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The Meniere attack: An ischemia/reperfusion disorder of inner ear sensory tissues ☆,☆☆

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ABSTRACT

We believe Meniere attacks arise as a chance association of endolymphatic hydrops and vascular risk factors for intracerebral ischemia. Hydrops acts as a variable Starling resistor upon the inner ear vasculature that is capable of inducing ischemic attacks only in people with reduced perfusion pressure in the ear. The unique characteristics of the attacks (loss of vestibular response and hearing acutely followed by a return to apparent normalcy over hours) are explained by the differential sensitivity of the inner ear tissues to transient ischemia, with the sensory tissues (dendrites, hair cells) vulnerable to hours-long ischemia/reperfusion injury, and the stria vulnerable to ischemia due to its high metabolic rate. Permanent hearing loss and vestibular damage after many attacks would result when small areas of irreversible sensory cell damage accumulate and become confluent.

This theory is supported by the strong correlation of hydrops with Meniere attacks, the finding that autoregulation of cochlear blood flow is impaired in the hydropic ear, and studies demonstrating that symptoms and signs in people and in animal models vary with conditions that alter perfusion pressure in the inner ear. Induction of Meniere attacks in animal models requires both hydrops and a mechanism that reduces perfusion pressure, such as epinephrine injection or head dependency. There is a strong clinical association between Meniere attacks and disorders that increase the risk for cerebrovascular ischemia, such as migraine. The excitable tissues in the sensory structures have long been known to be more vulnerable to ischemia than the remaining aural tissues, and are now known to be vulnerable to excitotoxicity induced by ischemia/reperfusion. This correlates well with autopsy evidence of damage to dendrites and hair cells and with strial atrophy in late Meniere disease cases.

If this hypothesis is confirmed, treatment of vascular risk factors may allow control of symptoms and result in a decreased need for ablative procedures in this disorder. If attacks are controlled, the previously inevitable progression to severe hearing loss may be preventable in some cases.

Introduction

Meniere disease is an idiopathic aural disorder that is defined as recurrent self-limited attacks of acute hearing loss, tinnitus and vertigo, which are followed by the gradual development of deafness in the affected ear [1]. The inner ear is a delicate membranous structure filled with endolymph and suspended in perilymph within a convoluted bony cavity of the temporal bone. In people with Meniere disease the affected membranous labyrinth is found to be dilated and endolymph is increased in volume with respect to perilymph, called endolymphatic hydrops (EH). There is no definitive objective test for Meniere disease other than finding EH at autopsy; diagnosis is based on the characteristic attacks and clinical course. The presence of attacks meeting 1995 American Academy of Otolaryngology/Head and Neck Surgery (AAOHNS) criteria for Meniere disease is highly specific for the presence of EH [1]. Since the first linkage of EH and Meniere disease in 1938 [2], a variety of mechanisms have been proposed to explain the attacks and the progressive deafness, but no answer has explained all aspects of the disorder, and no treatment based on these theories has proven capable of controlling the progression of the disease. A model that fully explains the condition is still needed.

An adequate model must provide explanations for all the key components of the disorder, including symptoms, signs, pathology, and epidemiology. The symptoms and signs of Meniere attacks (MAs) are well known [1,2]. During spells the affected ear has an

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acute, widespread but incomplete loss of function. There is aural fullness and a roaring tinnitus in the ear that corresponds to an acute hearing loss, usually in the low frequencies. There is profound vertigo with vomiting that is associated with a decrease in caloric responsiveness in the affected ear, and a horizontal-rotatory nystagmus is visible. This continues for 20 min to several hours, with a complete resolution of symptoms as the attack ends. Attacks recur repeatedly. Although each attack appears to be reversible, over time the affected ear gradually loses hearing and balance function. The ear will usually "burn out" with cessation of vertigo spells when the hearing loss becomes severe, but often some residual hearing is still detectable. In addition to the classic MA, Meniere patients experience other forms of dizziness due to this progressive damage, such as benign positional vertigo and the dizziness prior to compensation for permanent vestibular loss.

There are characteristic pathologic findings on autopsy. EH is ubiquitous in Meniere disease and is found in the affected ear in unilateral cases, and is sometimes bilateral [3–5] .Normal hair cell populations may be found in the cristae and cochlea until the disease is advanced [6]. With progression, atrophy of dendrites and of hair cells may be found [7]. Neuroepithelial degeneration with thickening of the basement membrane and loss of stereocilia have also been reported [8]. Strial atrophy and loss of dark cells in the cristae are often found, and strial abnormalities have also been identified in the contralateral ear in unilateral MD [9,10].

