Chapter 65

Chronic Migraines

Stephen D. Silberstein and Jes Olesen

CHRONIC MIGRAINE

International Headache Society (IHS) code and diagnosis: 1.5.1 Chronic migraine
World Health Organization (WHO) code and diagnosis: G 43.0 Migraine without aura
Short description: Migraine headache occurring on 15 or more days per month for more than 3 months in the absence of medication overuse
Previously used terms: Transformed migraine, mixed headache, evolutive migraine, chronic daily headache

Clinical Features

IHS diagnostic criteria for chronic migraine

A. Headache fulfilling criteria C and D for 1.1 Migraine without aura on ≥15 days per month for >3 months
B. Not attributed to another disorder (31)

Note:

When medication overuse is present and fulfills criterion B for any of the subforms of 8.2 Medication-overuse headache, it is uncertain whether criterion B is fulfilled until 2 months after medication has been withdrawn without improvement (see Comments).

Comments:

Most cases of chronic migraine start as 1.1 Migraine without aura. As chronicity develops, headache tends to lose its attack-wise (episodic) presentation. Medication overuse, when present, is the most likely cause of chronic headache. Therefore, the default rule is to code such patients according to the antecedent migraine subtype (usually 1.1 Migraine without aura) plus 1.6.5 Probable chronic migraine plus 8.2.7 Probable medication-overuse headache. When these criteria are still fulfilled 2 months after medication overuse has ceased, 1.5.1 Chronic migraine plus the antecedent migraine subtype should be diagnosed, and 8.2.7 Probable medication-overuse headache discarded. If at any time sooner they are no longer fulfilled because improvement has occurred, code for 8.2, Medication-overuse headache plus the antecedent migraine subtype, and discard 1.6.5 Probable chronic migraine.

Epidemiology and Comorbidity

Since chronic migraine is a newly defined entity, epidemiologic studies using the ICHD-2 criteria are not yet available. Chronic daily headache (CDH) is a collective term, not a diagnosis. It includes chronic migraine, chronic tension-type headache (CTTH), medication-overuse headache, and new daily persistent headache. Some previous studies of CDH have subdiagnosed and thus may allow a qualified guess about chronic migraine. However, these studies used the concept of transformed migraine, which, again, is difficult to translate into chronic migraine, because it does not distinguish medication-overuse headache. In the absence of more specific data, we make use of previous data on CDH and transformed migraine.

In population-based surveys, CDH occurred in 4.1% of Americans, 4.35% of Greeks, 3.9% of elderly Chinese, and 4.7% of Spaniards. Scher et al. ascertained the prevalence of CDH in 13,343 individuals aged 18 to 65 years in Baltimore County, Maryland. The overall prevalence of CDH was 4.1% (5% women, 2.8% men; 1.8:1 women-to-men ratio). More than half (52% women, 56% men) met criteria for CTTH (2.2%); almost one-third (33% women, 25% men) met criteria for transformed migraine (TM) (1.3%); and the remainder (15% women, 19% men) were unclassified (0.6%). Overall, 30% of women and 25% of men who were frequent headache sufferers met IHS criteria for migraine (with or without aura).

Castillo et al. (6) sampled 2252 subjects over 14 years of age in Cantabria, Spain. Overall, 4.7% had CDH: None had hemicrania continua (HC), 0.1% had new daily persistent headache (NDPH), 2.2% had CTTH, and 2.4% had TM. Acute medication overuse occurred in 19% of CTTH and

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-65 Olesen- 2057G GRBT050-Olesen-v6.cls August 5, 2005 20:18

TABLE 65-1 Possible Risk Factors for Chronic Migraine

1. High headache frequency
2. Female gender
3. Obesity (body mass index >30)
4. Snoring
5. Stressful life events
6. High caffeine consumption
7. Acute medication overuse
8. Depression
9. Head trauma
10. History of migraine
11. Less than a high school education

31.1% of TM patients. Eight patients had a previous history of migraine without aura and now had CDH with only the characteristics of TTH. These headaches met the criteria of TM but could have been migraine and coincidental CTTH.

