ABSTRACT

Frequent headaches are becoming increasingly recognized as an important medical and public health problem. Defined as headaches that occur 15 days or more per month, frequent headaches of long duration (i.e., lasting 4 hours or more) are commonly classified as transformed migraine (or chronic migraine) or chronic tension-type headache; less common possibilities are hemicrania continua and new daily persistent headache. The results of recent epidemiologic studies of frequent headache highlight the high prevalence and cost of headache to society, and underscore the widespread overuse of analgesics by people with these types of headaches. In the United States, revised diagnostic criteria have been proposed and tested. This paper reviews the epidemiologic burden of frequent headache and the results of recent studies that assess transformed migraine as a diagnostic concept.


This article is based in part on a presentation given by Dr. Lipton at Headache World 2000, London.

Frequent headaches (FH) occur 15 or more days per month. The current approach to FH is first to rule out secondary headache, then to define or classify the type of primary headache. Secondary causes of FH may include brain tumors, other mass lesions, giant cell arteritis, abnormal metabolic states, infections, and a range of other disorders. Frequent primary headaches are classified as headaches of either short or long duration. Short-duration (i.e., < 4 hours) FH are attributed to cluster headaches, paroxysmal hemicranias, hypnic headaches, and trigeminal neuralgia, among other causes. FH lasting more than 4 hours, sometimes termed chronic daily headache (CDH), are commonly classified either as transformed migraine (TM) or as chronic tension-type headache (CTTH); hemicrania continua and new persistent daily headaches are less common possibilities. This article focuses on primary FH of long duration, especially TM and CTTH.

There are numerous reasons for studying FH/CDH disorders, most notably the enormous burden of this family of diseases. FH/CDH represents an extraordinarily common group of disorders affecting 4% to 5% of the population. This means that about 1 of every 20 persons over the age of 12 suffers from FH. In fact, most consultations in headache subspecialty practices in the United States are for FH/CDH. The FH/CDH problem poses enormous challenges to rigorously establish the risk factors so that high-risk individuals can be classified and appropriately treated.

FREQUENT HEADACHE AND TRANSFORMED MIGRAINE

The classification of primary FH remains somewhat controversial. From one perspective, migraine...
Advanced Studies in Medicine

and CTTH are viewed as independent disorders that occur together by chance. From an alternative view, transformed migraine is offered as a distinct nosologic entity where episodic migraine progresses to daily or almost daily attacks of migraine and/or tension-type headache (TTH).

The issue of appropriate classification is important not only for treatment choices in such a highly prevalent disorder but also because patients are quite desperate to understand their disorder. For researchers, classification is important because it facilitates epidemiologic and biologic research as well as clinical trials. Public health advocates are concerned about classification because it affects reimbursement for patient care, the allocation of research money, and the development of preventive strategies. It is only by understanding the nature of these disorders and the factors that cause progression that we can find appropriate preventive strategies.

The concept of TM crystallized in 1982 in a seminal publication by Ninan Matthew and colleagues. TM is a clinical syndrome that begins with episodic migraine. The frequency of attacks increases over time. Sometimes, the average pain intensity and the severity of associated migraine symptoms (e.g., photophobia, phonophobia, nausea) may diminish. In some patients, a daily or near-daily headache disorder develops, often with superimposed attacks of migraine. Most individuals with TM are women; predominantly, these women have a history of migraine without aura.6-9

In studies from US specialty centers, TM is predominantly associated with the overuse of pain medications (e.g., analgesics, opioids, ergotamine, and triptans). However, even in specialty centers, transformation may occur without overuse.10 Most specialists believe that medication overuse is not just a consequence of FH, but an etiologic or contributing factor, primarily because treatment studies show that when medication overuse is reduced or eliminated, attack frequency dramatically falls.16-20 In population samples and in studies outside the United States, the prevalence of medication overuse is much lower (Lipton RB, data on file).2,21,22

Criteria for diagnosing TM are currently not included in the headache criteria established by the International Headache Society (IHS). Individuals with FH/CDH often have headaches that meet the criteria for CTTH, but clinic-based studies suggest that their headaches evolve from episodic migraine, raising questions about their appropriate classification.10 TTHs often have migrainous features that are not sufficient to be classified as migraine.

