



From Episodic to Chronic: A Discussion on Headache Transformation

Anna Pace and Bridget Mueller

“Chronic daily headache” (CDH) encompasses various headache syndromes, including chronic migraine, chronic tension-type headache, hemicrania continua, and new daily persistent headache. While there are some patients who initially present with a primary chronic daily headache, most patients begin with episodic headache and then progress, or transform, into chronic headache over time. Chronic daily headache has been reported to affect 3–4% of the population worldwide, and patients with CDH represent a significant number of referrals to tertiary care centers for headache. Chronic daily headache can lead to a significant degree of disability in many patients, especially when affecting young patients in the prime of their workforce capabilities.

According to proposed criteria by Silberstein et al. in 1994, used frequently by headache specialists, chronic headache can be subdivided into four entities—transformed migraine (TM), chronic tension-type headache (CTTH), hemicrania continua (HC), and new daily persistent headache (NDPH) [1]. Transformed migraine is found in patients who previously had a history of episodic migraine but have experienced more frequent attacks over time and whose nausea, vomiting, photophobia, and phonophobia have become less prominent features

of their headaches. These patients have this progression over at least 3 months, to result in daily or almost daily head pain for greater than 1 months’ time [1]. The group then subdivides into those with or without medication overuse: medication overuse is defined as involving simple analgesic use >5 days a week, combination analgesic use >3 days a week, or using narcotics at least 2 days a week for >1 month [1]. For chronic tension-type headache, which often evolves from episodic tension-type headache, Silberstein et al. proposes criteria to include an average headache frequency of more than 15 days a month with the duration of each attack lasting longer than 4 h a day, for 6 months’ time [1]. Patients should have a history of episodic tension-type headache in the past, with an evolution of their headaches increasing in frequency over a 3-month period; headache should involve a bilateral pressing/tightening type pain and associated with no more than one of nausea, photophobia, or phonophobia, and no vomiting. CTTH is also subdivided into patients with or without medication overuse, as previously described with TM. Hemicrania continua is defined as a strictly unilateral headache present for at least 1 month, with continuous pain that may have “jabs and jolts” superimposed, and may be associated with or without medication overuse. It has no precipitating mechanisms and is often unremitting [1]. New daily persistent headache is described as a headache that is acute on onset and is constant and unremitting, for >15 days a month for at least 1 month, and patients with NDPH do not have a previous

A. Pace (✉) · B. Mueller
Department of Neurology, Icahn School of Medicine
at Mount Sinai, New York, NY, USA
e-mail: anna.pace@mssm.edu;
bridget.mueller@mssm.edu

history of migraine or tension-type headache that has increased in frequency or decreased in severity over the past 3 months [1]. The focus of the following discussion will be primarily transformed migraine and chronic tension-type headache.

Pathophysiology of Chronic Headache

Serotonin Receptors

The pathophysiology of headache transformation is not completely well understood, but there have been proposed mechanisms of this headache process. One study published in *Headache* in 1994 proposed that an upregulation of 5HT-2 serotonin receptors may be implicated in transformed migraine [2]. This study, which looked at six patients with transformed migraine and seven controls, measured the 5HT-2 serotonin receptors on platelet membranes and found a significant increase in the maximal number of receptors on the platelets in migraineurs compared to the control patients [2]. The researchers deduced that, since there is a significant similarity in receptor characterization between platelet membranes and aminergic neurons, it could be postulated that aminergic neurons would also have higher levels of serotonin receptors. This was suggested to play a role in transformed migraine, as patients with episodic migraine have a decrease in 5HT-2 receptors on platelets during periods of headache freedom. Therefore, the increase in receptors may contribute to the lack of pain freedom in patients with transformed migraine. The researchers also postulated that the increase in serotonergic receptors may be due to “serotonergic hypofunction,” whereby there is a hyposecretion of serotonergic vesicles presynaptically which leads to decreased serotonin levels over time and results in the upregulation of postsynaptic serotonergic receptors [2].

