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Are Episodic and Chronic Migraine One Disease or Two?

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Abstract Migraine is a debilitating headache disorder that has a significant impact on the world population, in both economic and sociologic capacities. Migraine has two main categories: (1) chronic migraine (CM), defined as the patient having 15 or more headache days per month, with at least five attacks fulfilling measures for EM with aura or EM without aura, and (2) episodic migraine (EM), defined as less than 15 headache days per month. With this definition, CM can only exist in the presence of EM, and it questions whether the two are separate diseases. Migraine has a significant impact on the population, as each year, about 2.5 % of patients with EM develop new-onset CM (Manack et al., Curr Pain Headache Rep 15:70–78, 2011) (Loder et al. Headache 55:214–228, 2015), with certain risk factors being evident only with CM. In addition, there are comorbid diseases that are only associated with CM, suggesting two separate diseases rather than one. Differentiation in response to treatments, both preventive and abortive, demonstrates both a similarity and a difference in EM versus CM. Also, comparing the two processes based upon functional imaging has been a recent development, beginning to show a physiological difference in regional cortical thickness, cortical surface area, and regional volumes in patients with EM and CM. Evidence regarding whether EM and CM demonstrate one disease with a significant level of complication or if two independent processes is inconclusive, and additional research must be performed to further characterize their relationship.

Keywords Migraine · Chronic migraine · Classification · Epidemiology · Episodic · Comorbidity · Treatment

This article is part of the Topical Collection on *Episodic Migraine*

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Introduction

Migraine is one of the most significant causes of disability with substantial world economic and psychosocial impact. It is estimated to affect 14 % of the population worldwide [1••] with a prevalence of 11.7 % in the USA [2]. The World Health Organization (WHO) ranks migraine 19th among causes for years lived with disability [1••]. It was also ranked the third most prevalent disorder and seventh-highest specific cause of disability worldwide [3••]. Migraine is a disease that knows no geographic boundary as it has been described on every inhabitable continent; however, there is variance in ethnicities and sex.

Migraine is a clinical diagnosis that cannot be made through laboratory or radiologic investigations. Therefore, understanding the definition is imperative to arrive at an accurate diagnosis. Migraine is currently defined by the International Classification of Headache Disorder third edition (ICHD-3) as a recurrent headache disorder of at least five attacks lasting 4–72 h, which are required to fulfill the following criteria: (a) unilateral location, (b) pulsating quality, (c) moderate or

severe pain intensity, (d) aggravation by or causing avoidance of physical activity, and (d) at least one of the following criteria: nausea and/or vomiting and photophobia and phonophobia [3••].

It can be further subdivided into episodic migraine (EM) and chronic migraine (CM). EM is defined as migraine that lasts 0 to 14 headache days per month, while chronic migraine includes 15 or more headache days per month (tension-like and/or migraine-like) for more than 3 months [1••]. More specifically, CM is required to present migraine with or without aura on 8 or more days per month for at least 3 months or believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative [3••].

There is debate as to whether EM and CM are the same entity versus two distinct disease processes. Understanding the parameters of EM and CM allows for a practitioner to identify differences in severity of pain, forms of treatment, and debilitating factors. Associated comorbidities such as anxiety, depression, obesity, chronic pain disorders, and cardiovascular elements may guide treatment and education and ultimately impact patient outcomes.

This article will review several areas to determine whether EM and CM should be categorized under the same disease with a higher level of complication or whether the two are separate conditions. A more comprehensive understanding will better equip those in the medical profession as well as help those who suffer from these conditions deal with the disease, determine risk of complications, and decide on management and course of action. We will make our analysis based upon (1) definition of the conditions, (2) epidemiologic data, (3) comorbidities, (4) response to treatment, and (5) functional imaging. With the implementation of ICD-10 in the USA and the acknowledgment of ICD-11, it is also important to distinguish whether these are separate conditions or a complication of an underlying disease in order to better determine epidemiology coding and prognosticators.

Definition

The discussion of whether CM and EM are distinct versus similar entities should involve examination of their definitions. Currently, the diagnosis of CM is based upon the fulfillment of EM parameters. As per the ICHD-3, the diagnostic criterion for CM relies on the patient having at least five attacks fulfilling measures for EM with aura or EM without aura as opposed to being described independently using specific characteristics associated with CM [3••]. Essentially, CM can only exist in the presence of EM. As such, it can be argued that there is a direct connection between CM and EM (at least as per following ICHD-3 criteria) centered through the definition of each.

