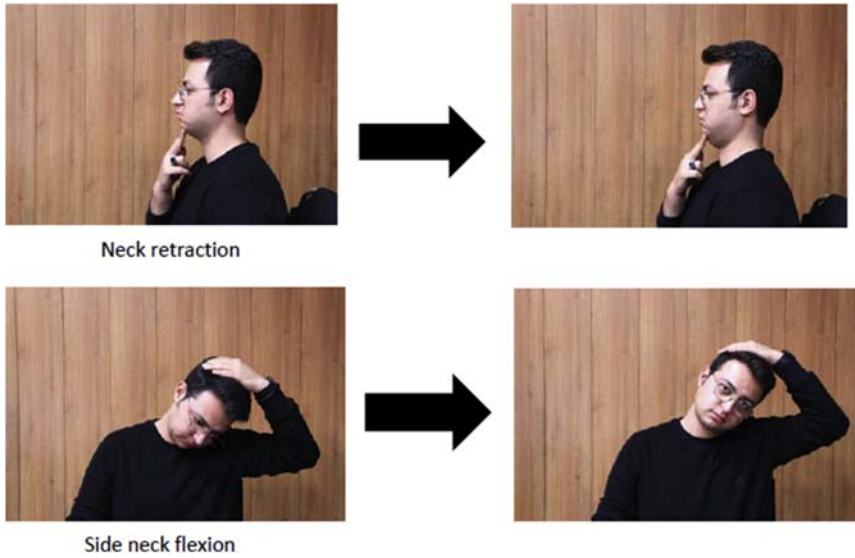


Figure 13b.4 Exercises for neck posture correction.

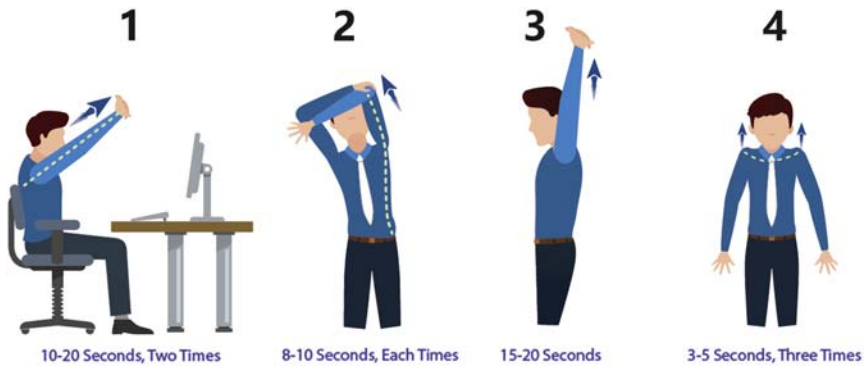


Figure 13b.5 Exercises while working on the computer.

10. To minimize pressure on the neck and back while typing, it is necessary to use a document holder.
11. The room temperature should be maintained between 19 and 23°C and the ideal humidity level is around 50%.
12. It is recommended to ventilate the room air regularly by opening the windows or using a ventilation system.

Some exercises for neck posture correction

The following exercises are recommended to prevent musculoskeletal pains in the head and neck while working on the computer:

Five simple exercises to relieve headaches [17]

Chin tuck stretch or neck retraction

Bend your head forward gently and press your chin against your chest with one hand until you start to feel a stretch at the back of the neck. Hold this position for 30 s and repeat 4 times (Fig. 13b.6).

Cervical extensor stretch

To further stretch these tight muscles at the skull base, bend the head forwards and turn it about 20–30° to one side. If you turn your head to the left, use the right hand to gently tilt the head forward. The right hand should hold the skull base to feel the stretch underneath your fingers. Hold the stretch for 5–10 s. Then, turn the head 20–30° to the opposite side, and use the other hand. Hold this position for 20 s. Repeat 4 times (Fig. 13b.7).

