Clinical course in migraine

Conceptualizing migraine transformation

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ABSTRACT

Migraine is currently conceptualized as a chronic disease with episodic manifestations, with attacks that increase in frequency in a subgroup (migraine transformation or progression). Transformation of migraine may be subdivided in three partially overlapping forms, although research in this area is still in infancy, and evidence is sometimes weak. Typically, transformation refers to increases in attack frequency over time leading to chronic migraine; this process is termed *clinical transformation*. Additionally, in some patients with migraine, physiologic changes in the CNS manifest themselves through alterations in nociceptive thresholds (allodynia) and alterations in pain pathways (physiologic transformation). Finally, in some individuals, definitive brain lesions including stroke and deep white matter lesions emerge (anatomic transformation). Herein we discuss the evidence that migraine may transform and then consider potential mechanisms as well as risk factors. We close with a brief discussion of clinical strategies that arise based on this perspective on migraine. *Neurology*® **2008;71:848-855**
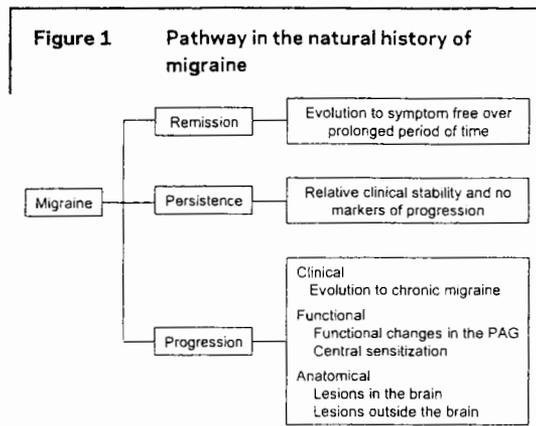
GLOSSARY

BBB = blood-brain barrier; **BMI** = body mass index; **CA** = cutaneous allodynia; **CDEA** = chronic disorder with episodic attacks; **CDH** = chronic daily headache; **CM** = chronic migraine; **CSD** = cortical spreading depression; **HFEM** = high-frequency episodic migraine; **LFEM** = low-frequency episodic migraine; **MMP** = matrix metalloproteinase; **NSAID** = nonsteroidal anti-inflammatory drug; **PAG** = periaqueductal gray; **PR** = prevalence ratio; **WMH** = white matter hyperintensity.

The conceptual framework for understanding migraine has evolved over the past decade. Seen as a purely episodic disorder for a large part of the 20th century,[1] more recent evidence supports the concept that migraine is a chronic disorder with episodic attacks (CDEA).[2] Between headaches, patients with migraine have an enduring predisposition to attacks including abnormalities in brain excitability and impaired health-related quality of life.[3] Emerging evidence also suggests that migraine has a variable clinical course. Some patients with migraine remit becoming free of migraine.[4] Others have a stable clinical course. Finally, a subset develops chronic migraine (CM), a condition characterized by headaches on 15 or more days per month.[5] This process is sometimes referred to as migraine transformation.[6,7] Accordingly, migraine is best conceptualized as a CDEA with attacks that increase in frequency in a subgroup.[6-8]

From a conceptual perspective, transformation of migraine has been recently subdivided into three non mutually exclusive forms.[9] Typically, transformation refers to increases in attack frequency over time leading to CM; this process, termed *clinical transformation*, occurs in about 3% of episodic migraine sufferers in the general population over the course of a year.[9-11] A less discussed and characterized issue is physiologic transformation,[9] physiologic changes in the CNS manifested through alterations in nociceptive thresholds (allodynia) and in pain pathways.[12] Finally, in some individuals, definitive brain lesions including stroke and deep white matter lesions emerge[13]; this process is of a potential anatomic transformation (as discussed below, the causal nature of the lesions is sometimes unclear) (figure 1). Although the data for anatomic changes are for patients with episodic migraine with aura only, herein we consider it a

Figure 1   Pathway in the natural history of migraine

PAG = periaqueductal gray.

form of migraine as transformation because the prevalence of brain lesions seems to increases with attack frequency.

