Migraine and Other Headache Disorders

edited by
Richard B. Lipton
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Migraine and Other Headache Disorders

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Preface

With this first edition of *Migraine and Other Headache Disorders*, we celebrate the remarkable progress in the art and science of headache during the last decade. With 32 chapters by 54 leaders in the field, the book provides health care professionals with practical approaches to patient care and reviews the scientific foundations of headache. We emphasize migraine because of its high prevalence, enormous burden, and the increasing availability of effective management strategies. At the same time, we provide broad coverage of all the primary headache disorders. Finally, although not focusing on specific subtypes of secondary headaches, we discuss strategies for diagnosing and excluding the ominous causes of headache, based both on clinical evaluation and, when appropriate, the use of diagnostic testing.

Our understanding of headache and the approach to treatment have been transformed by insights from many places. Based on the Second Edition of the International Classification of Headache Disorders, the book provides a series of diagnostic algorithms intended to simplify clinical practice. We also present up-to-date epidemiologic information on the primary headache disorders. Epidemiologic studies show that the overwhelming majority of headache sufferers who seek treatment in primary care settings have migraine. Diagnosis becomes more efficient when that fact is taken into account. Doctors should avoid oversimplifying the differential diagnosis of the primary headaches, however.

Our understanding of migraine as a disorder has significantly evolved over the past decade, based on genetic, epidemiologic, and translational studies. Once considered an episodic pain problem, treating the pain seemed like a sensible strategy. In the past few years, many lines of evidence have suggested that migraine and other headache disorders are best understood as chronic disorders with episodic manifestations. Painful episodes are the most prominent manifestation of migraine. Nonetheless, between attacks, there is an enduring predisposition to headache that characterizes the migraine brain. Furthermore, migraine is not only a chronic disorder with episodic manifestations, it is sometimes a disorder that progresses in several ways. Progression may be clinical, as attacks increase in frequency until chronic or transformed migraine develops. This clinical progression is sometimes accompanied by the development of allodynia with sensitization as its presumed substrate. In addition, in some individuals, morphological progression takes the form of deep white matter lesion or posterior circulation strokes that increase with migraine attack frequency, probably reflecting neuroplastic changes in the brain. Herein we highlight the emerging data on progression and on the modifiable risk factors for migraine progression.

Progress in treatment has also taken several forms. Since 1990, ten new acute treatments with a multiplicity of formulations and two preventive drugs have been

approved. Many studies show that acute treatments work best if given early in the attack. Combining acute treatments may improve treatment response in some individuals. In addition, recent epidemiologic data shows that, based on frequency and disability criteria, preventive treatment should be offered or considered in about 40% of migraine sufferers. The same studies show that only 12% currently receive preventive therapy. Preventive treatment decreases attack frequency and severity and possibly prevents migraine progression. The use of specific acute agents that act on the neural pathways of migraine pain, such as the triptans, dramatically improve patient outcomes.

Migraine and Other Headache Disorders highlights the treatment approaches developed at some of the best headache clinics in the world. It also reflects many of the strategies adopted at The Montefiore Headache Center. The Montefiore Headache Center was the first headache specialty care center in the world, founded in 1945 by Dr. Arnold Friedman, and it is where we are both proud to be.

We are extremely grateful to our mentors. Among them, Dr. Lipton wants to thank Dr. Seymour Solomon, who directed The Montefiore Headache Center for a quarter of a century, for being a wonderful mentor and teacher. He'd also like to thank his mentors and collaborators in research, particularly Drs. Philip Holzman, W. Allen Hauser, and Walter F. Stewart. Dr. Bigal wants to acknowledge Drs. Speciali and Bordini, from Brazil, and the teams at The New England Center for Headache (Rapoport, Sheftell, and Tepper) and at Montefiore (Lipton and Solomon) for their help and direction. We also want to thank the authors of the chapters in this book for their excellent work.

Finally, we owe special thanks to our families, particularly our wives (Amy Natkins Lipton and Janaína Maciel Bigal) and children (Lianna Lipton, Justin Lipton, Luísa Bigal, and Hanna Bigal) for supporting us through evenings and weekends spent writing and editing as we prepared this book.

Finally, to our readers, we hope this book furthers your efforts to improve the lives of headache sufferers. These common and disabling disorders are tremendously gratifying to treat. In a field where cures are rare, we can nonetheless help patients by empowering them with tools that relieve pain, restore their ability to function, and, perhaps, prevent disease progression.

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1
Headache—Classification

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INTRODUCTION

Headache is one of the most common symptoms in mankind (1,2). Given the range of disorders that present with headache, a systematic approach to headache classification and diagnosis is essential both for good clinical management and for useful research. The first edition of the International Classification of Headache Disorders (ICHD-1) (3) was the accepted standard for headache diagnosis, from its publication (1988) to the release of the ICHD-2 (2004) (4). It established uniform terminology and consistent operational diagnostic criteria for the entire range of headache disorders. It was translated into 22 languages, providing the basis for clinical trial guidelines for primary headaches (5).

Although the basic structure and most of the original categories are preserved in the ICHD-2, relative to the ICHD-1, there are many changes that will influence headache care and research. These changes include a restructuring of the criteria for migraine, new subclassification of tension-type headache (TTH), introduction of the concept of trigeminal autonomic cephalalgias (TACs), and addition of several previously unclassified types of primary headache.

In this chapter, we present an overview of the ICHD-2, highlighting the primary headache disorders and their diagnostic criteria. This chapter is complemented by Chapter 11, where we offer an algorithmic approach to primary headache diagnosis based on attack frequency and duration, using the ICHD-2. Details on diagnosis and treatment of primary headache disorders are discussed in specific chapters.

AN OVERVIEW OF THE ICHD-2

Like its predecessor, the ICHD-2 separates headaches into primary and secondary disorders (Table 1). The criteria for primary headaches are clinical and descriptive

Table 1 The ICHD-2 Classification: An Overview

1. Migraine
   1.1. Migraine without aura
   1.2. Migraine with aura
   1.3. Childhood periodic syndromes that are commonly precursors of migraine
   1.4. Retinal migraine
   1.5. Complications of migraine
   1.6. Probable migraine
2. TTH
   2.1. Infrequent episodic TTH
   2.2. Frequent episodic TTH
   2.3. Chronic TTH
   2.4. Probable TTH
3. CH and other trigeminal autonomic cephalalgias
   3.1. CH
   3.2. Paroxysmal hemicrania
   3.3. SUNCT
   3.4. Probable trigeminal autonomic cephalalgia
4. Other primary headaches
   4.1. Primary stabbing headache
   4.2. Primary cough headache
   4.3. Primary exertional headache
   4.4. Primary headache associated with sexual activity
   4.5. Hypnic headache
   4.6. Primary thunderclap headache
   4.7. Hemicrania continua
   4.8. NDPH
5. Headache attributed to head and/or neck trauma
   5.1. Acute post-traumatic headache
   5.2. Chronic post-traumatic headache
   5.3. Acute headache attributed to whiplash injury
   5.4. Chronic headache attributed to whiplash injury
   5.5. Headache attributed to traumatic intracranial hematoma
   5.6. Headache attributed to other head and/or neck traumata
   5.7. Postcraniotomy headache
6. Headache attributed to cranial or cervical vascular disorders
   6.1. Headache attributed to ischemic stroke and transient ischemic attack
   6.2. Headache attributed to nontraumatic intracranial hemorrhage
   6.3. Headache attributed to unruptured vascular malformations
   6.4. Headache attributed to arteritis
   6.5. Carotid or vertebral artery pain
   6.6. Headache attributed to CVT
   6.7. Headache attributed to other intracranial vascular disorders
7. Headache attributed to nonvascular intracranial disorder
   7.1. Headache attributed to high cerebrospinal fluid pressure
   7.2. Headache attributed to low cerebrospinal fluid pressure
   7.3. Headache attributed to noninfectious inflammatory disease
   7.4. Headache attributed to intracranial neoplasm
   7.5. Headache attributed to intrathecal injection
   7.6. Headache attributed to epileptic seizure
   7.7. Headache attributed to CM1

(*Continued*)

Table 1 The ICHD-2 Classification: An Overview (*Continued*)

- 7.8. Syndrome of transient HaNDL
- 7.9. Headache attributed to other nonvascular intracranial disorders