CSF Glutamate

Researchers Gallai and colleagues in 2003 found that there were elevated levels of CSF glutamate

and CSF nitrites, as well as subsequent increases in CSF cyclic guanosine monophosphate compounds (cGMP), in patients with chronic daily headache compared to healthy controls [3]. These findings help support the theory that the release of glutamate and nitrous oxide may play a role in chronic daily headache development. Substance P and calcitonin gene-related peptide (CGRP) were also found to be elevated in measured CSF samples of patients with CDH, though the study researchers did not find a relationship between these levels and that of the elevated levels of glutamate and nitrites [3]. The study investigators propose in patients with chronic daily headache that there is activation of NMDA and other non-NMDA receptors, which results in the release of glutamate and production of NO species that contribute to central sensitization, with the subsequent release of cGMP correlating with sustained nociception [3].

Calcitonin Gene-Related Peptide (CGRP)

Calcitonin gene-related peptide (CGRP) has also been implicated in headache chronification. In a study conducted by researchers in Spain and published in *Neurology* in 2013, women with episodic migraine and women with chronic migraine underwent testing to determine CGRP levels in the blood interictally between migraine attacks [4]. These patients were compared to healthy controls and patients with episodic cluster headaches. Results showed that the women with chronic migraine had significantly higher levels of plasma CGRP compared to women with episodic migraine, women with episodic cluster, and women who were in the healthy control group [4]. These levels were not affected by rescue medication use, comorbid psychiatric conditions, vascular risk factors, or age [4]. Researchers hypothesize that the presence of persistently elevated CGRP levels may be a marker for headache chronification.

Genetics

There are suggestions in the literature that there may be underlying genetic predispositions to

headache chronification, though there have been no concrete studies evaluating specific gene patterns implicated in chronic daily headache. One study by Cevoli and colleagues in 2008 evaluated family history for chronic headache and family history of drug overuse as possible contributors to headache transformation in patients [5]. One hundred five patients with chronic headache, either with tension-type (CTTH), chronic migraine (CM), or with medication overuse headache (MOH), were interviewed directly by investigators about family history of headache, psychiatric disorders, and substance abuse or dependence. Patients were asked to provide details about their first-degree and second-degree relatives regarding timing and onset of headache and headache frequency, substance use, and history of psychiatric disorders, the latter two being classified by DSM-IV criteria [5]. Researchers found that 38.1% of patients with chronic headache reported a family history of chronic headache, compared to only 13.7% of patients with episodic headache reporting a family history of chronic headache. Patients with chronic headache also reported an increased family history of medication overuse and substance abuse than those patients with episodic headache, but there was no significant difference noted in family history of psychiatric disorders when compared between the two groups. History was not distinguished between first-degree and second-degree relatives for the participants in the study. Investigators postulate, due to the high family history of chronic headache in patients with chronic headache, that there may be an underlying genetic etiology or predisposition that may contribute to chronification of headaches [5].

Another study in 2010 by Arruda, Bigal, and others surveyed 1994 children with headache to determine if maternal headache history and frequency could predict the frequency of headaches in the pediatric participants [6]. Participants, ages 5–12, were chosen based on their headache frequency as reported by their mothers, and divided into low frequency (1–4 headache days per month), intermediate frequency (5–9 headache days per month), high frequency (10–14 headache days per month), and CDH (15+ headache

days per month) [6]. The mothers of the participants were also surveyed with the same questionnaire and divided into the same frequency categories. Analyses found that if the mother was classified as having low-frequency headache, the prevalence of low-frequency headaches in the children was 27.3% and the prevalence of intermediate-/high-frequency headache was 4.8%, with the prevalence of CDH at 0.6% [6]. If the mother had high-frequency headaches, the prevalence of high-frequency headaches in the children was 16.1%, and the prevalence of CDH in the children was 1.3% [6]. If the mother had CDH, the prevalence of intermediate-/high-frequency headaches in the children was 15.8%, and the children were found to have a 12-fold increased risk of CDH, compared to children of mothers with low-frequency headaches [6]. While this study is not able to provide definitive evidence that CDH is genetic, the results imply some inheritable basis for headache chronification in families [6].