Use of the term *progression* to describe a subgroup of people with migraine is controversial. Most migraine sufferers do not worsen over time.[8,9,14] In addition, many individuals who develop chronic migraine eventually remit.[11] Nonetheless, migraine does worsen in a sizable subgroup. Therefore, identifying risk factors for migraine transformation and remission has emerged as an urgent public health priority, in order to avoid the future consequences of migraine. These risk factors provide insights into the mechanisms of disease as well as a foundation for interventions intended to modify the course of illness. Nonetheless, we emphasize that the extraordinary pain and disability caused by migraine[10] is sufficient to drive health care efforts that focus on ameliorating the pain and disability of migraine in the "current" rather than "future" time.

Accordingly, in this article we discuss potential factors associated with migraine transformation in the context of a transition model presented below. We emphasize that progression or transformation should be understood as the potential for evolution to a different

form. Migraine does not inexorably progress like the neurodegenerative diseases.

THE CLINICAL TRANSFORMATION OF MIGRAINE CM, the clinical consequence of migraine transformation, is a subtype of long-duration primary chronic daily headaches (CDHs). Although it is not well established if migraine may not progress abruptly, clinical evidence suggests that most frequently attacks increase in frequency over a period of time (figure 2).[6,15] We conceptualize this process in terms of a transition model. According to this model, individuals who do not have migraine may develop low-frequency episodic migraine (LFEM) with a transition rate of λ_1, LFEM may remit at a transition rate of λ_2, or it may progress to an intermediate state of high-frequency episodic migraine (HFEM), with a transition rate λ_3. HFEM may remit with a transition rate of λ_4, or may worsen until CM emerges with a transition rate of λ_5. CM may persist or remit with a transition rate of λ_6. All transition rates can be modeled as a function of demographic, environmental, and genetic risk factors. This model addresses the observation that transitions from one form of migraine to another are frequent and bidirectional. Additionally, the model provides a framework for understanding the influence of risk factors at various stages of illness and lends itself to the development and testing of stage specific intervention strategies. A risk of this model is inducing oversimplification of the issue, since many of the risk factors exposed herein are under biologic and environmental influence (e.g., obesity) and are also inter-related (e.g., chronic pain and medication use, or caffeine use and obesity).

Risk factors associated with migraine clinical progression. The factors that drive the onset of LFEM and its remission have not been well studied. The onset of LFEM is likely driven extensively by genetic predisposition,[16,17] although this transition is also influenced by environmental risk factors.[18] Similarly, remission of migraine is poorly studied, but at least older ages, male gender, and postmenopausal status seem to partially account for λ_2.

The transition to HFEM ($\lambda3$) may be determined by a variety of factors.[7,11] Based on previous studies of migraine transformation we propose dividing risk factors into those which can be modified and those which are nonmodifiable (table 1).[7] Modifiable risk factors are important because they provide an opportunity to prevent disease progression. Nonmodifiable risk factors include age, female gender, white race, low educational level, socioeconomic status, and genetic factors.

Figure 2   Conceptual framework for transitions in migraine
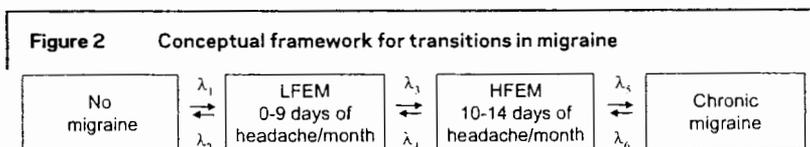
λ are described in the text. LFEM = low-frequency episodic migraine; HFEM = high-frequency episodic migraine.

Table 1	Risk factors for migraine progression	
Not readily modifiable	**Modifiable**	**Putative, currently being investigated**
Age	Attack frequency	Allodynia
Low education/ socioeconomic status	Obesity	Proinflammatory states
ſ	Medication overuse	Prothrombotic states
	Stressful life events	
Head injury	Caffeine overuse	Specific genes
	Snoring	
	Other pain syndromes	

Addressing modifiable factors may, at least theoretically, decrease the rate of migraine progression and increase the rate of remission. This article focuses on modifiable risk factors for migraine progression, which will be discussed in the following sections.

