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Medical Management of Migraine-Related Dizziness and Vertigo

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Historically, review of migraine-related vestibular symptoms has focused on the various clinical presentations that occur and the results of diagnostic studies of vestibular function. Treatment of vestibular symptoms related to migraine has been proposed similar to that used for headache control, but few examples of the effectiveness of this therapy have been published. The purpose of this study is to present the various approaches that can be used to manage vestibular symptoms related to migraine, and to evaluate the overall effectiveness of these treatment approaches. This was a retrospective review of 89 patients diagnosed with migraine-related dizziness and vertigo. The character of vestibular symptoms, pattern of cochlear symptoms, results of auditory and vestibular tests, and comorbidity factors are presented. Treatment was individualized according to symptoms and comorbidity factors, and analyzed regarding effectiveness in control of the major vestibular symptoms of episodic vertigo, positional vertigo, and nonvertiginous dizziness. Medical management included dietary changes, medication, physical therapy, lifestyle adaptations, and acupuncture. Complete or substantial control of vestibular symptoms was achieved in 68 (92%) of 74 patients complaining of episodic vertigo; in 56 (89%) of 63 patients with positional vertigo; and 56 (86%) of 65 patients with non-vertiginous dizziness. Similarly, aural fullness was completely resolved or substantially improved in 34 (85%) of 40 patients; ear pain in 10 (63%) of 16 patients; and phonophobia in 17 (89%) of 19 patients. No patient reported worsened symptoms following medical management. The conflicting concept of a central disorder (migraine) as the cause of cochlear and vestibular dysfunction that often has peripheral features is discussed.

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HISTORICAL REVIEW

Migraine is a complex, usually inherited, neurologic disorder in which headache is but one symptom. Headache, of all types, is a very common entity experienced by more than 90% of the population during any given year.[1] Although the majority of these headaches are not migraine, a fairly large segment of the population has migraine. Epidemiologic studies have indicated that 18% of women and 6% of men in the United States have migraine.[2] Migraine is not uniformly recognized by those who suffer from it. A questionnaire based on the International Headache Society (IHS) criteria for migraine was completed by 20,000 people representative of the general population.[3] Of those who warranted the diagnosis of migraine based on their answers, only 29% of the men and 41% of the women were aware that the headaches they were having could be diagnosed as migraine.

The IHS has published a classification system to standardize the diagnosis and reporting of migraine and other head pain.[4] The primary headache disorders are the first four designations in the new IHS classification: migraine; tension-type headache; cluster headache; and miscellaneous headaches. There is no universal agreement on where the dividing line should be drawn separating migraine from other headaches. Some experts believe that migraine should be "lumped together" with tension or muscle contraction headaches, with migraine representing one end of the spectrum of headache severity.[5] Other experts believe that migraine and tension headaches have completely different pathophysiologic bases and should remain separate entities or be "split apart." Over a lifetime, the headaches an individual experiences often change in terms of both intensity and quality. A patient frequently experiences more than one type of headache during a lifetime; that is, one type may predominate (such as migraine with aura) at one time, while another may predominate (such as tension headache) at another time.

The 1988 IHS classification[4] separates migraine into two major categories: migraine without aura and migraine with aura. Migraine without aura is the most common form of migraine. The headache occurs in recurring attacks lasting 4 to 72 hours. The diagnostic criteria for migraine without aura are shown in Table I.

The diagnosis of migraine[4] with aura is made based on the characteristics of the aura. While usually visual, this aura must be fully reversible and indicative of focal cerebral cortical and/or brainstem dysfunction. The aura typically develops over 5 to 20 minutes and usually lasts less than 60 minutes. Headache, nausea, and/or phono-

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TABLE I.
International Headache Society Criteria for Diagnosis of Migraine Without Aura.[4]

At least five attacks fulfilling A–C below:
A. Headache attacks lasting 4 to 72 hours (untreated or unsuccessfully treated)
B. Headache has at least two of the following characteristics:
Unilateral location
Pulsating quality
Moderate or severe intensity (inhibits or prohibits daily activities)
Aggravation by walking stairs or similar routine physical activity
C. During headache at least one of the following:
Nausea and/or vomiting
Photophobia and phonophobia
No evidence of organic disease or disease not temporally related to migraine onset

TABLE II.
Diagnostic Criteria for Basilar Migraine.[4]

Fulfills criteria for migraine with aura (two or more aura symptoms of the following types):
Visual symptoms in both the temporal and nasal fields of both eyes
Dysarthria
Vertigo
Tinnitus
Decreased hearing
Double vision
Ataxia
Bilateral paresthesias
Bilateral pareses
Decreased level of consciousness

phobia or photophobia usually follow the symptoms of neurologic aura, either directly or after an interval of less than an hour. The headache typically lasts 4 to 72 hours, but the headache may be completely absent. Basilar migraine,[4] previously referred to as basilar artery migraine, is a subclassification of migraine with aura. It usually occurs in adults, where it is characterized by aura symptoms originating from the brainstem or from both occipital lobes. Criteria for diagnosis of basilar migraine are given in Table II.

Although the majority of migraine sufferers do have headaches, migraine can also occur without headaches.[4] The latter was previously termed migraine equivalent,[6] or acephalgic migraine; under the IHS classification this has been termed migraine aura without headache. Particularly in middle or late life, the aura may become the predominant feature of the migraine attack with little or no headache.[7] It is uncommon to have always suffered exclusively from migraine aura without headache.[4]

The IHS criteria were designed to provide guidelines for making a clinical diagnosis for a neurologic disorder where no objective test exists. It was realized that a few patients would present with symptoms that were very suggestive of migraine but that would fall just outside the IHS criteria. For these patients, the category of migrainous disorder not fulfilling above criteria[4] has been designated. Patients who have had typical attacks but in insufficient numbers should be put in this category, as should patients who have had sufficient numbers of attacks that fulfill all but one IHS criteria for a particular diagnosis.

Migraine-Related Dizziness

Balance disturbances, including true vertigo as well as unsteadiness, have been described as symptoms accompanying migraine in both children and adults. Vertigo, occurring in the pattern of benign paroxysmal vertigo of childhood,[8] has been well accepted as a migraine-related phenomena.

The vertigo that has been associated with migraine in adults is a more difficult entity to classify. Although the clinical association of dizziness and migraine has been noted since the 19th century publication of Liveing in 1873,[9] it remains difficult to prove a causal relationship between migraine and any of the transient symptoms that may accompany it. Scintillating scotoma, universally associated with migraine for hundreds of years, has eluded efforts to explain its pathophysiologic link with migraine.[10] The diffuse nature of dizziness and the variety of disease entities that have been recognized as potential causes of dizziness make a relationship with migraine even harder to prove. One major difficulty is the categorization of the vertiginous symptoms into a single phase of a migraine episode. Such possibilities include vertigo as an aura, as an analog of the headache phase, or as an associated symptom similar to the migraine prodromes.

The realization that neurologic symptoms can be attributed to migraine without necessarily being temporally related to a headache has been recognized since Liveing's publication in 1873, as cited by Catino.[11] Bramwell and McMullen[12] in 1926 noted that many neurologic symptoms which occur with migraine headache may also occur without headache, including episodic vertigo. Since there is no diagnostic test to prove that migraine is the cause of any specific pattern of dizziness, many authors have tried to show that migraine is a likely cause by using two approaches. One approach has been to study randomly selected patients with typical migraine headaches to show that vertigo and dizziness occur more frequently in migraine patients than in the general population,[13–16] while the other approach has analyzed the history of patients with a particular character of dizziness for historical factors that were considered high-risk for the occurrence of migraine.[17–22]

Selby and Lance[13] in 1960 analyzed a group of patients who arrived at a neurologic center for headache management. In one group of 217 migraine patients, they found that 72 (33%) had experienced true vertigo. In another group of 131 migraineurs, 94 (72%) had complained of a sensation of dizziness, light-headedness, or unsteadiness. Kayan and Hood[14] in 1984 questioned a group of 200 unselected migraine patients who sought medical care for headache, to determine the incidence of vestibular and

cochlear symptoms. Dizziness or vertigo was reported by 109 (55%) of these 200 migraine patients, cochleovestibular symptoms of one type or another were reported by 118 (59%), vestibular symptoms alone by 78 (39%), and cochlear symptoms without vestibular symptoms by only nine (5%). Of the 109 migraine patients describing vertigo or dizziness, almost half (49%, or 53 patients) described the sensation of true vertigo, with the remainder (51%, or 56 patients) describing nonvertiginous dizziness or giddiness. Eighty-four (77%) of these 109 migraine patients describing vestibular symptoms experienced their vertigo or dizziness in association with their headache, while 25 (23%) experienced their vertigo or dizziness independent of the headache. In 8 of these 25 patients, the vertigo was accompanied by a typical migraine visual aura but without an ensuing headache. In this particular study, 116 tension headache patients served as controls, 35 (30%) of them reporting dizziness or vertigo.

Kuritzky et al.[15] in 1981 sent questionnaires asking about the presence of vestibular symptoms to 104 consecutive patients who presented to their clinic for headache management: 24 had migraine with aura; 60, migraine without aura; 12, tension headache; and eight, cluster headache. The authors looked specifically at vestibular symptoms that occurred independent of the headache. They separated the headache patients by diagnosis and compared them with a group of 54 control subjects accompanying patients to various outpatient clinics. Dizziness in general was described by 27 of all migraine patients: 15 (63%) of 24 patients with migraine with aura; and 12 (20%) of 60 patients with migraine without aura. Tension headache patients, cluster headache patients, and controls had similar incidences of dizziness (one, one, and seven patients, respectively). True vertigo was described slightly less frequently. Vertigo was reported by 20 (19%) of all migraine patients; 10 (42%) of 24 patients with migraine with aura; 10 (17%) of 60 patients with migraine without aura; two (17%) of 12 patients with tension headache; none of eight patients with cluster headache; and five (9%) of the 54 control subjects.

As noted above, migraine patients describe a variety of types of vestibular symptoms including true vertigo and nonvertiginous dizziness. Vestibular symptoms have been reported to occur before the headache in a pattern similar to an aura, during the headache, and completely independent of the headache. Several authors have tried to determine indicative patterns of vestibular symptoms that would be highly suggestive of vertigo attributable to migraine, much as the symptom triad of Meniere's disease is highly suggestive of endolymphatic hydrops. These specific clinical patterns of vestibular symptoms would ideally distinguish migraine-related vertigo from vestibular symptoms attributable to otologic diseases such as vestibular neuronitis, benign positional vertigo, and Meniere's disease, as well as from other neurologic conditions such as vertibrobasilar insufficiency and epilepsy.

The first described symptom complex of migraine-related vertigo was basilar artery migraine. Bickerstaff[17] in 1961 recognized that some patients experienced migraine aura suggestive of the aberrant function of cranial nerves and cortical areas supplied by the basilar artery rather than the more typical areas supplied by the carotid artery. Bickerstaff's basilar artery migraine patients described aura that usually started with visual symptoms including total loss of vision or positive visual manifestations throughout both visual fields. This was followed by vertigo, ataxia, dysarthria, and occasionally, tinnitus. Some patients described sensory manifestations such as tingling or numbness in the periphery of both hands and both feet and sometimes around both lips and on both sides of the tongue. These particular aura symptoms are in contrast to patients with aura symptoms relating to areas supplied by the ophthalmic or retinal vessels such as unilateral visual loss, altitudinous field defects, or various scotomata, or to areas supplied by the middle cerebral artery such as unilateral paraesthesia of face, hand, or arm; weakness of one arm; or even dysphasia if on the dominant side. All of Bickerstaff's patients experienced severe, throbbing headache following the brainstem symptoms. This headache was usually occipital, often accompanied by vomiting.

Seven years later, Eadie[18] reported a group of patients with a different type of migraine-related dizziness and coined the term "episodic giddiness." These 34 patients (23 females and 11 males) had a prior or present history of severe headache that warranted the classification of migraine. Some, but not all, of their migraine headaches were accompanied by vertigo. The time duration of the vertigo when present was compatible with an aura (i.e., less than 1 hour) in 38% (13) of this group. The vertigo lasted 1 to 24 hours in 35% (12 patients) and more than 24 hours in 24% (eight patients). Tinnitus and hearing loss were reported in 35% of a subgroup of 31 patients. A family history of migraine occurred in 35% (11) of the 31 cases where a family history was recorded. Eadie's episodic giddiness in migraine patients[18] differed from Bickerstaff's basilar migraine patients[17] in several respects. The time duration of the vertigo was too long for a typical aura in 20 (60%) of Eadie's episodic giddiness in migraine patients.[18] With the exception of one patient with unilateral paresthesia during her attack and another patient with facial paresis for several days after one attack, neurologic symptoms were limited to the cochleovestibular region. This contrasted with Bickerstaff's description of multiple brainstem symptoms occurring in progression, usually following a typical visual aura.[17] The necessity for vestibular symptoms associated with headache remained, although headache did not need to occur with every vertiginous episode.

Love[19] added the observation that a major sensorineural (SN) hearing loss could be attributed to migraine. In his series of six patients diagnosed with basilar artery migraine, Love described one patient presenting with episodic vertigo along with a fluctuating, low-frequency SN hearing loss and occipital headache. Pure-tone averages dropped to 45, 60, and 22 dB, respectively, during three described episodes of hearing loss that maintained an up-sloping configuration. Hearing returned to normal after each episode. Another patient experienced episodic vertigo concomitantly with a subjective hearing loss, aural fullness, and increase in tinnitus. An audiogram between spells was normal. These spells were not associated with headache, but the patient had a history of migraine.

Slater[20] in 1979 coined the term "benign recurrent vertigo" to denote the symptom complex of episodic vertigo without cochlear signs or aural symptoms. These patients were considered by Slater to have a disorder similar in origin to migraine, even though the vertiginous spells were not associated with headache. The denotation of vertigo completely independent of headache is what distinguishes benign recurrent vertigo from previously reported entities such as episodic giddiness in migraine and basilar artery migraine. The description of the vertigo was fairly stereotypical in the seven patients described by Slater. The vertigo developed suddenly and spontaneously and was accompanied by nausea, but not vomiting. Most spells lasted from 0.5 to 4 hours, the range being 1 minute to 24 hours. As the vertigo subsided, it was usually followed by positionally induced vertigo that often resolved over hours to days. This positional vertigo lasted for 1 month in one patient, while remaining permanently in another. Although none of these patients had hearing loss, some noted tinnitus or aural fullness that did not fluctuate in a consistent pattern coordinated with the vertigo. Slater noted that some features of this particular pattern of vertigo were similar to what is seen with migraine. Similarity was noted with benign paroxysmal vertigo of childhood, although the age of the Slater patients was older (adults) and the duration of the spells was longer. Four of the seven patients of Slater had a history of migraine headaches, either earlier in their life or presently, but never associated with the vertigo. One patient who did not have a headache history noted loss of vision for a split-second with attacks of vertigo. Family history was positive for migraine in four patients. Three patients noted that spells seemed to be precipitated by lack of sleep, alcohol use, or emotional stress, or that the attacks usually commenced upon awakening. These factors have also been recognized by other authors as precipitating factors for migraine headaches.[20] Female preponderance (five males, seven females) was also consistent with a migraine etiology.[2]

Moretti et al.[21] and Behan and Carlin[22] presented series of five and 32 patients, respectively, to further illustrate the symptom complex of benign recurrent vertigo. The patients Moretti et al. described had symptoms very similar to those of Slater's patients, although the duration of vertigo was slightly longer (from several hours to 5 days). Moretti et al. also noted a frequent pattern of the vertigo developing upon awakening and a tendency for positionally induced vertigo to follow the acute spells. Behan and Carlin[22] described 32 patients with symptoms similar to those reported by Slater, but with a few important changes made to the criteria for the diagnostic category of benign recurrent vertigo. Although all patients in their series described episodic vertigo lasting from hours to days, 31% (10) had headache as a prominent feature and all 32 patients noted some type of headache, usually described as a dull headache combined with a fuzzy feeling in the head and difficulty concentrating. The major modification to this diagnosis is the inclusion of two patients who complained of a hearing loss. These two patients had initially been given the diagnosis of Meniere's disease, but Behan and Carlin believed that benign recurrent vertigo, a migraine-related disorder, was a more appropriate entity for several reasons: their hearing loss was mild, they both had a strong family and personal history of migraine, and their hearing loss completely resolved with a normal audiogram following treatment with the antimigraine medication, pizotifen. Pizotifen was the primary drug used to manage the vertiginous symptoms. Twenty-three of the 32 patients so treated (72%) experienced complete relief, three obtained good to moderate benefit, and six had no response. Two of the six patients who did not respond were treated with propranolol, achieving almost complete relief.

