Chapter 25
Migraine, Headache, and Third Mobile Window Syndrome

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An illustrative summary that highlights the spectrum of the most common complaints from patients with perilymph fistula (PLF) was published over a quarter century ago [1]. No doubt many of these patients had third mobile window syndrome (TMWS) due to bony sites of dehiscence not yet discovered. In this publication the authors reported the percentage of their patients reporting each of the 13 most common complaints. The three most frequent complaints were disequilibrium, headache and dizziness. Other important clinical symptoms included cognitive dysfunction, nausea, visual disturbance, and objective as well as subjective hearing loss. The most common symptoms of superior semicircular canal dehiscence (SSCD), and other sites of TMWS, include pseudoconductive hearing loss (bone conduction hyperacusis), autophony, pulsatile tinnitus, and sound- or pressure-induced vertigo [2–11]. Some of the internal sounds that patients report as being particularly disturbing include hearing their eyes move and/or blink, hearing their heels strike loudly, chewing (often so loud they need to stop chewing to hear what others say), belching or borborygmi. Patients also experience aural fullness typical of endolymphatic hydrops. This spectrum of symptoms observed is summarized in Chap. 1.

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Headache and Migraine

Migraine is a symptomatically heterogeneous condition, of which headache is just one manifestation. Migraine is a disorder of altered sensory thresholding, with hypersensitivity among sufferers to sensory input. Advances in functional neuroimaging have highlighted that several brain areas are involved even prior to pain onset. Clinically, patients can experience symptoms hours to days prior to migraine pain, which can warn of impending headache. These symptoms can include mood and cognitive change, fatigue and neck discomfort. Epidemiological studies have suggested that migraine is associated with other systemic conditions such as depression, anxiety, irritable bowel syndrome, fibromyalgia, sleep disorders, and chronic fatigue, as well as cognitive disorders (for review see Karsan and Goadsby [12]). The association between migraine and psychiatric disorders has been well documented through numerous population-based studies. The results of these studies show an increased risk of suffering from depression, bipolar disorders, numerous anxiety disorders, especially posttraumatic stress disorder. Many reasons have been postulated for these associations, including comorbidities, cause and effect, and shared pathophysiological mechanisms [13]. Sarif et al. completed a systematic review of the association of migraine and cognitive dysfunction, including dementia [14]. All the reviewed studies put together showed an association between headache and cognitive dysfunction of any form. They showed that the frequency and duration of headache is a determinant for dementia. However, few studies also focused on how treating headaches with certain drugs can lead to dementia. The reviewed published literature showed that headaches of any sort and their treatment are potentially linked to dementia [14].

As one of the most common chronic daily headache (CDH) disorders, chronic migraine (CM) is featured by frequent headache attacks with at least 15 headache days per month [15, 16]. Chronic migraine sufferers usually have a history of episodic migraine (EM) and their headache frequencies increase with time. It is estimated that approximately 3% EM patients evolve to CM per year [17, 18]. This transformation can be bidirectional with about 26% of CM patients reverting to EM in a cohort followed for two years [19]. Because of this, it is difficult to confirm the true prevalence of CM. With the increasing headache frequency, CM can become less intense, but is associated with worse response to treatment. Both the undertreated headache and associated comorbidities cause greater disease burden for CM compared with EM [20–22]. Although regarded as the same spectrum illness with EM [23], the detailed pathophysiology of CM is not fully understood. The role of vestibular dysfunction due to TMWS in EM and/or CM remains understudied. Studies have recognized several predisposing factors and triggers such as specific olfactory stimuli, sleep deprivation, hunger, bright light, medication overuse, insufficient migraine prophylactic treatment, low socioeconomic status, stressful events and depression [19, 24]. Some epidemiological studies have suggested that migraine is associated in a bidirectional fashion with other disorders, such as mood disorders and chronic fatigue, as well as with other pain conditions such as fibromyalgia [12].