Attack frequency. In the Frequent Headache Epidemiology Study, individuals with episodic headache were followed over the course of 1 year.[11] The baseline characteristics of those who developed CM were compared with the characteristics of those who did not. One of the most important risk factors for progression was frequency of headache attacks at baseline. The risk increased in a nonlinear manner with baseline headache frequency; elevated risk for developing CM occurred in subjects who experienced three or more headaches per month. The risk exponentially increased with attack frequency. Additionally, the risk of HFEM also increased with attack frequency at baseline.

This observation agrees with the hypothesis that repetitive episodes of pain may lead to central sensitization and generation of free radicals and anatomic changes to the brain and brainstem[12,13] (see physiologic progression, below). However, although frequency of headaches predict future development of CM, it is not clear if this is truly the cause, or a consequence of biologic changes that predispose to migraine transformation.

Obesity. The link between obesity and the frequency of primary headaches has been demonstrated in four population studies. In the first study, the relative odds of CDH were five times higher in individuals with a body mass index (BMI) $\geq$30 than in the normal weighted. Overweight individuals (BMI ranging from 25 to 29) had a threefold increased risk of developing CDH.[11]

Two large epidemiologic studies further investigated the relationship between BMI and migraine progression.[19,20] In the first, BMI was associated with the frequency of headache attacks in migraineurs. In the normal weighted group, just 4.4% of migraine sufferers had 10–14 headache days per month. This increased to 5.8% of the overweight group (OR = 1.3, 95% CI = 0.6–2.8), 13.6% of the obese (OR = 2.9, 95% CI = 1.9–4.4), and 20.7% of the severely obese (OR 5.7, 95% CI = 3.6–8.8). Obesity was comorbid to CDH and was a much stronger risk factor for CM than for CTTH. For CM, the prevalence ranged from 0.9% of the normal weighted (reference group) to 2.5% of the severely obese (OR = 2.2 [1.5–3.2]).[20] More recently, obesity was shown to be an exacerbating factor for migraine, and not for headaches overall.[21]

Table 2 summarizes some key points of these four population studies assessing the relationship between headache and migraine progression.

Acute medication overuse. The importance of acute medication overuse as a risk factor for progression is still a matter of debate.[22,23] While most patients with CM seen in specialty care overuse acute mediations,[24] just one-third in the population do so.[11] Therefore, it is controversial whether medication overuse is a cause or consequence of CDH. Transitory worsening of

Table 2	Summary of the four population studies that investigated the relationship between obesity and migraine progression	
Reference no.	**Comments**	**Main findings**
13	Case-control followed by a longitudinal design. Only longitudinal study currently published. Sample size = 1,932.	In the longitudinal arm, the odds of CDH were 5 times higher in obese and 3 times higher in overweight, relative to normal weight.
14	Cross-sectional, assessing the influence of obesity on migraine frequency. Sample size = 30,215.	Relative to the normal weight group, the odds of having very frequent headache attacks were 2.9 in the obese and 5.7 in the severely obese.
15	Cross-sectional, assessing the relationship between obesity and CDH. Sample size = 30,215.	Chronic daily headache and obesity are associated. Obesity is a stronger risk factor for chronic migraine than for chronic tension-type headache.
16	Cross-sectional, assessing the relationship between obesity and several episodic headaches. Sample size = 30,703. This study has a longitudinal phase, ongoing.	Obesity was strongly associated with the frequency and severity of the attacks experienced by migraineurs, intermediately associated with probable migraine, and not associated with episodic tension-type headache.

CDH = chronic daily headache.

the headache after discontinuation of the offending symptomatic medication has been demonstrated in one placebo-controlled study.[25]

Acute medication overuse does not seem to cause de novo headache in patients without preexisting migraine. When nonsteroidal anti-inflammatory drugs (NSAIDs) were used daily for rheumatic pain, they did not cause CDH in subjects without preexisting primary headache disorders. In contrast, analgesics were a strong risk factor for CDH in individuals with preexisting migraine.[26] In another study, patients with a previous history of migraine who used daily opiates for treatment of bowel problems developed CDH, whereas the patients without preexisting migraine did not.[27]