Epidemiologic characteristics have also been identified. EH is found in all cases of Meniere disease, but many cases of EH are asymptomatic or show only hearing loss [3]. There is also an association with migraine in about half of MD cases [11]. MD is rare in children and increases in prevalence over the lifespan [12]. Identical attacks associated with EH occur in other disorders such as otosyphilis and neuroborreliosis [13–15].

Previous models

Prior to the 1938 Hallpike article, the mechanism of MAs was attributed to causes as disparate as viruses, hyperemia, and allergy. Many articles noted an association with migraine, leading to theories that vasospasm with resultant ischemia caused vertigo spells [16]. The Hallpike paper ascribed the symptoms to hypoxemia of the labyrinth due to impaired blood flow; this was believed to result from sudden large increases in endolymph pressure that impaired circulation within the ear [2]. Following the Hallpike paper, theories involving ischemia as a mechanism declined. Autopsy specimens showed an intact inner ear with few or no hair cell losses in some cases [17], which would have been difficult to explain if widespread aural ischemia was the cause. A consensus arose that hydrops alone was a sufficient cause for the symptoms through an unknown mechanism. Some authors suggested that increased endolymph pressure caused a direct mechanical effect on the sensory structures, [18] but this remained unproven.

In 1952 a new EH-based theory to explain completely reversible, non-damaging spells arose–the potassium intoxication theory [19,20]. Lawrence and McCabe autopsied a case of MD with a few areas of rupture along Reissner's membrane. They hypothesized that rupture could result in contamination of perilymph with potassium-rich endolymph. This could acutely elevate potassium in perilymph that would theoretically inhibit hair cell transduction and silence the sensory structures of the ear, presumably causing the spells. Sudden elevations in endolymph pressure were said to cause the ruptures. They went onto speculate that the vertigo spell ended as the pressure was released and the membrane healed, allowing a return of normal function without damage to the inner ear. The formation of a permanent rupture would permanently silence the cochlea, resulting in deafness.

The potassium intoxication theory has since been widely refuted [21]. Pressures in endolymph relative to perilymph are not elevated enough to cause ruptures during attacks [21,22], nor are ruptures found in all cases. Ruptures are incapable of healing over the minutes to hours of a typical attack. A permanent rupture does not provide an explanation for a slowly progressing hearing loss over many years. Direct injection of a potassium-rich solution in animal models does not result in signs typical for MA [23], and potassium levels in endolymph and perilymph show no changes in the presence of hydrops [24]. The rupture model does not provide any reason for the frequent association of MD and migraine. Bilateral strial atrophy in unilateral Meniere disease and the development of hair cell and epithelial abnormalities is also not explained. As this EH-based theory lost favor, the role of EH in the production of symptoms of MD in general has itself been seriously questioned [4]. However, EH remains strongly linked to a history of Meniere attacks and this linkage is likely to be causative [5].

The vascular theory of attack etiology has recently been resurrected. For several decades, an association between Meniere disease and migraine has been noted [25–30]. Migrainous vertigo does not frequently damage the ear [31], but there are case reports linking migraine to inner ear damage [32,33]. Since migraine is believed to be a genetic channelopathy with a vasospastic component, this raises the possibility that some cases of Meniere disease share this pathophysiology [34]. However, Meniere disease is usually characterized by recurrent spells of vertigo in just one ear, but migraine is a cerebrovascular condition that should affect both ears and so does not explain the focality of the disorder. Migraine does not provide a simple reason for the finding of hydrops in Meniere disease, nor has there been any published causative connection between hydrops and migraine. Migraine has never been shown to result in hydrops, nor has hydrops been shown to cause the onset of migraine headaches or aura. In the only autopsied case of Meniere disease with migraine, EH was found in the affected ear, suggesting that a chance combination of EH and migraine may be sufficient to cause MAs [32]. However, a large percentage of Meniere patients lack any personal or family history of migraine. Migraine, then, is neither necessary nor sufficient to cause MAs, but it has some connection to these attacks in a subpopulation of Meniere patients.