Kayan and Hood[14] in 1984 categorized the various presentations of neurotologic symptoms occurring in a group of 80 migraine patients referred for dizziness or hearing loss. Of the 78 patients with vestibular symptoms, episodic true vertigo was described by 59, positional or postural vertigo by 19, and nonvertiginous giddiness by 25, with 25 patients describing more than one vestibular symptom. The dizziness or vertigo was temporally related to headache in 42 of the 78 patients and completely independent of the headache in 36 of the 78. Both cochlear and vestibular symptoms occurred associated with headache in 55% (44) of the 80 patients; two patients described cochlear symptoms alone. Cochleovestibular symptoms preceded the headache in 17 of 80 patients and occurred with headache in 25 of 80 patients. Thirteen (16%) of the 80 patients described hearing loss: the loss occurred associated with headache in six patients and independent of headache in seven patients. Twenty-two of 80 patients (28%) had an SN hearing loss by audiogram.

Cutrer and Baloh[10] in 1992 similarly tried to avoid stereotyping the pattern of dizziness that occurred with migraine by using a more general term, "migraine-associated dizziness." In their study of 91 patients, they noted that although some patients with migraine-associated dizziness had their spells time-locked to headaches (five patients [5%]), the majority experienced vertigo either always independent of the headache (23 patients [25%]) or often independent of the headache (63 patients [69%]). Like most previous studies, the vestibular symptom reported by the majority of patients was true vertigo (63 patients [69%]), but a significant number of patients described nonvertiginous dizziness (28 patients [31%]). Almost one third (29 patients [32%]) of this group experienced both vertigo and nonvertiginous dizziness at different times. Eighty-four patients could confidently report the duration of their dizziness. Although the duration of these spells spanned from minutes to days, most of these 84 patients fell into two categories: 26 patients had spells from minutes to 2 hours, whereas almost half (41 patients) had spells that lasted longer than 24 hours.

Olsson[23] also found that the majority of his migraine-related dizziness patients experienced their dizziness independent of the headache, even though he limited his study to patients who satisfied a strict definition for basilar artery migraine. He reported the otoneurotologic symptoms of 50 patients who had vertigo, in combination with visual abnormalities and paresthesias (face, arms, or legs), occurring as an aura with a migrainelike headache following the vertigo within 1 hour. Eighty-four percent (42) of these patients also had episodes of either vertigo or nonvertiginous dysequilibrium without any accompany-

ing headache. The high incidence of hearing loss may be related to the selection of this particular type of migraine. Twenty-six of 50 patients (52%) reported difficulty hearing within 1 hour before the headache. The type of hearing loss Olsson noted on audiometry was similar to that reported by Guidetti et al.[16] and Behan and Carlin.[22] A low-frequency loss, primarily at 250 Hz and less frequently at 500 Hz, was measured in 80% of the 50 patients of Olsson.[23] This hearing loss primarily took the form of an up-sloping fluctuating pattern seen in 60% of the patients. Aural fullness or ear stuffiness was noted by 50% of the patients. Ear pain between headaches was described by 68% (34 patients), usually associated with vertigo or dysequilibrium, but it often could not be differentiated from a severe stuffiness.

Vestibular Tests

The results of vestibular studies on patients with migraine-related dizziness vary greatly, probably related to a combination of factors including the specific technique of the testing procedure. This is especially true with caloric testing and the subgroup of migraine-related dizziness that is being studied using this technology. It is of notable interest that when abnormalities are seen, they most often are the type that have been attributed to peripheral otologic disease.

A fairly high incidence of abnormal vestibular test results are seen in migraine patients unselected for vestibular symptoms. Toglia et al.[24] looked at 20 such patients with common migraine, none with specific complaints of vertigo, and found that 80% had abnormal caloric study results on electronystagmography (ENG). Rotary-chair studies were abnormal in 75% of these 20 patients. Kuritzky et al.[25] found similar results in their group of 20 migraine patients, again without selection for vestibular symptoms. In these 20 patients, spontaneous nystagmus was seen in 45%, caloric abnormalities in 80%, canal paresis in 45%, and directional preponderance in 15%. Rotary-chair abnormalities were found in 75%. Guidetti et al.[16] subdivided their study population of 53 headache patients into specific headache diagnoses, again unselected for vestibular symptoms. Abnormal ENG results were also common in this patient population (97%), with abnormal caloric test results in 89%. When patients were subdivided into specific headache diagnoses, abnormal caloric results were found in 12 of 12 patients with migraine with aura, 22 of 25 with migraine without aura, two of two with cluster headaches, four of four with tension headaches, five of seven with mixed headache, two of two with psychogenic headache, and none with Sluder's syndrome. It is not surprising that ENG studies of selected migraine patients with vestibular symptoms show similar abnormal findings such as spontaneous nystagmus, positional nystagmus, and caloric paresis.[14,22,23,26,27] Behan and Carlin[22] noted that one patient with benign recurrent vertigo had complete canal paresis on ENG. However, other authors have noted a significantly lower incidence of abnormal vestibular test results.[10,18,20] One of the more recent studies by Cutrer and Baloh[10] of a diverse group of 91 patients with migraine-associated dizziness had a fairly low incidence (31 patients, 34%) of ENG abnormalities. Caloric abnormalities were seen in 26 patients, with a unilateral caloric paresis of greater than 25% in 19 of their 91 patients. Spontaneous nystagmus was observed in six patients, and positional nystagmus in six patients. Slater's 1979 report[20] discussing benign recurrent vertigo notes normal results of caloric studies from all seven of his study patients, although all were also noted to have either spontaneous or positional nystagmus. Eadie[18] noted normal caloric test results in 17 of 19 patients (89%) with giddiness in migraine.

Dynamic posturography was performed on 48 of the 50 patients with basilar artery migraine reported by Olsson.[23] Poor amplitude scanning was found in 34 patients, abnormal toes-down perturbation in 32 patients, and abnormal sway when tested with a sway-referenced platform and sway-referenced visual surround in 27 patients.

Diagnosis

Migraine, like Meniere's disease, is a diagnosis made by the combination of an appropriate history and physical examination, along with the exclusion of other diseases. To consider migraine as an origin of clinical syndromes such as benign recurrent vertigo, episodic giddiness, basilar migraine, and migraine-associated dizziness, patients must have had a normal neurologic examination and exclusion of other diseases by a variety of techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) of the brain, electroencephalography, and/or metabolic blood tests.[10,18,19,21–23,26] The relationship of dizziness to migraine is fairly clear when the vertigo episode is consistently time-locked to a migraine-type headache, but this consistency was relatively uncommon overall in the study groups reported herein.[17,18,23] Most patients were presently experiencing migraine headaches or had a history of migraine headaches in the past. In Kayan and Hood's patient series,[14] headache history predated the onset of vertigo by 1 to 54 years. Often the patients were in total remission of the headache phase of their migraine when the vertigo developed. These authors noted that the higher the age at migraine onset, the shorter the interval between the headache and cochleovestibular symptoms. In 24 of 99 patients, the onset of headache and cochleovestibular symptoms was simultaneous. The vertigo preceded the migraine headache in only four of these 99 patients. Olsson[23] noted that 66% of his 50 patients with basilar artery migraine could trace a history of headaches since adolescence. Of these 50 patients, 16% had a headache history of less than 5 years and all were younger than 30 years of age. The neurologic symptoms developed before the headache in only four of 50 patients. Both Parker[27] and Aragones et al.[26] noted that it was common for the headache to occur before the vertigo by months to several years. Behan and Carlin[22] noted that some of their patients with benign recurrent vertigo had suffered for years with migraine headache, only to develop vertigo later. Thus, to make the diagnosis of migraine-related dizziness, the patient's past headache history must be carefully and thoroughly elicited, since many patients are not aware that their headaches can be appropriately classified as migraines.

When the headache history is remote from the period of vertigo, or when the headache history is nonexistent or

atypical for migraine, other factors can be used to raise the suspicion for a migraine etiology. These issues include the presence of other neurologic symptoms that can commonly occur with migraine such as visual scintillations and scotomata[22]; aggravation of symptoms by known precipitants of migraine such as alcohol, sleep deprivation, and emotional stress[20,22,23]; a history of motion sickness as a child[14,23,25] or an adult[15]; and a family history of migraine.[18,21,22,27]

Pathophysiology of Migraine

There is no consensus regarding the pathophysiology of vestibular or cochlear symptoms related to migraine. This is understandable, since dizziness or vertigo can occur at very different phases of the migraine episode. One would not necessarily expect the vertigo that occurs in a typical aura phase associated with a basilar migraine to be due to the same pathophysiology as positional vertigo following a spontaneous episode of vertigo in a patient having spells consistent with benign recurrent vertigo. Most authors, when they propose a mechanism for vestibular symptoms in migraine, base their conclusions on research that has focused on mechanisms responsible for the headache or aura of migraine. New drugs that function as selective agonists and antagonists of the neurotransmitters that participate in the migraine event have helped to explain some of the neurophysiology of migraine headaches. But it is not clear if the same mechanisms are involved in migraine-related symptoms such as vertigo lasting greater than 24 hours, positional vertigo, dysequilibrium lasting days or even weeks, aural fullness, ear pain, low-frequency fluctuating hearing loss, or tinnitus.

Migraine is presently believed to be the manifestation of a hereditary abnormal sensitivity of neurovascular reactions to sudden changes in the internal or external environment or to cyclic changes in the central nervous system (CNS).[28] Stated in simpler terms, patients with migraine are born with an abnormality of that part of the brain controlling or modulating incoming signals. These "pain control centers" control the gain or sensitivity of incoming information from touch or pain fibers in the head and neck, as well as from afferent nerves transmitting the sensations of vision, hearing, and motion. The gain control setting of these pain control centers can be affected by many different things, including changes in an individual's internal environment (such as hormonal fluctuations with the menstrual cycle, changes in one's sleep patterns, and emotional turmoil) and changes in one's external environment (such as dietary changes, altitude changes, and external causes of pain).

The anatomy of this "endogenous pain control system" is described by Lance[29] and diagrammatically represented in Figure 1. The spinal tract and nucleus of the trigeminal nerve which descends to the second cervical segment of the spinal cord plays a central role in this system as a pain center. Pain afferents from the second cervical root and from the trigeminal system converge on second-order neurons in an area called the nucleus caudalis. It is believed that primary sensory neurons containing enkephalin receptors use substance P, a polypeptide, as their neurotransmitter.[30] Interneurons within the spinal

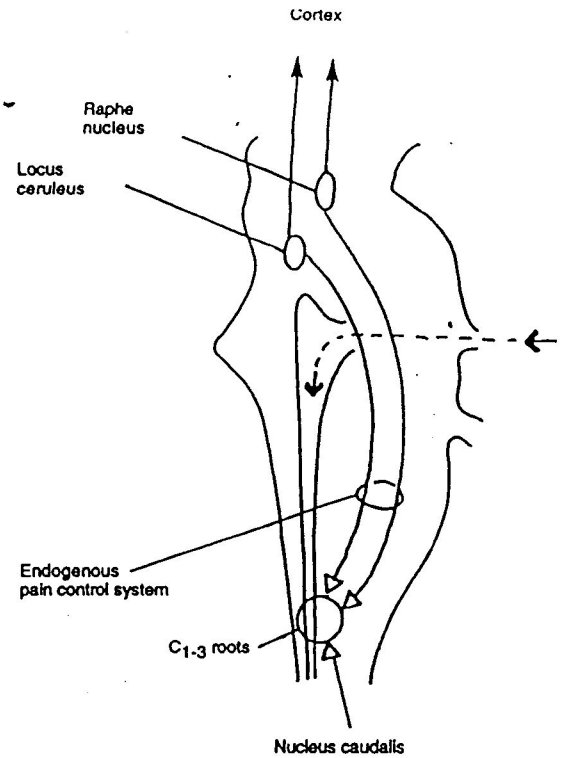

Fig. 1. Neuroanatomy of the noradrenergic locus ceruleus and serotoninergic raphe nuclei. Descending fibers in these two neural pathways comprise the endogenous pain control system.

tract of the trigeminal nerve regulate pain perception by using enkephalin, which binds to the enkephalin receptors on the primary sensory neuron, thus inhibiting neuronal transmission and preventing propagation of pain impulses from the periphery to the CNS. Bausbaum and Fields[31,32] have shown that γ-aminobutyric acid (GABA) may also be involved as an inhibitory neurotransmitter. These inhibitory interneurons are further modulated by two neural pathways descending from the brainstem, the raphe nuclei or midbrain raphe, and locus ceruleus. The raphe nuclei, consisting of serotonin-containing neurons, projects caudally from the periaqueductal gray (PAG) matter of the midbrain to the nucleus raphe magnus in the midline and lateral medullary nuclei[33] and terminates on the dorsal horn in the spinal cord, where it regulates the discharge of neurons in both trigeminal and spinal pain pathways. Stimulation of the PAG can produce potent analgesia in humans.[34] Rostral projections from the midbrain raphe course through the medial forebrain bundle and are distributed to the hypothalamus and dorsal thalamus and diffusely to the cerebral cortex.[35] These rostral projections are believed to be involved in both sleep and neuroendocrine control.[30]

The locus ceruleus is a noradrenergic pathway, which, like the raphe nuclei, projects caudally as part of the endogenous pain control system and rostrally to the cerebral cortex, where it alters cerebral blood flow. The locus ceruleus is located near the wall of the fourth ventricle in the upper pons. These neurons modulate the firing activity of the target neurons through alpha (α_1 and α_2) and beta (β_1 and β_2) adrenergic receptors.[36] The locus

ceruleus receives afferent fibers from insular and visual cortex, amygdala, hypothalamus, brainstem reticular formation, raphe, vestibular nucleus, and tractus solitarius. As Lance[29] pointed out, these are all areas that relate to internal and external sensory stimuli or to the affective state. The locus ceruleus projects to the cerebral cortex through a dorsal bundle of fibers, as well as to the thalamus, hypothalamus, medial and lateral geniculate nuclei, facial nerve nucleus, and spinal nucleus of the trigeminal nerve and spinal cord. The maximal activity in the locus ceruleus neurons is thought to occur at times of arousal and vigilance, with the effect on target organs being reduction of spontaneous activity and enhancement of the activity evoked by the sensory systems.[29]

This endogenous pain control system functions to allow the CNS to control impulses coming from the peripheral pain receptors via the descending pain-modulating systems. In the serotoninergic system (raphe nuclei), 5-hydroxytryptamine (5-HT) interacts with enkephalin neurons, whereas in the adrenergic system (locus ceruleus), norepinephrine uses GABA-containing interneurons.[37]

Neural pathways have been described that involve this endogenous pain control system, where painful stimuli in the head (sensory distribution of the trigeminal ganglia) can produce vascular dilation in both the intracranial and extracranial circulation. Moskowitz[38] has demonstrated the existence of neural connections between the trigeminal nerve and the cerebral blood vessels defined as the trigeminovascular system. The brain has been recognized as anesthetic ever since neurosurgeons discovered that the brain was not sensitive to pain when touched or stimulated. The early work by Ray and Wolff[39] showed that certain intracranial structures are sensitive to pain, however, and, when stimulated, refer this pain to the frontotemporal area. These sensitive structures include the great venous sinuses; the dural arteries; the proximal 20% of the larger arteries forming the circle of Willis; the pain-sensitive fibers of the fifth (trigeminal), ninth, and tenth cranial nerves and the upper cervical nerves; and the parts of the dura mater at the base of the skull. Early theories held that headache was caused by dilation of these intracranial arteries.[40–42] More recently, investigators have focused on the theory that a centrally mediated, neurogenic sterile inflammation of the intracranial and extracranial vasculature, mediated through the trigeminovascular reflex, is responsible for the headache in migraine.[43] Moskowitz[43] has described a plexus of nerves within the trigeminal system that supply sensory innervation to the cephalic blood vessels. The density of these sensory axons is greatest along the proximal arteries of the circle of Willis, diminishing in number over the convex surfaces. The basilar and vertebral arteries contain fibers that arise from the upper cervical ganglia,[44] which synapse with the spinal tract of the trigeminal nucleus at the nucleus caudalis. Terminals of sensory fibers surrounding the middle cerebral and basilar arteries have been found in the PAG,[43] the caudal projections of the serotoninergic raphe nuclei.

