Chapter 5

Pathophysiology of Meniere's Disease

Shazia Mirza and Sankalp Gokhale

Additional information is available at the end of the chapter

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Abstract

Meniere's disease, with its characteristic symptom triad of vertigo, balance and hearing disorders has yet to have its pathophysiology outlined conclusively. Any theory must elucidate all aspects of the natural progression, including vestibular and auditory symptoms. While the central dogma revolves around endolymphatic hydrops, this theory is not without flaws, such as its inability to explain all the physiological changes seen in patients, or the often absence of symptoms. While several degenerative changes are observed in temporal bone histopathology, they do not necessarily explain the sequence of events in the development and progress of the disease. This chapter explores the pathophysiology of the disease, focusing on the hydrops theory, while presenting evidence for and against it. Various changes in the inner ear physiology such as pressure changes, ionic disequilibrium, endocochlear potentials; in human and animal models are described. Alternative explanations for symptoms are discussed. This chapter touches briefly upon etiology associated with Meniere's (and hydrops), and aims to assist a deeper understanding of the relationship of the process to clinical and experimental findings. A clear understanding of the process guides not only the clinical management to improve quality of life but also the direction of future research endeavors.

Keywords: Meniere's disease, pathophysiology, etiology, mechanism, endolymphatic hydrops, deafness, vertigo

1. Introduction

Meniere's disease, with a symptom triad of vertigo, balance and hearing disorders, was reported as a disease of the inner ear by Prosper Meniere as far back as 1861 [1] and has yet to have its pathophysiology defined conclusively. Since a central theory of the pathophysiology involves endolymphatic hydrops, it is worthwhile be familiar with the terms.

Endolymph is the potassium-rich fluid in the membranous labyrinth, produced by the stria vascularis (cells in the scala media) of the cochlear labyrinth along with some contribution from the dark vestibular cells and planum semilunatum. There is a slow longitudinal flow and a fast radial flow of endolymph, also influenced by osmotic and hydrostatic forces. Endolymphatic hydrops refers to the over-accumulation of endolymph, pressing upon the perilymphatic space resulting in the characteristic symptom triad. The exact mechanism of this hydrops is unknown and can range from over-production, decreased absorption, to mechanical obstruction. If the cause of the distension or hydrops is unknown, the syndrome can be termed Meniere's disease (MD); conversely, if the cause is known, it is termed secondary endolymphatic blockage. The chapter intends to outline mechanisms for the hydrops; however, this theory is plagued with controversy as shown in a study of cadaveric temporal bone specimens wherein 100% of the diagnosed MD patients had evidence of hydrops, contrasted by findings of hydrops in 51/79 patients without an MD diagnosis, highlighting gaps in this theory [2].

2. Historical journey in pathophysiology

Prosper Meniere in 1861 observed the constellation of symptoms (such as tinnitus, hearing loss, falls, vertigo, nausea and syncope), when he postulated that the ear was the site of the disorder in contrast to the popular theory of apoplectiform cerebral congestion [1]. Building upon Flourens' experiments on pigeons, he further refined the site of the lesion to be the semicircular canals. In 1938, two independent studies by Yamakawa (in Japan) and Hallpike and Cairns (In England) described the hydrops as a pathological finding of the labyrinth; these anatomical findings were confirmed by various investigators through the decade to come [2].

3. Pathophysiology

MD is characterized during its active phase with the characteristic symptom triad, of episodic vertigo and tinnitus with fluctuations in hearing, followed by a symptom-free period, ultimately resulting in a more permanent dysfunction of the above symptoms. Any theory attempting to explain the pathophysiology of MD has to account for processes that result in a reversible dysfunction of both the cochlea and vestibule, with long-term chronic deficits. Examples of reversible causes include noise, toxins such as salicylates, viral infections and immune-mediated mechanisms, most of which do not show morphological changes unless they turn permanent.

This suggests a possibility of a final common pathway in a variety of conditions that could all result in fluctuating cochlear and vestibular dysfunction. The exact mechanisms are not clearly elucidated, with noise-related damage being a notable exception. In all cases, a persistence of the metabolic dysfunction results in permanence. Hence, it may be inferred that MD is modeled on the pathophysiology of disorders wherein abnormalities of metabolic dysfunction result in a permanent vestibulocochlear dysfunction.