Unlike migraine, EH provides an explanation for the focality of the attacks. Most Meniere disease affects a single ear, and on autopsy, hydrops is found in the affected ear. However, EH cannot alone explain Meniere disease. Most temporal bones with EH lack a history of MAs during life [3]. Animal models of EH have failed to provide a mechanism for attacks, because they do not show spontaneous attacks of vertigo and hearing loss. This suggests that EH is necessary but not sufficient to cause MAs. If EH is causative, there must be one or more other factors that are also necessary before MAs occur [5]. However, no prior theory of attack etiology has required an interaction between hydrops and one or more other disorders. Syphilis, neuroborreliosis, and migraine have already been linked to MAs and so these disorders must share one or more characteristics that give rise to this association, but not all MA patients have one of these disorders.

In summary, pre-existing hydrops appears to be necessary but not sufficient to cause MAs; migraine is strongly associated but alone is neither necessary nor sufficient to cause MAs; and migraine, syphilis or neuroborreliosis when combined with hydrops appear to be sufficient but not necessary to cause MAs. Therefore, there must be some characteristic of migraine that is also shared with syphilis, neuroborreliosis, and with other as-yet-unidentified disorders that, when combined with hydrops, reliably gives rise to attacks. We believe this shared characteristic is a heightened risk for ischemia, usually due to cerebrovascular disease sufficient to reduce perfusion pressure in the sensory structures of the inner ear, and we therefore present the following model for attacks.

The hypothesis

Our theory posits that there are three major interacting factors that combine to cause MAs. First, we believe that all patients with MAs have pre-existing hydrops in at the affected ear. Second, we believe that all individuals with MAs have a lowered threshold for intracerebral and intra-aural ischemia during the spells. Third, we believe the unique attack characteristics arise because aural tissues show a differential sensitivity to ischemia.

We hypothesize that the first key abnormality in hydrops is that inner ear pressures (perilymph and endolymph) fluctuate to a greater extent than in normal ears in response to exogenous pressure changes such as changes in atmospheric pressure, intracerebral fluid pressure, head position, and state of hydration. The sensory structures of the ear and the associated neural tissues lie between these two compartments. This exposes the sensory tissues and vasculature of the ear to intermittent mild over- and under-pressure. The hydropic ear thus acts as an intermittent Starling resistor to blood flow within the inner ear. In young individuals with hydrops who have normal vasculature and normal oxygen levels, the highest pressure reached does not exceed the critical perfusion pressure for the tissues and is therefore not sufficient to result in ischemia, explaining the presence of asymptomatic hydrops in young people. However, we believe this relationship is greatly changed by cerebrovascular disorders and other risk factors for ischemia.

For structures perfused by intracerebral vessels such as the inner ear, perfusion is determined by arterial pressure, venous outflow resistance and intracerebral fluid pressure and is further modulated by oxygen supply [35]. Typically perfusion pressures of greater than 50–60 mmHg are sufficient to prevent ischemia in the properly oxygenated brain, while higher pressures are needed in the face of hypoxia. Any process that reduces intracerebral arterial pressure, increases venous outflow resistance, chronically raises intracerebral CSF pressure or results in chronic hypoxia can lower the effective perfusion. These processes include migrainous vasospasm, atherosclerotic narrowing of arteries, autoimmune or infectious vasculitides, arteriovenous malformations, venous outflow obstructions, hypertension, hyperviscosity, and other related vascular disorders. Hydrocephalus and post-traumatic elevations of intracerebral pressure impair perfusion. Acute or chronic hypoxia due to sleep apnea, carbon monoxide exposure, anemia, or pulmonary disorders also lower the effective perfusion. Because the vascular supply to the ear is entirely intracranial and without collaterals, it has the same or greater vulnerability to ischemia as the adjoining brain.

The tissues of the inner ear vary in sensitivity to ischemia. The stria vascularis is particularly sensitive; ischemia results in immediate loss of the endocochlear potential and ultimately results in strial atrophy [36]. The sensory structures of the inner ear including the hair cells and associated sensory neurons are excitatory cells, and like the neurons of the brain are vulnerable to ischemia/reperfusion injury (excitotoxicity) [37,38]. While non-excitatory tissues at normal body temperature may be able to tolerate ischemia for hours, this is reduced to minutes in excitatory tissues [38,39]. During ischemia in excitable tissues glutamate is released into the extracellular cleft [40]. Upon reperfusion, the excess glutamate binds to NMDA, AMPA and other calcium channels, resulting in rapid uptake of large amounts of calcium by the cell [40,41]. This is sequestered by mitochondria, resulting in opening of the permeability transition pore, and activates intracellular proteases such as caspase and calpain. These factors result in the production of nitric oxide and reactive oxygen species, leading to apoptosis and death of the cell. This process is slow, with a duration of up to 6 h after an isolated ischemic event [40].