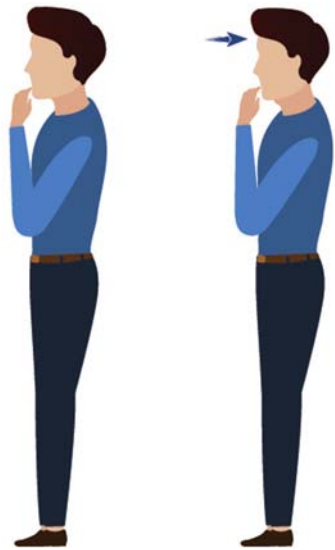


Figure 13b.6 Chin tuck stretch or neck retraction.

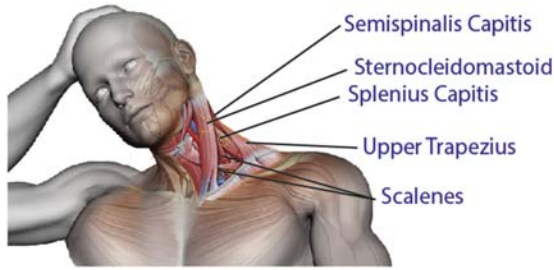


Figure 13b.7 Cervical extensor stretch.

Lateral flexion exercise

Sitting on your left hand, place your right hand over your head to touch your left ear. Gently pull your head to the right (you should feel a stretch down the left side of your neck toward the shoulder). Hold for 30 s. Repeat 4 times each side (Fig. 13b.8).

Figure 13b.8 Lateral flexion exercise.

Cervical rotation

Turn your head to the left to look over your shoulder as far as possible. Hold for 20 s, then turn to the right and hold and repeat. Repeat 4 times each side (Fig. 13b.9).

Figure 13b.9 Cervical rotation exercise.

Shoulder rolls

Use light weights (0.5—1 kg) in both hands. Gently roll both your shoulders forwards and downwards 10 times, then roll them backwards and upwards 10 times (Fig. 13b.10).

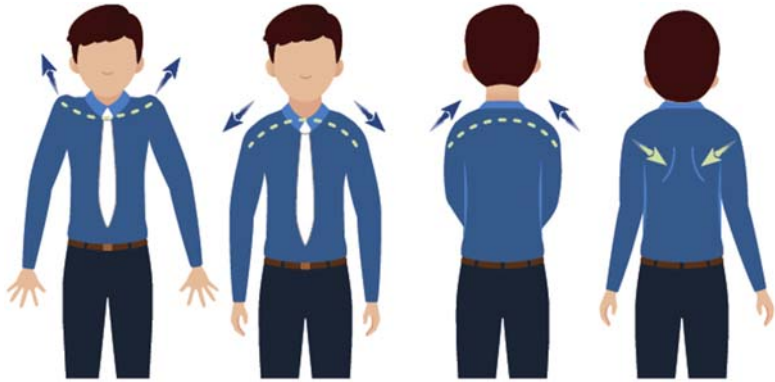


Figure 13b.10 Shoulder rolls exercise.

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CHAPTER FOURTEEN

Role of diet, food, and nutrition in prevention and treatment of headache

Soodeh Razeghi Jahromi[1,2]
[1]Department of Clinical Nutrition and Dietetics, Faculty of Nutrition and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Headache Department, Iranian Center of Neurological Research, Neuroscience Institute, Tehran, Iran

Introduction

Complementary and alternative medicines [1] are commonly used by patients with primary headache. Dietary recommendations are among the most popular CAM. The results of a study performed in the United States of America showed that 84% of the patients with headache used CAM [2]. There is a marked gap between the prevalence of CAM utilization and the number of well-designed studies in this field. Available evidence-based suggestions are not yet sufficiently studied to be supported by the majority of the medical organizations [3]. The dietary interventions that have been studied in patients with headache can be categorized into four categories:

Weight management

Both general and abdominal obesity increase the risk of more severe and frequent headaches [4–6]. Obesity is considered as an independent risk factor for migraine progression from episodic to chronic [7]. Relative to a BMI of 20, mild obesity (BMI of 30) was associated with roughly a 35% increase in the odds for experiencing headache, whereas severe obesity (BMI of 40) was associated with roughly an 80% increase in odds [8]. The contribution of obesity to worsening of migraine has potential biological causes. Several proinflammatory markers, including different cytokines [9], calcitonin gene–related peptide [9], leptin, and adiponectin [10] have fundamental roles in obesity and have recently been linked to migraine pain. Obesity and migraine also have other shared pathological features. As an example, an increase in neuropeptide Y is associated with abdominal obesity [11]

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and is reported during migraine attacks [12]. Moreover, male obesity correlates with an increase in the plasma insulin level. Recent studies have shown that the insulin level is also higher in migraineurs [13]. Weight loss through bariatric surgery [9,14] or lifestyle modification (diet, exercise, and cognitive-behavioral therapy) improved migraine attacks in adults [15], adolescents [16], and pediatric patients [17] in most studies.

Behavioral programming has modest effects on controlling migraine symptoms compared to weight loss surgery [15]. However, according to the promising results of the majority of the studies, the mainstay of treatment has to be diet and exercise.

For obese patients with a BMI of 27−30 and two risk factors or a BMI of 30−35 with or without risk factors, weight loss drugs are recommended beside lifestyle modification (Appendix 1) [18]. The choice of weight loss agents includes orlistat, liraglutide, lorcaserin, phentermine-topiramate, bupropion-naltrexone, or bulking agents, if not contraindicated [18]. SSRIs are weight neutral. However, patients receiving fluoxetine (60 mg/day) demonstrate an initial weight loss of up to 2−4 kg on average. However, weight regain occurs despite continued medication such that no difference is noted between fluoxetine and placebo over periods of up to 1 year [18]. Metformin does not produce enough weight loss (5%) to be qualified as a "weight loss drug." However, it would appear to be a very useful choice for overweight individuals at high risk for diabetes [18]. Obese patients receiving liraglutide have a greater weight loss. A number of other methods used for the treatment of headache, such as vagus nerve stimulation and vagotomy, are also effective in the management of obesity [19,20]. Surgical management is indicated in morbid obesity (body mass index>40 or >35 with one or more comorbidities) [15].

Specific food/nutrient avoidance

Elimination diet

Dietary triggers are a well-defined phenomenon in migraine. Several studies have investigated a number of dietary eliminations in migraine treatment. However, most of them were retrospective studies that used self-reported data and do not resulted in a generalizable recommendation [3]. The results of studies investigating the effect of oligoantigenic diet (Appendix 1) [21], vasoactive amine−restricted diet [21], and histamine-free diet [22,23] on headache control are heterogeneous. An alternate explanation for considering a food as a trigger is hypothalamic activity during the preictal phase of a migraine attack, suggesting a biological underpinning for the observed

food cravings during this phase. If these cravings encourage individuals to consume foods they may not otherwise eat (i.e., chocolate), this connection might explain why patients associate specific and infrequently eaten foods with migraine attacks [3]. Avoiding the consumption of suspected food triggers without evidence would result in needless restrictive diets. Unintended consequences of restrictive diets include nutrient deficiency and added demands on stress, anxiety, and executive function [3]. Different antibody tests have been used for immunologically targeting foods. Measurement of the IgG antibodies might be the most promising way to recommend elimination diet [3]. Overall, there is limited and controversial evidence about elemental diets. Likewise, caffeine is still a matter of debate. But according to the Mayo Clinic, daily limit to 400 mg is suggested. The most important factor regarding caffeine is consistency as to avoid it as a headache trigger. To date, it has not been established whether caffeine is either cure or cause of migraine attacks. There are many triggers for migraine, including dehydration, stress, lack of sleep, and fatigue. Therefore, caffeine withdrawal, that could produce many of the mentioned symptoms, might cause more frequent migraine headache. Caffeine also can contribute to urinary loss of magnesium. Results of a study showed that consuming three or more caffeinated beverages a day is associated with more headache days [24]. Tables 14.1 and 14.2 presented the foods which should be avoided in vasoactive amine-restricted and a histamine-free diet, respectively.