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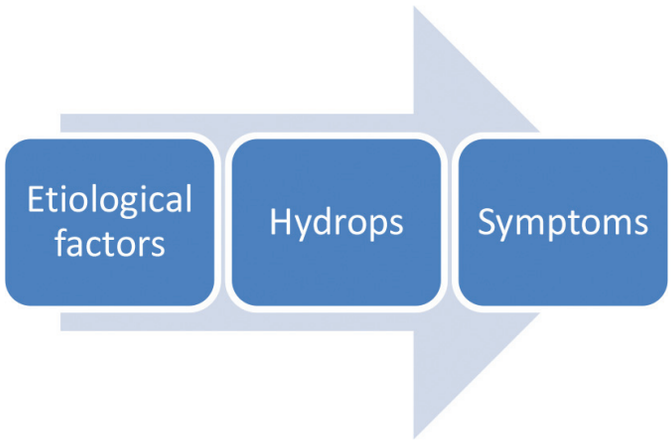
The problem in MD is thought to be malabsorption of endolymph, mainly in the duct or sac. This outflow dysfunction is usually a slow process, the inciting etiological event having occurred possibly years earlier.

4. Central theory of Meniere's disease

In simple terms, the central hypothesis of Meniere's disease pathophysiology is endolymphatic hydrops, due to a varied etiology (auto-immune, infectious, endocrine, allergic, vascular, autonomic, dietary, genetic, idiopathic, etc.) and is responsible for the symptoms of MD.



A discussion on the central theory necessarily focuses on the events leading up to the hydrops and the physiological consequences of the hydrops. Endolymphatic hydrops is the only consistently found anatomical abnormality in MD, with volume increases up to 200% in patients of MD versus health patients [3]. This correlation, however, does not imply causality, for if hydrops was causative then not only would every patient with Meniere's disease have hydrops but also the reverse; every case of hydrops would have symptoms of Meniere's disease, a statement we know does not stand true [2].

The theory regards that excess endolymph is due to overproduction or reduced resorption, either idiopathic or due to various etiologies, most likely being obstruction at the level of the duct or sac, which results in EH. The acuteness of attacks can be explained by the increased pressures within the scala media which result in a rupture of the membranous labyrinth. These ruptures are expected to occur frequently in MD and have been found in all parts of the inner ear in MD patients along with healed scars. This possibly explains the sudden attacks and fluctuation of symptoms. The Schuknecht theory is prominent for highlighting the ionic changes; ruptures of the membranous labyrinth cause a mixing of potassium-rich endolymph into the perilymph. This potassium is excitotoxic when exposed to CN VIII and hair cells as it causes depolarization of the nerve cells and subsequent inactivation. This results in decreased cochlear and vestibular function and symptoms of a Meniere's attack. When the ruptured membrane heals, symptoms subside [4].

While other pathological findings in hydrops include membrane ruptures, periductal sclerosis, damage to hair cells and spiral ganglion cells, studies also highlight other differences observed such as abnormal glycoprotein metabolism in the endolymphatic sac. And while fibrosis around the sac need not be present in each case of MD, the widespread glycoprotein imbalance could be of value in explaining EH formation through osmotic effect affecting inner ear homeostasis [5].

Hydrops has been experimentally found to be large enough to extend into the semicircular canal and thus disrupt the crista ampullaris, responsible for vertigo. The mechanical disruption of wave conduction by the hydrops is linked to the cochlear dysfunction.

Obstruction sites other than the duct and sac (secondary sites) such as in the ductus reunions may be responsible for the predominance of cochlear symptoms. Other involved sites (such as overactive vestibular cells and planum semilunatum) may result in excess production and mainly vestibular symptoms [6].

A combination of the mechanical and chemical factors is likely to be in play in the pathophysiology of MD. Since most of the theories on MD are derived from the study of temporal bone anatomy, the pathophysiology of MD has been inferred from the observed pathology. This is not always an ideal correlation as several insults, such as noise, can alter cochlear function without altering structure. Hence, one has to exercise caution while inferring the clinical condition of Meniere's disease from the pathological condition of hydrops.