We hypothesize that MAs occur when, due to a variety of cerebrovascular impairments listed above, perfusion pressure has been lowered to just above the ischemic threshold in an ear with pre-existing hydrops. In such a marginally-perfused ear, the relatively minor fluid pressure fluctuations caused by hydrops now become capable of resulting in ischemia in the stria vascularis and in the excitable tissues of the inner ear whenever inner ear pressures rise. We expect the stria to be the most sensitive, followed by the distal processes of sensory neurons, with the hair cells showing the least sensitivity of these excitable tissues. The remainder of the ear is relatively insensitive to ischemia and so will show no evidence of damage over time. The often slow onset of the attack, with increasing tinnitus and low tone hearing loss, reflect marginal ischemia that affects the stria vascularis at the apex of the cochlea, at the most distal branches of the internal auditory artery. An abrupt loss of strial blood flow results in acute low tone hearing loss with tinnitus due to loss of the endocochlear potential. Distal branches of the labyrinthine artery throughout the ear are affected in a patchy distribution and vertigo ensues when many of the calyces or boutons of sensory neurons in one or more cristae and maculae become ischemic. The distal processes of neurons serving cochlear hair cells and the spiral ganglia also become ischemic. Perfusion is not impaired long enough to cause necrotic tissue death, which would present as a sudden permanent sensorineural hearing loss with or without vestibular injury; during the MA it is only necessary that it last for between 5 and 60 min. During ischemia, glutamate is released into the synaptic cleft. When adequate perfusion is restored, non-sensory tissues quickly recover without damage, while ischemia/reperfusion pathways are activated in the most severely affected sensory structures. This is an hours-long metabolic process triggered by massive binding of the excess released glutamate to calcium channels. The calcium influx is taken up by mitochondria and if very great in extent overwhelms them, resulting in sensory cell death only in the most severely ischemic sensory tissues, surrounded by a zone of marginal ischemia, the penumbra, that recovers function over the next several hours. In the penumbra are calyces and boutons that are permanently damaged but with sparing of their associated neuronal cell bodies, as well as transiently impaired hair cells. This process is responsible for the hours-long duration of the spell and the gradual return to apparent normalcy. Because these zones of permanent cell death and calyceal damage are often small in the initial attacks, vestibular and auditory testing is not able to detect changes in function until several severe attacks have accumulated larger areas of sensory cell damage. Repeated destruction of calyces and boutons and hair cell ischemia eventually results in sensory neuron death and degeneration of hair cells. This results in slowly progressive hearing and vestibular impairments. Over time this patchy damage gradually becomes confluent in all the inner ear areas most vulnerable to ischemia, leading to the nearly dead ear of late stage Meniere's disease.

Evaluation of the hypothesis

Hydrops in every case

Our theory requires that hydrops is found on autopsy in the affected ear of every individual who has had recurrent MAs leading to SNHL in the ear. This has been demonstrated based on large double-blinded autopsy studies using 1995 AAOHNS criteria [34] and in a large review of autopsied cases [5].

The mechanism we propose also applies to bilateral MD, but this diagnosis cannot be made definitively without autopsy specimens. In order to be considered bilateral MD, each ear must be

shown to have had recurrent spells meeting 1995 AAOHNS criteria, with development of progressive hearing loss and vestibular damage in each. However, attacks affecting both ears simultaneously will not cause symptoms of classic MAs because simultaneous bilateral vestibular loss causes oscillopsia rather than rotational vertigo. It is also difficult to determine the source ear for a given attack, leading to the risk of over-diagnosis of bilateral disease. Autopsy studies with very careful clinical correlation will be necessary to prove or disprove our theory when applied to bilateral cases.