In a series with three different TMWS cohorts, depression, as measured with Beck's Depression Inventory (BDI), was significantly reduced after surgical management [5]. These same cohorts had significant reduction in their Headache Impact Test (HIT-6) scores after surgical management, underscoring the potential contribution of TMWS to depression and migraine. Moreover, recent neurophysiological and imaging studies have indicated that CM may be associated with both structural and functional alterations in some brain regions, especially cortical hyperexcitability and brainstem dysfunction [25–27]. Sensitization of the trigeminal system also plays a vital role, as allodynia is quite common in CM patients [28]. In addition, several molecular mechanisms have been implicated in the pathogenesis of CM, such as calcitonin gene-related peptide (CGRP), serotonin (5-HT), pituitary adenylate cyclase activating polypeptide (PACAP), and others [29–31]. Migraine should be considered a neural disorder of brain function, in which alterations in networks integrating the limbic system with the sensory and homeostatic systems occur early and persist after headache resolution and perhaps interictally. The associations with some of these other disorders may allude to the inherent sensory sensitivity of the migraine brain and shared neurobiology and neurotransmitter systems, rather than true comorbidity [32].

Pathophysiology of Chronic Migraine

Like EM, the pathophysiological basis of CM is not fully understood. However, recent data indicate that migraine is a disorder of brain dysfunction with both the genetic background and environment triggering [33]. The transformation of EM to CM is also related to the brain. Recent evidence has demonstrated both structural and functional alterations in the brain, in particular cortical hyperexcitability and abnormities in the brainstem [27]. More CM patients than EM patients report cutaneous allodynia [34], suggesting that sensitization of trigeminal system is involved in the development of the disease. Seo and Park investigated the clinical significance of allodynia compared with other sensory hypersensitivities in migraine patients [35]. They found that migraine particularly combined with allodynia resulted in poor clinical outcomes. In addition, several molecules, such as CGRP and 5-HT [29, 30], have been reported to be correlated with the transition from occasional migraine to EM to CM. In brief, both recurring headache attacks and the comorbid conditions (medication over use, anxiety, and depression) promote the derangement of top-down pain modulation and also atypical release of nociceptive molecules, which aggravates trigeminal sensitization induced by repeated nociceptive inputs. With this hypersensitive state, the EM finally progresses to CM. The neural plasticity induced by the risk factors of CM may in turn exert an influence.

Since migraine is characterized by altered sensory thresholding with hypersensitivity among sufferers to sensory input, we believe that the gravitational receptor asymmetries seen in TMWS are triggering migraine via this hypersensitivity-associated mechanism.

Measuring the Impact of Headache

When measuring the magnitude of headache and migraine headache in patients with TMWS and, equally importantly, the response to surgical intervention it is essential to incorporate a validated survey instrument into clinical practice. We have found the six-item HIT-6 to be an outstanding tool to accomplish these goals. The short-form HIT-6 is a widely used patient-reported outcome measure that assesses the negative effects of headaches on normal activity. Houts et al. completed a narrative literature review to examine existing qualitative research in patients with migraine and headache, and to provide insight into the relevance and meaningfulness of HIT-6 items to the lives of migraine patients [36]. This review demonstrated qualitative support for the relevance of the items of the HIT-6 in migraine patients, supporting its ongoing use in clinical migraine research and practice. The six-item HIT-6 includes the following questions: Question 1: *When you have headaches, how often is the pain severe?*; Question 2: *How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?*; Question 3: *When you have a headache, how often do you wish you could lie down?*; Question 4: *In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?*; Question 5: *In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?*; Question 6: *In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?* Each item has five descriptive response options, with each awarded a specific number of points: "Never" (6 points), "Rarely" (8 points), "Sometimes" (10 points), "Very often" (11 points), and "Always" (13 points). The score is the sum of item (points) responses. The index score ranges from 36 to 78, where scores 36–49 indicate little to no impact on life (Class I); 50–55 indicates some impact on life (Class II); 56–59 indicates substantial impact on life (Class III); and 60–78 indicates very severe impact on life (Class IV).