Quality of Life in CDH

When looking at quality of life for patients with episodic migraine versus chronic migraine, Meletiche et al. studied a group of 90 migraineurs by administering questionnaires including the Short Form 36 (SF36) and the Migraine Disability Assessment (MIDAS) [7]. These questionnaires look to quantify various domains of quality of life in these migraine patients, including assessing social functioning, general health, mental health, vitality, physical functioning, and bodily pain. When patients were grouped by ICH-D criteria as episodic migraine or transformed migraine (the latter following proposed criteria by Silberstein et al. [1]), the researchers found that patients with transformed migraines had significantly lower scores on seven out of the eight tested domains on the SF36 assessment and significantly higher scores on the MIDAS compared to patients with episodic migraine [7].

There is a significant economic burden of transformed migraine when compared to episodic migraine. According to the American

Migraine Prevalence and Prevention Study (AMPP), those migraineurs with transformed migraines utilize more primary care and neurologist outpatient visits, visiting emergency rooms more frequently, and incurred a 4.4-fold higher cost annually compared to patients with episodic migraine, and this cost includes both direct and indirect costs [8]. Patients with TM had more missed days at work or school due to their daily pain and were less productive when able to attend work or school compared to patients with episodic migraine [8].

This important data suggests that chronic headache, and specifically transformed migraine, is a major public health problem [8]. With the report of decreasing quality of life and an increased economic burden in patients with transformed migraine, it is evident that neurologists should look to identify risk factors for headache chronification and attempt to prevent this progression by helping to modify those risk factors. The transformation from episodic headache into a chronic headache disorder likely involves both an underlying genetic vulnerability and specific environmental risk factors. Medication overuse, obesity, sleep disturbances, stress, depression, and menstrual-related migraines have been shown to be potent triggers for headache progression.

Risk Factors for Transformation

Medication Overuse

Patients with chronic daily headache disorders are often self-medicating at frequencies that qualify as overuse. Population studies estimate ~30% of patients with transformed migraine is overusing pain-relieving medication [9, 10]. At headache tertiary centers, 80–85% of patients are overusing medication at time of presentation [10].

“Detox studies” have shown that medication overuse is often a reversible cause of headache transformation. In a large retrospective study, patients with chronic migraine and medication overuse who stopped all acute pharmacothera-

pies showed improvement in headache frequency, duration, and intensity [10]. The effectiveness of detoxification was again demonstrated in a controlled open-label trial that randomized chronic headache patients to either complete detoxification or restriction to medication 2 days per week [11]. Patients who stopped all acute pharmacotherapy interventions experienced twice as many headache-free days per month compared to patients who decreased medication usage to the recommended frequency of two to three times per week. In addition, 70% of detoxified patients reverted to episodic headaches, while only 42% of restricted patients reverted [11].

Not all drugs are created equal. Barbiturates and opioids increase the risk of transformation to chronic migraine by at least twofold, at any frequency of use [12]. Barbiturates exhibit a dose-response effect, with the heaviest users experiencing progression from episodic headaches to chronic headaches most frequently. These effects persisted after adjusting for headache severity. Triptans did not increase transition to chronic headache. Interestingly, NSAID use was associated with a decreased risk of headache progression in patients with low frequency of headaches and an increased risk of headache progression in patients with high-frequency attacks [12, 13].

Obesity

Obesity dramatically increases the risk of episodic migraines progressing to chronic daily headaches. In a longitudinal population study that followed episodic migraineurs over 1 year, obese migraineurs (BMI > 30) had a five-fold increased risk in headache transformation, while overweight individuals (BMI 25–29) had a three-fold increased risk of headache transformation [14]. The episodic migraineur and episodic chronic tension-type headache patient are not affected by obesity equally. While even modest weight gain significantly increases the risk of developing a transformed migraine, only morbid obesity increases the risk for progression to chronic tension-type headache [15, 16].

The pathophysiology underlying the association between obesity and headache transformation is likely multifactorial. It is well established that both migraine and obesity share a pro-inflammatory state. In addition, the hypothalamus and its associated peptides and neurotransmitters including 5-HT, adiponectin, and leptin play critical roles in headaches and energy balance. Interestingly, in addition to migraineurs having increased serum levels of leptin and adiponectin compared with healthy controls, chronic migraineurs have increased leptin and adiponectin compared to episodic migraine patients [17].

