Vestibular migraine: clinical aspects and pathophysiology

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Vestibular migraine is becoming recognised as a distinct clinical entity that accounts for a high proportion of patients with vestibular symptoms. 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 vestibular migraine but can be used to rule out other vestibular disorders with overlapping symptoms. The pathophysiology of vestibular migraine is incompletely understood but plausibly 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 vestibular migraine largely mirror those for migraine headache.

Introduction

Although recurrent vertigo in children was known to be associated with migraine since Basser's description in 1964,[1] in 1984 Kayan and Hood[2] alerted the clinical community to an important association between vestibular symptoms and migraine in adults. Since that time, appreciation of the role of migraine in the dizzy patient has grown. In fact, although a migrainous aetiology for vestibular symptoms was previously unknown or deemed highly speculative, members of the International Headache Society in collaboration with members of the Barany Society have published diagnostic criteria for a disorder called vestibular migraine.[3] As vestibular migraine is rapidly becoming recognised as a common vestibular disorder, and diagnostic criteria have been promulgated, the specialty is poised to make substantial advances in understanding the pathophysiology of this disorder and improving its management. In this Review, we provide an update regarding both the clinical aspects of vestibular migraine and the neurobiological basis for the disorder. Our current understanding of vestibular migraine is rudimentary but continues to evolve. We aim to provide both clinicians and clinician-scientists with the latest relevant information regarding this frequently encountered disorder and with the latest ideas and basic science findings germane to the pathophysiology and rational treatment of vestibular migraine.

Diagnostic criteria

Patients frequently present with a combination of migraine and vestibular symptoms.[2] The assessment of these patients needs to address the association between these disorders. That is, are the vestibular symptoms causally related to a migraine subtype; are the vestibular symptoms and the migrainous symptoms simply a chance co-occurrence, or is there some more complex comorbidity association? Currently, the only International Headache Society migrainous disorder that includes vertigo in its classification is basilar-type migraine, which is characterised by the occurrence of neurological symptoms originating from the brainstem or both cerebral hemispheres simultaneously. The diagnosis of basilar-type migraine might be more appropriately classified as a type of migraine with aura.[4] In two groups of patients with basilar-type migraine, 61–63% reported vertigo as a symptom.[5,6] However, few migraine patients with vestibular symptoms meet criteria for basilar-type migraine.[7] Additionally, although some patients with migraine have vertigo as a premonitory symptom, the vertigo cannot often be characterised as an aura because of its duration or temporal association with headache. Thus, with present International Headache Society classification criteria, the vestibular symptoms of many patients with migraine would be deemed unrelated to migraine. However, most migraine patients with vestibular symptoms do not have a recognised independent vestibular disorder such as Ménière's disease, benign paroxysmal positional vertigo, or vestibular neuritis. As a result, many patients with both migraine and vestibular symptoms do not have a specific diagnosis to account for their vestibular symptoms. In response to this deficiency when reaching an accurate diagnosis in many migraine patients with vestibular symptoms, Neuhauser and colleagues[8] developed diagnostic criteria for what is now termed vestibular migraine, a disorder in which vestibular symptoms are judged as part of the migrainous disorder itself. Nearly 1% of the general population meet these criteria,[8] which is five to ten times higher than the prevalence of Ménière's disease.[9]

Neuhauser and colleagues'[8] criteria for vestibular migraine have been reassessed favourably in a recent long-term follow-up paper.[10] A structured diagnostic interview using the criteria[11] has been used in studies of the clinical features, epidemiology, genetics, pathophysiology, and treatment of vestibular migraine. The most recent diagnostic criteria for vestibular migraine, a refinement of the 2001 Neuhauser and colleagues criteria, arose from a working group within the Barany Society (panel).[3] Recently, Cohen and colleagues[12] advocated the development of diagnostic criteria by the International Headache Society to account for the heterogeneity and natural history of vestibular migraine. Internationally proposed diagnostic criteria for vestibular migraine based on those developed by the Barany Society and the International Headache Society[3] will be included in an appendix of the third edition of the International

Classification of Headache Disorders. This appendix will suggest that vestibular migraine is a new disorder for which more research is warranted.