Wang et al. (37) found that 3.9% of elderly Chinese (over 65 years of age) had CDH. Significantly more women than men had CDH (5.6% and 1.8%, respectively; $p < 0.001$). Of the CDH patients, 42 (70%) had CTTH (2.7%), 15 (25%) had TM (1%), and 3 (5%) had other CDH. Significant risk factors for CDH included analgesic overuse (OR = 79), a history of migraine (odds ratio, OR = 6.6), and a Geriatric Depression Scale-Short Form score of 8 or above (OR = 2.6). At follow-up, patients with persistent primary CDH had a significantly higher frequency of analgesic overuse (33% vs. 0%; $p = 0.03$) and major depression (38% vs. 0%; $p = 0.04$) (Table 65-1).

Scher et al. (30) described factors that predict CDH onset and remission in an adult population. CDH was more common in women (OR = 1.65 [1.3–2.0]), those previously married (OR = 1.5 [1.2–1.9]), with obesity (body mass index [BMI] >30) (OR = 1.27 [1.0–1.7]), and those with less education. Obesity, high baseline-headache frequency, high caffeine consumption, habitual daily snoring, and stressful life events were significantly associated with new-onset CDH (29). Having less than a high school education was associated with a threefold increased risk of CDH. (OR = 3.56 [2.3–5.6]). (Table 65-1)

Anxiety, depression, panic disorder, and bipolar disease are more frequent in migraineurs than in nonmigraine control subjects (4,22). Since CM is a complication of migraine, one would expect to find a similar or accentuated profile of psychiatric comorbidity in CM patients. Many older studies do not clearly differentiate between CDH subtypes. In clinic-based samples, depression occurs in 80% of TM patients. CDH patients had significantly higher Zung and Beck Depression Scale scores than did migraine controls (15,16,19,28). Comorbid depression often improves when the cycle of daily head pain is broken.

Mitsikostas and Thomas (23) found that headache patients had significantly higher average Hamilton rating anxiety and depression scores than did nonheadache controls. Patients with CTTH, mixed headache, or drug abuse headache had the highest Hamilton rating depression and anxiety scores. Verri et al. (36) found current psychiatric comorbidity in 90% of primary CDH patients. Generalized anxiety occurred in 69.3% of patients and major depression in 25%.

Juang et al. (12) investigated the frequency of depressive and anxiety disorders in 261 consecutive CDH patients seen in a headache clinic. TM was diagnosed in 152 patients (58%) and CTTH in 92 (35%). Seventy-eight percent of patients with TM had psychiatric comorbidity, including major depression (57%), dysthymia (11%), panic disorder (30%), and generalized anxiety disorder (8%). The frequency of anxiety disorders was significantly higher in patients with TM after controlling for age and sex.

Peres et al. (25) estimated the prevalence of fibromyalgia (FM) in 101 TM patients and analyzed its relationship to depression, anxiety, and insomnia. FM was diagnosed in 35.6% of cases. FM patients had more insomnia, were older, and their headaches were more incapacitating than patients without FM. Fifty-seven patients (87.7%) had at least mild depression. Depression was also associated with FM ($p = 0.007$), insomnia ($p = 0.043$), and disability ($p = 0.05$).

Peres et al. (26) determined the prevalence of fatigue in 63 TM patients. Fifty-three patients (84.1%) had FSS scores greater than 27. Forty-two patients (66.7%) met the criteria for chronic fatigue syndrome established by the Centers for Disease Control. Fatigue as a symptom and chronic fatigue syndrome as a disorder were both common in TM patients.

Pathophysiology of Chronic Migraine

Underlying the pathophysiology of chronic migraine is, of course, the disposition to migraine without aura. This is discussed extensively in previous chapters of this book. Here, we focus on the question of why some migraine sufferers progress to become chronic. In this discussion, we disregard medication overuse, which is by far the most common cause of chronicity. Recent work suggests several mechanisms that could contribute: (1) increased peripheral nociceptive activation (perhaps due to chronic neurogenic inflammation) and activation of silent nociceptors; (2) peripheral sensitization; (3) altered sensory neuron excitability; (4) central sensitization of TNC neurons due to posttranslational changes in ligand- and voltage-gated ion-channel kinetics, altering excitability and strength of their synaptic inputs; (5) phenotype modulation due to alterations in the expression of receptors/transmitters/ion channels in peripheral and central neurons; (6) synaptic reorganization modification of synaptic connections caused

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-65 Olesen- 2057G GRBT050-Olesen-v6.cls August 5, 2005 20:18

by cell death or sprouting; (7) decreased pain modulation due to loss of local and descending input (39); or (8) a combination of these.