The unique aspect of the role of these trigeminovascular fibers in headache pain is that they are able to function in an antidromic fashion; that is, instead of their neuronal discharge going from the peripheral nerve ending to the brainstem nucleus, it goes in the reverse direction. Antidromic stimulation of the trigeminal nerve (central stimulation of the Gasserian ganglion) has been shown to cause release of the neuropeptiditic substance P,[45,46] neurokinin A,[47] calcitonin gene-related peptide (CGRP),[48] and galanin[49] from nerve fiber endings that surround the vessels of the circle of Willis. These fibers form an adventitial plexus of small-diameter, unmyelinated axons that exhibit electron microscopic characteristics of C-fibers[50] (pain fibers). The synaptic ends of these trigeminovascular axons contain these neuropeptides in vesicles, with their release from the vesicles mediated by calcium-dependent mechanisms.[51] The released neuropeptides interact with blood vessel walls, producing dilation, plasma extravasation, and sterile inflammation.[30] Electron micrographs of the interior of these blood vessels show platelet activation.[38] This neurogenic sterile inflammation has been shown to result in breakdown of the blood-brain barrier in the dura mater.[30]

Many of the drugs that are presently used to abort the headache in migraine have been shown to block trigeminovascular fiber release of the neuropeptides that cause neurogenic inflammation. Moskowitz[38] studied the leakage of radioactive albumin into the dura mater following stimulation of the rat trigeminal nerve. A twofold increase of radiolabeled albumin was found on the stimulated side, indicating inflammation and blood-brain barrier breakdown. Administration of the drugs sumatriptan or dihydroergotamine mesylate (DHE) prevented leakage of the albumin tracer; both drugs are agonists at the 5-HT_{1D} receptor (a subtype of the neurotransmitter 5-HT found in the serotoninergic raphe nuclei). However, neither drug blocked the production of inflammation when the neuropeptide was directly applied to the dural vessels.[52,53] These studies demonstrated that neurogenic inflammation can be prevented by blocking transmission within the trigeminovascular nerve fibers rather than through a vascular route.

Pathophysiology of Migrainous Cochleovestibular Symptoms

A large portion of migraine research has focused on explaining the pathophysiology of the focal neurologic symptoms (aura) and headache occurring with migraine. However, as has been discussed earlier, the majority of the patients who describe vertigo or dizziness associated with their migraine experience the vestibular symptoms unassociated with headache and in a time frame often different from a typical aura. The concept that the migraine patient may have a defect in the central pain control system that affects modulation of incoming signals has been demonstrated in a few ways. It is known that migraine patients are susceptible to head pains at times other than during a migraine episode. Raskin and Knittle[54] found that drinking cold drinks or eating ice cream elicited a headache in 93% of 59 migraine patients, but only in 31% of 49 nonmigraine control patients. Raskin and Schwartz[55] noted that 42% of 100 migraine patients were prone to sudden jabs of head pain ("ice-pick pains") compared with 3% of 100 nonheadache controls. Lance[28] has proposed that disinhibition of a segment of the trigeminovascular pathway may be a feature in migrainous pa-

tients, suggesting that the trigeminal system could also discharge excessively for hours or days, providing a neural origin for migraine. If central disinhibition (via the endogenous pain control system) occurred in the trigeminal pathways, disinhibition could also account for the phonophobia commonly associated with migraine. Woodhouse and Drummond[56] found that the auditory discomfort threshold decreased substantially during attacks of migraine. The threshold for hearing (an 8000-Hz tone) did not differ significantly for their 16 patients during a migraine attack, when compared with their headache-free period. The authors concluded that phonophobia in migraine is not a manifestation of loudness recruitment but, more likely, is a disruption of central sensory processing mechanisms. They reasoned that discharge of the locus ceruleus could increase auditory sensitivity to quiet sounds and therefore might also increase discomfort to loud sounds through a "sensory overload" phenomenon. Central involvement with auditory perception during migraine has been supported by the demonstration that latency of wave V in auditory brainstem response (ABR) is increased during migraine.[57,58] ABR differences between migraine patients and nonmigraine controls have also been found during the headache-free period.[59,60] Schlake et al.[59] compared the ABR of 38 migraine patients during a headache-free period and compared the results with 50 nonheadache patient controls. They found side differences in all peak latencies (except waves IV and VI) to be significantly increased (range, $P = 0.05$ to $P = 0.01$) in the migraine population when compared with controls. Similar results were reported by Bussone et al.,[60] who reported increased interear asymmetries of interpeak latencies for waves I to V in 20 migraine patients (both during and between attacks), compared with 20 nonheadache subjects. Further support for involvement of the central endogenous pain control system is the finding that evoked potentials are influenced by changes in cerebral metabolism that affect the noradrenergic and serotoninergic pathways such as the locus ceruleus and raphe nuclei.[61]

Cutrer and Baloh,[10] in their study of migraine-associated dizziness, proposed a similar mechanism to explain the varying types of vestibular symptoms that occur in migraine patients during the headache-free period. They suggested that a centrally mediated inhibition of efferent gating of vestibular sensitivity could be responsible for motion intolerance, if the two sides were affected equally. If, however, the changes in vestibular sensitivity were asymmetric, spontaneous vertigo would ensue. They suggested that this modulation of vestibular sensitivity is probably mediated by the release of neuropeptides by efferent nerve endings, as diagrammatically represented in Figure 2. It seems logical that an abnormality in the endogenous pain control system's ability to regulate incoming pain sensitivity would imply the possibility of a concomitant abnormality in the central control of vestibular sensitivity.

In developing a category of patients believed to have migraine-related dizziness, patients who have classic symptoms of known otologic diseases have been carefully excluded. A prime concern is excluding patients from migraine-related dizziness who have classic Meniere's disease. One approach is to consider only those patients who

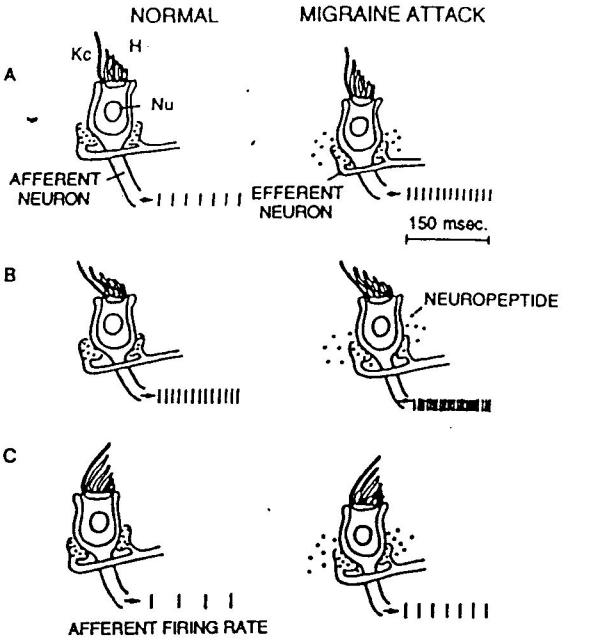

Fig. 2. Proposed mechanism of migraine-associated dizziness. **Panel A** represents efferent stimulation causing neuropeptide release, which increases the spontaneous baseline firing rate. **Panels B and C** show bending of the stereocilia toward or away from the kinocilium, which increases or decreases, respectively, the firing rate above baseline. Kc = kinocilium; H = hairs (stereocilia); Nu = nucleus. (Reprinted with permission from Cutrer FM, Baloh RW. *Headache* 1992;32:300–4.)

have vestibular symptoms without hearing loss.[20–22] Other authors have included patients with hearing loss as long as it was not classic for that attributed to Meniere's disease.[18] A mild, especially low-frequency or up-sloping, SN hearing loss has been described with migraine,[16,22,23] as has subjective hearing loss but with normal audiometry.[19] It should also be noted that, although not frequently reported, significant SN hearing loss has been attributed to migraine.[19,62,63] Viirre and Baloh[63] presented a series of 13 patients who came to medical attention with sudden SN hearing loss of unexplained origin who met the diagnostic criteria for migraine. Eleven of the 13 patients noted the hearing loss developing over seconds to minutes. One patient noticed the hearing loss upon awakening in the morning. Another only remembered that the hearing loss came on as a young child. The degree of hearing loss ranged from severe (up to 60 dB) to profound (>60 dB). The majority demonstrated a relatively flat loss. Two had involvement in the low-frequency range only; one had a high-frequency loss. Three patients experienced vertigo occurring with the hearing loss. Viirre and Baloh[63] suggested that a pattern of hearing loss developing over seconds to minutes is more consistent with a vasospastic origin than with a viral disease. Hupp et al.[64] reasoned that there is convincing evidence for vasospasm as the primary cause for ophthalmic migraine. Although such patients typically experience transient episodes of monocular blindness, permanent visual loss sometimes occurs. Tippin et al.[65] reported that vasospasm of the retinal arteries has been observed during periods of monocular visual loss

that occurred as a migraine aura. Therefore Viirre and Baloh[63] suggested that in a patient with migraine, sudden hearing loss, along with associated vertigo, could be explained by vasospasm affecting vestibular and/or cochlear branches of the labyrinthine artery.

Neurotransmitters in Migraine

Much of the present migraine research has focused on the role that neurotransmitters play in the pathophysiology of migraine. Serotonin (5-HT) and its various subtypes have been of primary interest. Research has focused on the various types of receptor sites that exist, the location of these receptor sites, and the results that occur when 5-HT (or drug that is an agonist or antagonist of 5-HT) reacts with these receptor sites. The 5-HT receptors consist of at least three distinct types of molecular structures: guanine-nucleotide-G protein-coupled receptors, ligand-gated ion channels, and transporters.[66] At least seven 5-HT receptors have been identified (5-HT_1 to 5-HT_7).[67] At least five 5-HT_1 receptor subtypes have been identified in humans: 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, and 5-HT_{1F}.[66] The inhibitory 5-HT_1 receptor appears to modulate neurotransmitter release presynaptically; the 5-HT_2 receptor is an excitatory postsynaptic receptor; and the 5-HT_3 receptor is excitatory.[68]

There are several lines of investigation that have shown a relationship of 5-HT and migraine. Reserpine is a drug believed to deplete the CNS of 5-HT, thus precipitating a migrainelike headache which can then be relieved by 5-HT or 5-HT agonists.[37,69] Two drugs that are used in the treatment of migraine are sumatriptan,[70] a serotonin analog, and DHE,[71] an ergot derivative. Both have been shown to be agonists at the 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors. These drugs block the development of neurogenically induced inflammation in rat dura mater, presumably by activating prejunctional 5-HT_1 receptors on the trigeminal nerve. This then blocks the release of neuropeptides at the neurovascular junction, including substance P and CGRP.[66] There is evidence that these drugs exert at least part of their activity on the central pathways of the endogenous pain control system. Radiolabeled DHE, when injected intravenously into the cat, passes through the blood-brain barrier and labels nuclei in the brainstem and spinal cord that are involved in pain transmission and modulation, including the caudate nucleus.[72] Experimental studies suggest that ergot alkaloids (ergotamine and DHE) and possibly sumatriptan exert their antimigraine effect by a receptor-mediated neural pathway in both the CNS and the trigeminovascular system, where they block neurogenic inflammation.[66] The other major classes of medication used as preventative treatment of migraine may also have activity at the 5-HT receptor sites.[66] These include beta-adrenergic blockers, antidepressants, calcium channel blockers, serotonin antagonists, and anticonvulsants. Many of these agents may interact with the 5-HT_2 or 5-HT_{2C} receptor sites, "down-regulating" the 5-HT_2 receptor or modulating the discharge of serotoninergic neurons.[67,68]

Sensory hyperacuity of migraine, including, perhaps, hypersensitivity to motion, remains to be explained.[29] The locus ceruleus, a noradrenergic system, projects to the medial geniculate nuclei and receives afferent fibers from the vestibular nucleus. If the pain gates are opened by removal of descending inhibition, sensitivity to noise may be caused by removal of ascending inhibition.[29] Increased sensitivity to pain around the ear could explain the ear pressure or ear pain sometimes described by patients with migraine-related dizziness. Increased vestibular sensitivity to motion, either symmetrically or asymmetrically, could account for the vestibular symptoms of motion intolerance, spontaneous or positional vertigo, or baseline instability.

Anatomy and Neurochemistry of the Peripheral and Central Vestibular System

Central vestibular pathways have been identified that involve brain nuclei which are affected by the central endogenous pain control system. The presence of cortical projections that serve to provide the subjective sensation of motion is supported by several observations.[73] Patients without vestibular function (acquired or congenital) do not experience a turning sensation when rotated in the dark, if visual and tactile cues are eliminated.[74] Focal cortical lesions in the nondominant parietal lobe affect the sense of spatial orientation.[75] Electrical stimulation of the superior sylvian gyrus and a region of the inferior intraparietal sulcus produces a subjective sensation of movement.[76] The ascending vestibulocortical system includes at least three synaptic stations: the vestibular nuclei, the thalamus, and the cerebral cortex.[77] Neurons in the superior and lateral vestibular nuclei project to two thalamic regions by two major pathways.[78] A large anterior projection terminates in the main sensory nucleus of the thalamus (nucleus ventralis posterior lateralis pars oralis). A smaller posterior projection ends near the medial geniculate. As these thalamic nuclei are also activated by proprioception and visual stimuli, it has been suggested by Baloh and Honrubia[73] that these vestibulothalamocortical projections appear to integrate vestibular, proprioceptive, and visual signals to provide one with a "conscious awareness" of body orientation.[73]

There is increasing evidence that adrenergic activity modulated through the central pathways of the locus ceruleus contributes to the regulation of the dynamic performances of the vestibulospinal pathways.[79–81] Unilateral lesions of the locus ceruleus cause asymmetric postural responses in decerebrate animals.[79] Resting activity of the locus ceruleus neurons has been shown to be modulated by labyrinthine and cervical proprioceptive afferent input.[81] Neural pathways from the locus ceruleus and the nucleus subceruleus, a secondary noradrenergic nucleus, projecting into the vestibular nuclear complex have been identified using immunoreactive techniques.[82] Schuerger and Balaban[82] described two major pathways: a lateral descending bundle projecting from the locus ceruleus to the superior vestibular nucleus and a medial descending bundle that provides afferent pathways to the lateral, medial, and inferior vestibular nuclei. Licata et al.[83] demonstrated that these pathways function to inhibit activity in the superior and lateral vestibular nuclei neurons by modulating the resting activity of central vestibular neurons through the noradrenergic α_2 receptors. Both α_1 and β-

noradrenergic receptors have also been detected within vestibular nuclei.[84,85]

Serotoninergic receptors that could originate from the dorsal raphe nuclei have also been identified in the vestibular nuclei.[86] The effect of serotonin varies between the different vestibular nuclei: responses vary between purely excitatory, purely inhibitory, or biphasic.[87,88] This varied effect can be explained by the presence of different 5-HT receptors in the different nuclei. The inhibitory responses are apparently mediated by 5-HT_{1A} receptors, whereas the excitatory responses result from the activation of 5-HT_2 receptors.[87,89]

Many other neurotransmitters have been identified in the peripheral and central vestibular system. De Waele et al.[36] gave a thorough discussion of the vestibular neurochemistry in their 1995 review. Some of these neurotransmitters and receptors play a potential role in the pharmacologic management of vertigo. Early studies suggested that acetylcholine was the neurotransmitter involved in synaptic transmission between the first-order and second-order vestibular neurons.[36] This hypothesis has been challenged with the discovery that the excitatory amino acids, aspartate and glutamate type, are probably involved, at least in the medial vestibular nucleus.[90] In some afferent fibers substance P is colocalized with glutamate.[91,92]

