Tracing transformation: Chronic migraine classification, progression, and epidemiology

Richard B. Lipton

Neurology 2009;72;S3-S7
DOI: 10.1212/WNL.0b013e3181974b19

Tracing transformation

Chronic migraine classification, progression, and epidemiology

Richard B. Lipton, MD

Address correspondence and reprint requests to Richard B. Lipton, MD, Department of Neurology, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461
rlipton@aecom.yu.edu

ABSTRACT

Migraine attacks sometimes increase in frequency over time. Headache experts conceptualize this process with a model that envisions transition into and out of four distinct states: no migraine, low-frequency episodic migraine (<10 headaches per month), high-frequency episodic migraine (10–14 headaches per month), and chronic migraine (CM, ≥15 headaches per month). Transitions may be in the direction of increasing or decreasing headache frequency and are influenced by specific risk factors. Overall, population studies estimate that patients who have low-frequency episodic migraine or high-frequency episodic migraine will transition to CM at the rate of about 2.5% per year. Two longitudinal population studies, the Frequent Headache Epidemiology study and the ongoing American Migraine Prevalence and Prevention (AMPP) study provide longitudinal population data that has defined the rates of and risk factors for transition. Launched in 2004, the AMPP study has followed a sample of >10,000 migraine sufferers annually for 4 years. Cross-sectional data from the Frequent Headache Epidemiology study and the AMPP study show that patients with chronic daily headaches have lower levels of education and household income. In addition, epidemiologic profiles show that CM sufferers tend to be older and have higher body mass indexes. These studies have also assessed a number of potential risk factors associated with the transition to CM. These include baseline high attack frequency, obesity, stressful life events, snoring, and overuse of certain classes of medication. In particular, opiate and barbiturate combination products contribute to migraine progression, and nonsteroidal anti-inflammatory agents are protective in patients with <10 headache days per month. The influence of medication is modified by both headache attack frequency and frequency of medication use. Although depression and anxiety are associated with an increased risk of new-onset CM, the influence of depression is accounted for by migraine disability assessment scale score, whereas the effect of anxiety may be independent of migraine disability assessment scale score. Emerging data on the longitudinal risk of CM suggest that, in a population at risk, CM may be a preventable disorder.

NEUROLOGY 2009;72 (Suppl 1):S3–S7

Migraine is a common neurologic disorder that has a wide variety of subtypes, many comorbidities, and a variable prognosis.[1] Because a broad range of disorders cause headache, a systematic approach to classification and diagnosis is essential for clinical management.[2] Classification of very frequent headaches is a controversial subject.[3] The International Classification of Headache Disorders (ICHD) is a comprehensive and hierarchical classification system for both primary and secondary headache disorders developed by the International Headache Society.[4] Its second edition, the ICHD-II, reflects improved understanding of some headache disorders and identifies new disorders.[2] It is hoped that the ICHD-II will continue to help improve clinical diagnosis and management of headache.[4]

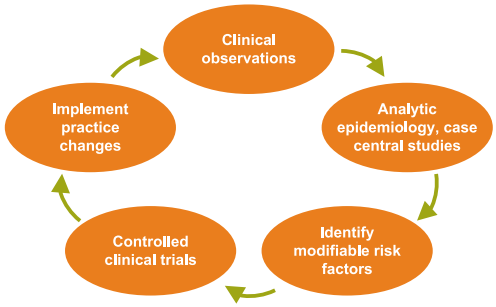
Although most people with primary headaches have two headache days per month or fewer, about 4% of adults experience headaches more days than not.[2,3] Chronic daily headache (CDH) is one of the

From the Department of Neurology, Albert Einstein College of Medicine, Bronx, New York.

Jointly sponsored by the Annenberg Center for Health Sciences at Eisenhower and CogniMed Inc. This program is supported by an independent educational grant provided by Allergan, Inc.

Disclosure: R.B.L. has participated on advisory boards for, consulted for, and received research support from Allergan, Inc., AstraZeneca, Bristol-Myers Squibb Company, GlaxoSmithKline, Novartis Pharmaceuticals Corporation, Ortho-McNeil Neurologics, Inc., and Pfizer Inc.

