Research Submission

Chronic Migraine, Classification, Differential Diagnosis, and Epidemiology

Richard B. Lipton, MD

Chronic migraine (CM) is the most disabling of the 4 types of primary chronic daily headache (CDH) of long duration, a syndrome defined by primary headaches 15 or more days per month for at least 3 months with attacks that last 4 hours or more per day on average. CDH of long duration includes CM, chronic tension-type headache, new daily persistent headache, and hemicrania continua. CM affects approximately 2% of the adult population in Western countries, imposing substantial burdens on individual sufferers and their families and, more broadly, upon society. Although this disorder is highly disabling and prevalent, it remains largely underdiagnosed and undertreated.

Diagnosing CM requires a systematic approach that includes these steps: (1) exclude a secondary headache disorder, and (2) diagnose a specific primary headache syndrome based on frequency and duration, for example, short-duration episodic, long-duration episodic, or long-duration chronic. CM usually develops as a complication of episodic migraine after a period of increasing headache frequency. This migraine transformation is associated with a number of risk factors, some of which cannot be modified, including age and race. Other risk factors for CM are modifiable, such as obesity, snoring, head injury, stressful life events, and overuse of opioids and barbiturates. However, risk factor modification has not yet been shown to decrease the likelihood of CM onset.

According to a cross-sectional analysis of data from the American Migraine Prevalence and Prevention study published this year in *Journal of Neurology, Neurosurgery, and Psychiatry*, when compared to patients with episodic migraine, patients with CM were significantly less likely to be employed full-time and almost twice as likely to be occupationally disabled. In addition, patients with CM were nearly twice as likely to have anxiety, chronic pain, or depression. Furthermore, patients with CM had higher cardiovascular and respiratory risk, were 40% more likely to have heart disease and angina, and were 70% more likely to have a history of stroke. These findings highlight the paramount importance of clinical vigilance, accurate diagnosis, and appropriate, effective management – including treatment or referrals – to improve patient outcomes.

Key words: chronic migraine, epidemiology, differential diagnosis

From the Albert Einstein College of Medicine, Bronx, NY, USA.

Address all correspondence to R.B. Lipton, Albert Einstein College of Medicine – Neurology, 1165 Morris Park Avenue Rousso Building, Room 332, Bronx, NY 10461, USA, email: rlipton@aecom.yu.edu

Chronic migraine (CM) is a complication of migraine characterized by headache attacks that occur more days than not. Although it is much less common than episodic migraine (EM), it is substantially more debilitating. Recent progress in the classification and diagnosis of CM, new findings in descriptive epidemiology, and emerging risk factors that predict the chronification of migraine are setting the stage for improvements in diagnosis, treatment, prevention, and monitoring.

CLASSIFICATION AND DIFFERENTIAL DIAGNOSIS

Refinements in the classification and differential diagnosis of CM reflect advances in our understanding of this highly disabling primary headache disorder. Of the established definitions, the Silberstein and Lipton revised criteria for transformed migraine (TM) are considered the most applicable to daily clinical practice.[1] Alternative definitions continue to be field-tested in an effort to establish broadly accepted criteria applicable to clinical practice as well as to epidemiologic studies and clinical trials.

Broadly, headache diagnosis can be conceptualized as a process:

- Exclude secondary causes of headache by searching for red flags based on a history, a general medical and neurologic examination, and diagnostic tests, if necessary[2];

- Classify the primary headache disorder according to attack frequency and headache duration into one of 4 categories: chronic daily headache (CDH) of long or short duration and episodic headache of long or short duration[2,3] (Table 1);

- Identify the specific headache disorder within that category.[2]

Chronic daily headache and episodic headache can be of long duration (attacks lasting ≥4 hours) or short duration (attacks lasting <4 hours on average).[2,3] Episodic headache is defined by a headache frequency of fewer than 15 days per month; CDH is defined by 15 or more headache days per month.

Table 1 outlines the most common disorders within the 4 major categories of primary headache. This article addresses the 4 disorders comprising CDH of long duration: chronic tension-type headache (CTTH), new daily persistent headache (NDPH), hemicrania continua, and CM.