Central sensitization is characterized by increased spontaneous discharge rate, reductions in threshold and increased responsiveness to both noxious and nonnoxious peripheral stimuli, and expanded receptive fields of central nervous system (CNS) nociceptive neurons (7,40,41). Central sensitization results in muscle tenderness and cutaneous allodynia in patients with migraine. Most migraineurs exhibit cutaneous allodynia inside and outside their pain-referred areas during migraine attacks (5). Evidence now exists that central sensitization, defined by the presence of cutaneous allodynia, exists in CM. Shukla et al. (32) studied dynamic mechanical (brush) allodynia (BA) in headache patients in an inpatient setting. This study demonstrated that mechanical dynamic BA is common in hospitalized CDH patients. Of a total of 78 patients, most of whom had migraine without aura, probable medication-overuse headache, and probable chronic migraine, 32 (41%) experienced BA. Allodynia was more common and more severe in V1, indicating the role of central sensitization in its development. Allodynia was significantly more common in patients with unilateral headaches and was usually ipsilateral to the headache.

Creach et al. (8) compared heat-pain thresholds in patients with so-called TM with and without medication overuse and patients with episodic migraine. Extracranial, but not face, allodynia was more common in both TM groups (39.5% vs. 12.1%). Using a questionnaire, Sobrino (35) found that 56.3% of so-called TM patients had cutaneous allodynia in their pain-referred areas. Interpreting these studies is difficult because internationally accepted diagnoses were not used.

Manjit et al. (14) reported eight patients with the IHS diagnosis of CM who showed a marked beneficial response to implanted bilateral suboccipital stimulators. Each patient was scanned in the following three states: (1) stimulator at optimum settings: patient pain-free but with paresthesia; (2) stimulator off: patient in pain and no paresthesia; (3) stimulator partially activated: patient with intermediate levels of pain and paresthesia. There were significant changes in regional cerebral blood flow (rCBF) in the dorsal rostral pons, anterior cingulate cortex (ACC), and cuneus, correlated to pain scores, and in the ACC and left pulvinar, correlated to stimulation-induced paresthesia scores. The activation pattern in the dorsal rostral pons is highly suggestive of a role for this structure in the pathophysiology of CM. The localization and persistence of activity during stimulation is exactly consistent with a region activated in episodic migraine and with the persistence of activation of that area after successful treatment. The dorsal rostral pons may be a locus of neuromodulation by suboccipital stimulation. In addition, suboccipital stimulation modulated activity in the left pulvinar.

Welch et al. (38) used high-resolution magnetic resonance techniques to map the transverse relaxation rates R2 (1/T2), R2′ (1/T2*–1/T2), and R2′ (1/T2*) in the brain, particularly the PAG, red nucleus (RN), and substantia nigra (SN). These measures are sensitive to free iron: R2′ is a measure of nonheme iron in tissues. They evaluated patients with TM, patients with episodic migraine, and nonmigraine controls. In the PAG there was a significant increase in mean R2′ and R2′ values in both the episodic migraine and TM patients. The value increased with disease duration. A decrease in mean R2′ and R2′ values in the RN and SN of only the TM group was observed; they attributed this to CBF changes due to head pain. Aurora (1) reported normalization of SN and RN but not PAG R2′ values following detoxification.

CM may result from a defective interaction between endogenous nociceptive brainstem activity and peripheral input. Physical or psychologic stress can increase the nociception that could trigger or sustain an attack in an individual with altered pain modulation. Emotional mechanisms may also reduce endogenous antinociception. Long-term potentiation of nociceptive neurons and decreased activity in the antinociceptive system could cause primary CDH. Sensitization of the trigeminal NC neurons can result in normally nonpainful stimuli becoming painful, producing trigger spots, an overlap in the symptoms of migraine and TTH, and activation of the trigeminal vascular system.