Additionally, to fulfill Section C of the ICHD-3 criteria, the patient may simply believe the headache is a migraine at onset [3••]. By common vernacular, migraine is considered to be a severe head pain. If the patient believes he or she was experiencing a migraine, but instead was experiencing another type of headache, this would be consistent with the ICHD-3 but would be very questionable in helping define the condition. The possibility of the patients experiencing a variety of cranial pains in CM suggests a more independent process and that other headache types may be involved with CM. There are specific characteristics of a headache that may have a higher correlation with the risk of developing chronic migraine, for example, nausea [4]. One could create a more independent definition of CM by referring directly to headache characteristics rather than referring to EM.

Response to treatment is also a key component in the diagnosis of CM by ICHD-3 standards [3••]. Section 1.3 C.3. includes that if the headache is relieved by a triptan or ergot derivative, a diagnosis for migraine can be established [3••]. Both of these treatments are known to be effective treatments for other types of diseases as well, such as cluster headaches. Triptan or ergot derivatives are not specific to a diagnosis of EM or CM and therefore do not necessarily support the possibility of one disease process. Using patient beliefs for definition and response to treatment is a poor substitute for evidence.

The number of headache days experienced per month is also an important element within the definition of EM and CM. The current designation of 15 headache days per month as a dividing point between EM and CM has been recently supported by functional imaging data. General consensus by professionals has also solidified its value in clinical practice. However, other studies suggest that the value of 15 headache days per month might be suboptimal when assessing a diagnosis of CM versus EM [5] and may be closer to 13. Furthermore, there is limited evidence that demonstrates comorbidity changes occurring at a value of <15 headache days per month, leading to the analysis that CM is closer associated to EM than previously thought [5]. To define CM separate from EM based on a speculative number of headache days devalues the concept that it is a separate diagnosis.

Epidemiology

Prevalence data from the American Migraine Prevalence and Prevention (AMPP) study suggests that the 1-year gender-stratified prevalence for EM was 17.1 % for women and 5.6 % for men [6•]. In addition, it is estimated that there is a prevalence of approximately 2 % for CM in the general population [7]. Prevalence among women is greater than that among men, with the prevalence among Hispanic women almost double compared with Caucasian counterparts (2.26 %

compared with 1.2 % for Caucasian women) [8, 9]. Prevalence was lowest among white men at 0.46 % [8]. A prospective study by Breslau et al. in 1996 indicated that the incidence rates of EM were 6 per 1000 person-years in men and 24 per 1000 person-years in women [10]. The incidence of CM within the general population has not been adequately elucidated [1••].

Incidence rates of CM and EM are important indicators of the progress of neurologic medical conditions. Each year, about 2.5 % of patients with EM develop new-onset CM [7, 9]. A long-term, prospective, clinic-based study of persons with one to six EM attacks per month showed that 1.6 % had developed CM at 10 years post assessment [7]. It is unusual for a patient to present initially meeting criteria for CM without first having EM. However, up to 60 % of patients with new daily persistent headaches will otherwise meet the criteria for CM without ever having suffered from EM [9]. Epidemiologic data tends to suggest a relationship between CM and EM as one disease within the paradigm of disease progression.

Since the evolution of EM to CM occurs in only a select number of people, it is valuable to consider associated risk factors. Risk factors that are found in both diseases are as follows: gender, family history of migraine, obesity, and presence of depression or anxiety. However, several risk factors are only linked with CM. These include sleep-related problems, temporomandibular disorders, medication overuse, and head or neck injury. Persons using hypnotics, as well as insomniacs, are associated with an increased risk of CM after adjusting for psychiatric illness [10]. Habitual snoring was also more frequent in CM patients (24 vs. 14 %) than in EM [10]. Furthermore, CM patients are more likely to experience cutaneous allodynia and tenderness in their masticatory muscles or temporomandibular joints compared with EM sufferers [7, 10]. Correlation in medication overuse and onset of CM showed the use of barbiturates and opiates over 5 and 8 days, respectively, per month increases risk of CM [10]. Lastly, studies show that head or neck injury may be a risk factor for CM, as both men and women have an increased risk with injury onset [10]. Difference in risk factors between EM and CM suggests distinct disease processes. However, the incongruence of risk factors may simply be underlying conditions of CM, that is, defining the risk of a more progressive, complicated disease.

Currently, annual direct and indirect costs from headache are estimated at $20 billion in the USA and €27 billion in Europe with significant difference between EM and CM [11]. Compared with EM, respondents with CM had lower levels of household income, were less likely to be employed full time, and were more likely to be occupationally disabled [7, 11]. Additionally, global results from the International Burden of Migraine Study (IBMS) indicate that patients with CM reported significantly more severe disability as assessed by MIDAS, lower HRQoL, higher levels of anxiety and depression, and greater health care resource utilization [7]. Annual total medical costs accrue to 4.4 times greater in patients with CM than in those with EM, $7750 and $1757, respectively, with about 70 % of the cost associated with CM being attributed to lost productive time [11]. This significant cost only augments the encumbrance of CM. Whether EM and CM are one disease or two, it is clear that CM carries a higher burden of disability and cost of care per individual [12].