Silberstein and coworkers proposed and then revised diagnostic criteria for TM.3 According to the most recent criteria (Table 1), individuals with TM must have 180 or more headaches per year with an average duration of at least 4 hours per day for at least 1 headache type, and either a current or previous history of migraine as determined by IHS criteria.

Table 1. Proposed Diagnostic Criteria for Transformed Migraine

| 180 or more headaches per year |
| Average duration ≥4 hours/day (untreated) for at least 1 headache type |
| At least 1 of the following: |
| History of migraine IHS 1.1 - 1.2, all criteria met |
| Current migraine IHS 1.1 - 1.2, all criteria met except duration (ie, duration > 72 hours included) |

Criteria for diagnosing TM are currently not included in the headache criteria established by the International Headache Society (IHS). Individuals with FH/CDH often have headaches that meet the criteria for CTTH, but clinic-based studies suggest that their headaches evolve from episodic migraine, raising questions about their appropriate classification.10 TTHs often have migrainous features that are not sufficient to be classified as migraine.

Table 2. Prevalence of Transformed Migraine in the United States

<table>
<thead>
<tr>
<th>Category</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine prevalence</td>
<td>19%</td>
<td>7%</td>
</tr>
<tr>
<td>CTTH prevalence</td>
<td>2.6%</td>
<td>1.6%</td>
</tr>
<tr>
<td>TM prevalence - expected</td>
<td>0.49%</td>
<td>0.11%</td>
</tr>
<tr>
<td>TM prevalence - observed</td>
<td>1.7%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Observed / expected</td>
<td>3.5</td>
<td>6.4</td>
</tr>
</tbody>
</table>

CTTH = chronic tension-type headache
TM = transformed migraine

According to the most recently revised criteria for TM, individuals with CDH in a subspecialty clinic could be successfully classified.23

Several lines of evidence support the existence of TM. The existence of TM cannot be accounted for by coincidental association of phenotypic CTTH and migraine. If TM represents the coincidental association of migraine and CTTH, TM should occur at the rate predicted by chance (ie, the product of the prevalence of migraine and the prevalence of CTTH). In a large population study of approximately 15,000 people in the United States, we estimated the prevalence of migraine and CTTH and compared their combined prevalences with the expected values. As shown in Table 2, TM is 3.5 times more common in women and 6.4 times more common in men than would be predicted on the basis of their chance association. We therefore suggest that TM is unlikely to result from coincidental association of migraine and CTTH.1

If migraine and TTH occur together by chance, then TTH in persons with and without migraine should have a similar response to various treatments. In the Spectrum study, we found that sumatriptan was an effective treatment for TTH in persons with migraine. However, sumatriptan was ineffective in treating attacks of TTH in persons without migraine (pure TTH). These data therefore suggest that TTH in persons with migraine is biologically different than TTH in persons without migraine or in persons with migraine that co-occurs by chance, supporting the TM concept as a different disease process.24,25

Other evidence to support the existence of TM has been derived from clinic-based observational studies suggesting that, in US headache centers, 40% to 80% of individuals with FH and migraine report a history of episodic migraine with attacks that escalate in frequency and severity.6-9

**FREQUENT HEADACHE: THE SCOPE OF THE PROBLEM**

Prevalence studies describe the scope and distribution of a disorder in a defined population over a defined period of time. Headache patients in clinics generally have more severe and frequent headaches than what is experienced by the general population. As a consequence, epidemiologic studies must be conducted in representative populations.

For CTTH, there have been several useful epidemiologic studies that used the IHS diagnostic criteria. Most of the studies showed a prevalence of 2% to 3%, indicating that CTTH is a common disorder (Table 3).1,2,6,30 Data on other forms of FH/CDH are limited because consensus has not been reached on the diagnostic criteria.

Two recent population-based studies (conducted in the United States and Spain) examined the prevalence and distribution of FH/CDH. In our US study, about 13,000 individuals aged 18 to 65 years were identified as having FH/CDH during a computer-assisted telephone interview. We applied diagnostic criteria that were consistent with the criteria proposed by Silberstein and colleagues.2 The study from Spain was smaller (approximately 2,200 people) but the evaluations were more intensive and complete. Each individual was screened by means of a telephone questionnaire evaluated by a primary care physician, and asked to keep a headache diary. Once the diaries were completed, the participants then saw a neurologist.2 Despite the differences in the “design” of the studies, the results were fundamentally very similar.