8. Headache attributed to a substance or its withdrawal
   - 8.1. Headache induced by acute substance use or exposure
   - 8.2. MOH
   - 8.3. Headache as an adverse event attributed to chronic medication
   - 8.4. Headache attributed to substance withdrawal
9. Headache attributed to infection
   - 9.1. Headache attributed to intracranial infection
   - 9.2. Headache attributed to systemic infection
   - 9.3. Headache attributed to HIV/AIDS
   - 9.4. Chronic postinfection headache
10. Headache attributed to disorder of homoeostasis
   - 10.1. Headache attributed to hypoxia and/or hypercapnia
   - 10.2. Dialysis headache
   - 10.3. Headache attributed to arterial hypertension
   - 10.4. Headache attributed to hypothyroidism
   - 10.5. Headache attributed to fasting
   - 10.6. Cardiac cephalalgia
   - 10.7. Headache attributed to other disorders of homoeostasis
11. Headache or facial pain attributed to disorders of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures
   - 11.1. Headache attributed to disorder of cranial bone
   - 11.2. Headache attributed to disorder of neck
   - 11.3. Headache attributed to disorder of eyes
   - 11.4. Headache attributed to disorder of ears
   - 11.5. Headache attributed to rhinosinusitis
   - 11.6. Headache attributed to disorders of teeth, jaws, or related structures
   - 11.7. Headache or facial pain attributed to TMJ disorder
   - 11.8. Headache attributed to other disorders of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structures
12. Headache attributed to psychiatric disorder
   - 12.1. Headache attributed to somatization disorder
   - 12.2. Headache attributed to psychotic disorder
13. Cranial neuralgias and central causes of facial pain
   - 13.1. Trigeminal neuralgia
   - 13.2. Glossopharyngeal neuralgia
   - 13.3. Nervus intermedius neuralgia
   - 13.4. Superior laryngeal neuralgia
   - 13.5. Nasociliary neuralgia
   - 13.6. Supraorbital neuralgia
   - 13.7. Other terminal branch neuralgias
   - 13.8. Occipital neuralgia
   - 13.9. Neck–tongue syndrome
   - 13.10. External compression headache
   - 13.11. Cold stimulus headache
   - 13.12. Constant pain caused by compression, irritation, or distortion of cranial nerves or upper cervical roots by structural lesions
   - 13.13. Optic neuritis
   - 13.14. Ocular diabetic neuropathy

(*Continued*)

Table 1 The ICHD-2 Classification: An Overview (*Continued*)

13.15. Head or facial pain attributable to herpes zoster
13.16. Tolosa–Hunt syndrome
13.17. Ophthalmoplegic "migraine"
13.18. Central causes of facial pain
13.19. Other cranial neuralgias or other centrally mediated facial pains
14. Other headaches, cranial neuralgias, and central or primary facial pain

Abbreviations: TTH, tension-type headache; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; NDPH, new daily-persistent headache; CVT, cerebral venous thrombosis; CM1, Chiari malformation type I; HaNDL, headache and neurological deficits with cerebrospinal fluid lymphocytosis; MOH, medication-overuse headache; TMJ, temporomandibular joint; ICHD, International Classification of Headache Disorders; CH, cluster headache.

and, with a few exceptions [i.e., familial hemiplegic migraine (FHM)], are based on headache features, not etiology. In contrast, secondary headaches are attributed to underlying disorders. The four categories of primary headaches are (i) migraine; (ii) TTH; (iii) cluster headache (CH) and other TACs; and (iv) other primary headaches. There are nine categories of secondary headache (against eight in the ICHD-1). Finally, there is a 14th category that includes headache not classifiable elsewhere (Table 1).

Key operational rules for the classification are summarized below, quoted or paraphrased from the ICHD-2 (4):

1. The classification is hierarchical, allowing diagnoses with varying degrees of specificity, using up to four digits for coding at subordinate levels. The first digit specifies the major diagnostic type, e.g., *migraine* (1.) The second digit indicates a subtype within the category, e.g., *migraine with aura* (1.2.). Subsequent digits permit more specific diagnosis for some subtypes of headache, e.g., *FHM*.
2. Patients should receive a diagnosis for each headache type or subtype they currently have (that is, have experienced within the last year). For example, the same patient may have *medication-overuse headache* (8.2.), *migraine without aura* (1.1.), and *frequent episodic TTH* (2.2.). Multiple diagnostic codes *should* be listed in their order of importance to the patient. This means that if a patient has four attacks of migraine without aura (1.1.) and eight attacks of frequent episodic TTH (2.2.) per month, but describes the migraine as being more incapacitating, the migraine diagnosis should be listed first.
3. For headaches that meet all but one of a set of diagnostic criteria, without fulfilling those of another headache disorder, there are "probable" subcategories, for example, *probable migraine* (1.6.) and *probable CH* (3.4.1.).
4. The diagnosis of any primary headache requires the exclusion, on clinical grounds or using subsidiary investigation, of any other disorder that might be the cause of the headache (i.e., of a secondary headache disorder).
5. Secondary headache diagnoses are applied when the patient develops a new type of headache for the first time in close temporal relation to onset of another disorder known to cause headache. Diagnosis of secondary headache in a patient with a preexisting primary headache can be challenging. Onset of a secondary headache is more likely when (i) there is a very close temporal relation to onset of the potentially causative disorder; (ii) exacerbation of the headache is marked, or differs in pattern from the preexisting

disorder; (iii) other evidence is strong that the potentially causative disorder can cause headache of the type experienced; or (iv) there is improvement or disappearance of headache, or return to the earlier pattern, after relief from the potentially causative disorder.

6. Although some headache types include frequency in their diagnostic criteria [i.e., chronic migraine (CM) and chronic TTH], the ICHD-2 does not specifically code frequency or severity. Frequency and severity may be specified parenthetically, at the discretion of the examiner.

CLASSIFICATION OF THE PRIMARY HEADACHES

The ICHD-2 divides the primary headaches into four major categories, which are discussed in sequence below.

Migraine

Migraine is subclassified into six major categories, the two most important of which are *migraine without aura* (1.1.) and *migraine with aura* (1.2.). This is unchanged from the ICHD-1, but there is a restructuring of the criteria for migraine with aura, and CM (1.5.1.) has been added. Ophthalmoplegic "migraine," now considered a cranial neuralgia, has been moved to item 13 (*Cranial Neuralgias and Central Causes of Facial Pain*) (Table 2).

Table 2 The ICHD-2 Classification of Migraine

1.1. Migraine without aura
1.2. Migraine with aura
1.2.1. Typical aura with migraine headache
1.2.2. Typical aura with nonmigraine headache
1.2.3. Typical aura without headache
1.2.4. FHM
1.2.5. Sporadic hemiplegic migraine
1.2.6. Basilar-type migraine
1.3. Childhood periodic syndromes that are commonly precursors of migraine
1.3.1. Cyclical vomiting
1.3.2. Abdominal migraine
1.3.3. Benign paroxysmal vertigo of childhood
1.4. Retinal migraine
1.5. Complications of migraine
1.5.1 CM
1.5.2 Status migrainosus
1.5.3 Persistent aura without infarction
1.5.4 Migrainous infarction
1.5.5 Migraine-triggered seizures
1.6. Probable migraine
1.6.1. Probable migraine without aura
1.6.2. Probable migraine with aura

Abbreviations: FHM, familial hemiplegic migraine; ICHD, International Headache Society Classification; CM, chronic migraine.

Table 3 ICHD-2 Criteria for Migraine Without Aura

Migraine without aura
Diagnostic criteria
A. At least five attacks[a] fulfilling B–D
B. Headache attacks lasting 4–72 hours[b,c] and occurring more than 15 days/mo[d] (untreated or unsuccessfully treated)
C. Headache has at least two of the following characteristics:
1. Unilateral location[e,f]
2. Pulsating quality[g]
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (i.e., walking or climbing stairs)
D. During headache, occurrence of at least one of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia[h]
E. Not attributed to another disorder[i]

[a]Differentiating between migraine without aura and episodic tension-type headache may be difficult. Therefore, at least five attacks are required. Individuals who otherwise meet the criteria for migraine without aura but have fewer than five attacks should be coded 1.6.
[b]If the patient falls asleep during migraine and wakes up without it, duration of the attack is until the time of awakening.
[c]In children, attacks may last 1 to 72 hours. (The evidence for untreated durations less than two hours in children should be corroborated by prospective diary studies.)
[d]If attack frequency is 15 days/mo or more and if there is no medication overuse, code 1.1. and 1.5.1. chronic migraine.
[e]Migraine headache is often bilateral in young children; an adult pattern of unilateral pain often emerges in late adolescence or early adult life.
[f]Migraine headache is usually frontotemporal. Occipital headache in *children*, whether unilateral or bilateral, is rare and calls for diagnostic caution; many cases are attributable to structural lesions.
[g]Pulsating means throbbing or varying with the heartbeat at rest or with movement.
[h]In young children, photophobia and phonophobia may be inferred from behavior.
[i]History and physical and neurological examinations do not suggest one of the disorders listed in groups 5–12; history and/or physical and/or neurological examinations do suggest such disorder, but it is ruled out by appropriate investigations; or such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder.
Abbreviation: ICHD, International Headache Society Classification.