There are alternative validated survey instruments such as the Chronic Headache Quality of Life Questionnaire (CHQLQ) which is a 14-item questionnaire, assessing the functional aspects of headache-related quality of life, producing three domain scores (role prevention, role restriction and emotional function) [37]. Haywood et al. compared the quality and acceptability of a new headache-specific patient-reported measure, the CHQLQ, with the six-item HIT-6, in people meeting an epidemiological definition of chronic headaches [37]. They concluded while both measures are structurally valid, internally consistent, temporally stable, and responsive to change, the CHQLQ has greater relevance to the patient experience of chronic headache. However, for the patient with TMWS, the CHQLQ questions are too similar to the Dizziness Handicap Inventory domains (functional, physical, and impact on disability) and it is likely that the TMWS patients would answer the CHQLQ questions based upon their vestibular dysfunction symptoms/experiences. For this reason, we find the HIT-6 to be more useful in this specific patient population.

Headache and Migraine in Third Mobile Window Syndrome

It is common for patients with TMWS to experience symptom complexes associated with headache and migraine headache. They can also experience the variants of migraine: vestibular migraine (VM), ocular migraine, and hemiplegic migraine. Table 25.1 summarizes the character of the headache, presence of headache, and the prevalence of migraine variants in six cohorts of patients that included: SSCD with plugging, TMWS with no visible site of dehiscence by high-resolution temporal bone CT (CT− TMWS) with round window reinforcement (RWR), both SSCD plugging and CT− TMWS with RWR, cochlea-facial nerve dehiscence (CFD) with RWR, CFD without RWR and surgically managed PLF. Of note there were patients with TMWS and no headache. In these same series the prevalence of no headache was 9.1% in SSCD with plugging, 7.1% in CT− RWR, 12.5% in CFD without RWR, and 12% surgically managed PLF [1, 4–6]. The remaining cohorts all experienced headache preoperatively. Ward et al. [38] reviewed the first 20 years of literature after SSCD, and regarding migraine and SSCD they stated, "*Many patients with [SSCD] also have migraine, but this may represent the high prevalence of migraine in the general population and that [SSCD] is an effective migraine trigger*." Another way of restating that is that SSCD and other sites creating TMWS induce migraine, in the same way that trigeminal nerve stimulation, olfactory stimulation, and ocular stimulation can induce episodes of migraine. Of course, both possibilities can be true and using a validated survey instrument, the HIT-6, to measure the scores before and after surgical intervention supports this.

Table 25.2 summarizes the HIT-6 scores and classifications before and after surgical intervention, as well as the statistical significance, for four different cohorts of patients with TMWS. Note that for all four comparisons, the improvement in the HIT-6 score was highly statistically significant ($p < 0.001$). However, based upon the postoperative classifications, there were a few patients with HIT-6 Class III or Class IV (next to worst and worst Class) suggesting that they were migraine patients whose TMWS made their migraine worse, but it persisted after surgical intervention. Figure 25.1 shows an example of individual patient data for eight CFD patients preoperatively and after RWR surgery.

As shown in Table 25.1, patients with TMWS can also experience VM (migraine-associated dizziness) which is recognized as a distinct clinical entity that accounts for a high proportion of patients with vestibular symptoms (for review see Furman et al. [39]). It is so common that VM should be considered in any patient presenting with dizziness, vertigo, or disequilibrium. A temporal overlap between vestibular symptoms, such as vertigo and head-movement intolerance, and migraine symptoms, such as headache, photophobia, and phonophobia, is a requisite diagnostic criterion. Physical examination and laboratory testing are usually normal in VM but can be used to rule out other vestibular disorders with overlapping symptoms such as TMWS. The pathophysiology of VM is incompletely understood but plausibly