The US study presented data on 3 mutually exclusive FH subtypes: TM (as defined by the Silberstein-Lipton criteria), CTTH (by IHS criteria), and other unclassified FH/CDH. The Spanish study provided data on TM, CTTH, hemianesthesia continua, new persistent daily headache, and other types. The prevalence

<table>
<thead>
<tr>
<th>Author (yr)</th>
<th>Country</th>
<th>Sample Size</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wong (1995)29</td>
<td>Hong Kong</td>
<td>7,356</td>
<td>0.1</td>
</tr>
<tr>
<td>Gobel (1992)26</td>
<td>Germany</td>
<td>406</td>
<td>1.0</td>
</tr>
<tr>
<td>Tekle Haimanot (1995)29</td>
<td>Ethiopia</td>
<td>15,000</td>
<td>1.7</td>
</tr>
<tr>
<td>Lavados (1997)27</td>
<td>Greece</td>
<td>1,385</td>
<td>2.5</td>
</tr>
<tr>
<td>Scher (1998)28</td>
<td>United States</td>
<td>13,343</td>
<td>2.2</td>
</tr>
<tr>
<td>Castillo (1999)2</td>
<td>Spain</td>
<td>1,883</td>
<td>2.2</td>
</tr>
<tr>
<td>Rasmussen (1991)29</td>
<td>Denmark</td>
<td>740</td>
<td>3.0</td>
</tr>
</tbody>
</table>

results are strikingly similar between the 2 studies with 4.1% and 4.7% of the population experiencing FH/CDH (Table 4). The percent distribution of FH/CDH subtypes was somewhat different between the US and Spanish study (CTTH: 53% vs 47%; TM: 32% vs 51%; other: 10% vs 2%, respectively).

The Spanish study also showed that secondary causes of FH are rare, as are new daily persistent headache, and hemicrania continua. Interestingly, Castillo et al reported that 24.7% of patients were overusing analgesics, whereas data from US specialty centers reported analgesic overuse in 80% of the individuals with FH/CDH. Also observed in the Spanish study, 8 individuals had a previous history of migraine without aura and had primary FH/CDH with characteristics only of TTH. These headaches met the criteria for TM but could have been migraine and coincidental CTTH.

Gender prevalences in the US study show that the prevalence of FH/CDH subtypes CTTH and TM in women are about twice that in men. Similarly, the prevalence of episodic migraine in women is nearly twice that in men, but the female-to-male ratio is virtually 1:1 in episodic tension-type headache (ETTH). TM has a gender prevalence ratio identical to that of ordinary migraine. Also in the US study, TM produced more pain and more disability than did CTTH (Figure 1) and the annual number of attacks for both men and women with CTTH or TM was approximately 270.

COMORBIDITY WITH PSYCHIATRIC DISORDERS

Psychiatric comorbidity is not uncommon with headache disorders. One study observed current psychiatric comorbidity in 90% of primary FH/CDH patients and 81% of migraineurs. Generalized anxiety disorders were the most common in each group (primary FH/CDH 69.3%, P < 0.001; migraine 59.5%, P < 0.05). The most common mood disorders were major depressive disorders, found in 25% of FH/CDH patients. In fact, several studies have shown that depression, anxiety, panic disorder, and bipolar disease are more frequent in migraineurs than in nonmigraine control subjects. Comorbid depression often improves when daily head pain is treated effectively, but psychiatric comorbidity is associated with intractability.

RISK FACTORS FOR FREQUENT HEADACHE

Several potential risk factors have been identified for FH/CDH: overuse of pain medications, depres-
sion, sleep disturbances, stress or traumatic life events, hypertension, and head injury. However, most of those observations have come from studies that simply report the proportion of individuals with both a headache and the risk factor (and no control group), so it is difficult to conclude any causal relationship. The criteria for determining risk factors are temporality (exposure precedes onset), strength of association (beyond the chance of co-occurrence), a dose-response relationship, consistency across multiple studies, biological plausibility, and (ideally) experimental evidence to support the hypothesis. Well-designed studies of risk factors are essential for developing preventive strategies.