Clinical Features

Many studies have described the process and associated features of CM (17,20,21,24,27,33), which is probably quite similar to what was called transformed migraine. Patients with CM often have a past history of episodic migraine that began in their teens or twenties (20,27,33). Most are women and the great majority, if not all, have a history of migraine without aura. Patients often report a process of transformation characterized by headaches that become more frequent over months to years, with the associated symptoms of photophobia, phonophobia, and nausea becoming less severe and less frequent (17,18,27). Patients often develop a pattern of daily or nearly daily headaches that phenomenologically resemble a mixture of TTH and migraine. That is, the pain is often mild to moderate and is not always associated with photophobia, phonophobia, or gastrointestinal features. Unfortunately the past literature does not exclude patients with medication overuse. Other features of migraine, including unilaterality, gastrointestinal symptoms, and aggravation by menstruation and other trigger factors, may persist. Attacks of full-blown migraine superimposed on a background of less severe headaches occur in many patients. The term transformation has been used to refer to this process. The term CM is now being used by the IHS, in part because a history of transformation is often missing.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-65 Olesen- 2057G GRBT050-Olesen-v6.cls August 5, 2005 20:18

If migraine transforms into apparent CM as a result of medication overuse it is called medication overuse headache (MOH); transformation may occur without overuse (19,21), although 80% of CDH patients seen in subspecialty clinics overuse acute medication (2,18,20,21,27).

ICHD-2 considers CM to be a complication of migraine. Its diagnosis requires migraine headache to occur on 15 or more days a month for more than 3 months without medication overuse. It must not be attributable to another disorder, including HC and NDPH. When medication overuse is present, the diagnosis is unclear until the medication has been withdrawn and there has been no improvement. Medication overuse (i.e., MOH) is often the cause of migraine chronicity. The IHS rule is to code these patients according to the antecedent migraine subtype (usually migraine without aura) plus probable CM plus probable MOH. If criteria for CM are still fulfilled 2 months after medication overuse has ceased, diagnose CM plus the antecedent migraine subtype and discard the diagnosis of probable MOH. If CM criteria are no longer fulfilled, change the diagnosis to MOH plus the antecedent migraine subtype and discard the diagnosis of probable CM (11).

The requirement that the daily headache must meet the criteria for migraine without aura each day may be a concern with the new IHS criteria. The early intake of acute antimigraine medicine may prevent the attack from full development and, hence, from fulfilling IHS criteria. Judgment must be exercised in such cases.

Differentiating Chronic Migraine From Other Chronic Daily Headaches

One must be sure that CM is not attributable to another disorder, the most common of which is MOH. Secondary causes of frequent headache include chronic posttraumatic headache, cervical spine disorders, vascular disorders, chronic meningitis, idiopathic intracranial hypertension, temporomandibular joint disorder, and sinus infection (3,34). Idiopathic intracranial hypertension is easily diagnosed when papilledema is present, but if the patient does not have papilledema, intracranial hypertension can mimic CM. Spontaneous intracranial hypotension can be missed, as the postural components may disappear over time (15). Magnetic resonance imaging plus magnetic resonance venography (MRV) (with gadolinium if needed) are the neuroimaging procedures of choice for patients suspected of having a secondary cause for CDH (10).

Prognosis

The "natural history" of CM has not yet been studied. There are now literature reports of spontaneous improvement of CDH in population-based studies (29). Scher et al. (30), in a population-based study, found that the 1-year remission rate to less than one headache per week was 14% and to less than 180 days per year was 57%. This was similar to the rate of remission in a population-based study in Taiwan, which demonstrated a 2-year remission rate of 65% (to <180 days per year) (13). The significant predictors for persistent CDH at follow-up included: older age (≥40 years) (risk ratio, RR = 2.4), CDH onset after 32 years (RR = 1.8), CDH duration greater than or equal to 6 years (RR = 2.0), medication overuse (RR = 1.8), and daily headache (RR = 2.1). Wang et al. (37) found that the 4-year remission rate in elderly Chinese was 33%.