GABA is one of the major inhibitory neurotransmitters in the vertebrate nervous system.[93] Its postsynaptic function is mediated by $GABA_A$ and $GABA_B$ receptors.[94] The $GABA_A$ receptor is an ionotropic receptor consisting of several subunits.[95] The γ subunit contains the target site for benzodiazepine regulation.[96] $GABA_B$ receptors are sensitive to the agonist b-r-chlorophenyl-GABA (baclofen).[36] GABA receptors have been found in several areas of the central and peripheral vestibular system. GABA has been shown to play a role as an afferent neurotransmitter in the vestibular hair cell.[97] Two subtypes of $GABA_A$ γ-receptors (γ_1 and γ_2 subunits) have been identified by immunohistochemical techniques in the peripheral terminal endings in the vestibular sensory epithelia, as well as in most vestibular ganglion cell bodies.[95] Within the central vestibular pathways, GABA has been shown to be involved in at least three types of central vestibular synapses: the synapses between Purkinje's cells of the anterior cerebellar vermis and the vestibular nuclei neurons, the synapses between commissural vestibular and medial vestibular nuclei neurons, and the synapses between inferior olive neurons and lateral vestibular neurons.[36]

Both animal and human studies have supported involvement of GABA in the regulation of vestibular function. Unilateral perfusion of the medial vestibular nucleus with $GABA_{inergic}$ agonists and antagonists induces a reversible spontaneous nystagmus and modifies the gain of the horizontal vestibuloocular reflex.[98] Postural asymmetries were reported following unilateral microinjections of $GABA_A$ and $GABA_B$ agonists and antagonists into the lateral vestibular nucleus.[99] Orally administered baclofen, a selective $GABA_B$ receptor antagonist, reduces nystagmus slow-phase velocity and oscillopsia in patients with upbeat and downbeat nystagmus.[100] These experiments suggested that $GABA_A$ and $GABA_B$ receptors play a functional role in central vestibular function.[36]

This discussion has concentrated on neurotransmitters and neural connections that appear most likely to be involved in the pathophysiology of migraine-related dizziness or in the pharmacologic management of dizziness or vertigo that has a migrainous origin. The complexity of the neurotransmitters that have already been identified and discussed and may play a role in future management are diagrammatically presented in Figure 3.[36]

MATERIALS AND METHODS

Patient Database

Patients for this study were selected from patients seen by a single practitioner of otology and neurotology at an academic medical center located in a rural area. Outpatient billing codes were used to identify 665 patients seen between January 1, 1992, and June 1, 1995, for the symptoms of vertigo and dizziness. The charts of these 665 patients were retrospectively reviewed to reveal 99 patients diagnosed with and treated for migraine-related dizziness. Follow-up of medical therapy was 3 months or more, as documented in the patient record of 74 patients. When chart documentation of medical follow-up was less than 3 months, additional patient information was obtained by telephone (in seven of 25 patients) or by an individually formulated questionnaire (in eight of 25 patients). Ten of 25 patients could not be contacted by telephone or letter to provide follow-up greater than 3 months and therefore were lost to this study. Thus participants in this study were 89 patients diagnosed with migraine-related dizziness or vertigo with follow-up greater than 3 months.

Diagnosis

Patients were considered to have dizziness attributable to migraine *1.* if their history, otoneurologic examination, audiogram, and any additional tests were inconsistent with other well-defined disorders such as vestibular neuronitis, benign paroxysmal positional vertigo, Meniere's disease, acoustic neuroma or other lesions of the cerebellar pontine angle or central nervous system, postconcussive syndrome, or vertibrobasilar insufficiency and *2.* if they had a present or past history of migraine satisfying the 1988 IHS diagnostic criteria or had a headache history that did not satisfy the IHS 1988 criteria but had a strong family history of migraine; had a history of motion sickness as a child; and/or had other neurologic symptoms well established as associated with migraine, such as typical visual aura.

All patients having subjective or objective symptoms of an asymmetric hearing loss or unilateral ear symptoms including aural fullness or ear pain were evaluated for an acoustic neuroma. This consisted of a gadolinium-enhanced MRI study in all but two patients; one patient had an asymmetric hearing loss that was purely conductive and explained by a prior tympanomastoidectomy in that ear, and the other patient had a unilateral, subjective, fluctuating hearing loss with a normal audiogram. An ABR and CT scan (including bone detail of the internal auditory canals with contrasted soft tissue study of the brain and internal auditory canal) were undertaken with the latter patient with normal results, and that patient was followed by yearly audiograms for 4.7 years, without showing any change in hearing.

Patients who had symptoms suggestive of classic Meniere's disease and migraine-related dizziness were included in this study only under one or more of the following specific conditions:

1. Meniere's disease symptoms preceded the dizziness attributable to migraine and were under good to excellent control with medical or surgical management before the onset of vertigo or dizziness not typical of Meniere's disease.

2. Symptoms were similar to but not typical of Meniere's disease, and there was a strong link to a classic migraine event

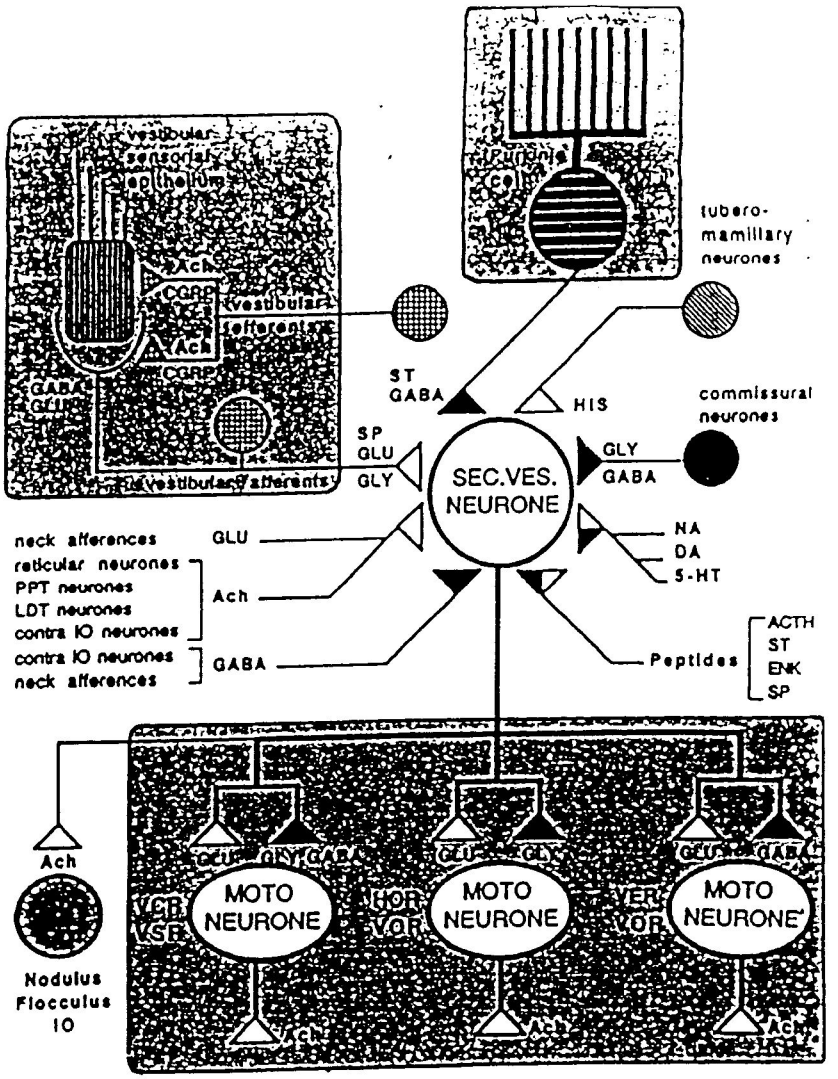

Fig. 3. Summary diagram of central and peripheral vestibular system neurochemistry. Ach = acetylcholine; CGRP = calcitonin gene-related peptide; DA = dopamine; ENK = enkephaline; GABA = γ-aminobutyric acid; GLU = glutamate; GLY = glycine; 5-HT = serotonin; IO = inferior olive; HIS = histamine; HOR VOR = horizontal vestibuloocular reflex; LDT = laterodorsal tegmental; NA = noradrenaline; PPT = pedunculopontine tegmentum; SEC VES = second-order vestibular neurone; SP = substance P; ST = somatostatine; VCR = vestibulocollic reflex; VER VOR = vertical vestibuloocular; VSR = vestibulospinal reflex. (Reprinted with permission from de Waele C, et al., *Brain Res Brain Res Rev* 1995;20: 24–46.)

(i.e., episodic vertigo always occurring with visual aura or typical migraine headache).

3. Symptoms were similar to but not typical of classic Meniere's disease and were not well controlled with a Meniere's disease medical or surgical approach, but were very well controlled with a migraine approach to medical management.

Treatment Modalities

Treatment included diet changes, medication, physical therapy, lifestyle adaptations, and acupuncture. More than one modality was in use for some of these patients, singly or in combinations.

Management of Neurotologic Symptoms

Assessment of management of neurotologic migraine symptoms was divided into the following categories:

1. Resolution (the patient could not have had any of the involved symptoms while on an effective treatment routine).

2. Substantial control (control of symptoms to the degree that they were no longer a bother to the patient, although an occasional, mild occurrence was acceptable).

3. Moderate control (symptoms were controlled sufficiently to no longer prevent the patient from going about a normal work or social schedule, although still occurring as an annoyance).

4. Minimal control (some improvement of symptoms, but symptomatic occurrence still interfered with the patient's work or social activities).

5. No improvement (no improvement in symptoms).

6. Worse (involved symptoms were worse than when entering the study).

Test Procedures

All patients received pure-tone threshold testing and speech audiometry during the initial evaluation and, if the patient reported the subjective sensation of hearing progression or fluctuation, subsequently. Evaluation consisted of pure-tone threshold testing using air- and bone-conducted tones of frequencies from 250 to 8000 Hz. Word recognition testing always accompanied pure-tone threshold testing.

Electronystagmography testing was not routinely performed on all patients; it was performed only if the study was thought to be potentially helpful in making a diagnosis. The test procedure was performed in a darkened room using electrodes at the lateral canthus to record horizontal eye movements. Testing procedure included oculomotor studies consisting of calibration measurements, saccadic and pursuit eye movements, and examination for spontaneous and gaze nystagmus. Position testing consisted of Hallpike maneuvers in the three standard positions.

Caloric examination included binaural monocaloric stimulation using an ICS Medical Corporation Model NCA-200 air caloric stimulator (Schaumburg, IL). Eye movement recordings used a Nicolet Nystar recorder (Nicolet, Inc., Madison, WI) with computed calculations of canal weakness using Jonkees' formula. An abnormal caloric response was defined as a unilateral caloric paresis greater than 20%.

Electrocochleography (ECoG) was performed early in this study when patients complained of aural fullness and episodic vertigo without objective hearing loss or with fluctuating hearing loss atypical of Meniere's disease. ECoG was not performed on patients once the diagnosis of migraine-related dizziness was made. ECoG testing was performed using a Tiptrode ear canal electrode (Nicolet, Inc.) with filtering from 5 to 3000 Hz. Averaging was completed on either a Nicolet 1170 or Compact 4 averager. The specific technique has been previously reported by Musiek and Baron.[101]

Magnetic resonance imaging was used to test for eighth-nerve tumors. MRI scanning was also performed, even in the presence of symmetric hearing, when the combination of headache and vertigo or unsteadiness appeared in a pattern atypical for otologic disease.

Auditory brainstem response testing was performed according to parameters previously reported by Musiek et al.[102] in the following clinical situations:

1. Combined with CT scanning to test for eighth-nerve tumors.
2. To assess brainstem function in patients in whom multiple sclerosis was considered.
3. Combined with a behavioral battery of audiologic studies to assess subjective hearing difficulties not explained by a standard audiogram, when MRI demonstrated no evidence of organic brain disease.

Rotary-chair evaluation was completed at an outside institution, if it was needed for overall evaluation and/or management of the patient. Before 1994, diagnostic platform posturography was performed at an outside center. Platform posturography became available at this medical center in 1994 and was performed primarily as an aid to vestibular rehabilitation therapy.

Neurologic consultation was obtained as follows:

1. When the headache history or neurologic symptoms were suggestive but not typical for migraine.
2. When headaches were frequent and/or severe and were not well controlled with the medical approach used to control dizziness.
3. When chronic daily headaches were occurring as a result of analgesic rebound.

Medical management in these circumstances was coordinated with the consulting neurologist to provide optimum control of both the dizziness or vertigo symptoms and headache.

Analysis

The charts, questionnaires, and results of telephone interviews of these 89 patients generated a database for the present review. Information regarding the patient's history, physical examination, audiologic and vestibular tests, imaging studies, prior diagnosis and treatment, concurrent diagnoses, treatment approaches, and results of treatment were compiled using FileMaker Pro, version 2.1 (Claris Corp., Santa Clara, CA).

RESULTS

Patient Logistics

Eighty-nine patients with a diagnosis of migraine-related dizziness or vertigo were followed for more than 3 months after diagnosis. Their ages ranged from 15 to 89 years, with an average age of 45 years and a median age of 43 years. Seventy-four patients (83%) were female and 15 patients were male; the female-to-male ratio was 5:1. The symptoms of dizziness or vertigo began 3 months to 44 years before beginning migraine management for their vestibular symptoms. Follow-up ranged from 3 months to 8 years; median follow-up was 2 years. Seventy (79%) of the 89 patients were followed for at least 1 year; 49 (55%) of the patients were followed for 2 or more years.

Symptoms

The 89 patients described in this study presented with a mixture of true vertigo and nonvertiginous dizziness in varying patterns. True episodic vertigo alone was described by 39 patients (44%), 15 (17%) experienced only nonvertiginous dizziness, and 35 (39%) experienced both true vertigo and nonvertiginous dizziness at different times. Vertigo or nonvertiginous dizziness occurred spontaneously without a positional component in 25 patients (28%). Positional vertigo or dizziness without spontaneous spells occurred in 11 patients (12%). Six patients (7%) described vertigo or dizziness as a constant feeling without spontaneous or positionally induced spells. The majority (47 patients [53%]) described some combination of spontaneous episodes, positionally induced vertigo or dizziness, and a constant or near-constant feeling of instability or lightheadedness.

The duration of episodic spells ranged from seconds to days. Episodes lasting seconds to 5 minutes were reported by 18 (20%) of the 89 patients. Spells lasting 5 minutes to 1 hour were reported by 12 patients (13%). Twenty-three patients (26%) described spells lasting 1 to 24 hours. Spells lasting greater than 24 hours were described by 19 patients (21%). Seventeen patients (19%) described near-constant, nonepisodic dizziness, which was accentuated by positional changes in 11 of these 17 patients.

The frequency of episodes varied from multiple spells per day to several per year. Twenty-nine (33%) of the 89 patients described one or more spells per day; 16 patients (18%) noted one or more spells per week; 25 patients (28%) had one or more per month; and two patients (2%) had one or more per year. Seventeen patients (19%) described near-constant spells.

The majority (81 of 89 patients) experienced dizziness or vertigo unassociated with headache. Only eight patients (9%) consistently noted an association of their vertiginous spells with a headache. Three of the eight patients described a vertigo pattern that was consistent with the time span of an aura (i.e., less than 1 hour). Two of the three had basilar migraine; one had migraine not fulfilling the 1988 IHS criteria. Fifty-one patients (57%) never had a headache that occurred right before, during, or shortly after a vertiginous spell, and thus was not associated with headache. Headache sometimes occurred associated with a vertiginous spell in 25 patients (28%). In this group of 25 patients, only two patients had vertigo in an aura time-span; one of these two patients had basilar migraine; the other had visual migraine, but with a headache that did not fit the IHS criteria for migraine. One patient remembered having headaches and vertiginous spells that were related in the past, but the two did

not occur together during the period when she sought medical help for the vertigo. Four patients were diagnosed with migraine aura without headache and presented no history of headache.

Migraine without aura (previously termed common migraine) was the most prevalent type of migraine in this series, accounting for 60 patients or 67% of the study group. Thirteen patients (15%) had migraine with aura; three patients (3%) had basilar migraine; four patients (5%) had migraine aura without headache; and nine patients (10%) had migrainous disorder not fulfilling the above criteria.

Only 28 patients (31%) were experiencing headache that they considered a significant problem at the time they were evaluated for their dizziness or vertigo. Thirty-five patients (39%) were experiencing a minor headache at the time of their dizziness. These headaches were well managed with over-the-counter analgesics; patients did not think that medical intervention was needed for control of these minor headaches. Twenty-two patients (25%) who had a history of headache denied any headaches occurring during the time they experienced dizziness or vertigo. In addition, four patients (those with migraine aura without headache) did not have a headache history.