The pain of CTTH is bilateral, nonpulsating, of mild to moderate intensity, and not aggravated by routine physical activity; generally, migrainous features are absent.[5] Photophobia, phonophobia, or mild nausea may occur, but as migraine features increase, a migraine diagnosis becomes more likely.[4]

New daily persistent headache pertains to persons whose headaches are unremitting from onset or within 3 days of onset.[4,5] The second edition of the International Classification of Headache Disorders

Table 1.—Classification of the More Common Primary Headache Disorders

Duration	Frequency	
	Chronic (15+ days/month)[2]	Episodic (<15 days/month)[4]
Long (≥4 hours)	Chronic daily headache of long duration • Chronic migraine • Chronic tension-type headache • New daily persistent headache • Hemicrania continua	Episodic headache of long duration • Episodic migraine • Episodic tension-type headache
Short (<4 hours)	Chronic daily headache of short duration • Chronic cluster headache • Chronic paroxysmal hemicrania • SUNCT	Episodic headache of short duration • Episodic cluster headache • Episodic paroxysmal hemicrania

SUNCT = short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing.

(ICHD-2) specifies that the headaches cannot have more than one migrainous feature (photophobia, phonophobia, or mild nausea).[5] However, experts are increasingly recognizing a subtype of NDPH in which migrainous features are fairly prominent (R. B. Lipton, oral communication, 2010).[4,6]

Hemicrania continua manifests as continuous, strictly unilateral pain of moderate intensity with exacerbations of severe pain.[5] The pain responds completely to therapeutic doses of indomethacin,[5] making hemicrania continua perhaps the only primary headache disorder defined in part by response to treatment.[4] During exacerbations of hemicrania continua, the patient may experience ipsilateral autonomic features, including a droopy eyelid, lacrimation, or rhinorrhea. Other features are possible nausea and photophobia.[7] Physicians who focus only on nausea, photophobia, and phonophobia may mistakenly diagnose migraine, observing the painful unilateral exacerbations with autonomic features. There is also a risk of a misdiagnosis of cluster headache.[4] Learning whether the patient's headache ever subsides completely will aid in distinguishing between chronic cluster headache and hemicrania continua.

The definition of CM has evolved considerably, but the essence of the definition is CDH linked to migraine. Migraine pain is defined by at least 2 of the following: unilateral location, moderate to severe, pulsating quality, and aggravated by physical activity.[5] Migraine-associated symptoms include nausea or photophobia or phonophobia. Ninan T. Mathew, MD, identified a syndrome of chronic daily headaches with migrainous features. In that 1982 publication, he argued that many patients thought to have mixed tension-vascular headache actually suffered from a syndrome that evolved from migraine.[4,8] This syndrome, termed transformed migraine, was associated with medication overuse in the majority of cases. Criteria for TM were subsequently proposed and tested. TM was defined as CDH of long duration (≥15 days/month) with headache duration of 4 hours or longer and at least one link to migraine, for instance, a history of EM or a history of current headaches that meet ICHD-2 criteria for migraine.[4,9] As with the other primary headache types, TM requires the exclusion of secondary headache.

Neither TM nor CM was included in the first edition of the ICHD, but CM was incorporated in ICHD-2 as a complication of migraine.[4] While the term TM has not been eliminated from common usage with the publication of ICHD-2, the term CM was codified. CM was defined initially as migraine without aura on 15 or more days per month for longer than 3 months in the absence of medication overuse.[5]

Field-testing soon revealed that the criteria for CM proposed by ICHD-2 are so restrictive that most patients with TM are excluded. Bigal and colleagues empirically tested 3 alternative criteria for CM by conducting a field test to evaluate the clinical records and headache diaries of 638 patients with CDH.[10] An analysis of the headache diaries revealed that 557 (87.3%) of the patients had TM according to Silberstein–Lipton criteria; 70.9% were female and ranged in age from 18 to 75 years. Of the 557 patients, 62.5% had TM with medication overuse.