Figure Epidemiologic cycle. Reproduced with permission[5]



more common headache presentations to headache specialty care centers.[2] There is much to be learned about the biologic mechanisms that lead to progressively worse headache symptoms, and the epidemiologic literature provides insight into factors that affect the risk of headache progression.[3]

It is now possible to design trials to explore the prevention of migraine progression.[1] The epidemiologic cycle provides a framework for linking risk factors discovered in epidemiologic studies to clinical trials and clinical practice (figure).[5] Clinical observations can be used to create hypotheses that support the development of analytic epidemiologic studies.[1] Potential risk factors can be identified from these studies.[1] Risk factor modification, or treatment intended to modify the course of the disease, can then be tested.[1] Ideally, repetition of this cycle will contribute to continued improved care of patients with headache.

Migraine is considered to be in remission when symptoms cease over a prolonged period, often 1 year. Persistent migraine is defined by relative clinical stability with no markers of progression. Migraine that undergoes progression clinically evolves to high-frequency episodic migraine or chronic migraine (CM). Functional changes may accompany migraine progression, including the development of allodynia, and changes in the periaqueductal gray matter. Anatomically, lesions occur both in and outside of the brain as a result of migraine progression.[1,6,7]

CDH comprises disorders characterized by a high frequency of headaches per month (≥15), including medication-overuse headaches.[8] CDH can be subdivided into primary and secondary. Primary CDH is unrelated to a structural or systemic illness and can be grouped into long- or short-duration disorders, whereas secondary CDH has an underlying cause, such as medication overuse, head trauma, cervical spine disorders, or vascular disorders. A headache duration of <4 hours, or short-duration CDH, includes differential diagnoses of cluster headache, paroxysmal hemicrania, idiopathic stabbing headache, hypnic headache, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing. A long-duration CDH is defined as a headache duration exceeding 4 hours. Its primary attributable disorders, with diagnostic criteria defined by ICHD-II, are CM, hemicrania continua, chronic tension-type headache, and new daily persistent headache. Long-duration CDH is a prevalent problem, with ~3% to 5% of the worldwide population experiencing daily or near-daily headaches. Most patients with long-duration primary CDH have CM.

One of the important new changes in ICHD-II was the inclusion of CM, which is defined as pain and symptoms associated with migraine without aura for 15 days or more per month for longer than 3 months, without medication overuse.[2,4] CM causes significant disability, resulting in a negative impact on quality of life and mental health and impairing physical, social, and occupational function.[8,9] Although the terms CM and transformed migraine (TM) were used synonymously in the past, ICHD-II does not recognize TM as separate.[2] One reason CM is now used in place of TM is that a history of transformation often was missing for patients in this subset.[8]

MIGRAINE PROGRESSION OR ESCALATION

Migraine can be a progressive disease in some patients and can transform into CM.[1,10] Many clinical observations have been made regarding migraine and CDH. CM is common and may emerge, remit, and re-emerge. Although ICHD-II does not include medication overuse in the definition of CM, CM is associated with medication overuse, as well as depression and other comorbidities. Further, medication overuse has been demonstrated to coexist in most patients with CDH, and improvement can occur once the overused headache medication is withdrawn.[11] In some studies, CM developed faster in patients who overused triptans and used fewer single dosages than patients who overused ergots or analgesics.[11] Patients with an intermediate headache frequency of 6 to 9 days per month were at greater risk for headache chronicity, and this risk was even higher for patients with the critical frequency of 10 to 14 headache days per month.[11]

Migraine shares common features with episodic pain disorders, such as postoperative pain or posttraumatic pain, and with chronic pain disorders, such as osteoarthritis or painful neuropathy.[1] Consequently, migraine can be considered a chronic disorder with episodic attacks.[1,12] Progression may be physiologic, anatomic, or clinical, which leads to CM.[1,13] Progression may be activated by mecha-

nisms that produce migraine attacks, such as cortical spreading depression, or by the results of the attacks, such as lesions in the periaqueductal gray matter.[13]