Sodium intake restriction

Cross-sectional studies have shown a link between hypertension and headache [25]. Furthermore, angiotensin converting enzyme inhibitors and angiotensin II receptor blockers are used as migraine prophylactic agents [25]. Low-sodium diets have a confirmed role in reducing the blood pressure [26]. Moreover, monosodium glutamate is a well-known headache trigger in some patients [26]. Low sodium diet (1150 mg/day) has been shown to be beneficial in reducing the risk of headache [27].

Table 14.1 Foods that should be excluded in a vasoactive amine-restricted diet.

Chocolate
Cheese and yogurt
Citrus fruits and citrus juice, banana, pineapple, raspberry, plum, pear
Pea, broad bean, avocado, squash
Shellfish
Smoked, pickled fish

Table 14.2 Food items that should be avoided in a histamine-free diet.

Fish	Tuna, Anchovy, Mackerel, Sardine
Cheese	Gouda, Roquefort, Tilsiter, Emmental, Harzer cheese, Camembert, Cheddar
Hard cured sausages	Salami, Dried ham
Vegetables	Spinach, Tomatoes (Ketchup), Pickled cabbage
Alcoholic beverages	White wine, Red wine, Bear, Sparkling wine

Dietary patterns

Many studies have been performed on changing the ratio of macronutrients in a diet (low carbohydrate/ketogenic diet, low carbohydrate/moderate fat intake, and low-fat diet) [3,21]. Prostaglandins play a role in trigeminal pain pathways. Intravenous administration of PGI2 and PGE2 induces migraine [28]. The amount and the composition of the consumed fatty acids affect the prostaglandin synthesis. Two studies evaluated the effect of treatment with low-fat diets on migraine prophylaxis. A quasiexperimental study limited the fat intake of adult migraineurs to 20 g/day for 12 weeks. The data showed a marked reduction in the headache intensity, frequency, and use of abortive headache drugs [29]. In an open-label, randomized, cross-over trial, a low-fat vegan diet in addition to removing trigger foods for 16 weeks improved headache in adult migraineurs [30]. Both of the above trials also reported weight loss in the fat-restricted group. Therefore, it is still unclear as to whether or not fat restriction can be effective in treatment of primary migraine. In one study, a group of adult patients with chronic headache was randomly assigned to dietary interventions, including a reduction of omega-6 fatty acids or a reduction of omega-6 fatty acids plus an increase in omega-3 fatty acids, for 12 weeks. The patients who received the low omega-6 and high omega-3 diet experienced more improvement in their headaches compared to individuals on the reduced omega-6 diet [31].

Omega-6 fatty acids are mainly found in the cell membrane of land animals; therefore, red meat, poultry, and animal fat are rich sources of omega-6 fatty acids. Omega-3 fatty acids are found in marine animals.

Most vegetable oils, especially safflower, corn, soybean, and cottonseed oil, are rich in omega-3 fatty acids. Soybean oil, canola oil, walnut oil, wheat germ oil, and flaxseed oil are also rich in omega-3 fatty acids [32].

Many of the migraineurs whose headaches are triggered with foods have a strong reaction to sugar-containing foods and beverages [33]. Different studies have assessed insulin sensitivity and glucose tolerance in migraineurs.

