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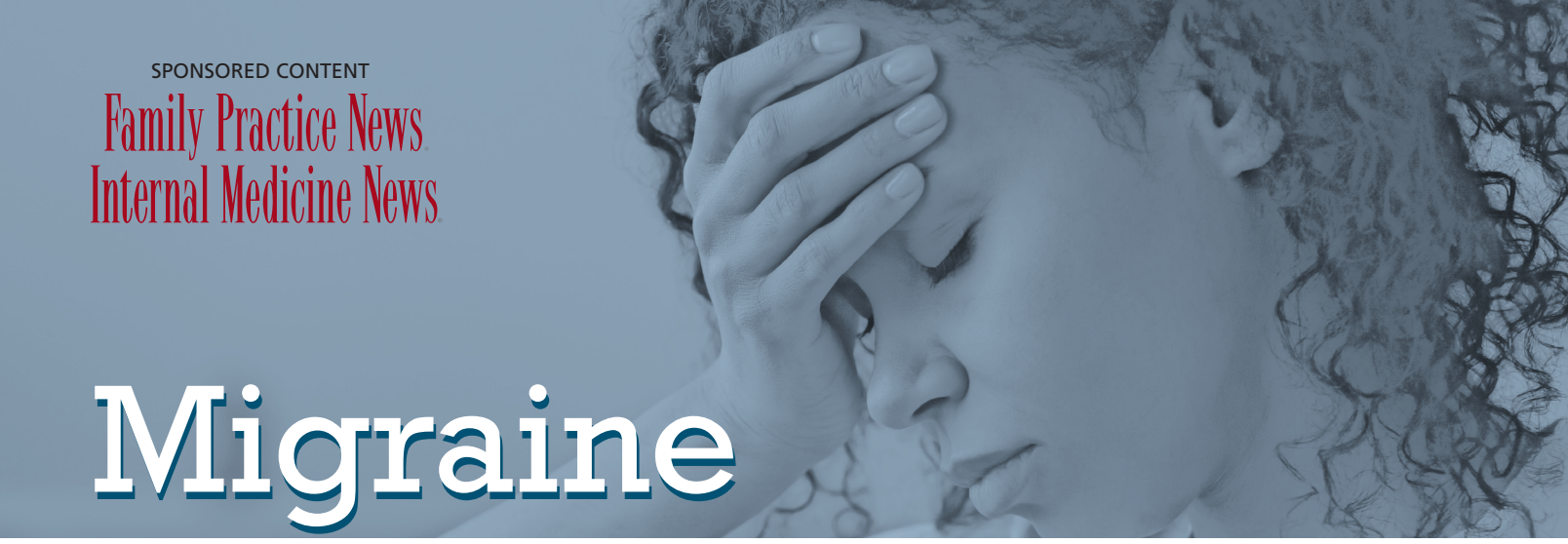

Migraine

More Than Just a Headache

Introduction

Migraine is a common and debilitating neurologic disease affecting more than 10% of the world's population (approximately 1 billion people globally).[1] In the United States, the prevalence of migraine is estimated to be around 12%.[2] Migraine is 2 to 3 times more common in women than in men, and its prevalence peaks in midlife (30–49 years of age), impacting individuals in their prime working years.[2,3]

Though a common disease with substantial impact, migraine is underdiagnosed and undertreated. The American Migraine Prevalence and Prevention study of 18,968 people found that 44% of subjects who met the International Classification of Headache Disorders 2nd edition (ICHD-2) criteria for migraine had never received a medical diagnosis of migraine.[4] Furthermore, in an observational study of 2991 subjects who had a medical or self-diagnosis of sinus headache, 88% met the International Headache Society (IHS) criteria for migraine-type headache.[5]