Comorbidity

Chronic and episodic migraine share a significant number of comorbidities. However, many have an increased association with CM including psychiatric disorders, medication overuse, obesity, and respiratory and cardiovascular diseases. It is the interaction between underlying disease process and presence of concomitant medical disorders that contributes to the significant disability associated with migraine. There are no comorbidities more commonly seen with EM than with CM (provided we accept CM to include migraine with aura as per ICHD-3).

Data from the AMPP study shows that psychiatric and pain disorders were more often associated with CM than with EM [13•]. Participants with CM were twice as likely to have depression according to multiple scales [13•]. In addition, they were also twice as likely to report anxiety [13•]. Chronic pain disorders followed a similar pattern of approximately double in CM when compared to EM. However, when assessing for arthritis, the difference was not as staggering (CM 33.6 % vs. EM 22.2 %) [13•]. The increased prevalence of psychiatric comorbidity and greater concordant disability among CM patient may suggest a possible alternative process from EM.

Medication overuse is an important comorbid factor to consider when determining the risk factors for CM and EM. The prevalence of CM in the general population with medication overuse, defined as the use of acute medications on more than 10 or 15 days per month, is about 1.5 % [15]. Specifically, excessive symptomatic medication (SM) use has been studied to be a risk factor for a change in migraine status [15]. Medications containing barbiturates and opiates had a twofold increased risk of developing CM to maintaining an EM status [15]. Furthermore, there has been a significant relationship between monthly NSAID use days and monthly headache frequency. It is suggested that increasing monthly NSAID use days is protective against transition to CM at low to moderate monthly headache days but is associated with increased risk of transition to CM at high levels of monthly headache days [15]. The separation of the protective effect of NSAID use and its influence on transition to CM may question a unifying disease process.

Chronic migraine and obesity have shown a strong relationship. A recent study provided that individuals with EM and obesity develop CM at more than five times the rate of normal weighted individuals [16]. The prevalence of EM does fluctuate considerably with body mass index (BMI), showing that obesity is a risk factor for migraine [17]. Obesity is a risk factor for EM and CM in those who already suffer from EM [18]. A study found that in the normal weighted group, 4.4 % of those with migraine had 10 to 14 headache days per month. The percentage rose in the overweight group to 5.8 %, 13.6 % in the obese group, and 20.7 % in the severely obese group [16]. Obesity shares similar comorbidities with CM such as depression and stressful life, sleep apnea, and medication overuse [16], suggesting that the two are closely related.

Respiratory disorders were also more prevalent with CM than with EM. CM reported higher rates of allergies/hay fever, asthma, and sinusitis [13•]. Rates of chronic bronchitis, bronchitis, and emphysema/chronic obstructive pulmonary disease (COPD) were also reported to occur with greater prevalence in CM versus EM [13•]. Cardiovascular disorders such as heart disease/angina and stroke had a propensity for CM versus EM [13•]. Additionally, cardiovascular risk factors were also shown to have a greater occurrence with CM including high blood pressure and high cholesterol [13•].

Studies have shown that EM and CM share a large percentage of comorbidities; however, they do not share the same rates of comorbidities. Higher rates among CM patients may represent a separation of a more severe disease process but does not contribute overall to evidence pointing to a single or dual disease process.

Response to Treatment

Response to treatment has important implications regarding whether EM and CM are similar or distinct entities. There are two main therapeutic approaches in migraine management, including preventive and abortive treatments. In clinical practice, the decision to prescribe a preventive therapy is multifactorial and depends on previous treatment history, patient preference, comorbidities, and a range of other factors [19]. FDA-approved preventive options include propranolol, timolol, valproic acid/sodium valproate, and topiramate; however, numerous other therapies have been adapted for migraine management, including additional antiepileptic drugs (AED) and β blockers as well as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers [1••, 18]. OnabotulinumtoxinA (or Botox) is the only drug that has received FDA approval for treatment of CM.