As a part of the American Migraine Prevalence and Prevention study, we selected a random sample of 24,000 severe headache sufferers from the population. Of those with migraine in 2005, 2.7% evolved to CM in 2006. Relative to acetaminophen, migraineurs who had been exposed to compounds containing butalbital had a twofold increased risk of developing CM (OR = 2.09, 95% CI 1.38–3.17). Opioid users were also twice as likely to develop CM (OR = 2.01, 95% CI = 1.43–2.83). Other classes of medication were not associated with transformed migraine (triptans: OR = 1.25, 95% CI = 0.89–1.75; anti-inflammatory medications: OR = 0.85; 95% CI = 0.63–1.17).[28]

Caffeine overuse. The role of caffeine in the development of CDH has been studied extensively due to wide exposure to dietary and medication caffeine.[29] Caffeine is the only substance shown to cause withdrawal headache with further improvement in the context of a double-blind study.[30] A case-control study[31] reported association between daily consumption of more than 100 mg of caffeine and CDH. The associations remained similar after adjustment for current depression and sleep problems, which may be present in individuals with high caffeine intake.

Snoring and sleep apnea. The relationship between headache progression and snoring has been studied in both case-control and population studies. In a large cross-sectional study of 3,323 Danish men, snoring was associated with any form of headache.[32] The authors reported that this association was independent of weight, age, gender, hypertension, and other sleep disturbances, including secondary to caffeine consumption. In a separate population-based case-control study, CDH were more likely to be habitual or daily snorers than controls.[31]

The mechanisms of relationship between obstructive sleep apnea and migraine progression are not fully understood, but may involve intracranial and arterial pressure fluctuations during snore in an individual susceptible to pain progression, hypoxia, hypercapnia, sleep fragmentation and disruptions and increased muscle activation during awakenings.

Psychiatric comorbidity and stressful life events. Although an association between migraine and several psychiatric conditions has been well demonstrated, few studies assessed the relationship with migraine progression. In a cross-sectional study, relative to chronic tension-type headache, patients with CM were more likely to have depressive (70% vs 59%, $p = 0.062$) and anxiety symptoms (43% vs 25%, $p = 0.005$).[33] More recently, CM was found to be more common in women with major depressive disorder (OR = 31.8).[34] Finally, recent history of stressful life events, such as divorce or separation, moving, work changes, or problems with children, is an independent risk factor for CDH.[11]

THE PHYSIOLOGIC TRANSFORMATION OF MIGRAINE

Herein, we use the term *physiologic transformation* to refer to sensitization of the second order sensory neurons whose cell bodies are in the trigeminal nucleus caudalis, and to the cutaneous allodynia (CA) which arises as a consequence.[35-38]

Clinic-based studies first suggested that about two thirds of migraine sufferers develop CA over the course of their attack.[37] In the population, we found that the prevalence of CA was significantly higher in CM (68.3%) than in episodic migraine (63.2% $p < 0.01$), and higher in both of these groups compared to other headaches.[39] The prevalence of severe CA followed the same pattern (figure 3). These findings suggest that functional progression (CA) is associated with clinical progression (CM), although the causal nature of this association is unclear. Nonetheless, these findings were recently supported by another population study.[40]

The mechanisms which link CA allodynia and migraine frequency (that is, physiologic and clinical progression) are poorly understood. The trigeminal nucleus caudalis is a structure that has reciprocal anatomic connections with the periaqueductal gray (PAG) area.[41,42] Repetitive activation of trigeminovascular neurons seems to lead to repetitive activation of modulatory pain pathways involving the PAG. In turn, this may lead to impairment of neuronal function through the liberation of free radicals, in the PAG (involved with migraine modulation) or eventually in areas involved with migraine generation.[43]

Modifiable risk factors for cutaneous allodynia. The development of CA is influenced by a number of potentially modifiable risk factors and some that are nonmodifiable. Among the nonmodifiable risk factors for CA, we found male gender (prevalence ratio