Pathophysiology

Many brain regions and systems are thought to be involved in migraine pathophysiology, including the cerebral cortex, hypothalamus, trigeminocervical complex, thalamus, and meningeal nerves and vessels.[6–10] Additionally, a range of neurotransmitters (eg, serotonin) and neuropeptides (eg, somatostatin) may contribute to the underlying biology of migraine.[11,12] Of these, the calcitonin gene-related peptide (CGRP), a 37-amino acid neuropeptide, is produced in central and peripheral neurons.[8,13,14] CGRP is now widely considered to play a central role in migraine pathophysiology through its interaction with the CGRP receptor, a G-protein coupled receptor expressed in the trigeminovascular system.[8,11,13,14]

Current clinical data suggest that the interaction between CGRP and this receptor regulates key events that underlie migraine pathophysiology, including trigeminovascular neuron sensitization and neuropeptide release.[15–17] Most recently, clinical evidence has demonstrated that monoclonal antibodies disrupting the interaction between CGRP and its receptor are effective preventive treatments for migraine.[18–21]

Diagnosing Migraine

Migraine diagnosis is described in the third edition of the ICHD (ICHD-3), developed by the IHS.[22] To meet ICHD-3 diagnostic criteria for migraine, a person must experience at least 5 headache attacks that each fulfill specific criteria for duration, quality, and severity, and are not better accounted for by a different diagnosis (**Figure 1**).[22]

The Course of a Migraine Attack

Migraine attacks occur over hours to days and consist of several phases. **Figure 2** illustrates potential symptoms that may be associated with each phase and indicates how the symptoms may vary in intensity and duration over the course of a migraine attack.

During the prodromal phase, which may last for up to 48 hours, fatigue, food cravings, sensitivity to light and sound, nausea, neck discomfort, and cognitive symptoms have been reported.[22–26] The aura phase may be shorter (5–60 minutes) and is often characterized by changes in vision, skin sensations, and/or language problems.[22] The ictal (headache) phase is defined by moderate-

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to-severe head pain, but may also include sensitivity to light and sound, nausea and/or vomiting, sensitivity to touch, neck discomfort, cranial autonomic symptoms, and cognitive symptoms.[22,25–27] This phase is the most debilitating and may last up to 72 hours.[22] During the postdrome, which follows headache during a migraine attack, patients may experience sensitivity to light and sound, nausea, fatigue, cognitive symptoms, and neck discomfort for up to 48 hours.[25,28,29] Some of these non-headache pain symptoms may continue into the interictal phase even in the absence of head pain.[27,30–32] Not every migraine patient will experience all symptoms and phases; for example, approximately 30% of patients report aura symptoms, and 60%–70% experience sensitivity to touch.[17,22,33–35]

The characteristic symptoms of migraine help facilitate differential diagnosis from other primary headache disorders including tension-type and cluster headache.[22] **Table 1** summarizes the pre-specified criteria that may be used to identify each headache type.[22] Key distinctive features of migraine are unilateral location, long duration (4–72 hours), frequency, associated symptoms such as nausea and/or vomiting, and sensitivity to light and sound or to touch.[22,33–35]

Figure 1. ICHD-3 Criteria for Migraine Diagnosis[22]

- ☐ ≥5 headache attacks
- ☐ Each attack lasting 4–72 hours
- ☐ Each attack including ≥2 of the following:
  - ○ Unilateral location
  - ○ Pulsating quality
  - ○ Moderate-to-severe pain intensity
  - ○ Aggravated by or causing avoidance of routine physical activity
- ☐ Each attack including ≥1 of the following:
  - ○ Nausea and/or vomiting
  - ○ Photophobia and phonophobia
- ☐ Not better accounted for by another ICHD-3 diagnosis