After applying the ICHD-2 definition of CM and including patients who overuse medications, only 5.6% of the cohort without medication overuse and 10.2% with medication overuse met the criteria for CM.[4,10] Evident was the need for a definition of CM that would be acceptable to ICHD-2 while including a larger population of patients with TM seen in clinical practice.[4]

A series of alternative definitions for CM were tested in patients who had headache diary confirmation of TM according to the Silberstein–Lipton definition.[11] A definition including patients who had migraine or probable migraine on at least 15 days per month captured 47.8% of the TM group. Including patients with migraine or probable migraine on at least 50% of the 15 or more headache days per month captured 87.9%. Recognizing patients with migraine without aura on at least 8 days per month or responding to migraine-specific treatment captured 92%.[4] By counting patients with 15 or more headache days per month and 8 or more days per month of migraine or probable migraine, 94.9% were captured.[11]

Based on these and other data, the Headache Classification Subcommittee of the International Headache Society developed a revision to the criteria for CM, referred to as CM-R, to enable headache physicians to diagnose CM and develop treatments
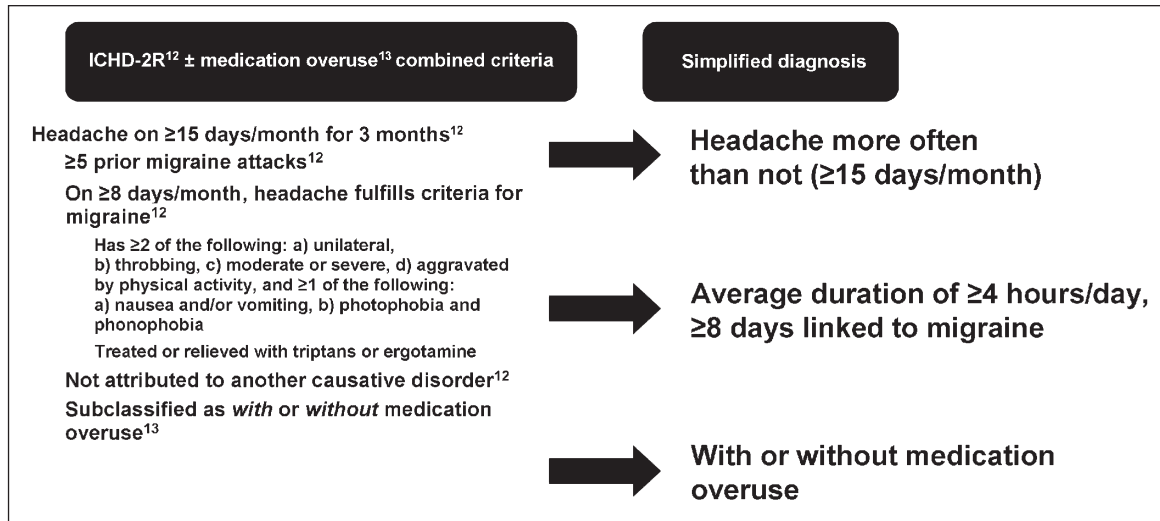
Figure.—Chronic migraine: current state of classification and diagnosis. ICHD-2R, International Classification of Headache Disorders, 2nd edition, revised.

for their patients. From the alternatives described above, the classification subcommittee chose to define CM as follows: The patient has CDH for at least 8 days per month for at least 3 months, and the patient meets the criteria for migraine without aura and/or has a response to migraine-specific medication.[4,12] That definition allowed investigators to capture 95% of the TM group, rather than merely 6%.[4]

Coincident with these events, Silberstein, Bigal, and Lipton were asked to recommend a definition for CM for clinical trials.[4] Their description, "migraine or probable migraine on at least 50% of days," largely overlaps with the ICHD-2 CM-R definition. Hence, the definition of CM used in some clinical trials for migraine therapies has diverged from the ICHD-2 CM-R definition.