TREATMENTS

Treatment of FH/CDH has been reviewed elsewhere. Individuals with CDH can be difficult to treat for several reasons previously mentioned (overuse of pain medication, comorbid psychiatric disease) as well as low frustration tolerance and physical and emotional dependency. As shown in Table 5 the approach should begin with excluding secondary headache disorders, diagnosing the specific primary headache disorder, and identifying comorbid medical and psychiatric conditions and exacerbating factors, especially medication overuse. Any new medication (for acute or preventive treatment) should be given with the explicit understanding that the drugs may not become fully effective until medication overuse has been eliminated and detoxification complete, which can take from 3 to 8 weeks for preventive medication.

Acute therapy can include drugs, psychophysiologic therapy (counseling, reassurance, stress management, relaxation therapy, biofeedback), or physical therapy such as heat, cold packs, ultrasound, electrical stimulation, improved posture, trigger point release, occipital nerve blocks, and a more balanced lifestyle (exercise, adequate sleep, balanced meals, stretching).

Individuals with chronic migraine who do not overuse pain medications can treat acute migraine attacks with triptans, dihydroergotamine, and nonsteroidal anti-inflammatory drugs (NSAIDs), although the use of these drugs should be limited to avoid superimposed “rebound” (or drug-induced) headache.

PREVENTIVE PHARMACOTHERAPY

Individuals with very FH should be treated with preventive medications. Table 5 outlines the principles that should guide the administration of preventive treatment. The number of well-designed, placebo-controlled studies on the effectiveness of preventive medications is limited, but some of the medications used for traditional migraine appear to be effective in preventing FH/CDH. Among the antidepressants, the most widely used are nortriptyline, amitriptyline, and doxepin. In particular, amitriptyline has been effective in many but not all of the studies. Among the SSRIs, fluoxetine has demonstrated efficacy in primary FH/CDH. Other SSRIs under consideration are fluvoxamine and paroxetine. Beta-blockers such as propranolol and nadolol have been successful in treating individuals with migraine, and are used for primary FH/CDH. Anecdotal evidence supports the use of calcium channel blockers (eg, verapamil, diltiazem, nifedipine) in TM.

The results of small, open-label studies with the antiepileptic drug divalproex sodium have supported

### Table 5. Guiding Principles of Preventive Therapy for CDH

1. From among first-line drugs, choose preventive agents on the basis of their side-effect profiles, comorbid conditions, and specific indications.
2. Start at a low dose.
3. Gradually increase the dose until efficacy is achieved, until the patient develops side effects, or until the ceiling dose for the drug in question is reached.
4. Be aware that treatment effects develop over weeks, and treatment may not become fully effective until rebound is eliminated.
5. If one agent fails, choose an agent from another therapeutic class.
6. Prescribe monotherapy but be willing to consider combination therapy.
7. Communicate realistic expectations.

its use in TM. Similarly, topiramate, a new antiepileptic agent, has shown benefit in a small, open-label study of 37 patients with more than 10 migraine headaches per month. Finally, NSAIDs can be used for both symptomatic and preventive headache treatment, although we believe that the use of short-acting NSAIDs should be moderated owing to their potential to cause rebound headache.

CONCLUSION

The prevalence of primary FH/CDH is a public health problem of enormous scope. The clinical classification remains controversial. Although the criteria for diagnosing CTTH are well accepted, debate continues on the existence, nature, and optimal criteria for diagnosing TM. The burden of FH/CDH is considerable; FH/CDH affects 4% to 5% of the population. From 40% to 80% of individuals with FH and migraine report a history of episodic migraine with attacks that escalate in frequency and severity. FH is a major source of disability, unemployment, and healthcare utilization. As with migraine, FH is underdiagnosed and undertreated. 55% do not have ongoing medical care and 73% do not take preventive medication (Lipton RB, data on file). Although acute and preventive treatments are available, the challenge is to rigorously establish the risk factors so that high-risk individuals can be identified. At that point, preventive measures can be implemented and their effect on disease progression can be evaluated.

REFERENCES