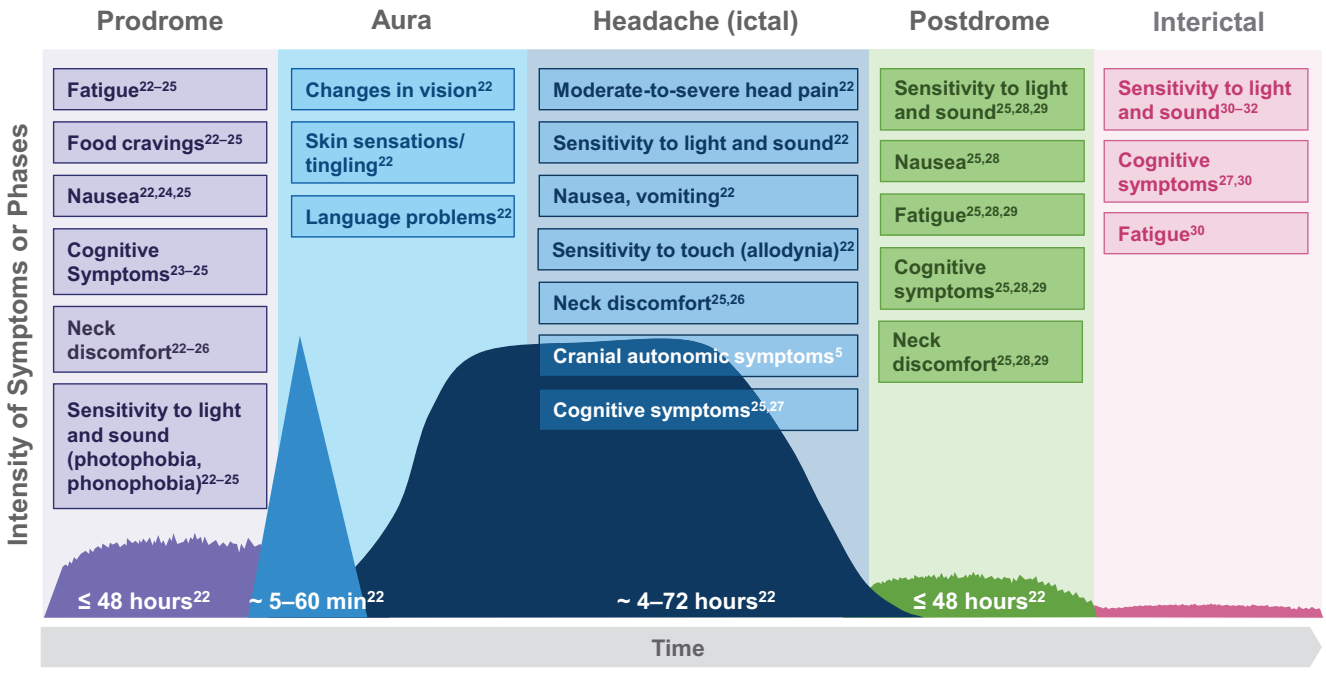
Abbreviation: ICHD, International Classification of Headache Disorders.

Diagnostic Tools and Migraine Classification

An accurate diagnosis of migraine headache depends heavily on obtaining an accurate patient history.[36] Validated diagnostic tools provide a systematic approach to recording and assessing possible migraine symptoms and facilitate diagnosis.[36,37] Both general headache and migraine-specific tools are available, which may be used concurrently to help exclude secondary headache and diagnose primary headache, including migraine.[36,37]

ID Migraine™ is a 9-question assessment that was validated in primary care practices and is considered the gold

Figure 2. Phases of Migraine[22-32,46]



Migraine patients may not experience all phases and listed symptoms, and not all possible symptoms are listed.

Adapted from Blau JN. *Lancet*. 1992;339:1202-1207.

standard for diagnosing migraine.[36,38] A simplified 3-item version assesses nausea, light sensitivity, and headache-related disability.[38] A "yes" response to 2 of the 3 items has high specificity and sensitivity for diagnosis of migraine.[38] In the primary care setting, ID Migraine™ has a positive predictive value of 93.3.[38] The ID Migraine™ tool may be used when migraine is suspected, as it does not screen for other headache types.[36]

For a general record of symptoms, a headache diary may be used by the patient to document the frequency, intensity, duration, and other characteristics of headaches.[36] Diaries can be used in digital or paper format, are simple to use, and may be customized based on the data of interest (eg, symptom history, medication use, or trigger identification).[36] The headache diary is beneficial because the patient can record their symptoms in real time instead of recalling them after a time delay.[36,39] The diary is used to assess general headache symptoms, to help determine whether migraine-specific tests and screening may be beneficial.[36]