4.1. Role played by the central theory

The central theory has not only dominated the pathophysiological dogma of MD but also influenced the design of various tests such as glycerol test or potential ratios (AP/SP; explained later) used to diagnose the “hydrops” and by extension MD. Most medical and surgical therapies in practice and in research are aimed at reducing the “hydrops.” Animal models are designed to recreate the “hydrops” as a model for MD. Most research is focused on discovering various etiologies or mechanisms of hydrops.

4.2. Etiology of the hydrops

Specific causes of hydrops include infectious (viruses and syphilis), allergic, genetic, trauma, autoimmune, otoconia or otoliths and low cerebrospinal fluid (CSF) pressures.

Viruses: Studies testing the endolymphatic sac of MD patients show the presence of viral DNA notably Varicella-Zoster virus (VZV), Epstein-Barr virus, cytomegalovirus and conflictingly absence of herpes simples viruses 1 and 2 [7] or its presence in the vestibular ganglion [8], with inactive serum titers during attacks, leading to a statistically based theory of latent inactive viral infections related to MD, with possible early VZV infection in childhood affecting the endolymphatic sac later in life. However, antiviral medications have no role in the treatment of MD.

Syphilis: Congenital or acquired syphilis was found to be the cause of MD in 6% of all cases, with pathogenesis of endolymphatic hydrops and osteitis of the capsule believed to cause the symptoms. This entity responds to steroid administration [9].

Hereditary: 34% of patients report a family history of hearing loss or recurrent vertigo, with 8.4% of patients having a relative with diagnosed definite MD. While genetic heterogeneity has been observed, most families had an autosomal-dominant inheritance pattern with anticipation. No clinical differences were found between sporadic and familial MD, except for an expected earlier onset in familial cases [10]. Studies have discovered two heterozygous single-nucleotide variants in FAM136A and DTNA genes, both from a Spanish family with three affected cases in consecutive generations, suggestive of autosomal-dominant inheritance [11] with various other gene mutations being explored in different familial groups.

Allergy: Studies found an inhalant allergy in 41.6% and a food allergy in 40.3% of patients with MD in comparison with rates of 27.6% and 17.4% in their control population [6]. The theory involves antigen exposure leading to a sudden influx of fluid into the endolymphatic sac (which is immunologically active), resulting in a rupture of Reissner's membrane. The resulting influx of potassium and its excitotoxicity causes the symptoms. Other theories involve deposition of circulating immune complex leading to inflammation. Patients on allergic immunotherapy have shown better control of their vertigo symptoms [6].

Autoimmunity: Immune stimulation of the endolymphatic sac may cause hydrops by disturbing its fluid regulatory function. This immune involvement is possibly type 2 (tissue antigen-antibody-related) or type 3 (circulating immune complex-related). A higher (30–50%) percentage of MD patients have circulating antigen-antibody complexes) compared to normal people; however, the detection of antibodies to vestibular antigens was lower (20%) and more variable. The deposition of the immune complexes possibly results in increased vascular permeability and hence an imbalance in the fluid electrolyte concentration [6]. Various cytokines such as interleukin-1alpha, tumor necrosis factor alpha, NF kappaB P65 and P50 have been found to be produced in cochlear cells such as type 1 fibrocytes and root cells of spiral ligament, demonstrating that local or systemic production of inflammatory ligands may play a role in cochlear dysfunction [12].

Otoconia: Studies using three-dimensional (3D) computerized tomography (CT) imaging in patients show that hydrops in MD patients might be caused by obstruction of the duct reunions by loose otoconia in the saccule [13].

Otitis media: Otitis media has been linked to the development of MD either later on in life (in childhood exposures, with vertiginous symptoms predominating) or concurrently with fluctuating hearing loss being the dominant presentation. The postulated pathophysiology involves the development of hydrops linked to labyrinthitis and or otitis media due to the under-development of the duct and sac due to the associated inflammatory sequelae in the mastoid [14]. Another possibility is the spread of infectious or inflammatory products into the perilymphatic space, which may disrupt the electrolyte homeostasis and osmotic pressures thus resulting in hydrops [6].