Table 25.1 Presence and characteristics of chronic headache/migraine and migraine variants in six cohorts of patients with third mobile window syndrome of different etiologies

Etiology of third mobile window syndrome and cohort studied	Chronic headache/ migraine	24/7 while awake	Daily or frequent	Occasional headache	No headache	Vestibular migraine	Ocular migraine	Hemiplegic migraine
SSCD with plugging (Wackym et al. [4, 5])	91% (10/11)	9.1% (1/11)	81.8% (9/11)	9.1% (1/11)	9.1% (1/11)	9.1% (1/11)	9.1% (1/11)	None
CT− with RWR (Wackym et al. [4, 5])	92.9% (13/14)	71.4% (10/14)	21.4% (3/14)	None	7.1% (1/14)	14.3% (2/14)	21.4% (3/14)	7.1% (1/14)
SSCD plugging + CT− with RWR (Wackym et al. [5])	100% (4/4)	None	100% (4/4)	None	None	None	25% (1/4)	None
CFD with RWR (Wackym et al. [6])	75% (6/8)	25% (2/8)	75% (6/8)	None	None	37.5% (3/8)	62.5% (5/8)	None
CFD without RWR (Wackym et al. [6])	87.5% (7/8)	None	75% (6/8)	12.5% (1/8)	12.5% (1/8)	62.5% (5/8)	25% (2/8)	None
PLF (Black et al. [1])	88% (51/58)	NR	NR	NR	12% (7/58)	NR	NR	NR

24/7 indicates migraine headache present constantly, 24 h and 7 days per week while awake; *CFD with RWR*, cochlea-facial nerve dehiscence with round window reinforcement surgery; *CFD without RWR*, cochlea-facial nerve dehiscence without round window reinforcement surgery; *CT− with RWR*, third window syndrome with no bony site of dehiscence seen on high-resolution temporal bone CT with round window reinforcement surgery; *PLF*, perilymphatic fistula; SSCD with plugging, superior semicircular canal dehiscence with plugging and resurfacing; *SSCD with plugging + CT− with RWR*, superior semicircular canal dehiscence with plugging and resurfacing plus third window syndrome with no bony site of dehiscence seen on high-resolution temporal bone CT with round window reinforcement surgery; *RWR*, round window reinforcement surgery. Published with permission, copyright © P.A. Wackym, MD

Table 25.2 Headache Impact Test (HIT-6) score preoperatively and postoperatively, statistical significance, and preoperative and postoperative classification

Etiology of third mobile window syndrome and cohort studied	Mean preoperative HIT-6 score	Mean postoperative HIT-6 score	Statistical significance (paired *t*-test)	Preoperative HIT-6 classifications	Postoperative HIT-6 classifications
SSCD with plugging ($n = 5$) ($n = 4$ with headache) (Wackym et al. [5])	69.8 (range 61–76, SD ± 6.34)	44.5 (range 36–61, SD ± 11.27)	$p < 0.001$	4 Class IV (plus 1 with no headache)	3 Class I, 1 Class IV
CT− with RWR ($n = 8$) ($n = 7$ with headache) (Wackym et al. [5])	74 (range 68–78, SD ± 4)	45.7 (range 42–49, SD ± 3.14)	$p < 0.001$	7 Class IV	7 Class I
SSCD plugging + CT− with RWR ($n = 4$) (Wackym et al. [5])	69.3 (range 57–78, SD ± 9.7)	46.8 (range 36–53, SD ± 8.10)	$p < 0.001$	3 Class IV, 1 Class III	2 Class I, 2 Class II
CFD with RWR ($n = 8$) (Wackym et al. [6])	64.9 (range 52–69, SE ± 1.1)	42.4 (range 36–55, SE ± 2.7)	$p < 0.001$	8 Class IV	7 Class I or Class II, 1 Class III