SNOOP is a diagnostic screener that may be used to help rule out secondary headaches, based on systemic and neurologic symptoms, onset, other associated conditions, and prior headache history.[37] The elements of SNOOP are red flags for further investigation: **S**ystemic symptoms, **N**eurological symptoms, **O**nset sudden, **O**lder (Onset after age 50), and **P**attern change.[36,37] Completing this screening takes only a few minutes and can help ensure a secondary cause is not overlooked.[37]

The Brief Headache Screen (BHS) is a 7-item self-administered questionnaire to help distinguish between different types of headaches, including episodic headache syndromes and daily headache syndromes. Within the daily syndromes, it can also identify medication overuse headache.[36] The BHS has demonstrated strong agreement with the migraine-specific ID Migraine™ tool.[40]

Once a migraine diagnosis has been established, it can be further refined based on the monthly frequency of headache days.[22,41] Episodic migraine is defined as fewer than 15 headache days per month, whereas chronic migraine is characterized by 15 or more headache days per month (including migraine-like or tension-type headache) for more than 3 months, with headaches fulfilling the diagnostic criteria for migraine on at least 8 of the headache days.[22] While diagnosis is assumed to be stable and is used to guide treatment decisions and gauge outcomes, some patients have natural fluctuations in the severity of the disease (eg, they may transition between chronic and episodic migraine), which may impact treatment decisions.[42]

Table 1. Distinguishing Migraine From Other Primary Headaches[22]

	Tension-type	Migraine	Cluster
Intensity	Mild to moderate	Moderate to severe	Severe or very severe
Location (of head pain)	Often bilateral	Often unilateral	Unilateral, usually behind or around one eye
Physical activity	**Not** aggravated by routine physical activity	Aggravated by routine physical activity	
Duration	30 min–1 week	4–72 hours	15–180 min
Frequency	Infrequent to daily	Recurrent, variable frequency	Once every other day to 8 times per day during clusters
Symptoms (in addition to head pain)	Light OR sound sensitivity (not both) Pericranial tenderness **No** nausea or vomiting	Light and sound sensitivity Nausea/vomiting Aura[17] Sensitivity to touch[33–35]	Eye redness or watering and constricted pupils Nasal congestion and facial sweating Eyelid swelling or drooping
Demographics	Higher prevalence in women than in men[47]	Prevalence in women 2–3 times higher than in men[2]	Prevalence in men 3 times higher than in women

Burden of Migraine

Migraine is one of the most burdensome neurologic diseases.[1] Headache disorders, including migraine, are the second leading cause of years lost to disability worldwide, after low back pain.[1,43] More than half of migraine patients experience severe impairment of daily activities or a need for bed rest during a migraine attack.[2] Many patients also report that their family activities are disrupted, and that they miss everyday activities, such as social obligations.[2,44] Migraine also imposes a substantial economic burden on society through increased health care costs and lost days of work.[45] On average, patients with migraine lose 2–4 work days each month (not including reduced productivity in people with migraine who do go to work).[45]

Conclusion

Migraine affects more than 1 in 10 individuals worldwide[1] and can have a severe and disabling impact on everyday life.[2,44] Migraine is underdiagnosed, undertreated, and frequently misdiagnosed as other common headache disorders.[5] The substantial direct and indirect costs associated with migraine impose a considerable societal burden.[45] While much remains unknown, there is an evolving understanding of the pathophysiology of migraine. A growing body of evidence suggests that the interaction between CGRP and the CGRP receptor and activation of the trigeminovascular system may play a central role.[8,13,14] In sum, migraine is more than just a headache. It is one of the most common and burdensome neurologic diseases.[1,2] Understanding the characteristics and features of migraine and the symptoms that differentiate it from other headache disorders may help facilitate diagnosis and treatment in the primary care setting.

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