For the 22 patients whose headache history preceded the onset of dizziness or vertigo, the time span between the end of their headache period and the onset of dizziness ranged from 1 to 55 years, with a median of 10 years. The time span between the end of the headache and the onset of dizziness was greater than 5 years in 17 patients, greater than 10 years in 13 patients, and greater than 20 years in eight patients.

Motion sickness, either during childhood or as an adult, was experienced by 43 (48%) of the 89 patients. Often, the motion sickness was a significant problem during childhood. Symptoms consistent with the periodic syndrome, such as cyclic vomiting or abdominal migraine, were reported by only one patient.

Forty-two of 89 patients were not sure enough about their family history to give a good indication of the presence of a family history of migraine. Of the 47 patients who had a good knowledge of their family history, 38 reported a positive family history and nine denied any family history of migraine.

Fifty-three of 89 patients (60%) had no complaints of a subjective hearing loss. Eight patients (9%) who described a symptomatic hearing loss had consistently normal audiograms over a follow-up period of 1.4 years to 6.7 years. This subjective-only hearing loss was described as unilateral and fluctuating in five patients; unilateral and stable in two patients; and bilateral and stable in one patient. Five of these subjective-only hearing loss patients had MRI studies. One had an ABR; one had an ABR and CT. The patient who did not have an MRI, ABR, or CT scan had complete resolution of cochlear symptoms with medical treatment of the migraine-related dizziness.

Twenty-eight patients had an objective hearing loss on audiologic testing. In 13 of 28 patients, the loss could be clearly attributed to reasons other than migraine. These included surgery for chronic otitis media including cholesteatoma in three patients; nonsurgically treated chronic otitis media in three patients; surgical procedures for Meniere's disease including an endolymphatic shunt, vestibular nerve section, and intratympanic gentamicin in one patient and endolymphatic shunt with high-frequency hearing loss in one patient; congenital SN hearing loss in two patients; hereditary SN progressive loss in one patient; otosclerosis in one patient; and noise exposure high-frequency loss in one patient. Four of 28 patients had a hearing loss that could be potentially attributed to an origin other than migraine: two patients had objective hearing loss with present or past symptoms compatible with both Meniere's disease and migraine; one patient had bilateral otosclerosis treated with bilateral stapedectomies; one patient had a hearing loss since a young age and therefore a congenital hearing loss could not be ruled out. Eleven of 28 patients had an objective SN hearing loss that could not be attributed to any otologic disease. The pattern of hearing loss seen with these 11 patients can be divided into three groups: *1.* sudden hearing loss, *2.* fluctuating hearing loss without progression over time, and *3.* fluctuating hearing loss with progression greater than 30 dB in one or more frequencies. Two of the 11 patients presented with a sudden hearing loss: the first patient developed a sudden, unilateral hearing loss immediately followed by a headache, just before her first episode of vertigo. The hearing improved over 7 months. The second patient presented with a sudden hearing loss that occurred with the initial episode of vertigo. The hearing loss progressed in a nonfluctuating pattern during the episodes of vertigo. Eight of the 11 patients showed a fluctuating SN hearing loss with no progression, or at most a 30-dB progression at one frequency, during the follow-up period ranging from 4.6 to 17 years (Figs. 4–6). One of the 11 patients showed a progression of the hearing loss in the left ear by 40 dB at 8000 Hz and by 25 dB at 250 and 4000 Hz (Fig. 7).

Aural fullness was described by 50 (56%) of the 89 patients. This aural fullness was unilateral in 32 patients. Unilateral aural fullness was combined with a unilateral subjective hearing loss in 20 patients, a unilateral subjective, fluctuating hearing loss in 17 patients, and a unilateral subjective and objective, fluctuating hearing loss in six patients. Thus 11 patients had subjective symptoms similar to unilateral Meniere's disease (i.e., unilateral aural fullness with fluctuating hearing loss) but without any objective hearing loss by audiogram. Of the six patients with combined unilateral aural fullness and unilateral subjective and objective fluctuating hearing loss, one patient had a concurrent diagnosis of Meniere's disease, one patient had postsurgical otosclerosis, and four patients had no identifiable otologic disease.

Bilateral aural fullness was noted by 14 (16%) of the 89 patients. This was combined with bilateral subjective hearing loss in four of the 14 patients or bilateral subjective, fluctuating hearing loss in two of the 14 patients. None of the 14 had bilateral aural fullness and both subjective and objective fluctuating hearing loss. Four additional patients described a fullness in the head.

Ear pain was described by 17 of the 89 patients. The ear pain was unilateral in seven patients and bilateral in 10. Five of those seven patients with unilateral ear pain

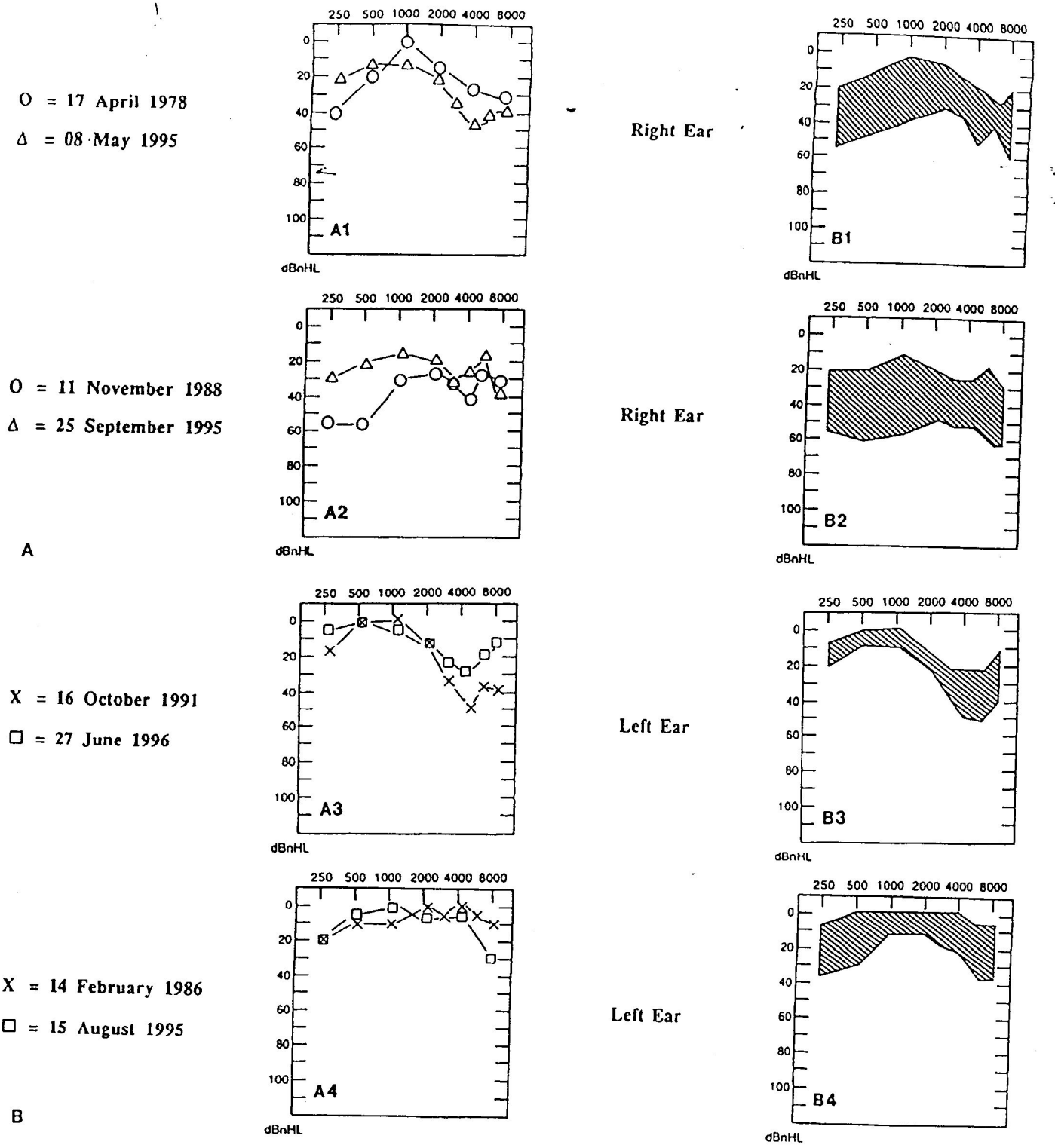

Fig. 4. (A) First and last audiograms of four patients (Panels A1, A2, A3, and A4) diagnosed with migraine-related vertigo and dizziness who suffered unilateral fluctuating hearing loss without progression. Hearing fluctuation during follow-up of these four patients (B) is shown in Panel B1 (17 years), Panel B2 (7 years), Panel B3 (4.6 years), and Panel B4 (9 years), respectively.

also complained of unilateral aural fullness. Five of the 10 patients with bilateral ear pain described bilateral aural fullness. Five of these combined 17 patients also had either myofascial pain syndrome, temporomandibular joint (TMJ) syndrome, or occipital neuralgia.

Phonophobia was noted by 44 (49%) of the 89 patients. The phonophobia was unilateral in 10 patients, and bilateral in 34 patients.

Additional complaints included eight patients with visual symptoms including blurred vision and diplopia,

eight patients who specifically described poor sleeping patterns, six patients with complaints of fatigue or generalized weakness, and three patients who noted the tendency for a leg to buckle under them while walking. Neurologic symptoms, noted by one patient each, were expressive aphasia, dysarthria, extremity weakness, and periorbital numbness. One patient had an episode of a prolonged aura consisting of hemiplegia and was evaluated with MRI and magnetic resonance angiography for possible stroke. These studies were normal, and the prolonged hemiplegia was considered a migraine manifestation. Extremity weakness followed multiple visual auras in one of the three patients with basilar migraine. Expressive aphasia occurred in one patient initially thought to have a seizure disorder, who was eventually diagnosed with migraine.

Concurrent diagnoses that may play some role in the neurotologic symptoms of migraine included three patients with Meniere's disease, four patients with anxiety disorder, 11 patients with depression, five patients with panic attacks, five patients with TMJ syndrome, and two patients with occipital neuralgia. Four patients were believed to have both myofascial pain syndrome and TMJ dysfunction. Two patients had both myofascial pain and TMJ disease. The true incidence of myofascial pain and occipital neuralgia may be underestimated in these results because the role of these disorders in the etiology of ear pain and aural fullness was not fully appreciated at the onset of this study. Other diagnoses singularly noted by one patient each included bipolar disorder, benign paroxysmal positional vertigo, hypertriglyceridemia, fibromyalgia, multiple head injuries, possible seizure disorder, thyroid abnormality, hypoglycemia, and diabetes mellitus.

Previously Diagnosed Conditions and Treatment

Most of the 89 patients in this study were referred for dizziness or vertigo of unknown etiology. Thirty-two of the 89 patients (36%) were diagnosed with some other condition believed to be the cause of the vestibular symptoms. By far the most common prior diagnosis was Meniere's disease (in 75% or 24 of these 32 patients). Three of the 32 patients were thought to have labyrinthitis. Five of the 32 patients were diagnosed with a spontaneous perilymph fistula.

Previous treatments in the 89-patient study group included 12 surgical procedures: four perilymph fistula repairs (one patient had a temporary facial paralysis after exploration), three endolymphatic shunt procedures, one vestibular nerve section, one intratympanic gentamicin treatment, two myringotomies and tube procedures for chronic otitis as a cause of dizziness, and one nasal procedure. Bed rest was tried with one patient suspected of having a perilymph fistula. Vestibular rehabilitation therapy was used in one patient. Prior medical management of the study group included a sodium-restricted diet in 23 patients, diuretic in 26 patients, and vestibular suppressant in 30, including a benzodiazepine of some type in 18 patients; steroids were tried in two patients, glycopyrrolate in two, antibiotics in three, and allergy management in one. Management of contributing disorders included depression in one patient, treated with imipramine; anxiety in one patient, treated with alprazolam; and an unknown condition in one patient, treated with amitriptyline.

Testing

Auditory brainstem response testing was performed on 32 of the 89 patients and interpreted as normal in all 32. A cranial MRI scan using gadolinium with targeted views of the internal auditory canal was performed on 80 of the 89 patients and was normal on all 80. Computed tomography of the temporal bone was performed on 55 of the 89 patients and was normal on all 55.

Electronystagmography was performed on 32 of the 89 patients; ENG was normal in 15 patients and abnormal in 17. One of the 17 abnormal studies was on a patient following vestibular nerve section, revealing an absent caloric response on the postsurgical side. The most common abnormality of the 16 remaining patients with abnormal studies was a unilateral caloric weakness, as seen in seven patients. The second most common abnormality was a bilateral caloric weakness, as noted in six patients. Spontaneous horizontal nystagmus was found in five patients; direction-fixed positional nystagmus in two patients; and horizontal-gaze nystagmus in one patient. Two patients had irregular pendular tracking.

Diagnostic rotary-chair testing was performed on three patients and was normal in all three. Platform posturography was performed on the same three patients and was normal in two. The third patient showed excessive visual dependence for postural stability, with a posterior bias in all positions.

Electrocochleography was performed on eight patients early in this study when patients complained of aural fullness and episodic vertigo without objective hearing loss or with fluctuating hearing loss atypical for Meniere's disease. All eight of these patients were initially considered to have either vestibular Meniere's disease or atypical Meniere's disease and treated with a diuretic and sodium restriction. ECoG was normal in three of eight patients and abnormal in five. Because symptoms of aural fullness and vertigo persisted in these eight patients, a more thorough headache history was obtained, with the change in diagnosis to migraine-related dizziness. When medical therapy was directed at the migraine, symptoms of aural fullness and vertigo either completely resolved or substantially improved. Two of five patients with abnormal ECoGs had symptoms of unilateral aural fullness with episodic vertigo without symptoms of hearing loss; one of these two patients was followed for 2.5 years, the other patient for 6.3 years. Both continue to have normal hearing. The ratio of the summating potential to the action potential (SP/AP) was 77% in the first patient and 50% in the second patient. Another two of the five patients with abnormal ECoGs demonstrated objective bilateral fluctuating hearing loss over the 3.6 and 4.6 years they were followed, respectively, but progressive hearing loss was not observed during that time. The SP/AP ratio was 50% in the more symptomatic ear of one of these two patients and was 50% in the right ear and 60% in the left ear in the other patient. The last patient of the five patients with an abnormal ECoG had persistent symptoms of

episodic vertigo, positional vertigo, nonvertiginous dizziness, aural fullness, and phonophobia following an endolymphatic shunt procedure, vestibular nerve section, and intratympanic gentamicin treatment. The caloric response on ENG testing was absent on the operated side, and the SP/AP ratios were 71% and 90% on two different trials of the symptomatic postoperative ear. All symptoms in this postoperative patient resolved with migraine medical management.

Additional studies performed on these 89 patients included diagnostic studies for multiple sclerosis consisting of visual-evoked response testing in three patients, somatosensory-evoked response testing in two patients, and spinal tap for monoclonal antibodies in one patient. A Holter monitor was used to look for episodic cardiac arrhythmias in two patients, and an electroencephalogram was performed on three patients to test for seizures. One patient had sphenopalatine ganglion block testing for sphenopalatine ganglion neuralgia (Sluder's lower-half headache) as a cause of the ear pain. All these additional studies were normal.

Treatment

Treatment was directed toward the patients' neurotologic symptoms of vertigo or dizziness, aural fullness, and ear pain. The primary treatment focus was the patients' vestibular symptoms. Patients who had significant headaches during the time period of the vertigo or dizziness were advised that their headaches may not improve with the treatment approach as outlined. If headache was a significant concern and the patient desired headache management, consultation with a neurologist was arranged. Thirteen of 89 patients requested consultation with a neurologist.

Dietary changes were recommended to 59 of the 89 patients (66%). This primarily consisted in an elimination of aspartame (NutraSweet); and reduction or elimination of chocolate, caffeine, and/or alcohol. Lifestyle adaptations were recommended in six patients (7%), including such issues as stress reduction, more regular sleeping patterns, and the initiation of regular aerobic exercise. Occasionally, referral to a psychologist for stress reduction techniques was suggested. Vestibular rehabilitation therapy was prescribed for 24 patients (27%): therapy alone was used in two patients and combined with pharmacologic treatment in the remaining 22 patients.