Trauma: Physical or acoustic trauma has been linked to MD through the dysfunction of cells involved in endolymphatic homeostasis or the traumatic displacement of cellular debris and otoconia which could physically or chemically result in hydrops [6]; studies in veterans with

such trauma, however, do not provide adequate backing to this theory [15]. The bilaterality of MD cannot be explained in cases of unilateral trauma.

Otosclerosis: Patients with otosclerosis have been found to have symptoms of MD due to the otosclerosis enveloping the aqueduct or invading the endosteum, resulting in changes in the flow and chemical composition of endolymph and perilymph [16].

Low cerebrospinal fluid pressures: Connections between the inner ear and CSF allow pressure changes to be transmitted, notably, a drop in CSF pressures such as postoperatively, leading to decreased perilymphatic pressures and a corresponding relative endolymphatic hydrops [17].

Other mediators: nitric oxide and vasopressin: Overexpression of the inducible nitric oxide synthase enzyme results in morphological (hair cell loss) and functional changes (endocochlear threshold and potential shifts) and stria vascularis toxicity, implicated in the development of MD, along with other free radicals [18]. Vasopressin levels have been shown to increase before and after a vertigo attack in MD patients, in humans and experimental models possibly contributing to the development of hydrops [19].

5. Physiology in Meniere's disease

The pathophysiology of Meniere's disease is tied to the physiology of the hydrops, which can be induced in experimental models by obliteration or blockage of the duct and/or sac in animals at a success rate approaching 100% in guinea pigs but with more variability in other species. The experimental animal models remain deficient, with no acute attacks of MD and lack of reported vestibular dysfunction despite severe hydrops, cautioning against direct equivalence from animal to human theories. This induced hydrops, despite being an incomplete model, is used to study the effects on the labyrinthine and cochlear physiology such as electrolyte homeostasis in the fluids and membranes, pressures and potentials.

6. Ionic homeostasis and hydrops

Despite logistical and technical difficulties in obtaining tissues and fluid (as composition is usually disturbed during surgical procedures), some human and animal studies show a change in the sodium-potassium levels of the cochlear and vestibular endolymphatic fluids in MD and experimental hydrops, respectively [20]. In addition to the theory of ruptures causing spillage of potassium ions into the perilymph, another possible explanation for the ionic and fluid imbalances in hydrops was postulated to be the Na, K-ATPase enzymes found in the cochlear lateral wall. However immunohistochemical studies of human temporal bones did not show statistically significant differences in hydropic ears consistent with the normal functioning of the stria vascularis in patients with MD [21]. Possible theories diverging from the traditional disruption of Guild's principle of longitudinal endolymphatic flow include ionic disequilibrium being responsible for the hydrops. Cellular changes in Reissner's membrane

are postulated to cause disruption of the endolymphatic flow and thus lead to ionic imbalance, a possible mechanism of hearing loss in endolymphatic hydrops [22].

7. Pressure changes and hydrops

Experimental models studying the effect of postural changes on endo- and perilymphatic space fluid pressures show a marked change in the hydropic versus control animals [23]. There is possibly an adaptation of the vestibular system to the increased endolymphatic pressures, given that the time period for the development of hydrops is over months. This adaptation is unlikely to remain in effect with changes in posture. This uncompensated disequilibrium of fluid pressures may be responsible for the vestibular dysfunction.

A second mechanism to consider is that an increase in pressures produced in the hydropic ear during postural changes compresses the microvasculature on the wall of the labyrinth, resulting in ischemia of the inner ear [24].

The cerebrospinal fluid pressure dictates the inner ear hydrostatic pressure through the cochlear aqueduct. Studies measuring the positional changes of intracranial CSF pressure and its corresponding effects on the perilymphatic pressures showed insignificant differences between MD affected and control ears [25]. Animal models measuring endo- and perilymphatic space fluid pressures before and after induced hydrops show no significance in pressure between the scala media and the scala tympani in either control or hydropic ears [26], with similar findings in humans, thus precluding the use of MMS-10 tympanic displacement analyzer (Marchbanks' test) in a diagnostic capacity [27].