Hydropic ear acts as a variable Starling resistor

In order for the hydropic ear to act as a variable Starling resistor, our theory requires that pressures in the sensory tissues of hydropic ears vary with pressure changes external to the ear to a greater extent than in non-hydropic ears. The inner ear is fluid-filled but its fluid volume is limited by its bony shell. Increases in fluid volume in either compartment must result in fluid displacement through the cochlear aqueduct, endolymphatic duct, or through compression of the soft tissues. According to our theory, the effect of EH must be to impair fluid displacement via these ducts in favor of compression of the soft tissues. Bohmer states that fluid pressure changes in the inner ear are buffered by the compliance of the soft tissues, particularly the veins within the inner ear. When fluid volumes increase, this directly compresses venules, increasing venous outflow resistance [42]. This is the definition of a Starling resistor. EH has been shown to impair autoregulation of blood flow to the cochlea, which is an anticipated effect of a Starling resistor [43–46].

There is a large literature on pressure fluctuation in the endolymph and perilymph compartments in normal subjects and animal models of hydrops. Because the membrane separating these compartments is distensible, pressures are rapidly equilibrated between the compartments and so pressure in either compartment can be used as a proxy for pressure in the sensory tissues within which the vasculature arborizes [47]. To the present, most studies have examined the differences in pressure between the two compartments and so the pressures to which the vasculature is exposed have not yet been studied. We predict that these pressures will fluctuate to a greater extent than in non-hydropic ears.

We state that pressure fluctuations in the hydropic inner ear due to atmospheric pressure, intracerebral fluid pressure, head position and state of hydration can raise intra-aural tissue pressures high enough to impair blood flow in a marginally-perfused ear. The inner ear is exposed to atmospheric pressure via the round and oval windows, and to intracerebral pressures via the endolymphatic duct, the cochlear aqueduct, and via the venous system. A number of papers have discussed exogenous pressure effects on the inner ear of Meniere's disease patients that our theory identifies as important.

Intracerebral fluid pressure and head position

CSF pressures range from <0 to >30 mmHg during daily physiologic perturbations, higher with the head inverted or when supine, and lowest in the standing position. The relationship between CSF pressures and inner ear pressures in hydrops suggests that intra-aural fluid pressures are elevated in the hydropic ear [48]. Meniere patients report worsening with head dependency [49]. Attacks of nystagmus can be initiated in hydropic ears in the guinea pig model by inverting the head of the animal [50,22].

State of hydration

Reduced sodium intake and diuretics have long been mainstays of therapy of MAs [51] with the belief that hydropic volume was reduced by these methods. The use of hydrochlorthiazide with triamterene to control vertigo symptoms is very common and has been supported by a double blind crossover study [52]. Andrews reported an association between MAs and perimenstrual fluid shifts; this was attributed to hyperviscosity with resultant decreased inner ear perfusion [53].

Atmospheric pressure

Up to 70% of patients prone to MAs note symptoms are brought on by weather changes and 45% with elevation changes [49]. A study of cold fronts, which are associated with larger and more sudden atmospheric pressure changes than warm fronts, identified worsening of symptoms in 36/70 Meniere patients studied [54]. MAs can be ended by acutely lowering atmospheric pressure in a pressure chamber [55].

These observations support our hypothesis that hydropic ears become symptomatic in response to pressure changes external to the ear. However, some have stated that EH cannot affect blood flow because the vessels pass through the perilymph space, and so are not affected by changes in endolymph volume [56]. Our theory avoids this problem because it is the pressure in the sensory tissues containing the capillary bed vasculature that changes, rather than pressure differences between endolymph and perilymph.

Development of a detailed model of the resistor will require intra-aural measurement of perivascular interstitial fluid, arterial and venous pressures during attacks in varying head positions with respect to the heart, and under varying barometric conditions. We suspect that the time course to equilibration of these pressures in normal and hydropic ears will differ.

Vascular risk in every case

Our hypothesis suggests that every person with MAs has one or more major risk factors for cerebral ischemia, including vascular disorders and/or chronic hypoxia. The presence of many cases of EH with no history of MAs is consistent with our theory [3], because we predict that those without vascular risk factors will not have such attacks. Since hydrops and cerebrovascular risk are linked in our theory by chance (hydrops is not caused by ischemia, and vascular risk factors do not result from hydrops), the proportion of Meniere cases caused by each risk factor should reflect the relative frequency of that risk factor found in the general population. Not all vascular risk factors are yet known, nor are all known risk factors easily testable, so we expect that some people may be found who seem to lack vascular risk. The proportion of Meniere cases without clear risk factors should be inversely proportional to the number of vascular risk factors evaluated in a

Table 1
Stroke risk factors by frequency in the general population.