Vestibular migraine can be thought of as a migraine variant with vestibular symptoms or a balance disorder that includes migraine. Although such a distinction might seem to have little clinical relevance, because patients with vestibular migraine can present to either otolaryngologists or neurologists, patients might receive different care depending on the type of specialist to whom they present. A study by Millen and colleagues[13] shows that specialists have different views regarding the manifestations of vestibular migraine. For example, more neurologists than otolaryngologists believe that vestibular migraine results from a CNS rather than a peripheral vestibular abnormality.

Epidemiology

Vestibular migraine is more prevalent than other vestibular disorders.[14] Lempert and Neuhauser[15] report a lifetime prevalence of migraine of 16%, a lifetime prevalence of vertigo of 7%, and a comorbidity of 3·2 %, rather than the 1·1% expected by chance alone. Neuhauser and colleagues[16] report that vestibular migraine has a 1-year prevalence of 0·89% and accounts for about 10% of patients seen for dizziness and about 10% of patients seen for migraine.[17] Hsu and colleagues[18] report that the 1-year prevalence of vestibular migraine in women aged 40–54 years is 1%.

Clinical characteristics

Symptoms

For most patients, vestibular migraine is an episodic disorder; however, the duration of attacks ranges from seconds to days. Vestibular migraine has a strong female predominance of up to 5 to 1,[11] and vestibular migraine often begins several years after typical migraine. Some patients can have a headache-free interval of several years before onset of vestibular migraine. Vestibular migraine might begin in place of headache especially in perimenopausal women.[19] Vestibular migraine is more common in patients without aura than in patients with aura. The temporal association between the vestibular symptoms and migrainous symptoms such as headache is quite variable between patients and the association might be inconsistent in an individual. Furthermore, patients might have migraine headache at the same time as their vestibular symptoms, which include spontaneous vertigo—ie, an illusory sensation of motion of self or surround, dizziness induced by head movement, positional vertigo, or gait instability. Other symptoms can include visual motion sensitivity and hearing loss, and migrainous symptoms such as photophobia or phonophobia. Episodes of vestibular migraine can be brought about by the same triggers as those for migraine headache, including menstruation, irregular sleep, stress, physical exertion, dehydration, food and drinks, and intense sensory stimulation.[17] Quality of life measures are

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Panel: Diagnostic criteria for vestibular migraine

Patients need to meet all four of the following criteria:

- At least five episodes with vestibular symptoms* of moderate or severe intensity† lasting between 5 min and 72 h
- Present migraine or previous history of migraine with or without aura according to the International Classification of Headache Disorders
- One or more migraine features with at least 50% of the vestibular episodes
    - Headache with at least two of the following characteristics: one-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity
    - Photophobia and phonophobia
    - Visual aura
- Not explained by another vestibular disorder

*Vestibular symptoms include: spontaneous vertigo, positional vertigo, visually induced vertigo, head motion-induced vertigo, head motion-induced dizziness with nausea. †Vertigo is rated as moderate if vertigo interferes with but does not prohibit daily activities and as severe if daily activities cannot be continued. Modified from Lempert and colleagues,[3] by permission of IOS Press.

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generally lower in individuals with vestibular migraine,[16] including problems with sleep and depression.[20]

Physical examination

The physical examination of patients with vestibular migraine is generally normal between episodes. During episodes of vestibular migraine, patients usually manifest a nystagmus that suggests either a central or peripheral vestibular abnormality.[21–23] Non-paroxysmal positional nystagmus is especially common during attacks of vestibular migraine.

Physiological testing

Physiological findings alone cannot be used to specifically diagnose patients with vestibular migraine because of their inconsistent pattern and high incidence in patients with migraine without vestibular complaints.[24] However, physiological testing can be used to help rule out other vestibular disorders and to establish the extent of vestibular abnormalities if they exist. Between 10% and 20% of patients with vestibular migraine have a unilateral reduction of vestibular function[24–26] and many patients have a directional preponderance.[25] Teggi and colleagues[27] and Celebisoy and co-workers[26] found that patients with vestibular migraine had higher postural sway than did patients without vestibular migraine. Two studies have documented abnormalities of vestibular-evoked myogenic potentials in patients with vestibular migraine including reduced amplitudes either unilaterally or bilaterally.[28,29]

Genetics

Several studies have investigated the genetics of vestibular migraine. Jen[30] concluded that vestibular

migraine might be monogenic and heterogeneous. Von Brevern and colleagues[31] found no evidence of an association between calcium and sodium channel genes linked to familial hemiplegic migraine and episodic ataxia type 2 and vestibular migraine. Lee and colleagues[32] found a region on chromosome 11q that is common in females in a family with vestibular migraine. Bahmad and colleagues[33] located a 12·0 MB interval on chromosome 5q35 that contained a disease gene for familial vestibular migraine. The pathophysiology of this disease gene remains unknown.