In a study of 74 migraine sufferers who associated their attacks to the mid-morning or mid-afternoon fasting state, patients performed a 5-hour, 100 g glucose tolerance test. The glucose tolerance curves of six patients were classified as diabetic and 56 patients exhibited a curve consistent with degrees of reactive hypoglycemia, i.e., a serum glucose level of less than 65 mg/L or a drop of 75 mg/L within 1 hour. Following dietary therapy with a low sucrose, six-meal regimen, all patients who had a diabetic glucose tolerance curve showed an improvement of greater than 75%, and three were headache free. Moreover, of the 56 patients with reactive hypoglycemia curves, 43 returned for follow-up after dietary instruction. Of these 43 patients with reactive hypoglycemia curves who returned for follow-up, 63% showed more than 75% improvement, 40% showed 50%–75% improvement, and 9% showed 25%–50% improvement [34]. Some other studies have also reported insulin sensitivity impairment in migraineurs [35,36].

Supplementation

Vitamin B groups

A case series, a number of open-label studies, and one RCT assessed the effect of vitamin B_2 in migraine prophylaxis based on the role of this vitamin in mitochondrial bioenergetics [26]. The RCT showed that vitamin B_2 was effective in migraine prophylaxis compared to placebo in adult migraineurs [37]. In another study, vitamin B_2 administration for 3 and 6 months had comparable effects with propranolol in adult migraine prophylaxis [38]. Current evidence suggests that vitamin B_2 (100–400 mg/day) is well tolerated and effective in migraine prophylaxis for adults [26]. A number of studies have evaluated the effect of vitamin B_2 in pediatric migraine, but the results are controversial [26]. Studies also point to the beneficial effects of other B vitamins. Daily supplementation with 2 mg of folic acid, 25 mg vitamin B_6, and 400 mcg of vitamin B_{12} for 6 months was reported to have favorable effect in reducing intensity and duration of migraine attacks [39,40]. In another study, a significant decrease in severity and frequency of migraine headaches was observed in individuals who received 80 mg pyridoxine plus 5 mg folic acid for 3 months, but not folic acid alone [41]. Folate, cobalamin, and pyridoxine are three necessary factors in homocysteine metabolism. Hyperhomocysteinemia can cause endothelial impairments by increasing the release of nitric oxide (NO). This, in turn, can be involved in initiation and maintenance of migraine headache, due to the role of NO in pain generation and inflammation [42].

Magnesium

Magnesium has received considerable attention in headache therapy. Magnesium is a cofactor of about 300 enzymes [43]. Magnesium deficiency has been linked to hyper excitability of the nervous system, cortical spread depression, neurotransmitter release, platelet aggregation, vasoconstriction, and substance P release [44]. A recent metaanalysis was performed on four RCTs about the efficacy of intravenous magnesium for migraine relief in adults. Of four recruited studies, one small trial reported the superiority of magnesium over placebo, two showed no difference between placebo and magnesium, and one indicated the superiority of placebo over magnesium. The authors concluded that intravenous magnesium is not likely to be effective for acute migraine improvement [45].

Oral magnesium (different doses and different compositions) has been assessed for pediatric and adult migraine prophylaxis. In a group of women with low magnesium levels, magnesium was effective for menstrual migraine prophylaxis compared to placebo. Three RCTs showed oral magnesium was effective for migraine prophylaxis in adults [26]. The American Academy of Neurology guidelines indicates that magnesium is likely to be effective for migraine prophylaxis in adults [46]. Three studies evaluated the role of magnesium in pediatric migraine prophylaxis [26], of which two reported the superiority of magnesium over placebo and one reported the synergistic effect of magnesium and acetaminophen/ibuprofen on acute headache relief. Moreover, magnesium has been shown to reduce the frequency of migraine attacks [26].