In clinical practice, it is challenging to operationalize the CM-R definition. Patients may not be able to retrospectively report the number of headaches with migraine, features, or a response to migraine-specific medication over a 3-month period, so detailed diaries may be employed to capture this information more accurately. The requirement "at least 8 days per month" may prove challenging in clinical practice and is not practical for epidemiologic studies unless diaries are available.[4] The Figure offers the simpler variant of that definition that many headache specialists apply.

Chronic migraine is often complicated by medication overuse.[13] Including absence or presence of medication overuse in the definition conveys information useful for clinical trials and clinical practice.[4] It is important to distinguish between CM with or without medication overuse because, although medication overuse does not alter the diagnosis, it does change the treatment approach.

EPIDEMIOLOGY

The estimated prevalence of CM worldwide ranges widely, but the majority of studies estimate 1% to 3%.[14-16] Although CM is generally thought to be an uncommon migraine subtype, especially compared with EM, it is more common than epilepsy and virtually all other neurologic disorders.[4] Recent epidemiologic studies continue to clarify the relationship between EM and CM.

The American Migraine Prevalence and Prevention (AMPP) study was a large-scale investigation of the prevalence and epidemiology of migraine and CM in the USA.[17] In the 2004 survey, Lipton and colleagues screened a representative sample of 120,000 households for data on 162,576 people aged 12 years and older. From 2004 to 2009, the investigators followed a subgroup of 28,601 people older than age 12 years with severe headache. In the 2005 follow-up, Lipton et al identified 15,757 people with episodic

headache, of whom 11,338 had migraine, 2929 had probable migraine, 1395 had tension headache, and 95 had other forms of headache. Of the 820 respondents who had CDH, 655 met the criteria for TM and 165 met criteria for other types of CDH (R.B. Lipton, written communication, 2010).

Study data indicated that CM sufferers were slightly older on average than EM sufferers, had a higher mean body mass index (BMI), and had somewhat lower educational levels and household incomes than did the EM group.[18] CM sufferers were less likely to be employed full-time (CM, 37.8%; EM, 52.3%) and almost twice as likely to be disabled (CM, 20.0%; EM, 11.1%). There were no major differences between the 2 groups in terms of gender, race, or insurance status.

Additional AMPP data indicated that a number of diseases and disorders are more common in patients with CM than in those with EM.[18] Psychiatric and pain disorders associated significantly more often with CM than EM include:

- Arthritis: CM, 33.6%; EM, 22.2%; odds ratio (OR), 1.71; 95% CI, 1.43-2.05; *P* < .001.
- Chronic pain disorders other than migraine: CM, 31.5%; EM, 15.1%; OR, 2.49; 95% CI, 2.08-2.97; *P* < .001.
- Anxiety: CM, 30.2%; EM, 18.8%; OR, 1.80; 95% CI, 1.51-2.15; *P* < .001.
- Depression (depression criteria were measured by a validated depression scale, a 9-item patient health questionnaire [PHQ-9], or by self-report of a physician diagnosis.): CM, 30.2%; EM, 17.2%; OR, 2.00; 95% CI, 1.67-2.40; *P* < .001.
- Depression (self-report of physician diagnosis): CM, 42.2%; EM, 25.6%; OR, 1.99; 95% CI, 1.68-2.34; *P* < .001.
- Bipolar disorder: CM, 4.6%; EM, 2.8%; OR, 1.56; 95% CI, 1.06-2.31; *P* = .024.

Comorbidity rates for obesity and certain cardiovascular disorders are also significantly higher in patients with CM than EM[18]:

- Obesity (BMI ≥ 30): CM, 25.5%; EM, 21.0%; OR, 1.24; 95% CI, 1.03-1.50; *P* = .020.

- Circulation problems: CM, 17.3%; EM, 11.4%; OR, 1.51; 95% CI, 1.21-1.87; *P* ≤ .001.
- Heart disease: CM, 9.6%; EM, 6.3%; OR, 1.43; 95% CI, 1.08-1.90; *P* = .012.
- High blood pressure: CM, 33.7%; EM, 27.8%; OR, 1.23; 95% CI, 1.03-1.47; *P* = .021.
- Stroke: CM, 4.0%; EM, 2.2%; OR, 1.65; 95% CI, 1.09-2.52; *P* = .019.