Pharmacologic treatment was used in 79 of the 89 patients (89%). The choice of drug therapy was based on the patient's age, general health issues, history of drug reactions or side effects, sleeping status, and coincident comorbidity factors such as anxiety disorder, panic attacks, or depression. That is, all available information was taken into consideration when any drug was chosen. Most patients had little difficulty tolerating the medications in effective doses. Some patients had such a low tolerance to some medications that different agents had to be tried, alone or in combinations, to achieve effective control of symptoms. The necessity of such a trial process was explained to patients at the initiation of medical management. Two patients privately initiated acupuncture as an adjunctive treatment.

Ten patients were managed without the use of medications. A variety of nonpharmacologic approaches was used in these patients: six were managed with dietary changes alone, one patient combined dietary changes with lifestyle changes and vestibular rehabilitation therapy, one patient combined diet with acupuncture, one patient combined lifestyle changes with vestibular rehabilitation therapy, and one patient used acupuncture alone.

Of the 79 patients treated with medications, benzodiazepines were used alone or in combination with other medications in 71 patients (90%). Clonazepam (Klonopin) a potent, long-acting benzodiazepine, was the most commonly used benzodiazepine; it was used in 68 patients (86%). Alprazolam (Xanax) was used in two patients; lorazepam (Ativan) was used in two patients; and prazepam (Centrax) was used in two patients. Tricyclic antidepressants were used in 33 patients (42%) as the second most commonly used medication. Amitriptyline was used in 29 patients, and nortriptyline in 11 patients. A beta blocker, propranolol, was used in 28 patients. The selective serotonin reuptake inhibitor medications were used in six patients. Sertraline (Zoloft) was used in three patients, fluoxetine (Prozac) was used in two patients, and paroxetine (Paxil) was used in one patient. A calcium channel blocker was used in three patients. Verapamil (Calan) was the calcium channel blocker used in two patients. Diltiazem (Cardizem) was tried in one patient. (Not one of the patients on a trial regimen of calcium channel blocker was symptomatically improved; therefore this class of drugs was discontinued after a clinical trial.) Hormonal management by the patient's gynecologist was used in two patients: estrogen and progesterone were added to the medical management of one patient experiencing perimenopausal symptoms, and the other patient had her birth control medication changed. Both of these patients found that the changes significantly improved the control of their vertigo or dizziness.

Metoclopramide (Reglan) was used adjunctively in one patient, and glycopyrrolate (Robinul) in three patients, for control of nausea accompanying the migraine and/or vertigo. Fourteen patients had been placed on a diuretic when the initial diagnosis was thought to be Meniere's disease or an atypical form of endolymphatic hydrops, but other medications were added when migraine-related dizziness was diagnosed.

Thirty-four (44%) of the 79 patients treated pharmacologically were acceptably managed with a single medication. Twenty-six (33%) patients required a second medication, either singly or in combination. Twelve patients (15%) required three different medications, four patients required four medications, two patients received five different medications, and one patient needed six different medications before achieving control of symptoms.

At the time of optimal control of each patient's neurotologic symptoms, 67% (53 patients) were taking a single medication. Twenty patients (25%) needed the combination of a second medication for symptomatic management, and three patients required the combination of three medications. No patients required more than three concurrent medications for symptomatic control. The dosage of each medication at optimal pharmacologic control of vestibular symptoms is shown in Table III.

TABLE III.
Medication Dosage (mg/d) for Optimal Control of Vestibular Symptoms.

Dose (mg)	Patients (n)
Benzodiazepines	
Clonazepam	
0.125	1
0.25	2
0.5	27
0.75	2
1.0	12
1.25	2
1.5	7
2.0	4
Alprazolam	
0.125	1
0.25	1
Lorazepam	
1.0	1
1.5	1
Prazepam	
30	1
β-Blockers	
Propranolol	
40	3
60	10
120	1
Selective serotonin reuptake inhibitors	
Sertraline	
50	2
Fluoxetine	
20	1
40	1
Tricyclic antidepressants	
Amitriptyline	
10	3
20	2
25	3
30	1
50	1
100	1
Nortriptyline	
10	2
30	1
50	1
60	1
75	2

For patients treated pharmacologically, an effective treatment routine may have taken several weeks to several months while gradually increasing the management dosage up to the therapeutic range. Even dietary management often took several weeks to clear, or significantly improve, symptoms.

At the last follow-up visit, all 10 patients treated nonpharmacologically were continuing their nonmedical treatment. Of the 79 patients treated pharmacologically, 60 were continuing that management at follow-up. Nineteen patients had stopped their medication: eight patients had their symptoms under complete control, seven patients had their symptoms under satisfactory but not complete control, three patients had unacceptable side effects and therefore stopped taking medication, and one patient stopped taking medication because satisfactory control could not be achieved. The 15 patients who stopped taking their medications with symptoms under complete or satisfactory control have been followed up to 291 days without recurrence of symptoms. Thus 75 patients are continuing pharmacologic management or have stopped medications with symptoms under complete or satisfactory control. The duration of medical therapy in these 75 patients ranged from 92 days to 7.2 years, with a median treatment duration of approximately 2 years.

Episodic vertigo was completely resolved in 40 of 74 patients and substantially improved in 28 patients; this represents a 92% success rate of complete resolution or substantial improvement. Three of the 74 patients received moderate control, one patient achieved minimal control, and two patients had no improvement of their episodic vertigo. Positional vertigo, described by 63 patients, was completely resolved in 33 patients and substantially improved in 23 patients; this represents an 89% success rate of complete resolution or substantial improvement. Four of the 63 patients had moderate control, one patient had minimal control, and two patients achieved no improvement of their positional vertigo. Nonvertiginous dizziness, as described by 65 patients, was completely resolved in 31 patients and substantially improved in 25 patients; this represents an 86% success rate of complete resolution or substantial improvement. Five of the 65 patients achieved moderate control, two patients received minimal control, and two patients had no improvement of their nonvertiginous dizziness.

Aural fullness was described by 50 patients, and medical management in 40 patients was assessed as completely resolved in 26 patients and substantially improved in eight patients; this represents an 85% success rate of complete resolution or substantial improvement. Four of the 40 patients noted minimal improvement, and two patients did not feel that medical management had any effect on their aural fullness.

Ear pain was described by 17 patients, and medical management in 16 patients was assessed as completely resolved in seven patients and substantially improved in three patients; this represents a 63% success rate of complete resolution or substantial improvement.

Phonophobia was reported by 44 patients, and medical management in 19 patients was assessed as completely resolved in 15 patients, substantially improved in two patients; this represents an 89% success rate of complete resolution or substantial improvement. One of the 19 patients felt that the phonophobia was minimally improved, and one patient felt that there was no improvement.

No patient in the present study felt that his or her symptoms were worse following medical management. Side

effects of the medications used were usually mild but occasionally occurred in sufficient intensity to limit dosage increase or continuation of that drug. Side effects reported by patients taking benzodiazepines included drowsiness in 15 patients; decrease in mental sharpness in six patients, and depression in two patients, with the following additional side effects, each singularly noted by a different patient: gastrointestinal tract upset, urinelike smell to their forearms, and a vague sense of feeling weird. Side effects of the tricyclic antidepressants included dry mouth in two patients, tachycardia in two patients (one with high doses of amitriptyline, the other with nortriptyline), drowsiness in one patient with amitriptyline, and irritability in one patient with both amitriptyline and nortriptyline. Loss of libido occurred in one patient with propranolol, and one patient taking propranolol developed gastrointestinal tract upset.

DISCUSSION

Migraine is a very common disorder. It has been estimated nationwide to occur in 18% of women and 6% of men.[2] True episodic vertigo has been shown to occur in 26% to 33% of unselected migraine patients seen for headache management in large headache clinics; nonvertiginous dizziness has been reported in 27% to 72% of migraine patients.[13–15] In contrast, Meniere's disease has an estimated frequency in the United States of 15 cases per 100,000 people,[103] or an incidence of 0.015%. Using these data, and making a random assumption that if only 1% of the migraine patients who had episodic vertigo had symptoms severe enough to seek medical evaluation, physicians should diagnose migraine-related dizziness 15 times for every one patient diagnosed with Meniere's disease. If this approximates a true representation, the otolaryngologic literature does not reflect the prominent role migraine-related dizziness should play in the differential diagnosis of vestibular symptoms, suggesting that this disorder is significantly underdiagnosed.

Migraine-related dizziness can present in ways that are similar to the symptom complex described as vestibular or atypical Meniere's disease. Like migraine-related dizziness, these disorders are diagnosed by clinical presentation, as one rules out other diagnosable clinical entities. The occurrence of vestibular symptoms with migraine has been frequently documented in the medical literature.[13–23,26] The reasonably successful result of medical management of migraine-related dizziness gives added impetus to the conscientious pursuit of this diagnosis.

Forty-six percent of the 89 patients in the present study had symptoms of episodic vertigo, sometimes accompanied by nonvertiginous dizziness, without symptoms of hearing loss. This group is consistent with Slater's diagnostic category[20] of benign recurrent vertigo.

Eleven patients in this series had objective hearing loss without identifiable otologic disease. Sudden hearing loss with or without improvement, although typically attributed to viral etiology in a young adult population, has been attributed to a vasospastic event of the cochlear vasculature associated with migraine.[19,23,27,62,63] Viirre and Baloh,[63] in their study of 13 patients with sudden hearing loss attributed to migraine, reasoned that the sudden development of hearing loss over seconds to minutes is more consistent with the pathophysiology of vasospasm than of viral inflammation. They argued that although the role of vasospasm in the production of migraine symptoms is controversial, there is convincing evidence for vasospasm as the primary cause for ophthalmic migraine.[63,64] These patients typically experience transient monocular blindness, with occasional permanent visual loss. Examination of the retinal arteries in patients experiencing ophthalmic migraine have shown vasospasm of the retinal arteries.[65] It seems reasonable that a similar pathophysiology could occur in the arteries supplying the cochlea.

Eight patients in the present study had objective fluctuating hearing loss with no progression or, at most, 30-dB progression in one frequency, at follow-up. These fluctuations were as small as 10 dB or as large as 40 dB. Fluctuating hearing loss without progression has previously been noted in patients with migraine-related dizziness.[19,23,27,62] Lipkin et al.[62] described one patient who had a history of migraine with aura for several decades who presented with two episodes of sudden hearing loss; the individual's hearing returned to baseline on both occasions. Parker[27] noted that three (19%) of his 16 patients with migraine-associated dizziness described transient hearing loss. Love,[19] in his study of six patients with neurotologic symptoms of migraine, described one patient who presented, first, with a single episode of a fluctuating hearing loss and then, with episodic vertigo accompanied by aural fullness. A single audiogram was normal. Another patient showed an SN fluctuating hearing loss on three separate occasions. Hearing was normal at 2-year follow-up audiometry. Olsson[23] noted a fluctuating hearing loss in 60% of his 50 patients with basilar migraine, although the presence of progression, or stability of hearing over time, was not noted.

The feature that sets hearing loss in these migraine patients apart from the hearing loss seen in classic Meniere's disease is the pattern of relative stability in the migraine patient over several years of symptomatic vertigo. Stahle[104] and Hedgecock[105] observed several hundred patients with nonsurgically treated Meniere's disease and reported that the hearing loss of these patients tended to stabilize after 3 years of symptoms at a pure-tone average of 50 to 60 dB. The eight patients in the present study with a diagnosis of migraine-related dizziness with objective fluctuating hearing loss had a hearing loss similar to early Meniere's disease and could not be easily distinguished from early Meniere's disease until those patients had been followed for several years. The argument can be made that these patients have classic Meniere's disease attributable to endolymphatic hydrops, and that the cochlear component has been so well controlled with medical management that the natural history of the progressive hearing loss associated with Meniere's disease has been averted. If the vertigo component had also been well controlled, this argument would seem appropriate. These eight patients, however, continued to experience sufficient dizziness to seek additional treatment for their vertigo. All eight patients had been managed with a sodium-restricted diet (sodium intake below 2000 mg per day), along with a diuretic. A migraine approach was initiated because of persisting vestibular symptoms,

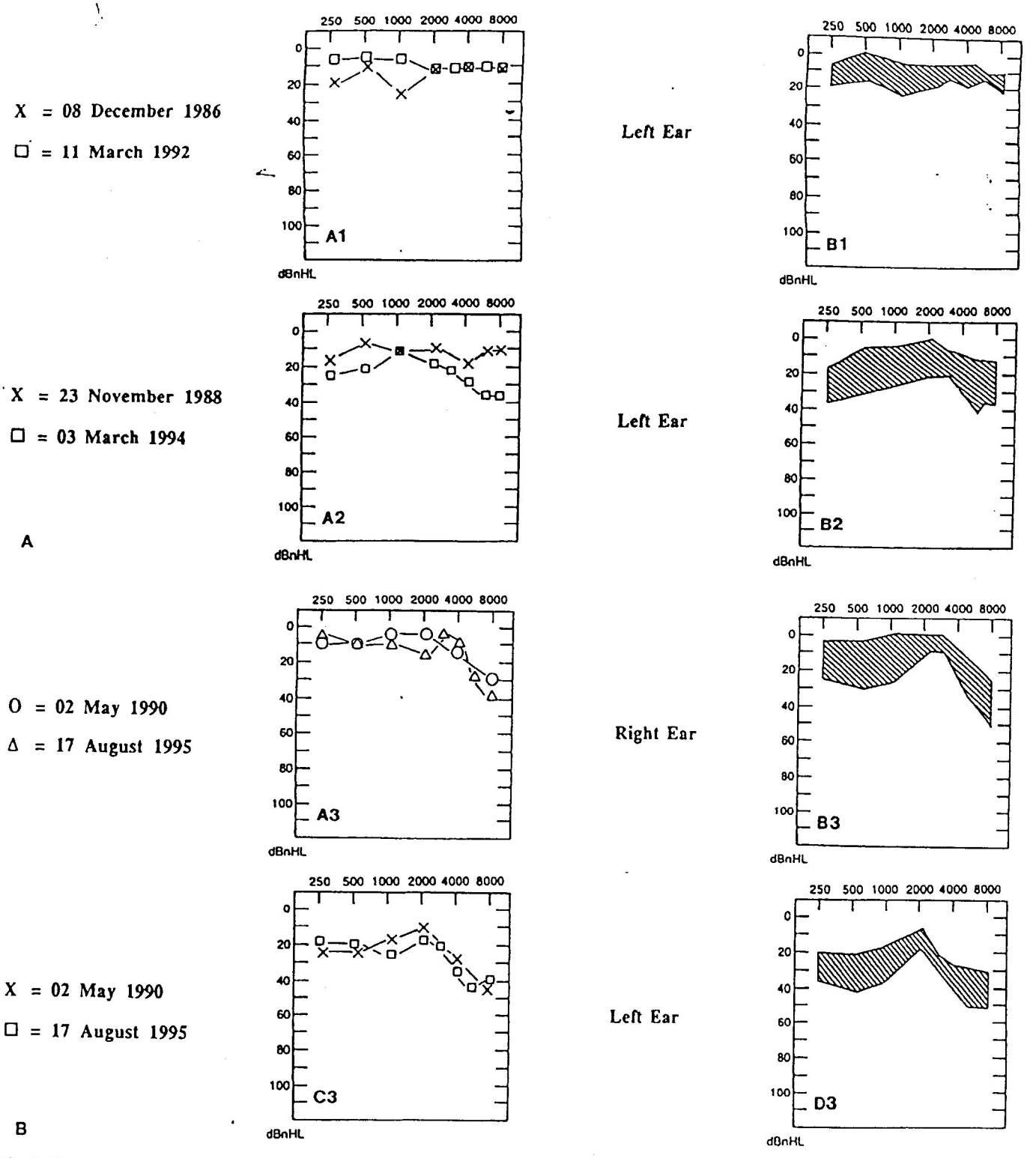

Fig. 5. First and last audiograms of three patients diagnosed with migraine-related vertigo and dizziness who suffered unilateral (Panels A1 and A2) or bilateral (right ear, Panel A3; left ear, Panel C3) fluctuating hearing loss without progression. Hearing fluctuation during follow-up of these three patients is shown in Panel B1 (5.2 years), Panel B2 (9 years), and the 4.6-year follow-up of the third patient in Panels B3 (right ear) and D3 (left ear).

supported by a history consistent with migraine. The change to, or addition of, a migraine approach was effective in achieving either complete control or substantial improvement in all eight patients. Whether this fluctuation over years without significant progression is due to neural events within the cochlea or vascular vasospasm of a degree that avoids permanent neural injury is presently open to speculation.