OnabotulinumtoxinA, according to the PREEMPT study, has been proven to be effective for prophylaxis of headache in adults with CM [11, 20] but never shown significantly to be helpful for EM. The PREEMPT study showed significant reductions from baseline that were observed for onabotulinumtoxinA for headache and migraine days, cumulative hours of headache on headache days, and frequency of moderate/severe headache days, which in turn reduced the burden of illness in adults with disabling CM [21]. In addition, although not FDA approved, amitriptyline was compared with onabotulinumtoxinA for prophylaxis and had similar benefits to CM patients [11]. The number of days with pain was reduced by at least 50 in 72 % of participants receiving amitriptyline and 67.8 % of those taking onabotulinumtoxinA [11]. Some open-label studies for treatment of CM also show several drugs that display evidence of care which include atenolol, memantine, zonisamide, pregabalin, gabapentin, and fluoxetine [1••, 11]. Topiramate is one of the only medications that have demonstrated to be effective for CM and EM in randomized placebo-controlled trials [1••, 18]. The problem, though, arises from the fact that three out of the four FDA-approved treatments of EM, along with the many others listed, have never shown to be effective prophylactically for the treatment of CM, raising the possibility of discrete disease processes [1••].

Abortive treatments further obscure the relationship between EM and CM. On the one hand, non-specific headache medications work just as well for both EM and CM, comprising of opiates, anti-inflammatory, and anti-nausea medications. Since the clinical distinction between CM and EM is based primarily on the frequency of headache and migraine days rather than the attack features or symptoms, both populations use acute therapies (analgesics and NSAIDs) or migraine-specific agents with vasoconstrictor properties (triptans and ergot derivatives) [1••]. There has never been a study showing an acute medication to be more effective in CM than in EM. This observation indicates that CM maybe a complication or more severe aspect of the episodic form. However, in patients with cutaneous allodynia (CA) which is a frequent feature of migraine and is associated with development of CM, effectiveness of abortive therapy is questionable, complicating the idea of a singular disease process [22].

Functional Imaging

Very recently, a paper has demonstrated that imaging modalities can be used to differentiate between EM, CM, and healthy controls [23•]. Using magnetic resonance imaging (MRI) to observe regional cortical thickness, cortical surface area, and regional volumes has been shown to be an accurate source of classification for those with migraine [23•]. The accuracy for migraine classification based on MRI was (1) 68 % of migraine (episodic and chronic) versus healthy controls, (2) 67.2 % for EM versus healthy controls, (3) 86.3 % for CM versus healthy controls, and (4) 84.2 % for CM versus EM [23•]. The study indicates CM is associated with aberrant

brain structure, and structural differences in CM are of a magnitude that allows for accurate differentiation from the brains of people with EM and from healthy controls [23•]. Specifically, this conclusion suggests that either (1) more frequent migraine attacks lead to more extensive brain structural change or (2) more severe brain structural aberrations predispose a migraine patient to a more severe or different form of migraine (i.e., CM).

Additionally, imaging has supported the clinical distinction of 15 headache days per month as the threshold separating EM and CM. Based on this study, brain structure models more accurately depict differences in subcohorts of migraineurs when 15 headache days per month was used as the break, despite testing other threshold levels that were less that 15 headache days [23•]. Imaging could be vital for migraine in the clinical setting, as physicians can utilize MRI scans to diagnose migraine subtypes more precisely, thus leading to improved clinical decision-making and outcomes.

Conclusion

Understanding the similarities and differences between EM and CM is imperative for the advancement of treatment and management paradigms in the migraine community. Through our debate, there is evidence to support two distinct processes as well as the same disease, but the answer still remains unclear. The thoughts and evidence we have provided falls into the following categories: (1) definition of the conditions, (2) epidemiologic data, (3) comorbidities, (4) response to treatment, and (5) functional imaging. Perhaps later editions of the ICHD may look to refine the definitions of EM and CM so that they comprise specific elements of each entity. Further epidemiologic studies should also be considered, looking at rates among different ethnicities with the goal of correlating to genetic data. Additional research is required for a more thorough understanding of the relationship between comorbidities and whether they are complicating factors or risk factors for progression. In regard to the response to treatment, further studies on preventive medications in separate populations of CM, EM, and high-frequency EM are necessary in hopes of preventing transformation to CM. Among acute treatments, future studies should have a focus on the effectiveness of migraine-specific treatment in CM controlled for allodynia. Likewise, further neuroimaging studies need to be conducted to obtain more concrete and reliable clinically relevant data. We do not have an answer to EM and CM as a singular process versus multiple processes; however, additional studies can help to understand and prevent complications of the diseases in both the academic and clinical settings.

Compliance with Ethical Standards

Conflict of Interest Reuben Burshtein, Aaron Burshtein, and Joshua Burshtein declare that they have no conflict of interest.

Noah Rosen declares personal fees, non-financial support, and other fees from Allergan for serving on the advisory board, in research, and speakers' panel; personal fees from Avanir and the American Headache Society; and other compensation from Curelator for consultation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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