Similarly, various respiratory conditions are significantly more likely to be comorbid in patients with CM than in those with EM[18]:

- Allergies or hay fever: CM, 59.9%; EM, 50.7%; OR, 1.47; 95% CI, 1.25-1.73; *P* ≤ .001.
- Asthma: CM, 24.4%; EM, 17.2%; OR, 1.53; 95% CI, 1.27-1.84; *P* ≤ .001.
- Bronchitis: CM, 19.2%; EM, 12.9%; OR, 1.54; 95% CI, 1.25-1.89; *P* ≤ .001.
- Chronic bronchitis: CM, 9.2%; EM, 4.5%; OR, 1.99; 95% CI, 1.49-2.65; *P* ≤ .001.
- Emphysema or chronic obstructive pulmonary disease: CM, 4.9%; EM, 2.6%; OR, 1.73; 95% CI, 1.18-2.54; *P* = .005.
- Sinusitis: CM, 45.2%; EM, 37.0%; OR, 1.39; 95% CI, 1.18-1.63; *P* ≤ .001.

In summary, CM and EM are associated with a number of psychiatric and medical disorders, and every comorbidity associated with EM is more strongly associated with CM.[18] Therefore, CM carries not only a burden of pain but also a burden of comorbid disorders[4] and is more disabling than EM.[18,19] The migraine disability assessment scale (MIDAS) captures lost days in 3 domains: paid work or school, household work, and non-work activities.[20] The mean MIDAS score in a population with CM is 63.4, compared with a mean score of 10 for people with EM (Table 2).[4] For EM, severe disability scores 20 or higher. Thus, the mean MIDAS score for chronic migraineurs is 3 times higher than for those with EM.

LONGITUDINAL RELATIONSHIP BETWEEN EM AND CM

When followed over time, a subgroup of persons with EM experience CM (headaches on more days

Table 2.—Migraine Disability Assessment Scale in Chronic Migraine and Episodic Migraine[4]

	Lost Days Per 3 Months†	
	Chronic Migraine	Episodic Migraine
Missed work or school	2.4	0.54
Reduced productivity at work or school of ≥50%	10.4	1.7
Missed household work or chores	21.4	3.5
Reduced productivity in household work or chores of ≥50%	18.7	2.6
Missed days of family, social, or leisure activity	10.5	1.7
Total	63.4	10.0

†Values represent the number of days in the past 90 days.

than not).[21] Chronification from low-frequency to high-frequency headache is often gradual, with eventual CM a possibility. Both EM and CM may improve or remit. In some patients, monthly headache frequency fluctuates above and below the diagnostic threshold for CM.[4]

The AMPP longitudinal study evaluated factors in persons with EM in a given year that predicted true new onset of CM in the subsequent year.[22] From 2005 to 2006, 8219 patients with EM provided follow-up data: 6805 (82.8%) were found to have migraine, 209 (2.5%) had new-onset CM or TM, and 1205 (14%) had other outcomes.

Study risk factors for chronification included lower socioeconomic status, obesity, snoring, comorbid pain, head or neck injury, stressful life events, high caffeine intake, and overuse of certain medications.[23] Several additional risk factors for chronification were reported: anxiety, depression, and allodynia.[24] In a 2009 review, Bigal and Lipton also cited these risk factors for the clinical chronification of migraine.[21]

Of 4 risk factors for chronification to CM (cutaneous allodynia, anxiety, disability, and depression), disability as measured by MIDAS was the best predictor of chronification (OR, 2.91; CI, 0.9-9.1).[24]

In recent years, a substantial amount of research has identified various risk factors for chronification from EM to CM. Furthermore, there has been a growing recognition that both EM and CM have refractory variants.[25,26] Even preliminary evidence clearly suggests that risk factor intervention prevents chronification, and headache physicians should take efforts not only to treat CM effectively but also to prevent its development in patients at risk for chronification from episodic to chronic disease.[4]

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