Related disorders

Several balance disorders are related to vestibular migraine. Ménière's disease, benign paroxysmal positional vertigo, and anxiety are more common in patients with vestibular migraine than would be expected by chance alone. The basis for this high comorbidity remains uncertain but might relate to overlaps between the clinical characteristics of these disorders and those of vestibular migraine, and because vertigo can serve as a migraine trigger.[34] Ménière's disease and vestibular migraine overlap extensively in their clinical manifestations, and in some patients it might be impossible to establish whether they have one or both disorders. Patients with Ménière's disease are twice as likely to have migraine as individuals without Ménière's disease,[35] and patients with migraine are more likely to have an earlier onset and bilateral hearing loss with Ménière's disease.[36] Cha and colleagues[37] discovered a frequent association among episodic vertigo, migraine, and Ménière's disease in closely related individuals. Like patients with Ménière's disease, patients with benign paroxysmal positional vertigo are more likely to have migraine than patients without benign paroxysmal positional vertigo.[38] Patients with migraine are also more likely to have benign paroxysmal positional vertigo than individuals without migraine.[39] The highly common finding of persistent rather than paroxysmal positional nystagmus in patients with vestibular migraine complicates this association.[22] Psychiatric illness, especially anxiety and depression, is especially common in patients with vestibular migraine.[40,41] In a prospective study of psychiatric illness in vertigo syndromes, only patients with vestibular migraine had increased rates of psychiatric illness 1 year after establishing a vestibular diagnosis.[42] Patients with vestibular migraine reported more vertigo, more somatic anxiety and autonomic arousal, and more vertigo-induced handicap than did other patients with vertigo.[43] Although not strictly a balance disorder, motion sickness susceptibility is more common in patients with migraine in general and patients with vestibular migraine in particular.[44,45]

Treatment

Treatment options for patients with vestibular migraine include reduction of triggers, pharmacotherapy, physical therapy, and mitigation of comorbidities. No dedicated evidence base is available and no randomised controlled trials for the treatment of vestibular migraine exist, mainly because of the hitherto lack of diagnostic criteria. Instead, treatments are based on those for migraine headache or are anecdotal. Avoidance of migraine triggers should always be the first avenue of treatment. Pharmacotherapy can be abortive, symptomatic for episodes, and prophylactic. Although diagnostic criteria for vestibular migraine are now available, no randomised treatment studies have been done, except for a small inconclusive study of zolmitriptan as an abortive agent.[46] Symptomatic treatment for acute episodes of vestibular migraine is similar to treatment for acute vertigo with peripheral vestibular causes, including vestibular suppressants such as promethazine, dimenhydrinate, and meclozine. Physical therapy has been reported to improve imbalance in patients with vestibular migraine in an uncontrolled study.[47] In general, the scientific literature suggests that drugs efficacious for prophylaxis of migraine headache are also appropriate for prophylaxis of vestibular migraine.[48] On the basis of mainly opinion, and not on controlled studies, researchers have advocated β-blockers such as propranolol or metoprolol; antidepressants such as amitriptyline, nortriptyline, fluoxetine, sertraline, or paroxetine; calcium-channel blockers such as verapamil or diltiazem; anticonvulsants such as valproate, topiramate, or lamotrigine; and carbonic anhydrase inhibitors such as acetazolamide.[49–51]

Proposed neurobiological bases

Present hypotheses of migraine mechanisms are based on results of combined genetic, in-vitro cell biological, animal model, and clinical studies in human beings.[52–58] This well developed published work provides a conceptual framework for understanding vestibular migraine as a variant produced by the convergence of vestibular information within migraine circuits; therefore, we provide a framework for further development of our understanding of vestibular migraine.