Risk factor	Prevalence % (in US adult population)
Dyslipidemia, any type	53
Obesity	36
Hypertension	30
Age >55	21 (of total population)
Smoking	19
Atherosclerosis	8–14
Diabetes	8
Sleep apnea	3–7
History of myocardial infarction	4
History of stroke	2–3
History of TIA	2

If Meniere attacks occur only in those with vascular risk factors for stroke, then the prevalence of the disorders listed above should be increased in patients with a diagnosis of Meniere disease compared to the general adult population.

given study. Table 1 lists the most common vascular risk factors in the general population and their frequency [57]. No studies have yet been performed to assess vascular risk factors in Meniere disease.

Animal models of Meniere disease support our contention that vascular risk factors combine with EH to cause MAs. Most animal models of EH do not demonstrate spontaneous MAs [58]. These can be triggered in EH models by injection of epinephrine into the middle ear [59] or by venous occlusion (blocking the vein of the vestibular aqueduct [60]). Both of these factors are known to impair perfusion pressure: epinephrine through arterial constriction, and venous occlusion by raising venous outflow resistance. Kimura states that EH causes hypoxia of the inner ear through impaired autoregulation of blood flow [60]. Autoregulation is imperative to prevent ischemia when cerebrovascular disease is present, so its impairment in the hydropic ear would increase the risk of ischemia over that seen in adjacent brain.

Vascular risk factors in Meniere's disease have not been extensively studied; the focus on research has been on the development of hydrops. We feel that the timing of onset and prevalence of attacks during the lifespan should reflect the development of vascular risk factors, since hydrops has been identified in people of all ages [12]. Migraine occurs throughout the lifespan but peaks in the teen and young adult years and is the most common risk factor for cerebrovascular ischemia in that age group. Our hypothesis is supported by articles describing a strong correlation between MAs and migraine in children and young adults [29]. Migraine can be difficult to diagnose because there is no objective test for it, vasospasm can occur without headache and headaches can remit for many years or begin later in life. This means that some young people with MAs and migraine may be misclassified as having no vascular risk factors because they have not yet developed typical headaches, so prolonged follow up of such cases may be required. Some forms of migraine are genetic channelopathies [61], so a family history of migraine should be sought, and inclusion of other migraine-associated symptoms such as motion intolerance, cyclical vomiting, depression and anxiety may be helpful in classification. If objective tests become available for migraine diagnosis, this would be of great benefit in such studies.

Classic vascular risk factors other than migraine arise in middle age, with strokes, myocardial infarction and death from these risk factors following with a lag of several years. The average age of onset of Meniere disease should occur earlier than the average age for stroke onset, since our theory predicts that hydrops makes the ear more vulnerable to ischemia than the adjoining brain. The mean age of onset of Meniere disease is 45, with myocardial infarction showing an epidemiologic increase at age 55–59 [62] and stroke following in the 65–74 age group [63]. Meniere disease prevalence increases with age [12], as do vascular risk factors, stroke and myocardial infarction as reported above. Aging has been shown to impair blood flow and result in capillary changes in the vestibular system and cochlea [64,65]. In older individuals, we predict that smoking, atherosclerosis, sleep apnea, diabetes, obesity, hypertension, elevated cholesterol, and a history of stroke, TIA or MI will be common associations (Table 1). Examples of rare causes should include coagulation disorders, sickle cell disease, genetic and autoimmune vasculopathies, vertebral dissection or vascular malformations near the ear, and chronic carbon monoxide exposure. The more exhaustively vascular risk factors are sought, the stronger the association with MD should be. Studies have already documented the association of Meniere disease with sickle cell disease [66], antiphospholipid antibody syndrome [67], giant cell arteritis [68], polyarteritis nodosa [69], systemic lupus erythematosis [70,71], Behcet's disease [72,73] , homocystinuria with jugular thrombosis [74], branch retinal artery occlusion [75], retinal vasculitis/Eales disease [76], and perimenstrual fluid shifts with hyperviscosity [53]. These directly support our theory.

Our definition of MAs does not exclude already known causes of hydrops with similar attacks, such as otosyphilis and neuroborreliosis. Our theory predicts that all such known causes should have elevated cerebrovascular risk factors in addition to hydrops. Both syphilis and neuroborreliosis cause meningovasculitis and have an enhanced risk for stroke, as predicted by our theory [77,78].