Migraine Without Aura

Migraine without aura is a clinical syndrome characterized by headache features and associated symptoms (Table 3). According to the ICHD-2, if a patient fulfills criteria for more than one type of migraine, each type should be diagnosed. It is important to emphasize that:

- Criteria for migraine without aura can be met by various combinations of features, and no single feature is required.
- Because two of four pain features are required, a patient with unilateral, throbbing pain may meet the criteria, but so does a patient with bilateral, pressure pain, if the pain is moderate and aggravated by physical activity.
- Similarly, only one of two possible associated symptom combinations is required. Patients with nausea but not photophobia or phonophobia fill the requirements as do patients without nausea or vomit, but with photophobia and phonophobia.

- Attacks usually last from 4 to 72 hours if untreated. If the patient falls asleep during migraine and wakes up without it, the duration of the attack is timed until the time of awakening.
- In children, attacks may last 1 to 72 hours, and in young children, photophobia and phonophobia may be inferred from behavior.

If attack frequency is 15 days/mo or more in a subject not overusing acute medications, the ICHD-2 establishes coding 1.5.1 CM [see also "Controversies in the Classification of Primary Chronic Daily Headaches of Long Duration"].

Migraine with Aura and Its Subtypes

The criteria for *migraine with aura* (1.2.) have been revised substantially. The typical aura of migraine is characterized by focal neurological features that usually precede migrainous headache, but may accompany it or occur in the absence of the headache (Table 4) (6,7). Typical aura symptoms develop over five minutes or more and last no more than 60 minutes, and visual aura is overwhelmingly the most common (7). Typical visual aura is homonymous, often having a hemianopic distribution and expanding in the shape of a crescent with a bright, ragged edge, which scintillates. Scotoma, photopsia or phosphenes, and other visual manifestations may occur. Visual distortions such as metamorphopsia, micropsia, and macropsia are more common in children (7–9).

Sensory symptoms occur in about one-third of patients who have migraine with aura (8–10). Typical sensory aura consists of numbness (negative symptom) *and* tingling or paresthesia (positive symptoms). The distribution is often cheiro-oral (face and hand). Dysphasia may be part of typical aura, but motor weakness, symptoms of brain stem dysfunction, and changes in level of consciousness, all of which may occur (10), signal particular subtypes of migraine with aura (hemiplegic and basilar-type) that are not characterized by typical aura.

Recently, typical migraine aura has been noted to occur with nonmigrainous headache (i.e., headache not fulfilling the criteria of 1.1.). Such cases are coded *Typical aura with nonmigraine headache* (1.2.2.). Reports have associated apparently

Table 4 ICHD-2 Diagnosis of Typical Aura

Diagnostic criteria

A. At least two attacks fulfilling criteria B–E
B. Fully reversible visual and/or sensory and/or speech symptoms but no motor weakness
C. At least two of the following three:
   1. Homonymous visual symptoms including positive features (i.e., flickering lights, spots, and lines) and/or negative features (i.e., loss of vision) and/or unilateral sensory symptoms including positive features (i.e., pins and needles) and/or negative features (i.e., numbness)
   2. At least one symptom develops gradually over 5 min or more and/or different symptoms occur in succession
   3. Each symptom lasts 5 min or more and 60 min or less
D. Headache that meets criteria B–D for migraine without aura (1.1.) begins during the aura or follows aura within 60 min
E. Not attributed to another disorder

Abbreviation: ICHD, International Headache Society Classification.

typical aura with CH, chronic paroxysmal hemicrania (CPH), and hemicrania continua (HC) (10,11). These cases are classified according to both disorders [e.g., CH (3.1.) plus *Typical aura with nonmigraine headache* (1.2.2.)].

Typical aura occurring in the absence of any headache is coded *typical aura without headache* (1.2.3.), a disorder most often reported by middle-aged men (12). Differentiating this benign disorder from transient ischemic attack (TIA), a medical emergency, may require investigation, especially when it first occurs after age 40, when negative features (i.e., hemianopia) are predominant, or when the aura is of atypical duration (13).

FHM (1.2.4.) is the first migraine syndrome to be linked to a specific set of genetic polymorphisms (14–18). Herein, aura includes some degree of motor weakness (hemiparesis) and may be prolonged for more than 60 minutes (up to 24 hours); additionally, at least one first-degree relative has had similar attacks (also meeting these criteria). Cerebellar ataxia may occur in 20% of FHM sufferers. The onset of weakness may be abrupt, but usually lasts less than one hour. A person with FHM may develop migraine with aura when adult and migraine without aura later in life.

In patients otherwise meeting these criteria but who have no family history of this disorder, the disorder is classified as *sporadic hemiplegic migraine* (1.2.5.), a disorder new to the revised classification (19).

Basilar-type migraine (1.2.6.) is a new term, replacing "basilar migraine." The change is intended to remove the implication that the basilar artery, or its territory, is involved. The distinguishing feature of basilar-type migraine is a symptom profile that suggests posterior fossa involvement (19). Diagnosis requires at least two of the following aura symptoms, all fully reversible: dysarthria, vertigo, tinnitus, decreased hearing, double vision, visual symptoms simultaneously in both temporal and nasal fields of both eyes, ataxia, decreased level of consciousness, and simultaneously bilateral paresthesias. Because 60% of patients with FHM have basilar-type symptoms, basilar-type migraine should be diagnosed only when weakness is absent. The headache meets the criteria for (1.1.) *migraine without aura*.

Childhood Periodic Syndromes That Are Commonly Precursors of Migraine

A number of more or less well-described disorders are classified under this heading (20–23). *Cyclical vomiting* (1.3.1.) occurs in up to 2.5% of schoolchildren (21). The hallmark of this disorder is recurrent and stereotyped episodes of intense but otherwise unexplained nausea and vomiting, which last one hour to five days in children free of symptoms interictally. Vomiting occurs at least four times in an hour, and no signs of gastrointestinal disease can be found.

Abdominal migraine (1.3.2.) afflicts up to 12% of schoolchildren, with recurrent attacks of abdominal pain associated with anorexia, nausea, and sometimes vomiting (22). The abdominal pain has all of the following characteristics: midline location, periumbilical or poorly localized; dull or "just sore" quality; and moderate or severe intensity. At least two of the following symptoms are present during the episode: anorexia, nausea, vomiting, and/or pallor. Physical examination and investigations exclude other causes of these symptoms.

Benign paroxysmal vertigo (1.3.3.) is a disorder characterized by recurrent (at least five) attacks, each comprising multiple episodes of severe vertigo resolving spontaneously in minutes to hours (23). Neurological examination and audiometric and vestibular functions are all normal between attacks, and the electroencephalogram is also normal.

Retinal Migraine

This disorder is rare. Recurrent attacks (at least two) of fully reversible scintillations, scotomata, or blindness, affecting one eye only, are accompanied or followed within one hour by migrainous headache (fulfilling criteria for 1.1.). Other causes of monocular visual loss, including TIA, optic neuropathy, and retinal detachment, must be ruled out by appropriate investigation (24). A recent study suggests that many patients with "retinal migraine" experience retinal infarction of migrainous origin (25). This disorder should be coded as *Migrainous infarction* (1.5.4.). In Chapter 16, Drs. Grosberg and Solomon present a detailed review of retinal migraine.

Complications of Migraine

The ICHD-2 lists five complications of migraine: *CM* (1.5.1.) (see section "Controversies in the Classification of Primary Chronic Daily Headaches of Long Duration") when headache is both present and meets criteria for migraine (almost invariably migraine without aura) on 15 days/mo or more for three months or more, in the absence of medication overuse. All cases evolve from episodic migraine, and most from migraine without aura, hence its classification as a complication of migraine. When medication overuse is present (acute antimigraine drugs and/or opioids, combination analgesics taken on 10 days/mos or more, or simple analgesics on 15 days/mo or more), it is a likely cause of chronic headache. Neither *CM* (1.5.1.) nor *medication-overuse headache* (8.2.) can be diagnosed with confidence until the overused medication has been withdrawn; improvement within two months is expected if the latter diagnosis is correct (and is necessary to confirm it), not if the former is present. Meanwhile, the codes to be assigned are that of the antecedent migraine (usually *migraine without aura*, 1.1.) plus *probable medication-overuse headache* (8.2.7.) plus *probable CM* (1.6.5.).