Vasculature, migraine mechanisms, and the inner ear

The large overlap between migraine pathways and vestibular pathways[41,59–61] is consistent with the view that vestibular migraine is a migraine variant with vestibular manifestations. Specifically, the vascular, neurogenic inflammation, and central neural mechanisms that have been implicated as peripheral and central triggers of migraine[52–56] are all present in central vestibular pathways and the inner ear. For example, the trigeminocerebro-vascular system[57] provided a focus to investigate the link between vascular responsiveness and pain as a physiological consequence of activation of trigeminal ganglion innervation of cerebral and meningeal vasculature. The trigeminovascular system also innervates the blood supply of the inner ear.[62,63] Iadecola[58] provided a more integrative context for migraine mechanisms, suggesting that a neocortical, extracellular release of

signals (eg, K^{+}, H^{+}, arachidonic acid, and nitric oxide) during cortical spreading depression would activate trigeminal afferents on cranial blood vessels, which would elicit a trigeminovascular reflex-mediated vasodilation in the meninges via a parasympathetic relay in the sphenopalatine ganglion. Simultaneously, as described by Moskowitz,[54] a sterile inflammatory response is elicited from meningeal vessels by peptide secretion from axon collaterals of the trigeminal ganglion cells.

Parallel events have been observed in the inner ear of animals.[64,65] The trigeminal innervation of the inner ear seems to be a component of trigeminal innervation of other intracerebral blood vessels,[62,63,66] and similar effects on inner ear blood perfusion have been seen in animal experiments.[67–70] Because the trigeminovascular reflex innervation of the inner ear is one component of the trigeminovascular reflex system, the innervation is a potential site of action for abortive effects of triptans, ergots, and calcitonin gene-related peptide antagonists on peripheral triggers in patients with vestibular migraine. Migraine prophylaxis drugs, such as acetazolamide and topiramate, have the potential to support endolymph homoeostasis by inhibition of carbonic anhydrase in the stria vascularis and supporting cells of the sensory epithelia.[71,72] The fact that spiral and vestibular ganglion cells in rodents and primates express the main serotonin receptor targets of the triptans and ergots (5-hydroxytryptamine [5-HT]$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$, and 5-HT$_{1F}$ receptors) is interesting because their binding affinities are within the clinical dose-related plasma concentrations of the drugs.[60,73–75] Hence, actions of ganglion cells might partly explain the efficacy of these agents in vestibular migraine. Finally, the effects of non-steroidal anti-inflammatory drugs might include a blunting of both the inflammation and extravasation responses by cyclooxygenase inhibition.

Integrative migraine mechanisms and vestibular pathways: translational rules from basic research

Because vasodilation is neither necessary nor sufficient for perception of headache pain,[56–58,76] migraine headache pain is attributed mainly to central processing of trigeminal afferent activation in ascending thalamocortical pathways.[53,56,58] Specifically, Ho and colleagues[53] expanded the idea of the migraine circuit from strictly trigeminal pathways for vascular regulation and pain perception to a framework that includes circuits for processing triggers and premonitory symptoms. External trigger circuits were proposed to include visual, auditory, somatosensory, and chemical (olfactory and gustatory) sensory pathways, and contributions from vascular phenomena. Internal triggers include hormonal fluctuations and stress.[77] Both internal and external triggers involve structures such as the hypothalamus and amygdala, which show altered activity associated with migraine in functional imaging studies,[78–82] and contain a dense calcitonin gene-related peptide-positive axon plexus among scattered positive neurons in

animals and human beings.[83–86] The central constituents of the migraine circuit include components of central vestibular pathways. For example, the regions affected by vestibular stimulation in human functional imaging studies include those involved in migraine and pain perception, such as the posterior insula, anterior insula, orbitofrontal cortex, and the posterior and anterior cingulate gyri.[87–93] Additionally, because the caudal parabrachial nucleus receives both trigeminal nociceptive[94–96] and vestibular inputs in rodents and primates,[97–100] the related pathways might contribute to symptoms of vestibular migraine, including motion sensitivity and its interaction with trigeminal pain in migraine patients.[97–104] Furthermore, the high expression of stress-response receptors in the amygdala and hypothalamus[105] suggests a role of stress interactions with development of migraine signs and symptoms.[77]