Differential sensitivity of inner ear tissues to ischemia

In a series of papers from 1956 to 58, Kimura and Perlman demonstrated differential sensitivity of the vestibular and cochlear tissues to arterial and venous obstruction by electrocautery. They demonstrated evidence of damage caused by arterial obstruction as follows: within 30 min in inner > outer hair cells, by 60 min in the stria vascularis, spiral ganglion, cochlear nerve fibers, hair cells of the cristae and maculae with sparing of the rest of the ear by several hours [79,80]. In a test of ischemia–reperfusion injury to the cochlea, synaptic endings of cochlear dendrites showed swelling indicating ischemic injury after as little as 15 min of ischemia, with outer hair cells less severely affected at 15 min and showing marked changes after 45–60 min of ischemia [38]. Inner hair cells were less affected than outer hair cells, with damage requiring greater than 60 min of ischemia followed by reperfusion [81].

For acute venous obstruction, by 60 min the stria vascularis showed changes, followed hours later by the outer > inner hair cells, the saccular, utricular and ampullary hair cells and their associated dendrites, with sparing of the remainder of inner ear structures for days to weeks [82,83]. In 1961 Griffith reconfirmed the differential sensitivity to ischemia induced by venous obstruction in the following order: stria, spiral ganglion, outer hair cells, then inner hair cells with sparing of the remainder of the inner ear epithelium; in the vestibular labyrinth the utricular and saccular hair cells were the most vulnerable. Chou in 1962 showed that the stria is more sensitive to ischemia than the maculae [84].

Strial ischemia initiates the spells

The increased sensitivity of the stria to ischemia compared to hair cells and dendrites provides an explanation for the hearing loss and tinnitus that usually initiate the classic Meniere attack. Typically the hearing loss is low tone, which we feel indicates apical ischemia of the stria [36]. Our theory predicts that the apex will be affected first because its vessels are the most distal; these vessels have been described as narrower and simpler than at the base [46]. The immediate effect of strial ischemia is acute loss of the endocochlear potential, with resultant silencing of the affected portion of the cochlea. Strial atrophy is a common finding in Meniere disease, and is also a known outcome of aural ischemia [85,86]. A recent paper has shown bilateral strial atrophy in Meniere disease [9], which suggests enhanced vascular risk in Meniere patients as our theory posits. According to our theory, strial atrophy must be a marker for impaired cerebral perfusion and vascular risk, but should be more severe and occur earlier in the hydropic ear because that ear is more prone to ischemia compared to the non-hydropic ear in the affected individual. This has not yet been studied.

Ischemia/reperfusion injury during spells

For our theory to be correct, the sensory tissues of the inner ear must be vulnerable to excitotoxicity and must respond to it with a cascade similar to that already identified in central neurons [40]. Several studies have shown excitotoxic responses in hair cells

and in vestibular calyces [87,38,88] The stria vascularis is also selectively vulnerable to ischemia due to its high metabolic rate [36,84,89]. The remainder of the inner ear structures are less vulnerable [80]. It is this differential response to ischemia that explains the apparent normalcy of non-sensory inner ear structures on autopsy in Meniere disease.

We explain the hours-long duration of spells on the basis of the prolonged time course of the excitotoxic cascade. This has been shown in neurons [90], and also occurs in hair cells [87,88] Dysfunction of the stria vascularis and damage to spiral ganglion cells have been shown in Meniere disease [9] and have been found to occur with ischemia–reperfusion injury to the inner ear [88]

Because our theory predicts that damage to sensory cells is cumulative, the severity of vertigo during attacks and measures of remaining vestibular function should decline over time, more rapidly when attacks are more frequent. A decline in both vestibular and auditory function over time has long been noted in this disorder. Attacks also have been shown to decline in severity over time [91]. The relationship between attack frequency and the rate of decline has not yet been studied.

Progressive excitable tissue damage with sparing of nonexcitable tissues

To confirm this hypothesis, autopsy specimens should show preferential damage to the stria vascularis, dendrites, neurons, cochlear hair cells, and neuroepithelia of the cristae & maculae with sparing of non-excitatory tissues. Damage to calyces and boutons should occur earlier than damage to the neurons themselves. Autopsies in cases early in the course of the disease should show patchy or minimal damage in sensory structures with complete sparing of non-excitatory tissues. In late-stage cases, there should be more widespread damage in sensory tissues.