Studies performed in obese migraineurs who underwent bariatric surgery suggest weight reduction is an effective way to decrease headache frequency in chronic migraine patients. Three months following surgery, five of the six chronic migraineurs reported at least a 50% reduction in headache frequency [18]. Additional studies are needed to replicate these results and determine if modest weight loss achieved through behavioral measures also influences headache frequency in chronic migraineurs.

Sleep

Poor sleep is a widespread complaint in patients with chronic headache. Approximately two-thirds of patients with chronic migraine suffer from insomnia on a daily or near-daily basis [19]. As measured by the Pittsburgh Sleep Quality Index, higher migraine frequency correlates with poorer sleep quality. Further, patients with chronic migraine report non-restorative sleep and a higher number of night awakenings compared to patients with episodic migraine [20].

The relationship between sleep and chronic headache presents the classic “chicken or the egg” question: do headaches interfere with sleep or does poor sleep produce headaches? In a randomized placebo-controlled study, chronic migraineurs who followed behavioral sleep modifications aimed at improving sleep quality and increasing sleep duration were more likely to revert to episodic migraine, suggesting a causal

relationship between poor sleep and the development of chronic migraine [21]. Interestingly, the degree of improvement in headache symptoms was proportionate to the number of sleep behaviors changed, further supporting a causal link between poor sleep and the development of a chronic headache disorder.

The importance of screening headache patients for obstructive sleep apnea (OSA) has been highlighted by several studies [22, 23]. A retrospective study examining the prevalence of OSA in patients with various headache disorders found 83% of chronic migraine patients without aura suffered from OSA while 50% of episodic migraineurs suffered from OSA [22]. Overall, chronic migraineurs without aura were 20 times more likely to have OSA than patients with other headache types including tension-type and episodic migraines. The effectiveness of continuous positive airway pressure (CPAP) to improve headaches was examined. Almost half of the chronic migraineurs without aura reported a 50% reduction in headache severity and frequency with CPAP, indicating CPAP may be an important tool for treating chronic headache disorders [22].

Acute Stress

It is a common complaint heard in the clinic: “Stress gives me headaches.” In fact, more than 90% of headache patients report that stress affects their headaches [24]. Determining the role of acute stress in progression of headaches is complex as experiencing pain can produce stress. Numerous studies have attempted to parse this relationship by establishing temporality of events. A retrospective study found 44.8% of patients with transformed headache report a stressful event correlated with transformation from episodic to a chronic disorder [25]. Health problems accounted for 35.6% of stressful events, marriage disputes accounted for 13.6% of events, bereavement accounted for 13.6% of events, and work accounted for 11.4% of events. A smaller percentage of patients said stress related to education, legal concerns, and immigration preceded worsening of their headaches. Events in this

study were characterized by severity using the Paykel score [26]. Approximately one-third of transformed migraine patients reported a major stressful event, characterized as bereavement, legal concerns, serious illness, change or loss of job, and retirement, preceding progression. Two-thirds of patients said minor stressors such as interpersonal conflict and suboptimal work conditions coincided with headache transformation.

There are several biological mechanisms likely underlying the relationship between stress and headache. Acute stress activates an opioid-mediated pain response, which temporarily decreases sensation of pain; this may be an evolutionarily preserved adaptive response permitting improved response to a perceived threat. However, recurring stimulation of this pain center can produce central sensitization leading to hyperalgesia [27]. In addition, animal studies have shown that chronic stress, but not acute stress, results in increased sensitivity to pain in peripheral nociceptors, which may play an important role in headache transformation [28].

While acute stress may play a role in headache transformation, therapies focused solely on stress reduction have had minimal success in alleviating pain burden and reverting chronic to episodic headache. Only 13% of those suffering from chronic headaches reported reduction in headache burden following behavioral therapy, while 52% of patients with episodic headaches reported improvement in headache [29]. A combination of pharmacologic and behavioral stress reduction appears to be more effective than either therapy alone. Patients with chronic tension-type headache who received behavioral intervention and antidepressant therapy were significantly more likely (64% of patients) to show a clinically significant decrease in headache activity than patients who received antidepressant medication (38% of patients) or cognitive behavioral therapy (35% of patients) alone [30].