CFD with RWR, cochlea-facial nerve dehiscence with round window reinforcement surgery; *CT− with RWR*, third window syndrome with no bony site of dehiscence seen on high-resolution temporal bone CT with round window reinforcement surgery; *HIT-6*, Headache Impact Test 6; *SD*, standard deviation, *SE*, standard error; *SSCD with plugging*, superior semicircular canal dehiscence with plugging and resurfacing; *SSCD with plugging + CT− with RWR*, superior semicircular canal dehiscence with plugging and resurfacing plus third window syndrome with no bony site of dehiscence seen on high-resolution temporal bone CT with round window reinforcement surgery; *RWR*, round window reinforcement surgery. HIT-6 classification: Class I (36–49), Class II (50–55), Class III (56–59), Class IV (60–78). Published with permission, copyright © P.A. Wackym, MD

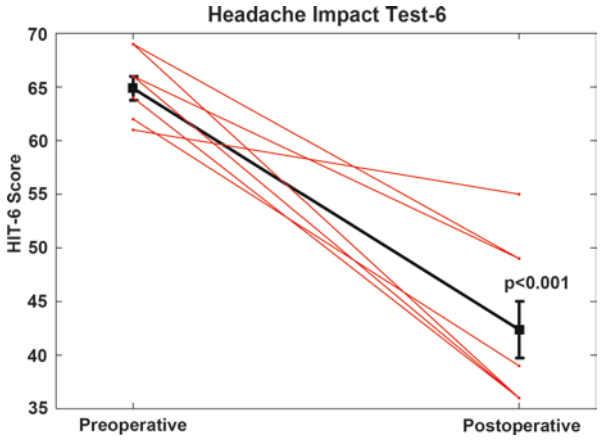

Fig. 25.1 Example of individual patient data for preoperative and postoperative Headache Impact Test (HIT-6) scores. The patients depicted are a cochlea-facial nerve dehiscence cohort who had round window reinforcement procedures performed. The preoperative mean HIT-6 score was 64.9 (SE 1.1, range 52–69). The postoperative mean HIT-6 score was 42.4 (SE 2.7, range 36–55). This improvement was highly statistically significant (paired *t*-test, $p < 0.001$). These data are plotted as a single black line. Individual patients are plotted as separate lines (red). (Used with permission, copyright © P.A. Wackym, MD)

could include neuroanatomical pathways to and from central vestibular structures and neurochemical modulation via the locus coeruleus and raphe nuclei. In the absence of controlled trials, treatment options for patients with VM largely mirror those for migraine headache. These treatment approaches include the prophylactic prevention of migraines with: (1) antiseizure medications such as topiramate (Topamax) or zonisamide (Zonegran); (2) calcium channel blockers such as verapamil (Verelan); (3) tricyclic antidepressants such as nortriptyline (Pamelor); or beta-blockers, for children, such as propranolol (Inderal). Approximately one-third of vestibular migraine patients have endolymphatic hydrops, which is typically bilateral.

VM patients do not have sound-induced dizziness and nausea or autophony; however, when these patients have endolymphatic hydrops, they can have sound sensitivity that borders on a Tullio phenomenon. For this reason, when a high-resolution temporal bone CT shows no evidence of TMWS, all patients suspected of having CT− TMWS are treated as a VM patient since medical management, if successful, avoids unnecessary surgery. Typically, CT− TMWS patients will have some improvement with medical management, and then regression as the dose is increased resulting in switching to another class of medication. Ultimately the patients never come under control and reassessment leads to a decision for surgical intervention.