Status migrainosus (1.5.2.) refers to an attack of migraine with a headache phase lasting more than 72 hours (26). The pain is severe (a diagnostic criterion) and debilitating. Nondebilitating attacks lasting for more than 72 hours are coded as *probable migraine without aura* (1.6.1.).

Persistent aura without infarction (1.5.3.) is diagnosed when aura symptoms, otherwise typical of past attacks, persist for more than one week. Investigation shows no evidence of infarction. It is an unusual but well-documented complication of migraine, which is now being introduced into the ICHD-2 (27).

Migrainous infarction (1.5.4.) is an uncommon occurrence. One or more otherwise typical aura symptoms persist beyond one hour, and neuroimaging confirms ischemic infarction. Strictly applied, these criteria distinguish this disorder from other causes of stroke, which must be excluded (28); the neurological deficit develops during the course of an apparently typical attack of migraine with aura and exactly mimics the aura of previous attacks.

Migraine and epilepsy are comorbid disorders (29). Headaches are common in the postictal period, but epilepsy can be triggered by migraine (migralepsy). The criteria for *migraine-triggered seizure* (1.5.5.) require that a seizure fulfilling the diagnostic criteria for any type of epileptic attack occurs during or within one hour after a migraine aura.

Probable Migraine

Between 10% and 45% of patients with features of migraine fail to meet all criteria for migraine (or any of its subtypes) (30). If a single criterion is missing (and the full

set of criteria for another disorder are not met), the applicable code is *probable migraine* (1.6.). Epidemiologic studies demonstrate that probable migraine is common and associated with temporary disability and reduction in the health-related quality of life (31).

Tension-Type Headache

TTH is the most common type of primary headache, with one-year period prevalences ranging from 31% to 74% (32,33). The ICHD-1 distinguished two subtypes, episodic TTH (less than 15 attacks per month) and chronic TTH (15 or more attacks per month). The ICHD-2 distinguishes three subtypes: *Infrequent episodic TTH* (2.1.) (headache episodes on less than 1 day/mo), *Frequent episodic TTH* (2.2.) (headache episodes on 1–14 days/mo), and *Chronic TTH* (2.3.) (headache on 15 or more days/mo, perhaps without recognizable episodes).

The diagnostic criteria for TTH are presented in Table 5. In contrast to migraine, the main pain features of TTH are bilateral location, nonpulsating quality, mild-to-moderate intensity, and lack of aggravation by routine physical activity. The pain is not accompanied by nausea, and just one of photo- or phonophobia does not exclude the diagnosis.

Chronic TTH invariably evolves from episodic TTH but, like CM, cannot be diagnosed in patients overusing acute medication. Such patients often meet criteria for, and in fact have, *medication-overuse headache* (8.2.), although withdrawal of the medication is required to confirm this diagnosis. A recently recognized disorder that phenotypically resembles chronic TTH, but is nosologically distinct from it (as far as is known), does not evolve from an episodic headache but is present daily and is

Table 5 ICHD-2 Classification of Tension-Type Headache

Diagnostic criteria
A. At least 10 episodes fulfilling criteria B–E. Number of days with such headache less than 1 day/mo (episodic infrequent), from 1 to 14 (episodic frequent), or 15 or more (chronic)
B. Headache lasting from 30 min to 7 days
C. At least two of the following pain characteristics:
  1. Pressing/tightening (nonpulsating) quality
  2. Mild or moderate intensity (may inhibit, but does not prohibit activities)
  3. Bilateral location
  4. No aggravation by walking stairs or similar routine physical activity
D. Both of the following:
  a. No nausea or vomiting (anorexia may occur)
  b. Photophobia and phonophobia are absent, or one but not the other may be present
E. Not attributed to another disorder
2.X.1. Associated with pericranial tenderness
Diagnostic criteria:
  A. Fulfills criteria for 2.X
  B. Increased tenderness on pericranial manual palpation
2.X.2. Not associated with pericranial tenderness
Diagnostic criteria
  A. Fulfills criteria for 2.X
  Not associated with increased pericranial tenderness

Note: X means the correspondent digit of infrequent episodic (i), frequent episodic (ii), or chronic (iii).
Abbreviation: ICHD, International Headache Society Classification.

unremitting from onset or within three days of onset. This condition is separately classified as *new daily-persistent headache* (4.8.).

When a headache fulfills all but one of the criteria for TTH and does not fulfill the criteria for migraine without aura, the diagnosis should be *probable TTH* (2.4.).

CH and Other TACs

The addition of the term TACs to the classification reflects the observation that CH is one of a group of primary headache disorders characterized by trigeminal activation coupled with autonomic activation. The ICHD-2 includes several disorders not in the previous edition.

Cluster Headache

The diagnostic criteria for CH have not substantially changed. This disorder manifests as intermittent, short-lasting, excruciating unilateral head pain accompanied by autonomic dysfunction (34). The pain of CH is described variously as sharp, boring, drilling, knife-like, piercing, or stabbing, in contrast to the pulsating pain of migraine. It usually peaks in 10 to 15 minutes but remains excruciatingly intense for an average of one hour within a duration range of 15 to 180 minutes. During this pain, patients find it difficult to lie still, exhibiting often marked agitation and restlessness, and autonomic signs are usually obvious. After an attack, the patient remains exhausted for some time.

CH is classified into two subtypes (Table 6). Attacks of *Episodic* CH (3.1.1.) occur in cluster periods lasting from seven days to one year separated by attack-free intervals of one month or more. Approximately 85% of CH patients have the episodic subtype. In chronic CH (3.1.2.), attacks recur for more than one year without remission, or with remissions lasting less than one month. Chronic CH can evolve from episodic CH, or develop de novo, and may revert to episodic CH (35).

Patients who have both CH as well as trigeminal neuralgia, and received the denomination of cluster-tic syndrome have been described (36). According to the ICHD-2, they should receive both diagnoses.

Table 6 ICHD-2 Classification of Cluster Headache

Diagnostic criteria

A. At least five attacks fulfilling B–D
B. Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 min untreated for more than half of the period (or time if chronic)
C. Headache is accompanied by at least one of the following symptoms or signs that have to be present on the side of the pain:
   1. Conjunctival injection, lacrimation, or both
   2. Nasal congestion, rhinorrhoea, or both
   3. Eyelid edema
   4. Forehead and facial sweating
   5. Miosis, ptosis, or both
   6. Headache is associated with a sense of restlessness or agitation
D. Frequency of attacks: from one every other day to eight per day for more than half of the period if chronic
E. Not attributed to another disorder

Abbreviation: ICHD, International Headache Society Classification.

Paroxysmal Hemicrania

As a group, the paroxysmal hemicranias have three main features: (i) at least 20 frequent (more than five per day) attacks of short-lasting (2–30 minutes), severe, and strictly unilateral orbital, supraorbital, or temporal pain; (ii) symptoms of parasympathetic activation ipsilateral to the pain (as in CH); and (iii) absolute response to therapeutic doses of indomethacin (37–39).

The ICHD-1 included CPH only. The ICHD-2 includes *episodic paroxysmal hemicrania* (3.2.1.) and CPH (3.2.2.). Like CH, these disorders are distinguished by the presence or absence of attack-free intervals lasting one month or more.

Some patients with both CPH and trigeminal neuralgia have been described (CPH-tic syndrome); they should receive both diagnoses.

Short-Lasting Unilateral Neuralgiform Headache Attacks with Conjunctival Injection and Tearing

The short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome (3.3.) and is a very rare primary headache. The diagnostic criteria require at least 20 high-frequency attacks (3–200 per day) of unilateral orbital, supraorbital, or temporal stabbing or pulsating pain, lasting 5 to 240 seconds and accompanied by ipsilateral conjunctival injection and lacrimation. The attacks are characteristically dramatic, with moderately severe pain peaking in intensity within three seconds and prominent tearing (40).

Headache attacks believed to be a subtype of TAC but fulfilling all but one of the diagnostic criteria for it are diagnosed as probable TCA.

Other Primary Headaches

This group of miscellaneous primary headache disorders includes some mimics of potentially serious secondary headaches, which need to be carefully evaluated by imaging or other appropriate tests. Some headaches, such as hypnic headache, primary thunderclap headache, HC, and new daily-persistent headache were not included in the ICHD-1.