Because migraine does not progress in most patients, applying risk factors to identify individuals at high risk for progression has become an important goal in public health research.[1,14] Risk factors can be divided into those that are easily modifiable and those that are not.[1] Age and gender are nonmodifiable risk factors, for instance, whereas socioeconomic status and head injury are not easily modified.[1] Easily modifiable risk factors for migraine progression include headache frequency, allodynia, obesity, acute medication overuse, depression, stressful life events, caffeine consumption, and snoring.[1] Attack frequency and obesity are among the most important risk factors for migraine progression.[1] Headache frequency and medication overuse act in concert as risk factors for chronicity of headache.[11,12] However, because some patients can experience CM without medication overuse and others overuse medication without experiencing chronic headache, medication overuse is not the sole determinant of migraine progression.[11] Important approaches that may reduce the risk of developing CDH include decreasing headache frequency with behavioral and pharmacologic interventions, weight loss and maintenance of ideal body weight, avoiding medication and caffeine overuse, treating sleep disturbances and snoring, and screening for depression and other psychiatric comorbidities.[15]

In clinic-based samples, the prevalence and severity of somatic symptoms were greater in patients with chronic headache and in those with severe headache-related disability.[16] Chronic headache, severe disability, and high somatic symptom severity were associated with major depressive disorder. Major depression may increase pain perception, and painful symptoms may be a manifestation of major depression.

Recognizing risk factors for CDH is an important step toward identifying methods to manage CDH more effectively and determining preventive strategies.[17] Head and neck injuries have long been associated with headache.[17] A recent study suggested that headache related to head and neck injuries may be a unique subclassification of CDH, based on increased frequency of migraine with aura and the significant increase in frequency of daily headache (>30 per month).[17] Sleep disorders may result from or may cause headache.[18] Chronic headache and depression may cause disturbed sleep, and sleep deprivation or excessive sleep may cause migraine attacks.[18] Sleep-disordered breathing has also been strongly associated with cluster headache.[18] Frequent snoring, even in the absence of sleep apnea, has been associated with headache.[18] Correcting obstructive sleep apnea has been reported to decrease or eliminate headache for some patients.[18] Women are approximately twice as likely as men to be affected by CDH.[3] Individuals with migraine or frequent headache are more likely to have coexistent nonheadache pain, especially related to musculoskeletal pain or arthritis, compared with those without headache.[19] Lower socioeconomic status is a risk factor for CDH incidence and is also associated with a poorer prognosis.[3]

RESULTS FROM THE AMERICAN MIGRAINE PREVALENCE AND PREVENTION STUDY Migraine affects ~12% of adults in Western countries, and its prevalence in the United States is about 18% in women and 6% in men.[20] The American Migraine Prevalence and Prevention (AMPP) 2004 study was undertaken to reassess the prevalence of migraine in the United States and further investigate the need for and use of preventive headache treatment. The epidemiology, burden, and patterns of migraine treatment were assessed using methods that permitted comparisons with the results of the American Migraine Studies (AMS)-I and AMS-II.

Questionnaires were mailed to a representative sample of 120,000 US households.[20] The survey included questions about use of health care, preventive medication use, and the migraine disability assessment scale to determine the level of impairment. A panel of headache experts defined operational criteria for preventive treatment, which resulted in three groups being identified in terms of their need for preventive treatment. The first group was offered preventive treatment, the second group was considered for preventive treatment, and prevention was not indicated for the third group. These recommendations were based on reported headache days per month and degree of impairment during headache attacks. The group offered preventive treatment comprised migraine patients who reported headache 6 days or more per month, 4 days or more with at least some impairment, or 3 days or more with severe impairment or impairment requiring bed rest. Prevention was considered for migraine patients with four or five migraine days per month with normal function, three migraine days with some impairment, or two migraine days with severe impairment. Preventive treatment was not offered if there were <4 headache days per month and no impairment or if there were ≤1 headache day per month regardless of impairment level.