Vestibular migraine is an example of the integral overlap between vestibular pathways and migraine circuit triggers and central mechanisms for premonitory symptom generation [39]. Information transmitted by peripheral vestibular sensory organs and the vestibular nerve to the medulla and pons is an external trigger within

the migraine circuit construct proposed by Ho and coworkers [40, 41]. This model is based upon the distribution of the neuropeptide CGRP, which has a complex distribution within the vestibular periphery [42]. The neurotologist author (PAW) has observed that migraine headache is nearly always present in patients with gravitational receptor dysfunction type of vertigo caused by TMWS, but infrequently with rotational receptor dysfunction type of true rotational vertigo [4–6, 8–10]. This is an important concept as TMWS can induce migraine symptoms consistent with three variants of migraine—ocular migraine, hemiplegic migraine and VM. This is why patients with TMWS, who normally have gravitational receptor dysfunction type of vertigo (disequilibrium) as their dominant vestibular dysfunction, can have episodes of vestibular migraine and infrequent true rotational vertigo attacks. However, as shown in Table 25.1, surgical management of TMWS typically improves the migraine symptoms. However, sometimes there is a marked decrease of the frequency and intensity of the migraines, as migraine has a high incidence overall (Table 25.2 and Fig. 25.1) [4–6, 8–10].

Headache and migraine headache have been reported to be associated with idiopathic intracranial hypertension (IIH), which has also been reported in patients with SSCD and CT− TMWS [43–45]. Visual alterations and headache are the two main symptoms of idiopathic intracranial hypertension, although additional features including cranial nerve palsies, cognitive deficits, olfactory deficits, and tinnitus are not uncommon [43]. The headache associated with idiopathic intracranial hypertension frequently has a migrainous phenotype. The underlying cause of the disorder has not yet been determined, although obesity is thought to be a risk factor. In a series of 12 patients with comorbidities complicating the recovery of their surgical management of TMWS, Wackym and collaborators reported a patient with bilateral SSCD who had recurrent TMWS symptoms and subsequently had multiple bilateral middle ear surgeries to manage her CT− TMWS [44]. She was ultimately found to have IIH and it was only after ventriculoperitoneal shunt placement to control her intracranial pressure that her migraine headaches were controlled and she no longer experienced recurrent CT− TMWS symptoms that required surgical intervention. Berkiten et al. studied 57 patients (114 ears), 20 who were controls and 37 who were IIH [45]. All patients were evaluated with high-resolution temporal bone CT for superior semicircular canal bony roof thickness and SSCD. In the IIH group, while dehiscence was detected in 25 of 74 ears, no dehiscence was detected in 49 ears. In the control group, while dehiscence was detected in five ears, no dehiscence was detected in 35 ears. The difference was statistically significant ($p = 0.015$). In contrast, Kuo et al. reported 121 patients who had both a lumbar puncture performed to determine opening pressure and high-resolution temporal bone CT imaging, of which 24 patients (19.8%) met the criteria for IIH with an opening pressure >25 cm H_2O [46]. The remaining 97 patient cohort (80.2%) did not have elevated opening pressures and served as the controls. None of the 24 patients with IIH had radiographic SSCD, whereas eight of the 97 patients (8.2%) without IIH had radiographic SSCD. The average opening pressure in patients without radiographic SSCD was 20.2 cm H_2O compared to 19.3 cm H_2O in patients with radiographic SSCD ($p = 0.521$). These findings suggest that the relationship between IIH and

SSCD is not clear. Finally, Kutz and Tolisano reported a series of patients with spontaneous CSF leaks and encephaloceles [47]. They noted that there was an increased incidence of obesity in this cohort and that concurrent superior semicircular canal dehiscence was seen in up to 15% of cases.

Summary

Migraine is a symptomatically heterogeneous condition, of which headache is just one manifestation. Migraine is a disorder associated with altered sensory thresholding, with hypersensitivity among sufferers to different sensory inputs. Hence, we suggest that sensitivity to the gravitational receptor asymmetries seen in TMWS is triggering migraine symptoms via this hypersensitivity-associated mechanism. When measuring the magnitude of headache and migraine headache in patients with TMWS and, equally importantly, the response to surgical intervention it is essential to incorporate a validated survey instrument into clinical practice. We have found that the six-item HIT-6 has documented a highly statistically significant improvement postoperatively in symptom reporting.

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