Management

Patients with CM can be difficult to treat, especially when the disorder is complicated by comorbid psychiatric disease, low frustration tolerance, and physical and emotional dependency (20,28). It is important to identify comorbid medical and psychiatric conditions and exacerbating factors. All acute medications (with the possible exception of the long-acting nonsteroidal anti-inflammatory drugs) should be limited. European centers mostly make patients totally free of symptomatic medication for 1 or 2 months before starting preventive medications. U.S. centers often start on preventive medication early, with the explicit understanding that the drugs may not become fully effective until medication overuse, if present, has been eliminated. Most preventive agents used for CM have not been examined in well-designed double-blind studies. Their use is based on their efficacy for episodic migraine. In some cases, CM reverts to the episodic variety when preventive medication is initiated and acute medication limited. In other cases, there may be only moderate or no improvement. Patients often need additional treatment (which we call *headache terminators*) to break the cycle of CM and/or help with the exacerbation that occurs when overused medications are discontinued. Terminators are given orally, by suppository, or by injection, and some (dihydroergotamine, neuroleptics [prochlorperazine, chlorpromazine, and droperidol], corticosteroids, valproate sodium, magnesium, and ketorolac) can be given repetitively intravenously. The route of administration depends on both the setting and the intensity of treatment. Outpatient options, including outpatient infusion in an ambulatory infusion unit, are available. If outpatient treatment proves difficult or is dangerous, hospitalization may be required (9,34,42).

REFERENCES

1. Aurora SK. Imaging chronic daily headache. *Curr Pain Headache Rep* 2003;7:209–211.
2. Bigal ME, Sheftell FD, Rapoport AM, et al. Chronic daily headache in a tertiary care population: correlation between the International Headache Society diagnostic criteria and proposed revisions of criteria for chronic daily headache. *Cephalalgia* 2002;22:432–438.

P1: KWW/KKL P2: KWW/HCN QC: KWW/FLX T1: KWW
GRBT050-65 Olesen- 2057G GRBT050-Olesen-v6.cls August 5, 2005 20:18