Vestibular processing and migraine circuits

Vestibular migraine is an example of the integral overlap between vestibular pathways and migraine circuit triggers and central mechanisms for premonitory symptom generation (figure). 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 colleagues.[53] Hence, the abortive effects of drugs in the inner ear (eg, triptans, ergots, calcitonin gene-related peptide antagonists, non-steroidal anti-inflammatory drugs, lamotrigine, calcium-channel blockers, and topiramate) can attenuate a peripheral trigger specific for vestibular migraine, and affect a central migraine circuit. Similarly, the perceptual and sensorimotor consequences of unilateral or bilateral disruptions of peripheral vestibular function constitute internal triggers of vestibular migraine within their framework because the migraine circuit overlaps extensively with the vestibular-related pathways that have been discussed in the context of comorbidity of balance disorders, migraine, and anxiety disorders.[59–61] The central vestibular pathways that overlap with internal trigger mechanisms for the migraine circuit have been parsed conceptually into a cognitive-behavioural component, a neurological sensorimotor performance component, and an interoceptive component, which are each modulated by the dorsal raphe nucleus and locus coeruleus (figure).

The cognitive-behavioural domain encompasses vestibulo-thalamo-cortical networks that produce perceptual responses to vestibular, visual, proprioceptive, and somatosensory afferent inputs. The domain also includes pathways related to premonitory symptoms associated with balance control, such as circuits involving the ventral lateral prefrontal cortex, orbitofrontal cortex, and the ventral aspect of the cingulate cortex that communicate with the interoceptive domain for regulation of affect. The sensorimotor performance component generates somatic and visceral motor responses to afferent
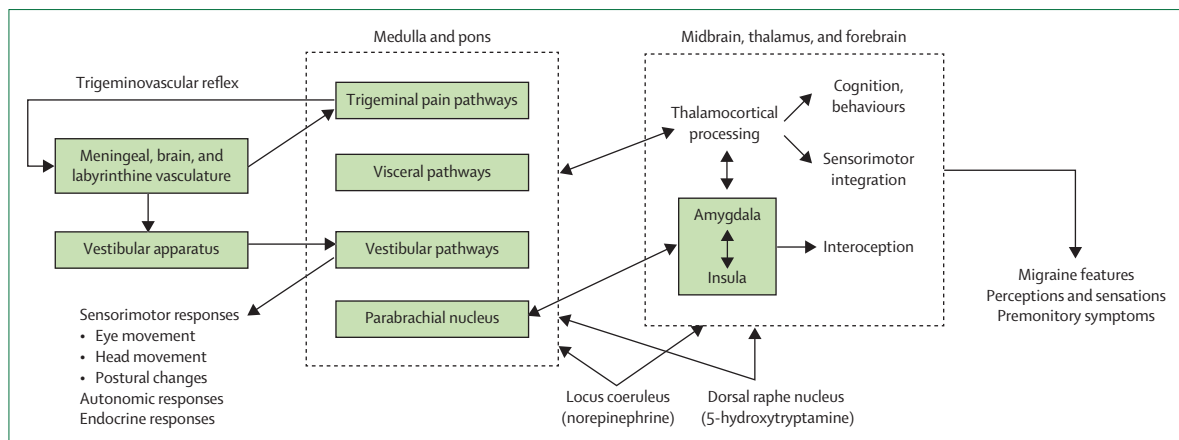
Figure: **Vestibular migraine pathways**
Pathways related to sensorimotor performance, interoceptive, and cognitive-behavioural domains within migraine circuits are shown diagrammatically. The boxes that represent brainstem sensorimotor structures include parallels in peripheral neurochemical organisation between vestibular pathways and migraine mechanisms.[41,106]