Figure 3 Relative frequency and severity of cutaneous allodynia according to the headache subtype (from reference 44)
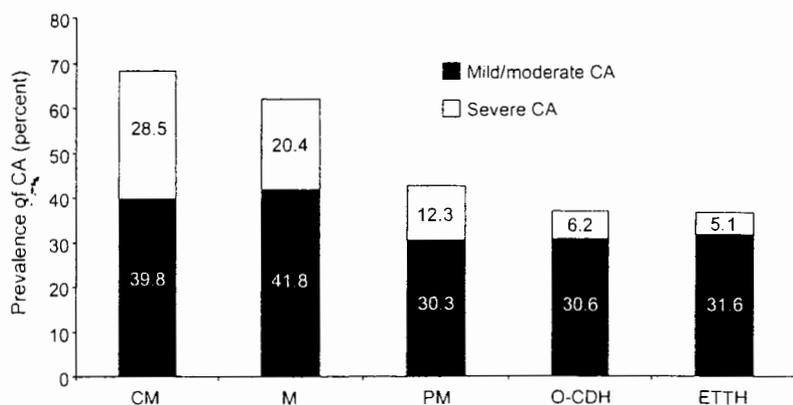
CA = cutaneous allodynia; CM = chronic migraine; M = migraine; PM = probable migraine; O-CDH = other chronic daily headaches; ETTH = episodic tension-type headache.

PR] = 1.7, 95% CI = 1.55–1.82), African American race (PR = 1.14, 05% CI = 1.04–1.25), and decreased educational level (graduated vs less than high school, PR = 0.68, 95% CI 0.55–0.83).[44] Potentially modifiable risk factors for CA include high attack frequency, high pain intensity, and high levels of headache related disability. These associations were demonstrated in cross-sectional studies so causal sequence is uncertain.[43,44] Two other risk factors were independently associated with CA (and are also associated with CM), obesity and depression.[44]

THE ANATOMIC PROGRESSION OF MIGRAINE

The study of brain lesions in migraine is in its infancy. Most published studies are cross-sectional so inferences about worsening over time are at best hypotheses. We elected to discuss them here to foment further research and conceptual thinking. However, caution is advised regarding the overinterpretation of these data.

Limited cross-sectional data, as discussed below, show that the number of deep white matter lesions and the number of strokes is associated with migraine aura (primary analyses) and with attack frequency (a secondary finding of the study).[45] This pattern suggests that brain lesions may arise as a consequence of multiple attacks. Alternatively, the brain lesions and frequent attacks may have a common underlying cause. Longitudinal imaging studies are required to resolve this issue particularly since some deep brain lesions associated with migraine seem to remit.[46]

Deep brain lesions. White matter hyperintensities (WMHs) have traditionally been considered to be more common in migraineurs. In a meta-analysis of published studies, WMHs were more common in migraineurs than controls (OR = 3.9, 95% CI = 2.2–6.7) and the risk was independent of age and vascular risk factors.[47] More recently, in the Dutch population, male subjects with migraine with aura, and women with

migraine with or without aura were at a higher risk of deep white matter lesions, compared to controls.[45] The white matter lesions increased with attack frequency, possibly demonstrating progression of the disease. This study showed a dose-response effect, in that the number of lesions increased with migraine attacks frequency, even after adjusting for confounders.

The association between migraine, especially with aura, and stroke has been suggested for many years. In a population study in the Netherlands, migraine with aura was a risk factor for subclinical ischemic lesions in the posterior fossa and in the brainstem.[13] Migraineurs with infratentorial ischemia were more likely to have supratentorial white matter lesions as well and hemodynamic changes may give rise to both deep white matter lesions and posterior fossa strokes.[48] Finally, two large population studies in the United States confirmed this association. In the Women's Health Study, a cohort study that followed nearly 28,000 women for an average of more than 10 years, migraine with aura increased the risk of nonfatal ischemic stroke by twofold. The association remained significant after adjusting for many cardiovascular risk factors and did not occur in the most common type of migraine, migraine without aura.[49] In the Physicians Health Study, similar findings were found for men.[50]

Risk factors for anatomic progression. Because brain lesions have only been clearly related to migraine with aura, and because they increase in frequency with number of attacks, the mechanisms of aura may be linked to the mechanisms of anatomic change.[51]

Cortical spreading depression. Cortical spreading depression (CSD) is believed to be the substrate of the migraine aura; CSD is a self-propagating wave of neuronal and glial depolarization that marches across the cortical mantle.[52]