3. Bousser MG, Russell RR. Cerebral venous thrombosis. In: Bousser MG, Russell RR, eds. *Major problems in neurology.* London: Saunders,1997:175.
4. Breslau N, Davis GC. Migraine, physical health and psychiatric disorders: a prospective epidemiologic study of young adults. *J Psychiatric Res* 1993;27:211–221.
5. Burstein R, Yarnitsky D, Goor-Aryeh I, et al. An association between migraine and cutaneous allodynia. *Ann Neurol* 2000;47:614–624.
6. Castillo J, Munoz P, Guitera V, et al. Epidemiology of chronic daily headache in the general population. *Headache* 1999;39:190–196.
7. Cook AJ, et al. Dynamic receptive field plasticity in rat spinal cord dorsal horn following C primary afferent input. *Nature* 1987;325:151–153.
8. Creach C, Radat F, Laffitau M, et al. Cutaneous allodynia in transformed migraine with medication overuse [Abstract]. *Cephalalgia* 2003;23:656–657.
9. Freitag FG, Lake A, Lipton RB, et al. Inpatient treatment of headache: an evidence-based assessment. United States Headache Guidelines Consortium. *Headache* 2004;44:342–360.
10. Gladstone J, Eross E, Dodick D. Chronic daily headache: a rational approach to a challenging problem. *Semin Neurol* 2003;23:265–276.
11. Headache Classification Committee. The international classification of headache disorders, 2nd edition. *Cephalalgia* 2004;24 [Suppl 1]:1–160.
12. Juang KD, Wang SJ, Fuh JL, et al. Comorbidity of depressive and anxiety disorders in chronic daily headache and its subtypes. *Headache* 2000;40:818–823.
13. Lu SR, Fuh JL, Chen WT, et al. Chronic daily headache in Taipei, Taiwan: prevalence, follow-up and outcome predictors. *Cephalalgia* 2001;21:980–986.
14. Manjit SM, Thorsten B, Ward N, et al. Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study. *Brain* 2003;1:220–230.
15. Mathew NT. Chronic daily headache: clinical features and natural history. In: Nappi G, Bono G, Sandrini G, Martignoni E, Micieli G, eds. *Headache and depression: serotonin pathways as a common clue*. New York: Raven Press,1991:49–58.
16. Mathew NT. Drug induced headache. *Neurol Clin* 1990;8:903–912.
17. Mathew NT. Transformed migraine. *Cephalalgia* 1982;13[Suppl 12]:78–83.
18. Mathew NT. Transformed or evolutional migraine. *Headache* 1987; 27:305–306.
19. Mathew NT, Kurman R, Perez F. Drug induced refractory headache—clinical features and management. *Headache* 1990;30:634–638.
20. Mathew NT, Reuveni U, Perez F. Transformed or evolutive migraine. *Headache* 1987;27:102–106.
21. Mathew NT, Stubits E, Nigam MR. Transformation of episodic migraine into daily headache: analysis of factors. *Headache* 1982;22:66–68.
22. Merikangas KR, Angst J, Isler H. Migraine and psychopathology: results of the Zurich cohort study of young adults. *Arch Gen Psychiatry* 1990;47:849–853.
23. Mitsikostas DD, Thomas AM. Comorbidity of headache and depressive disorders. *Cephalalgia* 1999;19:211–217.
24. Olesen J, Tfelt-Hansen P, Welch KMA. *The headaches*. New York: Raven Press, 1993.
25. Peres MF, Young WB, Kaup AO, et al. Fibromyalgia is common in patients with transformed migraine. *Neurology* 2001;57:1326–1328.
26. Peres MF, Zukerman E, Young WB, et al. Fatigue in chronic migraine patients. *Cephalalgia* 2002;22:720–724.
27. Saper JR. *Headache disorders: current concepts in treatment strategies*. Littleton: Wright-PSG, 1983.
28. Saper JR. Ergotamine dependency—a review. *Headache* 1987;27: 435–438.
29. Scher AI, Lipton RB, Stewart W. Risk factors for chronic daily headache. *Cur Pain Headache Rep* 2002;6:486–491.
30. Scher AI, Stewart WF, Ricci JA, et al. Factors associated with the onset and remission of chronic daily headache in a population-based study. *Pain* 2003;106:89.
31. Scher AI, Stewart WF, Liberman J, et al. Prevalence of frequent headache in a population sample. *Headache* 1998;38:497–506.
32. Shukla P, Richardson E, Young WB. Brush allodynia in an inpatient headache unit. *Headache* 2003;43:542.
33. Silberstein SD, Lipton RB, Sliwinski M. Classification of daily and near-daily headaches: field trial of revised IHS criteria. *Neurology* 1996;47:871–875.
34. Silberstein SD, Lipton RB. Chronic daily headache including transformed migraine, chronic tension-type headache, and medication overuse. In: Silberstein SD, Lipton RB, Dalessio DJ, eds. *Wolff's headache and other head pain*. New York: Oxford University Press, 2001:247–282.
35. Sobrino FE. Cutaneous allodynia in chronic migraine [Abstract]. *Cephalalgia* 2003;23:750.
36. Verri AP, Cecchini P, Galli C, et al. Psychiatric comorbidity in chronic daily headache. *Cephalalgia* 1998;18[Suppl 21]:45–49.
37. Wang SJ, Fuh JL, Lu SR, et al. Chronic daily headache in Chinese elderly: prevalence, risk factors and biannual follow-up. *Neurology* 2000;54:314–319.
38. Welch KMA, Nagesh V, Rozell K, et al. Functional MRI of chronic daily headache. *Cephalalgia* 1999;19:462–463.
39. Woolf CJ, Mitchell MB. Mechanism-based pain diagnosis issues for analgesic drug development. *Anesthesiology* 2001;95:241–249.
40. Woolf CJ. Evidence for a central component of postinjury pain hypersensitivity. *Nature* 1983;306:686–688.
41. Woolf CJ, Wall PD. The relative effectiveness of C primary afferent fibres of different origins in evoking a prolonged facilitation of the flexor reflex in the rat. *J Neurosci* 1986;6:1433–1443.
42. Zed PJ, Loewen PS, Robinson G. Medication-induced headache: overview and systematic review of therapeutic approaches. *Ann Pharmacother* 1999;33:61–72.