Probiotics

The submucosal plexus, ganglia belonging to the ENS, is found in the submucosa layer and provides the chance for the microbiota to affect migraine by influencing the cross-talk between the CNS and ENS through the gut—brain axis. Gut microbiota affect human health in different ways, including [1] facilitating the absorption of several nutrient [2], defending against the colonization of pathogens in the gut [3], guiding the host immune system function, and [4] modulating neuronal functions. The above actions of the gut microbiota might affect the CNS through metabolic, immunological, neural, and endocrine pathways. Intestinal microbiota are affected by several factors, including genetics, diseases, environment, medication use, and diet. Between single dietary items, low saturated fat intake and avoiding overconsumption [47], adequate fiber (esp. trying to have high-fiber diet as shown in Table 14.3), and vitamin D intake are necessary for preserving

Table 14.3 Guidelines for high-fiber diets.

1. Consuming: 6–11 servings of whole-grain cereals, breads, and other products like wheat and barley bulgur per day (each serving is about 30 grams)
2. Consuming 5–8 servings of legumes, vegetables, nuts, edible seeds, and fruits per day (each serving is about a glass of raw or half a glass of cooked vegetables, a medium size fruit, or 30 grams of nuts and edible seeds)
3. Try to bring fiber intake to 38 g/day in men and 25 g/day in women.
4. Increase fluid consumption to 2 L/day or more.

microbiota health. Two open-label trials and two RCTs studied the effect of probiotics on adult migraine and showed promising results. All studies in this filed documented an improvement in chronic and episodic migraine attacks. In one study, after administering a supplement containing multiple species (*Lactobacillus bulgaricus*, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, and *Enterococcus faecium*), multivitamin, bioactive peptides, and amino acids for 90 days, about 60% of the patients reported approximately total relief from migraine symptoms [48]. Further studies are required to justify the results of the above study.

Vitamin D

In recent years, a number of studies have focused on the role of vitamin D in headache/migraine prophylaxis. Observational studies reported that serum vitamin D level higher than 22.8 ng/mL might reduce the risk of headache [49]. Also, 22% reduction in migraine headache occurrence was achieved for every 5 ng/mL rise in serum vitamin D levels [5] and migraineurs have less VDR levels compared to healthy subjects [50]. Furthermore, reduction in vitamin D concentration is associated with more frequent headache days [51]. Daily dose of 2000–4000 IU vitamin D for 4–6 months was reported to reduce headache frequency and improve disability score in migraine sufferers, especially in those with aura [52]. Combination of 1000 IU vitamin D and 20 mg simvastatin reduced number of headache days [53]. Similarly, another combination therapy of vitamin D in three doses of 400, 800, and 5000 IU with amitriptyline for 6 months decreased the frequency of migraine attacks among children and adolescents with migraine [54]. The hypothesized mechanisms for the observed effect of vitamin D in headache control are modulating NO and PGE2 production, controlling the release of antiinflammatory agents such as IL-4, IL-5, and IL-10 through suppression of NF-KB expression, and reducing CGRP level [55].

Coenzyme Q10

Coenzyme Q10 (2,3 dimethoxy-5 methyl-6-decaprenyl benzoquinone) is known as a fundamental factor for the oxidative phosphorylation process and cellular bioenergetics in mitochondria through playing a role as a cofactor in the mitochondrial electron transport chain [56]. Coenzyme Q10 is hypothesized to have a probable role in migraine prevention and management, based on its antioxidants, antiinflammatory, and bioenergetics activities. Daily supplementation with 150 mg coenzyme Q10 for 3 months could diminish the number of days with migraine headaches by more than 50% [57]. In a clinical trial by Dahri et al. receiving 400 mg Q10 daily resulted in almost 50% reduction not only in frequency but also in intensity and duration of migraine attacks. To add, significant changes were observed in the serum levels of TNF-a and CGRP [58]. In a study by Dalla Volta et al., in addition to frequency and intensity, responses to trigger factors were also among the improvement that was followed by Q10 supplementation [59].

Conclusion

Current evidence supports the positive effects of weight reduction, increased consumption of whole grains, vegetables, fruits, and lean proteins (especially plant-based proteins and fish), sodium and fat restriction, supplementation with vitamin B groups, magnesium, vitamin D and prebiotics, CoQ10, and elimination of IgG-inducing trigger foods on primary headache prophylaxis. However, well-designed studies are needed before recommending these dietary interventions.