sensory information. The balance-related sensorimotor component includes brainstem pathways that generate somatic (eg, vestibulo-ocular and vestibulospinal reflexes) and visceral (vestibulosympathetic and vestibuloparasympathetic)[107,108] motor responses. These vestibular sensorimotor responses are modulated by the cerebellum,[107,109] which has been activated in human imaging studies during migraine attacks[81,110,111] and shows prominent expression of calcitonin gene-related peptide receptors in association with Purkinje cells in animals.[112] The trigeminal nociceptive sensorimotor pathways include afferent sensory thalamocortical pathways, the periaqueductal grey, and the trigeminovascular reflex circuit. More importantly, neuroanatomical tracing studies have shown extensive interconnections among the spinal trigeminal nucleus, vestibular nuclei, and the solitary nucleus[100,113–117] and that small cervical dorsal root ganglion cells contribute to primary afferent projections to vestibular nuclei.[118,119] These observations clearly show that the vestibular nuclei contribute to the migraine circuit at the level of the caudal brainstem.

Interoceptive circuits assess information about present sensory and motor processes relative to the physiological status of the individual,[120] and translate this information into subjective awareness and feelings (often termed the sentient self).[121] Interoceptive circuits for vestibular, visceral sensory, and nociceptive information include a network that contains the parabrachial nucleus, central amygdaloid nucleus, and bed nucleus of the stria terminalis, several posterior thalamic intralaminar nuclei, the hypothalamus, and the insular cortex. Neuroanatomical studies have shown that this network is notable for its large concentration of calcitonin gene-related peptide immunoreactive neurons,[84,122–125] which include regions related to visceral, vestibular, and nociceptive pathways in the rostrodorsal and caudoventral parabrachial nucleus,[94,95,97,98,100,126–128] several posterior thalamic

intralaminar nuclei including the subparafascicular nucleus[84,129] and periventricular regions of the hypothalamus. These cells give rise to dense calcitonin gene-related peptide-immunopositive terminal fields in the insular cortex, central amygdaloid nucleus, bed nucleus of the stria terminalis, and the amygdalo-strial transition region.[84] This strong co-localisation of calcitonin gene-related peptide with central interoceptive pathways raises the possibility that central calcitonin gene-related peptide antagonism is a strategy to both alter the interpretation of premonitory sensory activity as a symptom and interrupt the progression of external and internal trigger activity.

The closely connected network between the locus coeruleus and dorsal raphe nucleus is a likely target for calcitonin gene-related peptide antagonists and triptans in vestibular migraine (figure). This network has the potential to modulate vestibular migraine-associated premonitory symptoms and triggers of vestibular migraine (eg, stress and pain perception) through widespread efferent projections to central migraine and vestibular circuits. The locus coeruleus and the dorsal raphe nucleus have long been included as modulators of both central migraine circuits[52,56] and vestibular sensorimotor[130–134] and interoceptive circuits.[59–61] Locus coeruleus unit activity in rats and monkeys increases with exposure to novel or imperative sensory stimuli, particularly during reorientation of attention in contexts associated with stress or anxiety.[135–137] A large proportion of locus coeruleus neurons are immunoreactive for calcitonin gene-related peptide in mammals (including human beings)[84,125,138] and express the stress response-related corticotropin-releasing hormone, glucocorticoid, and mineralocorticoid receptors.[105] The dorsal raphe nucleus neurons do not show appreciable calcitonin gene-related peptide expression but do express corticotrophin-releasing hormone and mineralocorticoid

receptors highly.[105] Raphe neurons and their targets also express 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors,[139,140] which provide both presynaptic and postsynaptic targets for triptans. Activity of the dorsal raphe nucleus seems to be associated with the selection of a behavioural strategy to either act or orient and gather more information. Activation of the dorsal raphe nucleus in rats and monkeys accompanies facilitated motor activity, inhibited sensory information processing, and concomitant expression of hormonal and neuroendocrine activity.[141] During orienting responses, reduced activity of these neurons occurs in conjunction with motor activity disfacilitation and sensory processing disinhibition. Hence, the interplay between the locus coeruleus and dorsal raphe nucleus might modulate perceptual and trigger-related activity in migraine circuits.