Primary Stabbing Headache

Episodic localized stabs of head pain occurring spontaneously in the absence of any structural cause (formerly referred to as "jabs and jolts") are diagnosed as *primary stabbing headache* (4.1.). Pain is exclusively or predominantly in the distribution of the first division of the trigeminal nerve (orbit, temple, and parietal area). It lasts for up to a few seconds and recurs at irregular intervals with a frequency ranging from one to many per day. Other features such as autonomic signs are lacking (40,41).

Primary Cough Headache

This headache is brought on suddenly by coughing, straining, or Valsalva maneuver, and not otherwise, in the absence of any underlying disorder such as cerebral aneurysm or, especially, Arnold–Chiari malformation (42). Diagnostic neuroimaging, with special attention to the posterior fossa and base of the skull, is mandatory to differentiate secondary and primary forms of cough headache.

Primary Exertional Headache

This disorder is triggered by physical exercise, and not otherwise, and is distinguished from *primary cough headache* (4.2.) and *headache associated with sexual activity* (4.4.). Primary exertional headache is pulsating and lasts from 5 minutes to 48 hours. After the first occurrence of any exertional headache of sudden onset, appropriate investigations must exclude subarachnoid hemorrhage and arterial dissection (43–45).

Primary Headache Associated with Sexual Activity

Headache precipitated by sexual activity usually begins as a dull bilateral ache as sexual excitement increases and suddenly becomes intense at orgasm (46). Two subtypes are classified: *preorgasmic headache* (4.4.1.), a dull ache in the head and neck, and *orgasmic headache* (4.4.2.), explosive and severe, and occurring with orgasm. Diagnosis of the latter requires exclusion of subarachnoid hemorrhage and arterial dissection.

Hypnic Headache

This primary headache disorder of the elderly is characterized by short-lived attacks (typically 30 minutes) of nocturnal head pain, which awakens the patient at a constant time each night, in many cases on more nights than not. It does not occur outside sleep (47). Hypnic headache is usually bilateral (though unilaterality does not exclude the diagnosis) and mild to moderate, very different from the unilateral orbital or periorbital knife-like intense pain of CH. Autonomic features are absent.

Primary Thunderclap Headache

Severe headache of abrupt onset, which mimics the pain of a ruptured cerebral aneurysm, is classified as *primary thunderclap headache* (4.6.), although this code is not applied to thunderclap headache meeting the criteria for 4.2, 4.3, or 4.4. Intensity peaks in less than one minute. Pain lasts from 1 hour to 10 days and may recur within the first week after onset but not regularly over subsequent weeks or months (48). This diagnosis can be established only after excluding subarachnoid hemorrhage.

Hemicrania Continua

This daily and continuous strictly unilateral headache is defined by its absolute response to therapeutic doses of indomethacin. Pain is moderate, with exacerbations of severe pain, and autonomic symptoms accompany these exacerbations although less prominently than in CH and CPH (49,50). Some bilateral or alternating-side cases have been reported (51).

New Daily-Persistent Headache

The essence of this headache, which according to the ICHD-2 but not accepted by all, otherwise resembles *chronic TTH* (2.3.), is that it is present daily and is unremitting from or very soon (less than three days) after onset. There is no history of evolution from episodic headache. Diagnosis is not confirmed until it has been present for more than three months, and cannot be made if this manner of onset is not clearly

recalled by the patient. Nor can it be made in the presence of medication overuse. NDPH is typically bilateral, pressing or tightening in quality, of mild to moderate intensity, and unaffected by routine physical activity, although the diagnostic criteria require only any two of these features. There may be any but not more than one of photophobia, phonophobia, or mild nausea.

SECONDARY HEADACHES

Discussing the classification of the secondary headaches in depth is beyond the scope of this chapter. In brief, the classification of all secondary headaches follows the same format:

1. The secondary disorder known to be able to cause headache has been demonstrated.
2. Headache occurs in close temporal relation to the secondary disorder, and/or there is other evidence of a causal relationship.
3. Headache is greatly reduced or disappears within three months (this may be shorter for some disorders) after successful treatment or spontaneous remission of the causative disorder.

There are exceptions to this general rule. Chronic post-traumatic headache does not disappear three months after the trauma. We will briefly discuss their classification.

HEADACHE ATTRIBUTED TO HEAD AND/OR NECK TRAUMA

This category includes headaches that occur for the first time in close temporal relation to a known trauma (52). If there is remission within three months after the trauma, the headache should be classified as *acute post-traumatic headache*. Otherwise, *chronic post-traumatic headache* is the diagnosis. The same rule applies to *acute and chronic post–whiplash injury headache*. The ICHD-2 also classifies under this group those headaches secondary to *intracranial hematoma and postcraniotomy*.

HEADACHE ATTRIBUTED TO CRANIAL OR CERVICAL VASCULAR DISORDERS

This category encompasses a large group of headaches that fulfill the following criteria: symptoms and/or signs of a vascular disorder; appropriate investigations indicating the vascular disorder; and the headache developing in close relationship with the vascular disorder. This group includes headaches related to (i) ischemic stroke and TIAs; (ii) nontraumatic intracranial hemorrhage; (iii) unruptured vascular malformations; (iv) arteritis (including giant cell arteritis); (v) carotid or vertebral artery pain (including arterial dissection, postendarterectomy headache, etc.); (vi) cerebral venous thrombosis; and (vii) other intracranial vascular disorders, including CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), etc. (53–59).

In many of these conditions, such as ischemic or hemorrhagic stroke, headache may be unrecognized because of focal signs and/or disorders of consciousness. In others, such as subarachnoid hemorrhage and giant cell arteritis, headache may be the most prominent symptom and an initial warning symptom.

HEADACHE ATTRIBUTED TO NONVASCULAR INTRACRANIAL DISORDERS

This category includes an extensive and heterogeneous group of disorders (7). They are: (i) high cerebrospinal fluid pressure; (ii) low cerebrospinal fluid pressure; (iii) noninfectious inflammatory diseases; (iv) intracranial neoplasm; (v) headache related to intrathecal injections; (vi) postseizure headache; (vii) Chiari malformation type I (CM1); and (viii) syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis (60–62).

HEADACHE ATTRIBUTED TO A SUBSTANCE OR ITS WITHDRAWAL

When new headaches occur in close temporal relation to substance use or withdrawal, they are coded to this group. The ICHD-2 classifies in this group those headaches following *acute* exposure to (63,64) (i) nitric oxide donor substances; (ii) phosphodiesterase inhibitors; (iii) carbon monoxide; (iv) alcohol; (v) food components and additives; (vi) monosodium glutamate; (vii) cocaine; (viii) cannabis; and (ix) other acute substance use.

In addition, *chronic* medication overuse is a risk factor for the development of CDH (65,66). Using the ICHD-2, if a subject has a frequent headache associated with medication overuse and meets otherwise the criteria for CM, a diagnosis of probable CM and probable medication-overuse headache should be assigned. Definite diagnosis of medication-overuse headache requires that headaches remit or improve when the overused medication is withdrawn. Prior to withdrawal, the use of the ''probable'' term exemplifies the difficulty of causal attribution (see section ''Controversies in the classification of primary chronic daily headaches of long duration'').

HEADACHE ATTRIBUTED TO INFECTION

This is a very straightforward group where headaches secondary to intracranial and extracranial (systemic) infections are classified. This group also includes headaches related to HIV/AIDS and chronic postinfectious headaches (67).

HEADACHE ATTRIBUTED TO DISORDERS OF HOMEOSTASIS

This group of headaches was formerly referred as headaches associated with metabolic or systemic diseases. They include the following headaches: (i) headache attributed to hypoxia and/or hypercapnia (high altitude, diving, and sleep apnea); (ii) dialysis; (iii) arterial hypertension; (iv) headache attributed to hypothyroidism; (v) headache attributed to fasting; (vi), cardiac cephalgia; and (vii) headache attributed to other disturbances of homeostasis (68,69).

HEADACHE OR FACIAL PAIN ATTRIBUTED TO DISORDERS OF CRANIUM, NECK, EYES, EARS, NOSE, SINUSES, TEETH, MOUTH, OR OTHER FACIAL OR CRANIAL STRUCTURES

This is a very heteronegenous group classifying headache and facial pain due to disease of the cranium, the neck, and the facial structures. Cranial neuralgias are not classified under this chapter. The ICHD-2 includes criteria for cervicogenic headache (70).

HEADACHE ATTRIBUTED TO PSYCHIATRIC DISORDERS

This group provides a link to classify those extremely rare headaches that are causally attributable to a psychiatric disorder. The headache may be attributed to a somatization disorder or to a psychotic disorder. This should be distinguished from psychiatric comorbidities where a headache disorder (e.g., migraine) and a psychiatric disorder (e.g., depression) occur together in the same person (71).