In concert with previous studies, the AMPP 2004 study demonstrated that the epidemiologic profile of migraine has remained stable in the United States

Table 1 MIDAS in CM and EM: lost days per 3 months[9]

	CM	EM
Missed work or school, d	2.4	0.54
≥50% Reduced productivity at work or school, d	10.4	1.7
Incomplete household work or chores, d	21.4	3.5
≥50% Reduced productivity in household work or chores, d	18.7	2.6
Missed time with family, social, or leisure activities, d	10.5	1.7
Total	63.4	10.0

MIDAS = migraine disability assessment scale; CM = chronic migraine; EM = episodic migraine; d = days.

during the past 15 years.[20] It also confirmed major findings of the AMS-I and AMS-II: migraine prevalence was higher in whites than in blacks, higher in women compared with men, and higher in individuals with lower family income.[20] The negative impact of migraines on quality of life was also confirmed, because >50% of all individuals who reported migraines experienced severe impairment during attacks (table 1).[9]

Another finding of the 2004 study was the underutilization of preventive treatment, such that only 12.4% of respondents were using preventive treatment though 38.8% were potentially candidates for it.[20] Although the levels of disability caused by migraine in France and Latin America are similar to that in the United States, only 6% of migraine patients in France and 2% in Latin America received preventive treatment, illustrating the variable application of preventive treatment in different parts of the world. Strengths of this AMPP 2004 study include the sample size, its representativeness of the US population with respect to demographic characteristics, and the use of questionnaires that were compatible with the AMS-I and AMS-II. The AMPP 2004 study was followed up with the 24,000 surveys of the AMPP 2005 study.[9] This study compared the prevalence, characteristics, and comorbidity of CM and episodic migraine (EM). The CM group had lower educational levels and lower household incomes than the EM group. Major depression, anxiety disorder, and other chronic pain disorders were more likely to occur with CM than with EM. CM was also more likely to have a greater negative impact on quality of life and cause impairment. The AMPP 2006 study involved 20,639 surveys and attempted to reach all available headache sufferers from 2005.[21] On the basis of the updated information, the rate of new onset TM/CM was determined to be 2.5%. Interestingly, the use of barbiturates and opiates in 2005 predicted CM in 2006. Other significant risk factors for CM in the longitudinal analysis included obesity, migraine disability assessment scale score, allodynia, anxiety, and depression (table 2).

The results from the AMPP 2006 study also suggested that risk factors vary by transition.[22] Age, sex, depression, and anxiety were implicated in the transition from no migraine to EM, and obesity, allodynia, and anxiety were determined to be risk factors when EM transitions to CM (table 3).

REMEDIABLE RISK FACTORS FOR CDH FROM FREQUENT HEADACHE CDH was found to be more prevalent in women, individuals with lower educational and socioeconomic levels, white patients, and those who were previously married.[23] Risk of CDH was increased in individuals with lifetime injuries to the head or neck, even if the injuries were remote to the onset of CDH.[3] CDH was also associated with diabetes, arthritis, and obesity.[23] Obesity, which is defined as a body mass index 30 or higher, has been shown to be predictive of 1-year CDH incidence.[3] Headache remission was more likely to occur in non-white patients, individuals with higher education, and those who are married.[23] Ultimately, the identification of individuals at higher risk of head-

Table 2 Use of barbiturates and opiates in 2005 predicts CM in 2006[21]

	Women		Men		
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Overall Adjusted OR (95% CI)
Acetaminophen	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Prescribed medication + NSAIDs	0.88 (0.62–1.26)	0.97 (0.67–1.41)	0.85 (0.46–1.55)	0.93 (0.46–1.88)	0.96 (0.69–1.34)
Triptans	1.11 (0.76–1.63)	0.93 (0.62–1.40)	2.37 (1.20–4.71)	2.11 (0.97–4.63)	1.05 (0.73–1.50)
Barbiturate compounds	2.29 (1.44–3.64)	1.97 (1.21–3.23)	1.42 (0.43–4.72)	1.29 (0.38–4.37)	1.73 (1.10–2.73)
Opiates	1.74 (1.15–2.63)	1.28 (0.81–1.97)	3.48 (1.74–6.96)	2.76 (1.20–6.38)	1.44 (1.10–2.08)
Isometheptene compounds	0.94 (0.41–2.16)	0.85 (0.36–2.02)	1.64 (0.38–7.09)	1.60 (0.34–7.54)	0.93 (0.44–1.98)

CM = chronic migraine; OR = odds ratio; CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug.