The pattern observed in one patient of the present study is that of an SN hearing loss that fluctuated and progressed to more than 30 dB in one frequency and has not previously been described in the literature on neurotologic symptoms of migraine. It is not, however, inconsistent with prior observations. SN hearing loss, as a one-time observation without description of prior audiograms, has been reported in patients diagnosed with migraine-related dizziness.[27] Parker[27] noted abnormal hearing by audiogram in 12 (75%) of his 16 patients with neurotologic symptoms associated with migraine. Seven of 12 patients had identifiable otologic disease that could explain their abnormal hearing. Five of the 12 patients had no identifiable ear disease. Parker suggested migraine as a probable origin of the hearing loss.

Hearing loss in the present study was consistently associated with the vestibular symptom of episodic vertigo. The 15 patients who described nonvertiginous dizziness without concurrent episodic vertigo, also denied any cochlear symptoms with the exception of one patient who also had chronic middle-ear disease.

Electronystagmography testing was performed on 32 of 89 patients (36%) in the present series. A normal study was found in 15 of the 32 patients (47%), and an abnormal study in 17 patients (53%). The most common abnormal findings, in the order of most to least occurrence, were unilateral caloric weakness, bilateral caloric weakness, spontaneous horizontal nystagmus, direction-fixed positional nystagmus, irregular pendular tracking, and horizontal-gaze nystagmus. Only two patients had ENG abnormalities suggestive of central disease; both patients showed irregular pendular tracking, a relatively soft central sign. A mixture of normal ENG studies, along with abnormal studies with a preponderant peripheral pattern, is consistent with the findings of previous authors.[10,14,16,18,20,22-27]

True objective vertigo, especially when presenting in a spontaneous or positionally induced pattern, has traditionally been considered highly suggestive for vertigo of a peripheral origin.[106,107] The addition of unilateral ear symptoms such as fluctuating hearing loss, aural fullness, or ear pain is considered further indication of peripheral end-organ disease.[107] Audiologic confirmation of a unilateral hearing loss, especially fluctuating, has been considered very strong evidence of peripheral disease and suggestive for classic Meniere's disease.[108] ENG abnormalities including unilateral caloric weakness, bilateral caloric weakness, horizontal gaze, and direction-fixed positional nystagmus are considered manifestations of peripheral vestibular dysfunction.[109] Migraine as the cause of vertigo of the type described in the present study is counter to many concepts that have been maintained through the years in the otolaryngologic literature. How, then, can these time-honored concepts of peripheral dysfunction be reconciled with a pathologic entity that is central dysfunction. There are several possible theories that can be proposed to explain this dichotomy.

One theory is that migraine-related vertigo or dizziness is a centrally mediated abnormality of peripheral vestibular function. The function of the peripheral vestibular neuroepithelium has been shown to be modulated by efferent fibers synapsing in a complex plexus on the neurosensory cell bodies.[36,110] The anatomy of vestibular efferent neurons is not known, although several studies[110,111] have shown that acetylcholine (ACh) is the primary neurotransmitter of the vestibular efferent system. These efferent neurons are thought by Ishiyama et al.[110] to modulate the afferent function of the vestibular neuroepithelium through the effects of the neurotransmitters, CGRP and ACh. They hypothesized that with efferent stimulation, CGRP would up-regulate synthesis of the nicotinic ACh receptor and thereby alter the sensitivity of primary afferent neurons to ACh. Prolonged application of CGRP has been noted to affect the temporal pattern of afferent discharge by the primary afferent neuroepithelium, supporting this hypothesis.[112] This pathophysiology of migraine-related dizziness, proposed in 1992 by Cutrer and Baloh,[10] would be consistent with the peripheral-type abnormal ENG findings seen in previously published articles,[10,14,16,18,20,22-27] as well as in the patients reported in the present study.

Another theory of the central effect on vestibular function can be hypothesized as a modulation of neural input through the afferent vestibular pathways. This is more analogous to theories of the hypersensitivity syndromes of photophobia, phonophobia, and increased sensitivity to pain ("ice-cream headache") that occur with migraine. Neural pathways linking the central noradrenergic locus ceruleus with the vestibular afferents have been identified.[82] These central pathways have been shown to inhibit activity in the vestibular nuclei through modulation of the resting activity of central vestibular neurons, mediated through noradrenergic α_2-receptors.[83] Serotoninergic receptors have also been identified within the vestibular nuclei.[86] Serotonin can modulate the sensitivity of vestibular input in a variety of excitatory and inhibitory ways including biphasic patterns,[87,88] depending on the presence of inhibitory 5-HT_{1A} receptors or excitatory 5-HT_2 receptors.[87,89] Thus either serotoninergic or noradrenergic central pathways could alter the gain of afferent vestibular input, even though the peripheral end-organ functioned normally and symmetrically. Since eye movements are used to record vestibular function, modulation of the vestibular afferent input through these central pathways could alter the vestibuloocular response in an asymmetric or symmetric pattern. ENG function could be normal, as it was in approximately half (15) of the 32 ENG patients in the present series, or it could show a variety of abnormal findings including unilateral or bilateral caloric weakness, horizontal-gaze nystagmus, or positional nystagmus. If the gain in vestibular input was increased in a symmetric pattern, there would be a mismatch between vestibular sensation and visual and/or somatosensory perception of motion.[14] This would most likely be perceived as lightheadedness, or nonvertiginous dizziness. When the mismatch is greater, as with fast movement, a greater sense of dysequilibrium would be experienced, causing motion sickness or positional vertigo. If the gain of vestibular input were modulated in an asymmetric fashion, true vertigo would be the expected perception.

Permanent vestibular dysfunction could also occur as a result of vasospastic events similar to what has been proposed as a cause of permanent hearing loss, especially, sudden hearing loss, associated with migraine.[14,15,27] It is

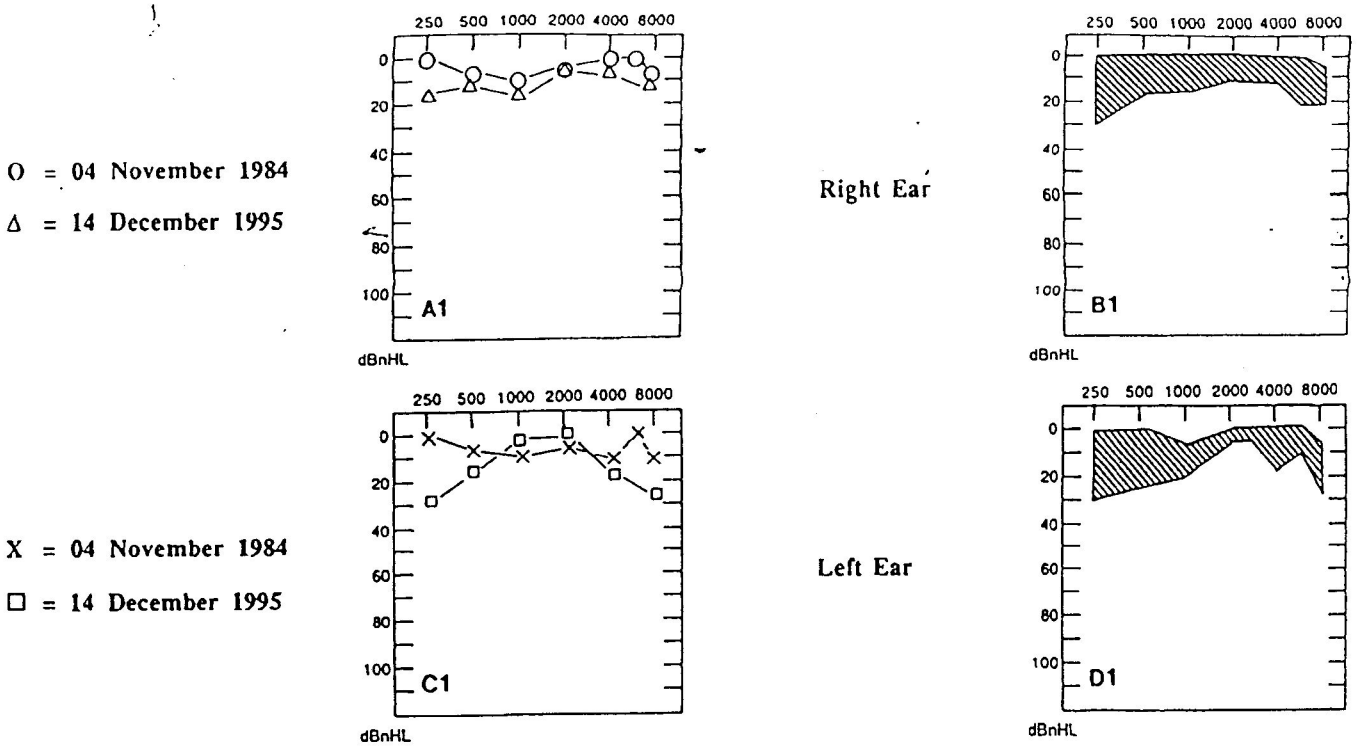

Fig. 6. First and last audiograms of a patient diagnosed with migraine-related vertigo and dizziness who suffered fluctuating bilateral hearing loss without progression (right ear, Panel A1; left ear, Panel C1); hearing fluctuation during the 11-year follow-up of this patient is shown in Panel B1 (right ear) and Panel D1 (left ear).

unlikely that permanent vestibular dysfunction, attributable to a vasospastic event, is the sole cause of symptoms in migraine-related dizziness, since if this were the case, patients would be expected to compensate for the unilateral vestibular loss with or without vestibular rehabilitation therapy. Vestibular rehabilitation remains a useful modality for treatment of dizziness attributable to migraine, although rarely used in the present study without adjunctive medication treatment (two of 89 patients).

The origin of hearing loss and vestibular dysfunction may be different depending on the relationship of these symptoms to the various stages of migraine. Sudden hearing loss and spontaneous vertigo preceding a migraine headache, especially if associated[17] with other aura symptoms, are likely to have a vasospastic component like that observed with ophthalmic migraine. Vertigo or nonvertiginous dizziness not associated with headache, especially the long-duration pattern of hours or even days to months, is unlikely to have a similar pathophysiology as an aura. Neural events involving modulation abnormalities of the endogenous pain control system (locus ceruleus and raphe nuclei) are more consistent with these long-duration vestibular symptoms. Since many patients with migraine-related dizziness can have episodic vertigo with or without an associated headache, in both an aura time span and longer periods of vertigo, it is probable that a patient can have different pathophysiologic events causing the migraine-related vertiginous symptoms. Therefore treatment strategies must address the full spectrum of migraine symptoms.

Proposed management of migraine-related vestibular symptoms has evolved over the course of the present study, taking a multifactorial approach that included dietary changes (or elimination of migraine triggers), management of sleep disturbances, physical therapy, and pharmacologic treatment. Dietary changes were directed toward the elimination of foods or chemical additives that have been associated with the precipitation of migraine. In the early part of this study sleep disturbances were infrequently mentioned spontaneously by patients during the initial interview, but as the study progressed, sleep disturbance quickly became part of the initial interview and its management an integral part of therapy, as many patients voiced improved sleeping patterns with pharmacologic treatment of migraine-related vestibular symptoms. More specifically, better sleeping patterns frequently occurred concomitantly with effective drug dosing. Pharmacologic management was initiated with single-drug therapy, the choice of drug depending on multiple factors including history of adverse drug reactions or drug sensitivities, sleep patterns, patient age, and the presence of anxiety, panic attacks, and/or depression. Patients complaining of significant ear pain or aural fullness often manifest physical examination findings consistent with myofascial pain syndrome or related abnormalities. Physical therapy was bidirectional—balance therapy and chronic pain management—because patients receiving therapy for their balance also had findings consistent with varying degrees of myofascial pain syndrome, occipital neuralgia, and/or TMJ dysfunction. Early in the present study, physical therapy was added after the patient reached an effective drug regimen if symptoms of dysequilibrium or positional

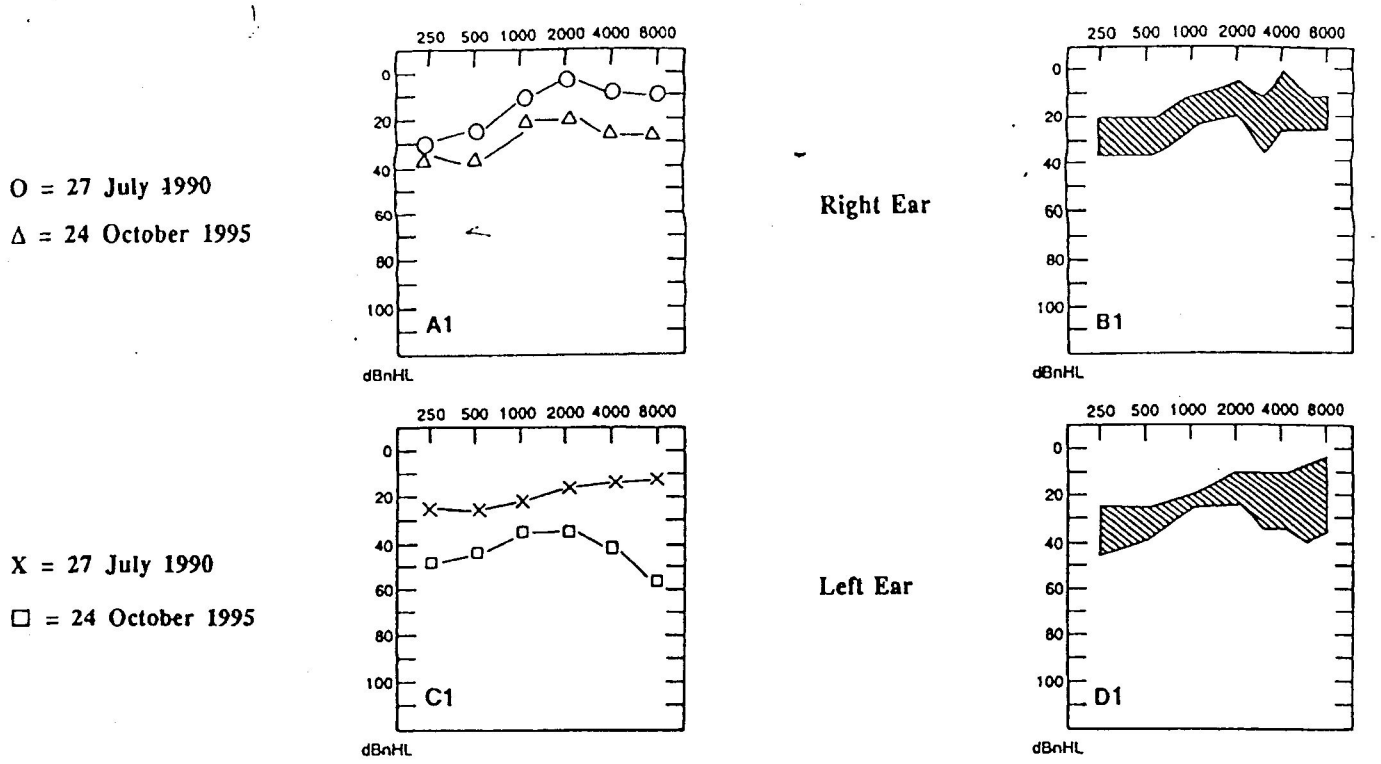

Fig. 7. First and last audiograms of a patient diagnosed with migraine-related vertigo and dizziness who suffered bilateral fluctuating hearing loss with progression (right ear, Panel A1; left ear, Panel C1); hearing fluctuation during the 5-year follow-up of this patient is shown in Panel B1 (right ear) and Panel D1 (left ear).

vertigo were not effectively controlled with medication. As the study progressed, physical therapy was begun as part of the initial management when physical findings were suggestive of myofascial pain, occipital neuralgia, and/or TMJ dysfunction.