In addition to the direct influence of stress on progression of headache disorders, stress likely exerts important indirect effects by influencing factors known to contribute to headache progression. Stress can lead to poor sleep as well as increase the risk for obesity and medication overuse [31, 32]. Clinicians should be encouraged to

screen for stress in their headache patients and consider a multipronged management approach to help patients reduce stress.

Depression

There is extensive literature showing a bidirectional link between migraine and depression [33]. Psychiatric comorbidity has been shown to be a risk factor for headache progression, and, not surprisingly, living with chronic pain adversely affects mood. Patients with chronic daily headache have higher levels of anxiety and depressive disorders than episodic migraineurs. In episodic migraineurs, 1 year of depression (as determined by PHQ-9 scale) was a significant predictor of progression to a chronic headache disorder. This effect was present after controlling for sociodemographic variables, headache frequency, comorbidities, and medications. Further, authors demonstrated a dose-dependent effect of depression on transformation risk, with the most severely depressed patients having odds risk of 2.65 and mild depression with an odds risk of 1.77 [34].

As postulated by Lipton and Silberstein, there are several hypotheses to account for the linkage between depression and onset of chronic migraine, including shared risk factors, depression resulting from increasing number of headache episodes, and a direct influence of depression on headache progression through sensitization of central pain pathways [35].

Chronic stress is a well-established risk factor for both depression and chronic migraine. Chronic stress has been shown to induce neuroinflammation in the brain, which may lead to hyperalgesia through suppression of the nociceptive threshold [36].

There is also evidence that depression may result from increasing headache burden. Treating chronic migraine with onabotulinumtoxinA produced not only a reduction in headache burden but also alleviation of depression, demonstrating that decreasing headache frequency leads to improved psychological outcome even in the absence of interventions aimed at improving mood [37].

Finally, depression may influence headache progression through centrally mediated alterations

in pain sensitization. Imaging studies show depressed patients have increased amygdala activity and neuroplastic changes, which may contribute to central pain activation and sensitization [38]. Similarly, rodents with chemically induced chronic migraine show evidence of depression and anxiety behaviors as well as decreased levels of dopamine and serotonin in the frontal cortex [39].

These hypotheses are not mutually exclusive, and it is probable that, for any specific individual suffering from episodic headaches and depression, one or all three of these factors can influence headache progression.

Menstrual-Related Migraines

It has been known for decades that the premenstrual decline in estrogen can precipitate a migraine [40]. In one study, 70% of female migraineurs report headache episodes associated with their menses. The attacks occurring during menstruation are reported to be longer, more painful, and resistant to therapy [41]. Patients with MRM often present to a headache center in the setting of a chronic headache disorder. In a retrospective study, Calhoun and colleagues tried to determine whether alleviation of menstrual-related migraines (MRM) reverted a chronic headache disorder to an episodic disorder [21]. Ninety-two percent of patients with MRM met the criteria for chronic migraine disorder, and 72% met the criteria for medication overuse. Treatment of MRM achieved with oral contraceptive therapy to prevent the premenstrual decline in estrogen led to resolution of MRM in 81% of compliant subjects. Further, alleviation of MRM led to reversion of chronic migraine to episodic migraine in 59% of patients, while only 18% of patients with persistent MRM showed reversion to an episodic phenotype. Interestingly, the resolution of MRM often correlated with decreased headache frequency outside the menstrual week. This improvement likely stemmed from the significant decrease in medication overuse. Women with persistent MRM used 41.6 acute agents per month, while women with resolved MRM only averaged 15.7 acute agents per month. This data suggests

that hormonal therapy should be considered in women not only to reduce MRM but also medication overuse headaches.

Conclusion

While the exact pathophysiology of headache transformation is not entirely well understood, there have been many studies providing evidence that there are several modifiable risk factors that can contribute to headache chronification. Understanding how risk factors shift an episodic disorder to unremitting, daily or near-daily headache may lead to novel treatment and prevention strategies, and help provide headache patients with an improved quality of life.

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