Structural changes are more likely to be reported in more recent studies using electron microscopy than in earlier studies using only light microscopy. Nadol and Thornton have shown damage to synapses at the base of inner and outer hair cells in hydropic ears [92]. Others have shown loss of hair cell stereocilia, formation of an epithelial monolayer, perinuclear vacuolization, and thickening of the basement membrane in the cristae and maculae of Meniere patients [8]. The stria vascularis is often noted to be atrophic in Meniere disease [4]. Ischemic damage has been shown to result in strial dysfunction that may alter endolymph production and so have a feedback effect on EH [86]. Loss of stereocilia and vacuolization of sensory cells has also been demonstrated in ischemic animal models of hydrops [93].

Consequences of the hypothesis and discussion

Present treatment for Meniere disease relies upon methods that are thought to reduce fluid pressure in the inner ear, such as diuretics and sodium restriction, and anti-inflammatory treatments such as steroids. Treatment failures are often followed by destructive procedures such as gentamicin perfusion. If our theory is correct, treatment of vascular risk factors should result in a decrease in the need for ablative surgeries. No prior treatments have been shown to prevent progressive hearing loss or vestibular damage in Meniere disease. Treatment of vascular risk factors holds the potential to delay or prevent this progression.

Some of the well-known treatments for Meniere disease may be useful because of their effects on vascular risk factors rather than solely because they regulate inner ear pressure. For example, a low salt diet is a mainstay of Meniere treatment but is also frequently prescribed for treatment of hypertension, a common vascular risk factor. Avoidance of monosodium glutamate (MSG) as part of sodium restriction has also been advocated [51]. MSG is a common migraine trigger and can enhance the risk of excitotoxicity, so avoidance of this eliminates a dietary vascular risk factor. Diuretics such as hydrochlorthiazide with triamterene or furosemide are used both in Meniere disease and in hypertension. A number of authors are reporting successful results with migraine prophylactic medications in Meniere disease, some of which are also antihypertensives, such as propranolol or verapamil [94]. By reducing migrainous vasospasm, another vascular risk factor is controlled in these patients. Acetazolamide is a diuretic thought to reduce intra-aural pressure, but it also reduces vasospasm in migraineurs and lowers CSF pressure, which can improve perfusion [95].

However, there are many other treatable vascular risk factors that presently are not addressed in Meniere patients. Sleep apnea is common and the vascular side effects are serious, including stroke and MI [96]. If our theory is confirmed, all patients with MAs should be questioned regarding snoring and nighttime apneas, and a sleep study should be performed in positive cases. We have treated a number of Meniere disease patients with CPAP and have noted a resolution of MAs after previous medical treatment failures.

Migraine is likely to be the most common vascular risk factor for MAs in people under the age of 40 [29]. It would behoove otologists to develop a migraine treatment protocol to be used in these patients, with referral to neurologists specializing in the disorder for patients who fail to respond. In our practice, migraine prophylactic treatments such as tricyclic antidepressants, calcium channel blockers, and topiramate are helpful, while medications for acute headache control such as the triptans are of no benefit. The use of exogenous hormones in female patients increases migraine and overall vascular risk and these should therefore be withheld in Meniere patients if our model is correct.

Evaluation and treatment for common vascular risk factors, such as obesity, hypertension, diabetes, elevated cholesterol, and a history of myocardial infarction or stroke should be provided for these patients. Smoking is a major vascular risk factor and all patients with MAs should received counseling and medication needed to end this addiction. If we are correct, the presence of MAs indicates an elevated potential for stroke. The hydropic inner ear acts as a "canary in the coal mine", the first to experience ischemic symptoms. Treatment of this symptom may protect the patient against more disabling cerebrovascular ischemia in later life.

Otologists will need to work closely with internists, rheumatologists and hematologists when treating Meniere patients with less common vascular disorders such as temporal arteritis, autoimmune vasculitides, clotting disorders, and inflammatory diseases. Neurosurgical consultation may be needed for those with vascular malformations, particularly those in or near the ear that alter perfusion. Not all vascular disorders are presently treatable, and for these patients who also have Meniere disease, other modalities such as transtympanic steroids and ablative procedures will likely remain the treatment of choice. However, if this theory is correct, the majority of patients with Meniere disease should have new treatment options available to prevent or reduce disabling vertigo spells and progressive deafness.

Conflict of interest

The authors have no conflicts of interest to disclose.

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