The drugs used in the present study for the management of migraine-related dizziness and vertigo include many of the drugs used in the prophylactic management of migraine headache, concomitantly with the benzodiazepine class of drugs. The prophylactic drugs used included the β-adrenergic receptor blockers (propranolol), tricyclic antidepressants (amitriptyline, nortriptyline), selective serotonin reuptake inhibitors (sertraline, fluoxetine, paroxetine), and calcium channel blockers (verapamil, diltiazem). The effectiveness of these drugs in migraine management was often a result of discovering actions unrelated to the agent's original clinical purpose.[113] Evidence presented by Raskin[113] suggested that propranolol's antimigraine effect is mediated by an action other than, or in addition to, β-receptor blockade. The effect of amitriptyline is probably not as an antidepressant. It has been suggested that the antimigraine effect of both propanolol and amitriptyline is mediated through stabilization of serotoninergic transmission.[113]

Two of the drugs described in the literature as effective in the management of migraine-related dizziness are pizotifen[21,22] and amitriptyline.[21] Both of these drugs have been shown to be potent 5-HT_2 receptor antagonists, although it is not clear whether this is their only mechanism of action, since they both have other effects.[70] In addition, antidepressants have been shown to block 5-HT reuptake[30] and decrease postsynaptic adrenergic beta receptors, consistent with a strong interaction between the noradrenaline and 5-HT systems.[67] Calcium channel blockers inhibit 5-HT release, and beta blockers modulate serotoninergic neurons.[30]

CGRP, one of the two neurotransmitters identified at the synaptic cleft between the vestibular end-organ and vestibular efferents, has been identified as a mediator of sterile neurogenic inflammation.[30] Antidromic stimulation of the trigeminovascular fibers releases CGRP along with substance P from sensory C-fibers, which interact with the blood vessel wall producing dilation, plasma extravasation, and sterile inflammation. Elevated CGRP levels have been found in the jugular blood during a migraine attack, and 5-HT_{1D} receptor agonists have been found to reduce CGRP to control levels concurrent with the abortion of the headache.[114] Although the anatomy of the vestibular efferents is not known, it is plausible that drugs that function as 5-HT_{1D} receptor agonists play a role in modulating CGRP at the vestibular efferent nerve terminal in much the same way as they affect the trigeminovascular terminals on intracranial blood vessels.

Clonazepam, although use is limited in migraine prophylactics,[115] has been used extensively in the management of chronic facial pain,[116] TMJ, myofascial pain,[117] and trigeminal neuralgia.[118] Clonazepam, as with all the benzodiazepines, expresses its activity at the $GABA_A$ receptor site.[119] GABA receptors have been found in multiple areas of both the central and peripheral vestibular system. In the peripheral vestibular system, GABA has been implicated as a vestibular hair cell neurotransmitter[97] and GABA re-

ceptors have been identified in most vestibular ganglion cell bodies.[95] Within the central vestibular pathways, GABA receptors have been identified within synapses between Purkinje's cells of the anterior cerebellar vermis and the vestibular nuclei neurons, synapses between commissural vestibular neurons and medial vestibular nucleus neurons, and synapses between inferior olive neurons and lateral vestibular neurons.[36] Drugs that function to modulate these GABA receptors would seem well suited to alter the activity within the vestibular afferents.

Clonazepam is a potent, long-acting benzodiazepine. It takes 1 to 2 hours after oral administration to reach maximum concentration,[118] so it is not well suited for treatment of acute attacks. However, its long half-life of 24 to 36 hours[118] makes it ideal for regular use as a prophylactic medication. (Dosing increases should not be made more frequently than every 2 weeks because it takes 12 days of regular use to reach a steady-state concentration.[118])

Patients with migraine-related dizziness present with a diverse complex of symptoms, thus prohibiting a focused-protocol approach to clinical management. There are, however, guidelines that can be suggested based on the approach taken in the present study. These treatment guidelines have several steps. Explanation of migraine as the cause of the vestibular symptoms is step 1. This includes a discussion of diagnosis with the patient, the rational for that diagnosis, and a realistic appraisal of treatment expectations. Migraine is not a disease that can be cured; thus the goal of management is minimization of disabling symptoms to allow the patient to live a life as normal as possible. It is often helpful to elicit the patient's involvement in the treatment and encourage his or her active involvement in discovering precipitating factors.

Nonpharmacologic control of dietary items that have been identified as precipitators of migraine[120] is step 2. The food items most often identified in the present study were aspartame (NutraSweet) and chocolate. Stress has been frequently identified as a precipitator of migraine,[120,121] and such a relationship can be discussed with patients, although specific stress management is reserved for patients in whom stress is considered to play a major role. Sometimes, when symptoms were not disabling, or the patient chose not to use medications, a trial of avoidance of precipitating factors and management of stress issues was tried as the treatment of choice.

Pharmacologic management is step 3. The major concerns of drug treatment are side effects, drug interactions with each other as well as with medications the patient might be taking for other conditions, and the dosage range needed for migraine control. These issues go beyond the scope of this study, but a good primer on side effects and dosage ranges was given in a recent review by Schulman and Silberstein.[122]

The patient's sleeping patterns should be considered in the choice of initial drug therapy. Several studies have recognized the relationship between sleep and migraine,[13,123] and it has been suggested that the neurophysiologic disregulation of sleep may be linked to the development of migrainous episodes.[124,125] Both amitriptyline and clonazepam are associated with changes in sleeping patterns,[119,122] and if there are no contraindications to their use, either of these medications would be a reasonable choice for a patient with poor sleeping patterns. It was frequently noted by patients in the present study that dizziness or vertigo was brought under control concurrently with improved sleeping patterns. When sleeping patterns were not a concern, or for those patients who became excessively sedated with clonazepam or the tricyclic antidepressants, beta blockers, calcium channel blockers, or the selective serotonin reuptake inhibitor class of drugs was an option.

In the present study, treatment dosage was initiated at a low concentration and increased gradually until successful management of symptoms or the development of annoying side effects. This dosage was usually increased every 2 to 4 weeks. It was observed that most patients developed a sedation tolerance, and if started low enough and advanced slowly enough, a therapeutic dosage could be achieved without excessive sedation.

In general, single-drug therapy was the ideal choice in the present study, but for some patients better control of symptoms with fewer side effects was achieved with a combination of medications. Fifty-three (71%) of the 75 patients successfully managed with medication were controlled with a single drug, albeit not without a trial to find an appropriate medication at an ideal dose. Twenty (27%) of the 75 patients were managed with two drugs in combination, while two patients received three different medications used concurrently. The primary concern of multiple-drug therapy is combinations that do not have overlapping side effects (especially sedation overlaps). Beta blockers and calcium channel blockers are often combined with clonazepam or the tricyclic antidepressant class of drugs. Occasionally, selective serotonin reuptake inhibitor drugs are combined with clonazepam to counteract its sedating side effects.

Duration of drug therapy is difficult to predict. The general goal is to continue medication only as long as needed using the lowest effective dosage. Once symptomatic control is reached, that dose schedule should be continued for approximately 4 to 6 months and then gradually tapered. The drug is tapered at least as slowly as it was started, or until the patient redevelops symptoms of dizziness or vertigo. The dose is then increased, returning back to the lowest dose that controlled symptoms, and continued at this level for another several months; then a tapering trial is retried. This approach is continued until the patient is completely off the medication. Patients often develop transient symptoms such as dizziness or sleeplessness when medications are tapered, which may be due to drug withdrawal, not a recurrence of migraine-related dizziness. Therefore patients in the present study were encouraged to persist with the lower dosage for several days, whereupon symptoms typically resolved. Often, patients were so reluctant to reexperience the disabling vertigo or dizziness that they were hesitant to attempt a withdrawal schedule. If a low dose was effective and the patient was not experiencing any adverse side effects, long-term drug therapy was continued. Sixty of the 75 patients (80%) successfully managed with medication were continuing the use of such at the time this study was compiled. Fifteen of the 75 patients (20%) were able to taper,

then discontinue, their medication with symptoms remaining under complete or satisfactory control.

Physical therapy and vestibular rehabilitation therapy comprise step 4. Patients complaining of ear pain or ear fullness along with physical signs of myofascial pain syndrome or occipital neuralgia are good candidates for physical therapy. Balance rehabilitation therapy is used primarily for the treatment of baseline instability or motion-induced vertigo or instability. It is not used for the symptoms of spontaneous vertigo. Twenty-two of the 24 patients (92%) treated with vestibular rehabilitation therapy in the present study received this therapy in combination with pharmacologic management. Early in the study a rehabilitation approach had been initiated with several of these patients, but they were so motion intolerant that they could not comply with the recommended exercises. The addition of medication, although it did not necessarily resolve their symptoms, often reduced the degree of motion intolerance such that each patient could then successfully complete a balance rehabilitation approach. Patients who had completely resolved their imbalance or motion-induced vertigo with medications were not routinely treated with balance rehabilitation; thus it is not known whether the addition of a rehabilitation approach could have allowed a more rapid or successful withdrawal from the use of medication.

Clonazepam, as a potent benzodiazepine, is used to treat generalized anxiety disorders and panic attacks.[126] Of the 89 patients in the present study, nine had anxiety or panic attacks along with migraine; therefore it is difficult to ascertain whether the benefit received from clonazepam was relevant to the migraine disorder or, instead, was the result of the modulation of anxiety or panic attacks. Although clearly separate entities, generalized anxiety disorders and panic attacks have been considered comorbidity disorders with migraine.[127,128] Although anxiety or panic attacks were considered a possible consequence of migraine, a recent longitudinal study[128] suggested that migraine and panic disorder might share common predispositions. In their study, Breslau and Davis[128] found that persons with a history of migraine were 12 times more likely to develop panic disorder than those with no history of migraine. Migraine patients were also found to have an increased incidence of major depressive disorder,[128–130] with the Breslau and Davis study[128] showing a fourfold increase of major depression in patients with migraine. The acknowledgment of these comorbidities does not necessarily implicate a common pathophysiology, although there are some interesting similarities in serotonin neurochemistry with migraine and that of depression; low levels of platelet 5-HT and low maximum velocity for 5-HT uptake have also been associated with both depression and migraine attacks.[129]

The association of migraine, especially migraine-related dizziness, with panic attacks is complicated by the inclusion of dizziness as one of the symptoms occurring with panic attacks. The criteria outlined by the American Psychiatric Association for diagnosis of panic attacks requires, among other requirements, the presence of at least four of 13 listed symptoms, dizziness or unsteady feelings being one of those symptoms.[131] Vestibular function has not been well studied in patients with panic attacks, but one study found vestibuloocular abnormalities in all 19 patients studied, when using the vestibular autorotation test.[132] The time-duration of dizziness may be one way to differentiate between dizziness attributable to panic attacks and dizziness attributable to other causes including migraine, although considerable overlap occurs. Symptoms attributable to panic attacks, including dizziness, generally resolve within 10 to 30 minutes.[131] The 10- to 30-minute time-durations were not specifically pursued in the present study, but 30 of the 89 study patients (34%) had dizziness or vertigo lasting less than 60 minutes.

Anxiety, panic attacks, and depression comorbidities have important implications for treatment. For the migraine patient with depression, tricyclic antidepressants are useful. The use of beta blockers is not a desirable option in a patient with migraine and depression. Patients with migraine-related dizziness or vertigo and anxiety disorders or panic attacks are appropriate candidates for clonazepam. The selective serotonin reuptake inhibitors can be used for migraine associated with both panic disorder and with generalized anxiety disorders.

Patients with symptoms compatible with migraine-related dizziness, but who have previously undergone surgical management for suspected otologic disease, present particular difficulties. The most common examples of previous surgical management seen in the series of patients presented in this study included endolymphatic shunting for vestibular or suspected early classic Meniere's disease and perilymph fistula (PLF) repair (spontaneous PLF or poststapedectomy PLF). Several features of migraine made the distinction between migraine and PLF symptoms particularly difficult. Physical activity can be an aggravating factor for migraines and was included in the IHS diagnostic criteria as one of the diagnostic features of migraine.[4] Childbirth is also recognized as an event that can be associated with the precipitation of migraine,[133] although hormonal and psychological issues were implicated.

Of particular importance is the need for caution in attributing temporary improvement in migraine-related symptoms to the direct effect of any surgical procedure on the function of the inner ear, especially when evaluating the improvement in dizziness or vertigo following tissue packing of the round and oval window and endolymphatic shunting. For reasons not clearly elucidated, migraine is often improved following surgery. Graham[133] cautioned care in the assessment of changes in migraine symptoms following surgery, when he said: "This period of freedom from headache following any major operation, illness or accident, has led to misconceptions regarding specific relief to migraine by hysterectomy, gall bladder and colon surgery. It should be recalled in evaluating any new surgical procedures designed for migraine relief." Caution may be equally applicable to the assessment of migraine-related vertigo and dizziness following inner-ear surgery.

CONCLUSION

Migraine is a common neurologic disorder affecting 6% to 18% of the adult United States population. It is characterized by headache and commonly accompanied by neurologic symptoms including episodic vertigo, posi-

tional vertigo, and nonvertiginous dizziness. These vestibular symptoms can occur in a wide variety of patterns: some are defined by a consistent symptom complex such as benign recurrent vertigo, or basilar migraine, while others are best described by the all-inclusive term migraine-related dizziness. Complaints of hearing loss are often absent; but when they occur they frequently present with a fluctuating pattern, accompanied by aural fullness similar to that of early Meniere's disease. The absence of significant progressive hearing loss is the major differentiation between the fluctuating hearing loss attributable to migraine and the fluctuating hearing loss attributable to Meniere's disease.

Noradrenergic (locus ceruleus) and serotoninergic (raphe nuclei) pathways within the CNS have been identified which function to modulate the intensity of incoming sensory input. External influences such as dietary changes or physical exercise, or internal changes related to sleep or hormonal cycles can initiate a malfunction within these endogenous pain control pathways that can cause an increase in the gain of these incoming sensory signals. Neural connections from the vestibular system to these same endogenous pain control pathways have been identified. Changes in the gain of afferent vestibular input may cause the perception of motion intolerance, spontaneous vertigo, or unsteadiness depending on the speed and asymmetry of the change in input gain. These same symptoms could also occur as the result of efferent modulation of vestibular end-organ sensitivity.

The medical management of migraine-related vestibular symptoms optimally includes a multifaceted approach modeled from the literature describing prophylactic control of migraine headache. This approach includes modulation of precipitating factors such as elimination of certain food substances, stress management, sleep improvement, vestibular rehabilitation therapy, and pharmacologic therapy. Drugs used include those established for use in the prophylactic management of migraine headaches as well as benzodiazepines, particularly clonazepam, which exerts its effect on GABAinergic receptor sites found in multiple areas of the peripheral and central vestibular system.

The favorable results of this medical approach to vertigo and dizziness associated with migraine lends support to the validity of the diagnosis of migraine-related dizziness. Complete resolution or substantial improvement of the vestibular symptoms attributable to migraine in the 89 patients reported in the present study was achieved in 92% of the 74 patients with episodic vertigo, 89% of the 63 patients with positional vertigo, and 86% of the 65 patients with nonvertiginous dizziness.

The symptoms of episodic true vertigo, especially when accompanied by fluctuating hearing loss and aural fullness, have traditionally indicated peripheral end-organ disease within the cochlea. Electronystagmography abnormalities of spontaneous nystagmus, direction-fixed positional nystagmus, horizontal-gaze nystagmus, and unilateral and bilateral caloric weakness have all supported the diagnosis of end-organ disease. By changing the gain of vestibular afferent input or changing the sensitivity of vestibular neuroepithelium via efferent connections, a migrainous neurologic disorder can produce symptoms and vestibular test results that look like end-organ dysfunction. Vasospastic events attributable to migraine may also cause both temporary and permanent changes in end-organ vestibular and cochlear function.

The diagnosis of vertigo and dizziness relies primarily on the identification of certain patterns based on history, physical examination, and test results of cochlear and vestibular function along with the elimination of identifiable conditions such as acoustic tumors through imaging or electrophysiologic studies. The favorable response of migraine-related vestibular symptoms to a medical approach, and the frequent occurrence of this condition, make migraine a diagnostic entity that should be pursued before undertaking a surgical procedure on the peripheral end-organ of the inner ear. Management of migraine requires familiarization with the effects and adverse reactions of medications that have not been in the traditional armamentarium of the otolaryngologist. As specialists in the management of vertigo and dizziness, it is a skill that we must acquire.

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