8. Endocochlear potential and hydrops

Experimental models report a decrease in the endocochlear potential (EP) developing after inducing hydrops [26]. Measurements of the evoked responses of the cochlea such as cochlear microphonic potential (CM) show decreased maximum output and threshold levels. Auditory brainstem responses also show progressive deficits. Electrophysiological tests such as electrocochleography (ECoG) are commonly used in the diagnosis of MD which includes both the compound action potential (CAP) and the summating potential (SP). The CAP is the summation of responses from the auditory nerve which would be reduced in patients with hearing loss. The SP is the summation of responses from the hair cells. Since hydrops would push the basilar membrane closer toward the scala tympani, in the absence of hair cell damage or loss (seen in the early stages of the disease), this effect of hydrops would increase the SP. While the absolute values of these two components may differ, they do covary and hence the ratio between the two is often used in MD diagnosis.

Studies show that while rupture of the membranous labyrinth in hydrops was believed to be responsible for the inner ear dysfunction (through large volume injections into the endolymphatic sac), the pattern of pressure changes in conjunction with techniques examining temporal

bones via a micro-CT and functional electrographic recordings shows that they are not solely responsible for the acute ear dysfunction, rather the hydrops is a continuing, prolonged process with Non-rupture mechanisms in play, which can be correlated clinically with MD too [28].

9. The role of CNS in MD

The CNS modulates functions of the inner ear by several mechanisms, which may have a bearing on the pathophysiology of MD. Alterations in autonomic activity may modulate vascular tone which could set off an acute attack with longer term effects resulting in a chronic damage. Since cochlear fine tuning is compromised in MD, it is likely that efferent pathways are likely to be involved in acute attacks. The role of the neuroendocrine system causing metabolic dysfunction is yet to be elucidated.

10. Physiology of clinical symptoms and hydrops

10.1. Fluctuating hearing loss and episodic vertigo

As outlined earlier, a possible explanation for the fluctuating hearing loss and episodic vertigo seen in MD patients is brief, acute rises in pressures resulting in membranous ruptures, resulting in cochleovestibular dysfunction due to ionic disequilibrium (potassium excitotoxicity). Healing of these ruptures sets the stage for symptom resolution. The correlation of electron microscopic damage visualized in animal models of hydrops, such as hair cell loss, neuronal damage and spiral ganglion cell and ligament damage, is purported to be responsible for the hearing deficits.

A physiological basis of the Hennebert sign (vertigo occurring when static pressure is applied to the ear) is the presence of vestibular fibrosis (part of the pathological manifestations of the disease which may form band-like connections between the footplate of the stapes and the utricular macula [29].

10.2. Aural fullness

Patients often complain of aural fullness (a blocked or full sensation) which, while colloquially has been attributed to the hydropic swelling, has no scientific basis due to the lack of inner ear receptors to relay this information to the brain and the improbability that a minute increase in endolymphatic volume would be adequate to stretch the round window to results in this fullness sensation. A possible explanation could be the childhood association of a common middle ear disease (otitis media) with its prominent sensation of fullness with the low-frequency hearing loss which accompanies middle ear conductive pathologies. In essence, the low-frequency hearing loss experienced by the patient is accompanied by fullness as a learned association.

10.3. Recruitment

Loudness intolerance or recruitment also seen in MD patients is due to the loss of the outer hair cell function which serves to fine-tune or evoke region-specific responses of the basilar

membrane to varying frequencies. As a result, larger regions of the membrane and hence a larger population of neurons are excited for a stimulus which is usually interpreted as increased signal intensity. Altered perception of pitch, a symptom of MD, is similarly explained by the abnormal recruitment of neurons. The brain thus perceives different signals from the "normal" and the "affected" ear for a given sound, resulting in the perception of two sounds. This unusual symptom is notable in MD due to the asymmetry of the disease process.

10.4. Tinnitus

A possible explanation for the tinnitus could be related to a similar broad tuning of the cochlear membrane. A reduced functioning of the receptors and nerves at the cochlear apex may allow the CNS to interpret the boundary zone between the active cochlea and the inactive apex as tinnitus. Another mechanism could involve channels getting inputs from the inactive area of the nerve fibers, which would optimize their gain, leading to amplification of internal signals thus resulting in tinnitus.