CRANIAL NEURALGIAS AND CENTRAL CAUSES OF FACIAL PAIN

Finally, the last chapter of the ICHD-2 codes the cranial neuralgias and facial pain, including (72,73) (i) trigeminal neuralgia; (ii) glossopharyngeal neuralgia; (iii) nervus intermedius neuralgia; (iv) superior laryngeal neuralgia; (v) nasociliary neuralgia (Charlin); (vi) supraorbital neuralgia; (vii) other terminal branch neuralgias; (viii) occipital neuralgia; (ix) neck–tongue syndrome; (x) external compression headache; (xi) cold stimulus headache; (xii) constant pain caused by compression, irritation, or distortion of cranial nerves or upper cervical roots by structural lesions; (xiii) optic neuritis; (xiv) ocular diabetic neuropathy; (xv) herpes zoster; (xvi) Tolosa–Hunt syndrome; (xvii) ophthalmoplegic migraine; and (xviii) central causes of facial pain.

Criteria for trigeminal neuralgia, the prototype of a cranial neuralgia, are summarized in Table 7.

CONTROVERSIES IN THE CLASSIFICATION OF PRIMARY CHRONIC DAILY HEADACHES OF LONG DURATION

Primary CDH is defined as a group of primary headaches that occur more than 15 days a month (or 180 days a year) with a duration of four or more hours per day

Table 7 ICHD-2 Classification of Trigeminal Neuralgia

A. Paroxysmal attacks affecting one or more divisions of the trigeminal nerve lasting from a fraction of a second to two minutes
B. The pain has at least one of the following characteristics: intense, sharp, superficial, stabbing, precipitated from trigger areas, or by trigger factors
C. There is no clinically evident neurological deficit
D. Attacks are stereotyped in the individual patient
E. Not attributed to another disorder

Abbreviation: ICHD, International Headache Society Classification.

(see Chapter 27 for the clinical features, diagnosis, and treatment of CDH). Studies reported difficulties using the ICHD-1 to classify CDH sufferers (74,75). As a consequence, a few proposals for the classification of these patients have emerged. Of these proposals, the Silberstein and Lipton (S-L) criteria have been most widely used (76). The S-L criteria divide the CDH into four main diagnoses: (i) transformed migraine (TM); (ii) chronic TTH; (iii) new daily-persistent headache; and (iv) HC. The system subclassifies these main diagnoses as "with medication overuse" or "without medication overuse."

As a syndrome, CDH is addressed neither in the ICHD-1 nor in the ICHD-2, which, however, provides criteria for the CDH subtypes. Controversies exist regarding the differences between CM and TM and the best way to classify NDPH.

TM and CM have been used synonymously in the past, but this is no longer appropriate. CM has a specific definition in the ICHD-2, and TM is a headache syndrome not included in the ICHD-2. Patients with TM typically have a past history of migraine, usually migraine without aura. Subjects report a process of transformation (chronification) over months or years, and as headache increases in frequency, associated symptoms become less severe and frequent. The process of transformation frequently ends in a pattern of daily or nearly daily headache that resembles chronic TTH, with some attacks of full migraine superimposed.

The S–L criteria classify TM in two situations: First, a primary CDH develops in a person with previous history of headaches. Second, one of the three following links with migraine are satisfied: (i) a prior history of migraine; (ii) a period of escalating headache frequency; or (iii) concurrent superimposed attacks of migraine that fulfill the IHS criteria.

A revision of the criteria for CM is currently being considered by the International Headache Society Classification Committee. As of the writing criteria for CM would require 15 or more days of headache per month and at least 8 days of migraine. This issue is fully discussed in Chapter 27.

NDPH is characterized by the relatively abrupt onset of an unremitting primary CDH, i.e., a patient without a previous headache syndrome develops a chronic headache that does not remit. It is the new onset of this primary daily headache that is the most important feature. According to the S-L criteria, the clinical features of the pain are not considered in making the diagnosis, which only requires absence of history of evolution from migraine or episodic TTH. The S-L classification allows the diagnosis of NDPH in patients with migraine or episodic TTH if these disorders do not increase in frequency to give rise to NDPH. The IHS criteria consider NDPH in those cases where the headaches resemble TTHs (in other words, NDPH with migrainous features or coexisting new-onset migraine does not meet the criteria for this diagnosis according to the ICHD-2) (77–80).

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2
The Epidemiology and Impact of Migraine

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INTRODUCTION

Headache disorders are divided into two major categories. Secondary disorders have an identifiable underlying cause such as an infection, a brain tumor, or a stroke. Primary headache disorders have no apparent underlying cause (1,2). Of the primary headache disorders, tension-type headache is the most common in population studies (3), but migraine is most common among patients who seek medical care for headache (4). The most important forms of migraine are migraine with and without aura as well as a condition termed ''probable migraine'' (PM) (1).

In this chapter we review the epidemiology and risk factors for migraine in population studies, as well as the patterns for health care use. We discuss the burden and the costs of migraine, as well as risk factors for disease progression. We close by linking the epidemiological data to treatment strategies directed to reducing the burden of migraine and preventing disease progression. The epidemiology of the other primary headaches is described in the respective chapters.

THE EPIDEMIOLOGY OF MIGRAINE

Efforts to improve the diagnosis and treatment of migraine should begin with epidemiologic data, which helps to describe the prevalence and burden of migraine and its scope and distribution.

Epidemiological data can be used to identify the groups at highest risk for migraine, including those in need of medical care among migraine sufferers. It also helps to identify individuals at higher risk to progress to chronic daily headache (see Chapter 27). Finally, epidemiologic data may provide clues to preventive strategies or disease mechanisms.

Epidemiological studies focus on the incidence and prevalence of disease in defined populations (5). Incidence refers to the rate of onset of new cases of a disease in a given population over a defined period. Prevalence is defined as the proportion of a given population, which has a disease over a defined period. Prevalence is determined by the average incidence and average duration of disease (6).

The Incidence of Migraine

The incidence of migraine has been investigated in a limited number of studies. Using the reported age of migraine onset from a prevalence study, Stewart et al. (7) found that, in females, the incidence of migraine with aura peaked between ages 12 and 13 (14.1/1000 person-years); migraine without aura peaked between ages 14 and 17 (18.9/1000 person-years). In males, migraine with aura peaked incidence several years earlier, around five years of age at 6.6/1000 person-years; the peak for migraine without aura was 10/1000 person-years between 10 and 11 years (Fig. 1). New cases of migraine were uncommon in men in their 20s. From this data, we can conclude that migraine begins earlier in males than in females and that migraine with aura begins earlier than migraine without aura.

A study performed in a random sample of young adults (21–30 years) found that the incidence of migraine was 5.0 per 1000 person-years in males and 22.0 in females (8), supporting the findings reported above (9). However, a study using a linked medical records system showed a lower incidence (probably because many people with migraine do not consult doctors or receive a medical diagnosis) (8). In this study, the average annual incidence rate per 1000 person-years was 3.4 (4.8 in women and 1.9 in men). In women, incidence rates were low at the extremes of age and higher for ages 10 to 49, with a striking peak at the age of 20 to 29. In this study, incidence also peaked later than in other studies, because medical diagnosis may occur long after the age of onset.

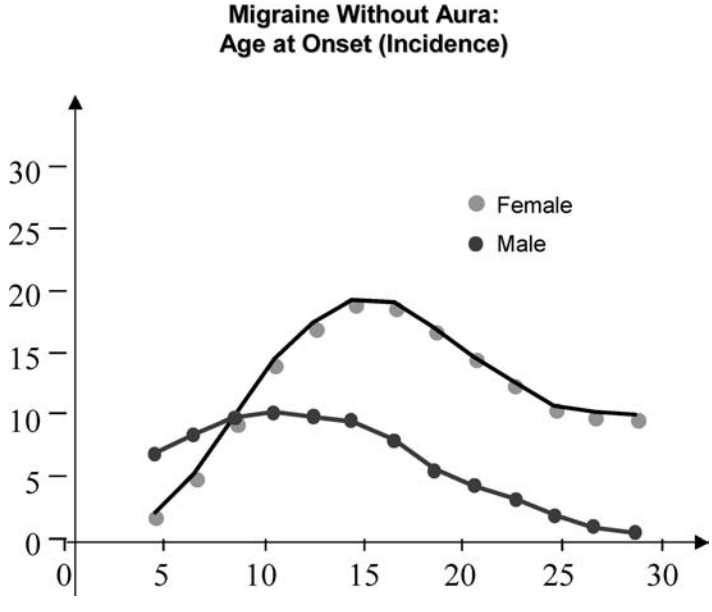

Figure 1 Incidence of migraine, by age and sex. *Source*: From Ref. 7.