Ca$_v$2.1 channels and the sodium–potassium ATPase α2 subunit

In view of the many components of the migraine and vestibular migraine circuits, it is not surprising that identification of one major susceptibility locus has been elusive in genetic linkage studies.[30,31] However, some candidate mutations from family association studies affect molecules in the inner ear (peripheral trigger mechanisms) and the brain. For example, functional mutations of a neuronal voltage-gated calcium channel (Ca$_v$2.1) in familial hemiplegic migraine type 1 and the glial catalytic α2 subunit of sodium–potassium ATPase (NaKA α2) in familial hemiplegic migraine type 2 have been discussed in the framework of neuron-glial-vascular contributions (neurovascular unit[142,143]) to cortical spreading depression.[144] However, the Ca$_v$2.1 (P/Q type) channels have many potential roles in vestibular migraine. Experiments in animals show that these channels are mediators of the trigeminovascular reflex[145] and they can modulate transmission at dural trigeminocervical afferent relays in the spinal cord.[146] Additionally, Ca$_v$2.1 channels help regulate calcitonin gene-related peptide release from neuronal processes in the dura, trigeminal ganglion, and the spinal trigeminal nucleus.[147] The same effect is likely in the inner ear trigeminovascular terminals. Other mutations of Ca$_v$2.1 are associated with vertigo in episodic ataxia type 5 (*CACNB4* mutation) or vertigo plus migraine in episodic ataxia type 2 (*CACNA1A* mutation).[30] Reduced otolithocular function is also associated with *CACNA1A* mutations in patients with episodic ataxia type 2 and spinocerebellar ataxia type 6.[30] The trigeminal ganglion,[148] vestibular ganglion,[149] and spiral ganglion[150] express Ca$_v$2.1 mRNA in rodents, suggesting that mutations can potentially affect both the fifth and eighth cranial nerves. Immunoreactivity for NaKA α2, on the other hand, is associated with fibrocytes below vestibular sensory epithelia and in the cochlea.[72,151] Hence, the antimigraine actions of the butterbur root sesquiterpenes S-petasin, iso-S-petasin, and eudesmol might show preferential actions as use-dependent antagonists of the Ca$_v$2.1 channel[152] in vestibular ganglion cells. A similar mechanism of action is plausible for lamotrigine, calcium-channel blockers, and topiramate[153] in the attenuation of peripheral trigger susceptibility in vestibular migraine.

Conclusions and future directions

Vestibular migraine is becoming recognised as a highly prevalent vestibular disorder that is a subtype of migraine. Recently developed diagnostic criteria have helped clinical research, allowing a more complete understanding of the clinical aspects of vestibular migraine. The challenge now is to better understand the pathophysiology of vestibular migraine from both a clinical and basic science perspective to enable improved rational management of this disorder. Recent studies of vestibular psychophysics[154] and motion sickness susceptibility[155–157] in vestibular migraine are yielding exciting new insights. An expanded view of the migraine circuit motivates basic science studies of the individual and interactive roles of vestibular and nociceptive mechanisms in vestibular migraine. For example, studies of the role of inner ear trigeminovascular reflexes in blood flow regulation, endolymph-perilymph homoeostasis, vestibular transduction, and vestibular nerve function are needed to develop rules for understanding the different effects of drugs on the vestibular symptoms and headache. Additionally, basic studies are needed to elucidate neuronal processing interactions between nociceptive and vestibular information processing, interactions of nociceptive and vestibular processing with stress-related receptor mechanisms—eg, arginine vasopressin, corticotrophin-releasing hormone, glucocorticoid and mineralocorticoid receptors[105] in migraine circuits—and the effects of antimigraine medications on vestibular nerve and vestibular nucleus activity. Finally, in view of the parallel neurochemical organisation of pain and vestibular pathways, it will be fruitful to investigate the common genetic bases for vestibular migraine, craniofacial pain[158] and interactions between stress and pain,[159] including pharmacogenetic features that might affect drug efficacy.[160] These studies will provide essential new knowledge to guide controlled treatment trials for vestibular migraine.

Search strategy and selection criteria

We searched Medline for articles in English published between Jan 1, 1980, and Dec 31, 2012, with the search words: "migraine", "dizziness", "vertigo", "vestibular", "balance", and "headache". Terms were expanded using the 'exp' (explode) function and the Boolean 'AND' function was used to select subsets. Studies of human beings and animals were included. Both original research and review articles were included. Additional citations were obtained by searching for additional articles by first authors of articles identified through the primary search and by reviewing citation lists within retrieved papers.

Review

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