10.5. Chronic symptoms

Irreversibility of symptoms and chronic deterioration in hearing are explained by the permanent morphological changes such as distortions in the ampulla walls, utricular macula and atrophy of the cristae. Such distensions of the lateral ampulla have been shown to be associated with impaired vestibular function tests [30]. While light microscopy may not always show obvious pathology, electron microscopy showing degeneration of unmyelinated axons may explain the symptoms such as loss of speech discrimination despite intact hair cells and spiral ganglion cells [31].

11. The evidence-based findings between hydrops and symptoms

Hyperosmolar agents and diuretics, such as glycerol and furosemide, respectively, have been used since several decades in the evaluation of patients with suspected hydrops. Several studies show that the hydrops is temporarily relieved by their mechanism of action [32–34], resulting in an improvement of hearing and or vestibular symptoms in some case, thus strengthening the case for hydrops being responsible for MD symptoms.

The results of electrocochleographic observations in MD patients also support a temporal correlation. This increase of the SP in patients with early MD, along with studies showing a positive temporal correlation of enhanced SP and symptom reporting and finally a decrease of the SP with the use of hyperosmolar agents [35], all strengthen the premise of hydrops being responsible for symptom constellation.

To explain the lack of symptoms in animal models of EH and as an alternative to the argument that hydrops cannot occur rapidly enough to cause an acute attack of symptoms, it was postulated that acute attacks of MD can be attributed to the biochemical effects of endolymphatic ruptures (not traditionally seen in animal models) specifically of Reissner's membrane. However, human temporal bone studies also do not consistently reveal theses ruptures or

they have been attributed to postmortem-processing artifacts, strengthening the theory that the pressure effects along with biochemical effects act in concert. With regard to the theory that ruptures are responsible for the acute attacks, studies have questioned the likelihood of a rupture in one anatomical area impacting the function of other areas, or the likelihood of simultaneous rupture of both the cochlear duct and saccule (not supported by histology findings) affecting cochlear and vestibular functions [36]. It is also logical extension of theory to expect relief of symptoms after rupture, as relief of the pressure should alleviate symptoms.

Vestibular symptoms such as nystagmus were induced in animal models with an injection of artificial endolymph into the perilymphatic space, presumed to represent the actual events in play during an attack of episodic vertigo [37].

Imaging studies in vivo using gadolinium-contrasted magnetic resonance imaging (MRI) demonstrated that in MD, different areas affected by the EH (vestibular vs. cochlear) were correlated to different symptoms experienced by patients as seen in the distinct cochlear or vestibular variants of Meniere's disease [38]. Such imaging studies also found a correlation between the progress of the EH imaged with the clinical deterioration of the inner ear functional measurements [39], strengthening the role of hydrops in the pathophysiology of MD.

Measuring the cross-sectional area of the scala media in vivo overcomes the drawbacks of histological shrinking and other artifacts. It has been used in animal models of hydrops with an endolymphatic marker, to study the temporal relation in the development of hydrops, post duct ablation (occurs within days). Functional deficits, measured electrophysiologically (such as cochlear potentials), were surprisingly initially only small changes and most marked at the 8- to 16-week time period when no further hydrops or endolymphatic expansion occurred. The logical extension, if it holds true in humans, would imply that factors apart from or in addition to the hydrops could be responsible for symptoms and relieving the hydrops may not restore normal functioning [40].

Studies determined that the hydrops causes a displacement of the basilar membrane toward the scala tympani which due to anatomical considerations is predominantly at the apex of the cochlea affecting its mechanical-electrical properties. This displacement results in sensorineural hearing loss of frequency below 100 Hz (due to anatomical locations of receptors) which is unlikely to result in clinically appreciated hearing loss, usually tested at frequencies of 250 HZ and higher. Thus, this in endolymphatic hydrops, the pathological findings do not correlate to the low-frequency hearing lost observed in Meniere's disease [41].