In the Danish population, the annual incidence of migraine for ages 25 to 64 was of 8/1000, being 15/1000 in males and 3/1000 in females. Prevalence peaked in younger women (20/1000) (10).

As shown below, the gap between peak incidence in adolescence and peak prevalence in middle life indicates that migraine is a condition of long duration.

The Prevalence of Migraine

The published estimates of migraine prevalence have varied broadly, probably because of differences in the methodology (for reviews see 5,11–13). A meta-analysis, restricted to studies that used the International Headache Society (IHS) criteria and gender-specific models (females and males were modeled separately), found that age and geography accounted for much of the variation in prevalence (14). Herein, we present primarily studies that used the IHS definition (Table 1).

Prevalence by Age

Before puberty, migraine prevalence is higher in boys than in girls; as adolescence approaches, incidence and prevalence increase more rapidly in girls than in boys. The prevalence increases throughout childhood and early adult life until approximately age 40, after which it declines (Fig. 2) (14). Overall, prevalence is highest between 25 to 55 years of age, the peak years of economic productivity. These dramatic age effects account for some of the variation in prevalence estimates from previous studies.

Although studies suggested that migraine prevalence may be increasing (9,15), the stability of prevalence in studies in the United States over the past decade does not support the view that prevalence is increasing (16,17). It is possible that the demonstrable increases in medical consultation and diagnosis may have caused an apparent rather than a real increase.

Prevalence in Children and Adolescents

The prevalence of headache in children, as investigated in a number of school- and population-based studies (18–24), is summarized in Table 2. By age 3, headache occurs in 3% to 8% of children. At age 5, 19.5% have headache and by age 7, 37% to 51.5% have headaches. In 7- to 15-year-olds, headache prevalence ranges from 57% to 82%. The prevalence increases from ages 3 to 11 in both boys and girls with higher headache prevalence in three- to five-year-old boys than in three- to five-year-old girls. Thus, the overall prevalence of headache increases from preschool age to mid-adolescence, when examined using various cross-sectional studies.

Two relatively recent studies report the prevalence of pediatric migraine in the Asian Middle East. The first one, performed in southern Iran, evaluated a random sample of 1868 teen-aged girls (aged 11–18) (507 reported headache). Overall prevalence rate for migraine was 6.1% (95% CI, 5.0–7.2) and for tension-type headache, 12.1% (95% CI, 10.6–13.6). Migraine and tension-type headache were significantly associated. The exposure of subjects to sunlight, type of food, and a family history of headache were the most significant factors associated with migraine and tension-type headaches (25). The second study evaluated 1400 randomly selected Saudi children in grades 1 through 9. Overall, the headache prevalence was 49.8%. The prevalence of migraine was 7.1%. For both boys and girls, the age-specific prevalence rate for nonmigraine headache rose steadily from around 15% at age 6 to age 7 to nearly 60% after age 15. For migraine, there was a sharp increase in the prevalence rate

Table 1 Gender-Specific Prevalence Estimates of Migraine from 25 Population-Based Studies Using IHS Diagnostic Criteria

Author (year of publication)	Country	Source	Method	Sample size	Time frame	Age range	Migraine prevalence (%)			Comments
							Female	Male	Total	
Abu-Arefeh (1994)	Scotland	School	Clin interview	1,754	1 yr	5–15	11.5	9.7	10.6	Prevalence is higher in boys prior to age 12 (1.14:1). After age 12, more common in girls (2.0:1)
al Rajeh (1997)	Saudi Arabia	Community	Face-to-face/ clin interview	22,630		All	6.8	3.2	5.0	
Alders (1996)	Malaysia	Community	Face-to-face	595	1 yr	5+	11.3	6.7	9.0	
Arregui (1991)	Peru	Community	Clin interview	2,257		All	12.2	4.5	8.4	
Bank et al. (2000)	Hungary	Community	Questionnaire	813	1 yr	15–80			9.6	
Barea (1996)	Brazil	School	Clin interview	538	1 yr	10–18	10.3	9.6	9.9	2–48 hr duration allowed
Breslau (1991)	United States	Community	Face-to-face/ telephone	1,007	1 yr	21–30	12.9	3.4	9.2	
Cruz (1995)	Ecuador	Community	Clin interview	2,723	Lifetime	All	7.9	5.6	6.9	Community endemic for cysticercosis
Cull (1992)	United Kingdom	Community	Face-to-face	16,002		16+	11.0	4.3	7.8	Without aura only
Dahlof et al. (2003)	Sweden	Community	Telephone interview	1,668	1 yr	18–74	16.7	9.5	13.2	
Deleu et al. (2002)	Saudi Arabia	Community	Face-to-face	1,158	1 yr	10+	5.6	4.5		
Göbel (1994)	Germany	Community	Mail SAQ	4,061	Lifetime	18+	15.0	7.0	11.0	
Hagen et al. (2000)	Norway	Community	Clin interview	51,833	1 yr	20+	16.0	8.0	12.0	

Haimanot (1995)	Ethiopia	Community	Face-to-face/ clin interview	15,000	1 yr	20+	4.2	1.7	3.0	
Henry (1992)	France	Community	Face-to-face	4,204	1 yr	15+	11.9	4.0	8.1	
Henry et al. (2002)	France	Community	Face-to-face	10,585	1 yr	15+	11.2	4.0	7.9	
Jabbar (1997)	Saudi Arabia	Community	Face-to-face	5,891	Lifetime	15+			8.0	
Jaillard (1997)	Peru	Community	Clin interview	3,246	1 yr	15+	7.8	2.3	5.3	
Kececi et al. (2002)	Turkey	Community	Face-to-face	1,320	1 yr	All	17.1	7.9		
Lamp et al. (2003)	Sweden	Community	Face-to-face	997	1 yr	15+	13.8	6.1	10.2	
Lenore et al. (1999)	Netherlands	Community	Questionnaire and telephone	6,491	Lifetime 1 yr	18–65	33 25	13.3 7.5		
Lipton et al. (2001)	United States	Community	Telephone	29,727	1 yr	12+	18.2	6.5		
Lipton et al. (2002)	United States	Community	Telephone	11,863	1 yr	18–65	17.2	6		
Merikangas (1993)	Switzerland	Community	Clin interview	379	1 yr	28–29	32.6	16.1	24.5	Weighted prevalence
Michel (1995)	France	Community	Mail SAQ	9,411	3 mo	18+	18.0	8.0	13.0	
Miranda et al. (2003)	Puerto Rico	Community	Telephone	1,610	1 yr	All	6	16.7	13.5	
O'Brien (1994)	Canada	Community	Telephone	2,922	1 yr	18+	21.9	7.4	15.2	
Raieli (1994)	Italy	School	Clin interview	1,445	1 yr	11–14	3.3	2.7	3.0	
Rasmussen (1992)	Denmark	Community	Clin interview	740	1 yr	25–64	15.0	6.0	10.0	
Russell (1995)	Denmark	Community	Clin interview	3,471	Lifetime	40	23.7	11.7	17.7	
Sakai (1996)	Japan	Community	Mail SAQ	4,029	1 yr	15+	12.9	3.6	8.4	Female:male prevalence ratio = 3.6. Regional differences
Steiner et al. (2003)	England	Community	CATI	4,007	1 yr	18–65	14.3	7.6	18.3	
Stewart (1992)	United States	Community	Mail SAQ	20,468	1 yr	12–80	17.6	5.7	12.0	

(*Continued*)

Table 1 Gender-Specific Prevalence Estimates of Migraine from 25 Population-Based Studies Using IHS Diagnostic Criteria (*Continued*)

Author (year of publication)	Country	Source	Method	Sample size	Time frame	Age range	Migraine prevalence (%)			Comments
							Female	Male	Total	
Stewart (1996)	United States	Community	Telephone	12,328	1 yr	18–65	19.0	8.2	14.7	Racial differences
Takeshima et al. (2004)	Japan	Community	Questionnaires and telephone	5,758	1 yr	18+	9.1	2.3	6	Study done in the rural area of western Japan
van Roijen (1995)	Netherlands	Community	Face-to-face	10,480	1 yr	12+	12.0	5.0	9.0	
Wang (1997)	China	Community	Clin interview	1,533	1 yr	65+	4.7	0.7	3.0	
Wong (1995)	Hong Kong	Community	Telephone	7,356	1 yr	15+	1.5	0.6	1.0	
Zivadinov et al. (2001)	Croatia	Community	Telephone and face-to-face	5,173	Lifetime 1 yr	15–65	22.9 18	14.8 12.3	19	

Abbreviations: CATI, computer assisted telephone interview; IHS, International Headache Society; SAQ, structured administered questionnaire.