Table 3 Risk factors for new onset of M (λ_1) and progression of EM (λ_2) vary by transition[22]

	No migraine $\xrightarrow{\lambda_1}$ EM $\xrightarrow{\lambda_2}$ CM	
	No migraine $\xrightarrow{\lambda_1}$ migraine	EM $\xrightarrow{\lambda_2}$ CM
Age	+	–
Sex	+	–
Obesity	–	+
MIDAS score	?	+
Allodynia	–	+
Depression	+	–
Anxiety	+	+

M = migraine; λ = transition rate; EM = episodic migraine; CM = chronic migraine; MIDAS = migraine disability assessment scale

ache progression may improve the treatment of CDH.[23] Such individuals may be advised to lose weight, avoid or limit barbiturates and opiates, modify stress, and seek treatment for snoring, if needed.

REFERENCES

1. Lipton RB, Bigal ME. Looking to the future: research designs for study of headache disease progression. Headache 2008;48:58–66.
2. Lipton RB, Bigal ME, Steiner TJ, Silberstein SD, Olesen J. Classification of primary headaches. Neurology 2004;63:427–435.
3. Scher AI, Midgette LA, Lipton RB. Risk factors for headache chronification. Headache 2008;48:16–25.
4. Olesen J, Steiner TJ. The international classification of headache disorders, 2nd edn (ICDH-II). J Neurol Neurosurg Psychiatry 2004;75:808–811. Editorial.
5. Lipton RB, Bigal ME. Looking to the future: research designs for study of headache disease progression. Headache 2008;48:58–66.
6. Welch KM. Concepts of migraine headache pathogenesis: insights into mechanisms of chronicity and new drug targets. Neurol Sci 2003;24(suppl 2):S149–S153.
7. Welch KM, Nagesh V, Aurora SK, Gelman N. Periaqueductal gray matter dysfunction in migraine: cause or the burden of illness? Headache 2001;41:629–637.
8. Silberstein SD. Chronic daily headache. J Am Osteopath Assoc 2005;105(4 suppl 2):S23–S29.
9. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. Neurology 2008;71:559–566.
10. Bigal ME, Rapoport AM, Sheftell FD, Tepper SJ, Lipton RB. The International Classification of Headache Disorders revised criteria for chronic migraine: field testing in a headache specialty clinic. Cephalalgia 2007;27:230–234.
11. Katsarava Z, Schneeweiss S, Kurth T, et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. Neurology 2004;62:788–790.
12. Haut SR, Bigal ME, Lipton RB. Chronic disorders with episodic manifestations: focus on epilepsy and migraine. Lancet Neurol 2006;5:148–157.
13. Bigal ME, Lipton RB. Concepts and mechanisms of migraine chronification. Headache 2008;48:7–15. Review.
14. Bigal ME, Lipton RB. Modifiable risk factors for migraine progression. Headache 2006;46:1334–1343.
15. Bigal ME, Lipton RB. Modifiable risk factors for migraine progression (or for chronic daily headaches): clinical lessons. Headache 2006;46(suppl 3):S144–S146.
16. Tietjen GE, Brandes JL, Digre KB, et al. High prevalence of somatic symptoms and depression in women with disabling chronic headache. Neurology 2007;68:134–140.
17. Couch JR, Lipton RB, Stewart WF, Scher AI. Head or neck injury increases the risk of chronic daily headache: a population-based study. Neurology 2007;69:1169–1177.
18. Scher AI, Lipton RB, Stewart WF. Habitual snoring as a risk factor for chronic daily headache. Neurology 2003;60:1366–1368.
19. Scher AI, Stewart WF, Lipton RB. The comorbidity of headache with other pain syndromes. Headache 2006;46:1416–1423.
20. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF; AMPP Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68:343–349.
21. Bigal ME, Serrano D, Buse D, et al. Acute migraine medications and evolution from episodic to chronic migraine: a longitudinal population-based study. Headache 2008;48:1157–1168.
22. Bigal ME, Lipton RB. Clinical course in migraine: conceptualizing migraine transformation. Neurology 2008;71:848–855.
23. Scher AI, Stewart WF, Ricci JA, Lipton RB. Factors associated with the onset and remission of chronic daily headache in a population-based study. Pain 2003;106:81–89.

Tracing transformation: Chronic migraine classification, progression, and epidemiology

Richard B. Lipton

Neurology 2009;72;S3-S7
DOI: 10.1212/WNL.0b013e3181974b19