12. Hydrops and diagnosis

Given the prevalence of EH in patients of MD, diagnostic tests developed to visualize the EH in vivo have been studied such as gadolinium-based contrast media using heavily T(2)-weighted 3D FLAIR [42]. The advent of such dynamic imaging technologies provides new insights into the pathophysiology of MD such as differential involvement of cochlear and vestibular compartments and the fact that EH occurs in the asymptomatic or unaffected ear with a high (75%)

frequency [38]. Studies also confirm the diagnostic value of such techniques to image the hydrops as essential in the workup of other conditions such as vestibular migraine versus MD [43].

13. Physiology of hydrops and treatment

Most treatment strategies are geared toward the hydrops theory of etiology [44, 45]. Irrespective of the treatment instituted, the success rate of controlling vertigo episodes hovers at 60–80%, strongly suggesting nonspecific therapeutic effect or placebo effect in play. While studies are not always optimally designed with adequate controls; subjective symptoms and the fluctuating nature of the disease itself may compound the results making it difficult to distinguish spontaneous remission versus drug effect versus placebo effects.

Most commonly employed treatments include diuretics and dietary salt restriction which are used based on the rationale of altering the fluid and electrolyte balance; thus decreasing the hydrops, which has shown conflicting results in studies from being effective [46] versus flawed [47].

Several surgical procedures have been devised, such as endolymphatic sac decompressions, shunts and vestibular ablation. The aim of a majority of sac procedures is to decompress the EH and provide a path for drainage. This is conceptually flawed as most shunts created undergo fibrosis and loss of patency and endolymph would not drain into a higher pressure area such as CSF. Ventilation tubes placed in the tympanic membrane were shown to reduce vertigo [48], suggesting that middle ear pressures are involved in the pathophysiology of vertigo. The variable results noted that post-surgery gives credence to the nonspecific placebo effect theory [49].

An interesting result of endolymphatic sac surgery for patients with MD has been the knowledge contributed toward the pathophysiology during revision surgery due to recurrence of symptoms. Extensive granulation tissue and fibrosis found in the mastoid area, in the region of the sac, create a secondary compression coupled with color changes in the implants suggesting that transudative processes in play provide evidence toward endolymphatic malabsorption as the basis of the secondary (induced) MD.

14. Future

Despite advances in technologies, the fundamentals of the pathophysiology in MD remain incomplete. The gaps in knowledge are wide ranging, from natural progression of the disease to etiology, pathophysiology and treatment. To reconcile these controversies, research endeavors should adhere to standardized definitions of MD, selection criteria, control development and results reporting, which will allow comparable analysis across studies.

Animal models and experimental designs more closely reflecting the clinical entity of MD should be the pillar for future research. Overcoming the shortcoming of traditional animal models may allow breakthroughs in answering these questions. Newer models more closely resembling the pathophysiological process in play in MD include mice with vasopressin

administration and exploring the role of Latanoprost in MD therapy [50]. Technological advancements in inner ear imaging, histology, immunohistochemistry, genetic testing and functional measurements will allow a more molecular and refined examination of the pathophysiological process.

15. Summary

The pathophysiology of MD remains elusive despite intense research. It is likely that hydrops may not be the cause of MD symptoms, rather an epiphenomenon. Theories on the pathophysiology of MD thus leave several important gaps, mainly around the central theory of EH causing hydrops. They include the following:

- EH cannot comprehensively account for all the physiological changes seen in MD patients.
- EH need not be associated with the characteristic triad of symptoms of MD.
- Several differences exist in the physiological responses in hydropic animals versus MD patients. While this can be accounted for by innate differences between human and animal ears, it is likely related to alternate or additional processes involved in MD.
- The central role played by the endolymphatic sac in the pathophysiology of MD is also challenged, due to the low proportion of hydrops that develops in most animal species following obstruction of the sac and duct. Alternative mechanisms of endolymph production or resorption are likely to be in play in different regions of the labyrinth.

However, given a 100% association of EH in at least one ear of patients with MD, it is likely that EH is more than just an epiphenomenon, rather it is a condition that is necessary but not sufficient for the clinical picture of MD.

Author details

Shazia Mirza* and Sankalp Gokhale

*Address all correspondence to: shazia.mirza@utsouthwestern.edu

UT Southwestern Medical Center, Dallas, Texas, USA

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