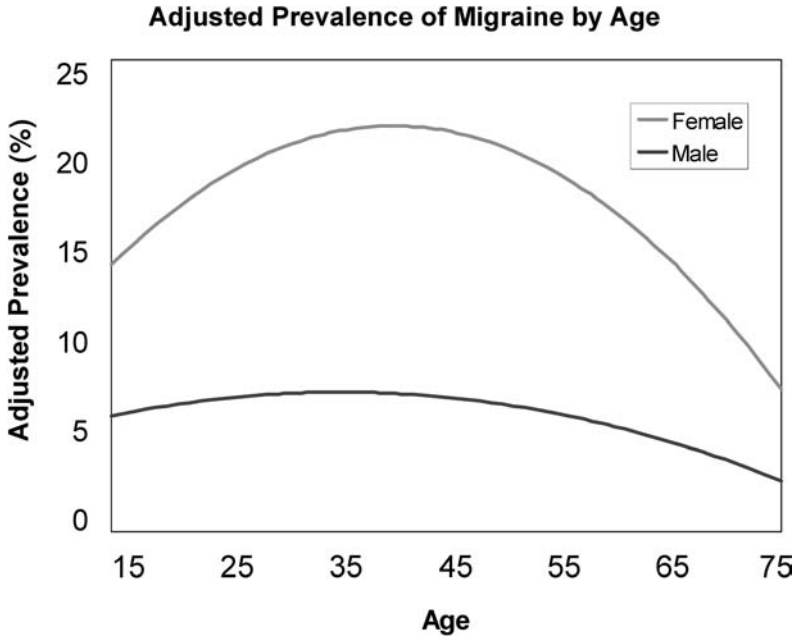

Figure 2 Adjusted prevalence of migraine by age from a meta-analysis of studies using IHS criteria. *Abbreviation*: IHS, International Headache Society. *Source*: From Ref. 14.

(from around 2% to around 9%) at age 10 to 11, both in boys and girls. Age-adjusted prevalence for migraine between ages 6 and 15 was 6.2% (26).

Another study evaluated the evolution over five years of juvenile migraine without aura in adolescents. Sixty-four subjects out of 80 previously selected were reevaluated. Thirty-two (50%) had migraine without aura. After four years, migraine without aura persisted in 56.2%, converted to migrainous disorder or non-classifiable headache in 9.4% and 3.1% of cases, respectively, changed to episodic tension-type headache in 12.5%, and remitted in 18.8% (27).

Prevalence in the United States

In the United States, the American Migraine Study-1 (AMS-1) collected information from 15,000 households representative of the U.S. population in 1989 (16). The AMS-II used virtually identical methodology 10 years later (17). Finally, the American Migraine Prevention and Prevalence (AMPP) study replicated, in its first research phase, the methods of the AMS-I and AMS-II (28). In these three very large studies, the prevalence of migraine was about 18% in women and 6% in men (Fig. 3).

Table 1 summarizes several prevalence studies conducted in the last 12 years. We present the prevalence of migraine in different geographic locations, overall and by gender.

Prevalence of Migraine by Socioeconomic Status

The relationship between migraine prevalence and socioeconomic status is uncertain. In physician- and clinic-based studies, migraine appears to be associated with high intelligence and social class. In his studies of children, Bille did not find association between migraine prevalence and intelligence (18,19). Similarly, in adults, epidemiologic studies do not support a relationship between occupation and migraine

Table 2 Prevalence of Headache and Migraine by Age in Selected Community and School-Based Studies

Author (Y) Country	Type of population	Sample size	Age range (years)	Time Frame	Migraine definition	Headache prevalence			Migraine prevalence		
						Males	Females	Overall	Males	Females	Overall
Ayatollahi (2002) Iran	School teenage girls	1,868	11–18	NS	IHS				–	6.1%	–
Al Jumah M (2002) Saudi Arabia	School Children	1,400	6–18	NS	IHS				6.4%	7.7%	7.1%
Abu-Arafeh (1994) U.K.	School Children	1,754	5–15	1 yr	IHS						10.6
Bille (1962) Sweden	School Children	8,993	7–15	Lifetime	Vahlquist	58.0	59.3	–	3.3	4.4	–
Linet (1989) USA	Community	10,132	12–29	1 yr	2 of NV/U/VA	90	95	–	5.3	14	–
Mortimer (1992) UK	General Practice	1,083	3–11	1 yr	IHS	40.6[a]	36.9[a]	38.8[a]	4.1	2.9	3.7
Raielli (1995) Italy	School Children	1,445	11–14	1 yr	IHS	19.9	28.0	23.9	2.7	3.3	3.0
Sillanpaa (1976) Finland	School Children	4,825	3	NS			4.3				
			7	NS	Vahlquist				3.2	3.2	3.2
Sillanpaa (1983) Finland	School Children	3,784	13	1 yr	Vahlquist	79.8	84.2	–	8.1	15.1	–

[a]age adjusted definitions: N, nausea; U, unilateral; V, vomiting; VA, visual aura; NS, not specified.

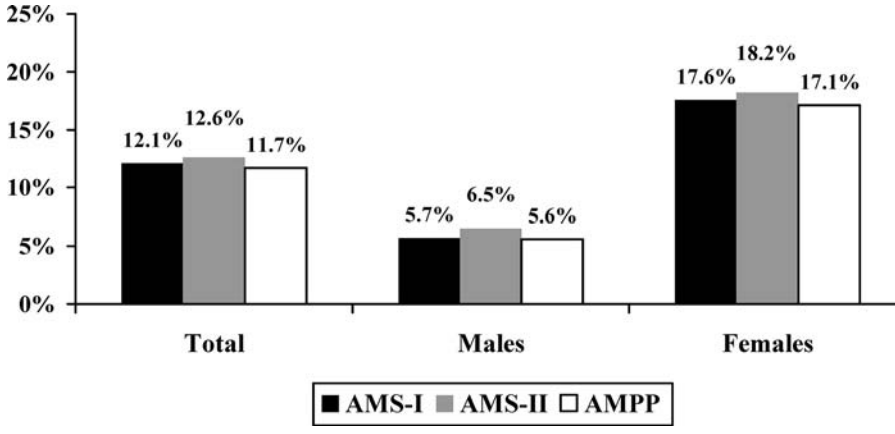

Figure 3 Prevalence of migraine in the AMS-I, AMS-II, and AMPP, overall and by gender. *Abbreviations*: AMS, American Migraine Study; AMPP, American Migraine Prevention and Prevalence.

prevalence (29). In both the AMS-I and AMS-II and the AMPP, migraine prevalence was inversely related to household income (i.e., migraine prevalence fell as household income increased) (17,18,28). This inverse relationship between migraine and socioeconomic status was confirmed in another U.S. study based on the members of a managed care organization and in the National Health Interview Study (29). Finally, although the genetic epidemiology of migraine study (GEM) failed to demonstrate an association between migraine and socioeconomic status (30), a recent study in England showed this relationship (31).

Prevalence of Migraine by Geographic Distribution

Migraine prevalence also varies by race and geography. In the United States, it is highest in Caucasians, intermediate in African Americans, and lowest in Asian Americans (5). Similarly, a meta-analysis of prevalence studies suggests that migraine is most common in North and South America and Europe, but lower in Africa, and often lowest in studies from Asia (Fig. 4) (4). The influence of reporting bias on these findings cannot be excluded. Nonetheless the data suggest that race-related differences in genetic risk may contribute. If and how these differences apply to the pediatric population (of if these differences have later expression) is still to be determined.

THE BURDEN OF MIGRAINE

Individual Burden of Migraine

Migraine is a public health problem of enormous scope, which has an impact on both the individual sufferer and on society (17,18). Nearly one in four U.S. households have someone with migraine. Twenty-five percent of women in the United States who have migraine experience four or more severe attacks a month; 35% experience one to four severe attacks a month; 38% experience one, or less than one, severe attack a month. Similar frequency patterns were observed for men (18,28).

In the AMS-II, 92% of women and 89% of men with severe migraine had some headache-related disability. Similar findings were reported by the AMPP. About half were severely disabled or needed bed rest (32). In addition to the attack-related