CSD alters the permeability of the blood–brain barrier (BBB) and activates matrix metalloproteinases (MMPs).[22] In particular, MMP-9 is activated within 15 to 30 minutes of CSD onset. Human studies show that, relative to controls, levels of MMP-9 are elevated in individuals with migraine, and this has been suggested to increase vascular permeability in the CNS as a consequence of migraine attacks.[53] Furthermore, the CSD cascade includes the formation and release of oxygen free radicals, nitric oxide, and proteases.[54] While the diminution in cerebral blood flow during CSD does not generally fall below the ischemic threshold at the macroscopic level, emerging evidence suggests that small regions of focal ischemia occur and that on occasion frank ischemia may occur.[54] These changes in perfusion may help explain why migraine with aura is a risk factor for stroke and deep brain lesions.

Shared biologic risk factors. CSD may at least partially explain the brain lesions associated with mi-

Table 3 Clinical intervention on selected risk factors for migraine progression

	Intervention	Comments
Attack frequency	Effective preventive treatment	
Obesity	Weight loss	Most migraine preventive medications are not weight neutral.
Medication overuse	Detoxification	Evidence suggests that detoxification only is associated with chronic daily headache remission over a 1-year period.
Stressful life events	Stress management	.
Caffeine overuse	Reduction in caffeine consumption	
Snoring (sleep apnea)	Weight lossCPAP	
Allodynia	Effective early acute treatmentPreventive treatment	
Other pain syndromes	Treatment of chronic pain	

graine with aura, but other factors may play a role. Two studies add to our knowledge in this regard.[55,56] In comparison with controls, MA was associated with a significantly increased risk for hyperlipidemia, hypertension, and elevated Framingham scores. Furthermore, a polymorphism in the methyltetrahydrofolate reductase gene (*C677T*) is associated with moderately elevated levels of homocysteine which, in turn, is associated with risk of stroke. The same polymorphism is overexpressed in migraine with but not migraine without aura.

CLINICAL IMPLICATIONS Herein we have argued that clinical progression (increasing attack frequency) is associated with physiologic progression in the form of allodynia and perhaps anatomic progression in the form of brain lesions. The temporal and causal sequence linking increasing attack frequency, allodynia, and brain lesions remains to be determined.

Because migraine progresses in some but not most individuals,[57-59] research will increasingly focus on the identification of factors associated with progression. In the future, the assessment of the patient with migraine may include an evaluation of risk factors for progression. Risk assessments may include screening for demographic features, concomitant conditions (obesity, depression), environmental risk factors (stressful life events, head injury), and eventually biomarkers and genes.[60] If studies demonstrate benefits, individuals at high risk for progression may be treated more aggressively to prevent progression. In this context, the goals of treatment will be to decrease current burden and prevent future burden.

Based on our current knowledge, modifiable risk factors for migraine progression should be assessed in clinical practice. While we await clinical trials regarding the benefits of intervention in the prevention of CM, several interventions are justifiable based on their other established benefits

(table 3). For example, decreasing headache frequency with behavioral and pharmacologic interventions will decrease current disability even if it does not modify clinical course. Monitoring the BMI and encouraging maintenance of normal body weight is good practice in patients with and without migraine. Avoiding overuse of medications and caffeine is desirable apart from its potential benefit in preventing progression. Sleep problems should be investigated and treated. Psychiatric comorbidities should be identified and addressed.[60] For these interventions, the possibility of preventing progression may motivate clinicians to offer good care and patients to engage in the treatment plan.

It is not clear that modifying the candidate risk factors for CA will prevent or ameliorate CA or produce clinical benefits. Among risk factors for CA (functional progression), one potential strategy is to treat the migraine attack early with effective medications; this may avoid central sensitization and prevent damage to the PAG. In appropriate patients, using preventive medications to decrease headache frequency is therefore desirable and may prevent CA.

For anatomic progression, most patients with migraine have migraine without aura and, therefore, are not at increased risk of cardiovascular disease. Theoretical interventions include targeting CSD. Clinicians should also have heightened vigilance for modifiable cardiovascular risk factors (e.g., hypertension). Future studies should investigate the possibility that screening for homocysteine and administering folate for those in need as well as antiplatelet therapy might reduce the risk of cardiovascular disease in patients with migraine with aura.

So far, none of the recommendations has been demonstrated to improve outcomes in longitudinal studies.

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