Appendix 1

Oligoantigenic diet

Foods given up/foods eaten frequently

This will be determined by individual test results. The oligoantigenic diet is initially implemented in five phases. Foods allowed in each phase are determined by the results of the Mediator Release Test, starting with the least reactive foods first. All foods in Phases 1 through 5 are low-reactive foods (indicated by a green bar on the test results).

During the five phases, it is strongly recommended that no untested foods or ingredients be consumed. Only tested foods that show a low/no reaction can be consumed during this time. The very lowest reactive foods

are started in Phase 1. Phase 1 is the most difficult phase since it is the time when food is most restricted. It is also the phase with the highest potential for symptom relief when the healing process begins. Phase 1 typically lasts 10–14 days, and Phase 2 may start when there has been significant symptom resolution.

When Phase 2 begins, one food at a time can be introduced. It may be best to add the new food and consume it multiple times over 3 days to make sure no reaction occurs. If not, this food is considered safe. It can take weeks to months to make it through all the phases. Generally, moderately reactive foods are strictly avoided for at least 3 months and highly reactive foods for at least 6 months before reintroducing. After the phases are completed, a rotation diet is recommended and guidance is provided. The rotation diet ensures that certain foods and food families are not overconsumed to the point that the person loses oral tolerance to those foods or food families. Oral tolerance is the ability to consume a food without it causing a hypersensitive or inflammatory response.

The dietitian helps with dietary planning and provides sample menus and recipes that teach the client/patient how to use the allowed ingredients together in creative ways. Daily food and symptom recording is required for success; therefore, the client should be committed to this before getting started.

Meal frequency and portion size

Three meals and two to three snacks are generally recommended. The diet is not a calorie-restricted diet and is balanced. Portioning should be sensible.

Supplements/vitamins

Ideally, no supplements are taken during Phase 1, and medications are researched by the oligoantigenic diet therapist for reactive ingredients. If reactive ingredients are found in medications, the oligoantigenic diet therapist, the client/patient, and the prescribing doctor should work together to find a suitable alternative or make a decision to continue the medication based on the clinical judgment of the prescribing doctor with input from the oligoantigenic diet therapist and the client/patient. The oligoantigenic diet therapist can help sort out what supplements are necessary to restart after Phase 1, if any, and can help find high-quality supplements that do not contain reaction-causing ingredients and excipients.

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HEADACHE AND MIGRAINE IN PRACTICE

EDITED BY
MANSOUREH TOGHA
ELHAM JAFARI

SEYED EHSAN MOHAMMADIANINEJAD
SAMANEH HAGHIGHI
HOSSEIN ANSARI

Headache and Migraine in Practice provides practical and precise approaches to the headaches and facial pains commonly encountered in hospitals and clinics. This book pays specific attention to the clinical features of headaches to present treatment solutions and recommends differential diagnoses based on ICHD3 diagnostic criteria. Topics developed by colleagues with expertise in Neurology, Nutrition, Psychiatry, Physical Medicine, and Sports Medicine provide collaborative authorship that adds interdisciplinary value. With the first section of this book devoted to dealing with a patient with a headache, distinct, practical chapters on diagnosis and treatment of various types of headaches in children, the elderly, and women during different periods of pregnancy, lactation, and hormone-related stages are all featured. This book is recommended for general practitioners, internists, neurologists, headache nurse specialists, and all others who would like to contribute to better diagnoses and more effective treatment of patients with headaches and facial pains.

Key features

- Provides practical guidance on the diagnosis and treatment of different primary and secondary headaches
- Includes classification of headaches according to latest international headache classifications
- Covers a variety of migraine and headache types, as well as disorders affecting cervical structures and cranial nerves

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