Pathogenesis and pathophysiology of Meniere’s disease: An update

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ABSTRACT
Meniere’s disease is known with certain clinical symptoms such as fluctuating hearing loss, episodic vertigo, and tinnitus and characterized by endolymphatic hydrops found on post-mortem examination. The pathophysiology of Meniere’s disease is still questionable, and it has not been fully understood despite almost a century of research. Many determinants are effective in the occurrence of endolymphatic hydrops and in the pathogenesis of relevant cochleovestibular dysfunction. This review discusses research studies conducted in recent years concerning the pathogenesis and pathophysiology of Meniere’s disease. Histopathological research studies conducted in recent years on patients with Meniere’s disease have often focused on certain subjects as follows: aquaporins, oxidative stress, genetics, cochlear lateral wall changes, longitudinal flow blockage, intraskeletal channels of the otic capsule, hydropic and cellular changes in Reissner’s membrane, cochlear hair cells and spiral ganglion cells, round window thickness, basement membrane pathology, and otolithic membrane damages. Recent studies conducted on pathogenesis mechanisms of Meniere’s disease would provide an insight for the improvement of diagnosis and treatment of this weakening disease.

Keywords: Endolymphatic hydrops, Meniere’s disease, pathogenesis.

The mechanistic etiology of Meniere's disease (MD) is still questionable and has not been fully understood yet even following almost a century of research. Endolymphatic hydrops was firstly diagnosed in a temporal bone study in a patient with MD in 1938, and it was described as the initial histopathological indicator of the disease.[1,2] Endolymphatic hydrops has been defined in a variety of conditions involving genetic anomalies, otitis media, otosclerosis, trauma, viral infection, and autoimmune diseases of the ear.[3] This review aims to shed light into recent histopathological studies in patients with MD, to extend this initial simplistic view of the disease, and to support for a better comprehension of the mechanism of its pathogenesis and pathophysiology. Herein, the structural alterations seen through MD including bony changes from the otic capsule bone of the vestibular aqueduct and soft tissue changes to the endolymphatic sac and the round window will be defined. In addition, these changes in the endothelial structures within the

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membranous labyrinth including the otolithic membrane, Reissner’s membrane (RM), cochlear hair cells, spiral ganglion cells, cochlear lateral wall changes, and basement membrane (BM) pathology will be discussed. Furthermore, the cellular mechanisms behind this pathology will be examined within the following scopes: genetic markers, aquaporins, and oxidative stress.

**Longitudinal flow blockage of endolymph**

Within the inner ear, there are two terminal structures of membranous labyrinth: the endolymphatic duct and sac. It is considered that the function of the two is to resorb endolymph. Endolymph is produced more proximally in the cochlea and vestibule.\[4\]

Several previous researches have reported a variety of developmental or congenital anomalies which influence the longitudinal endolymphatic drainage system, probably causing hydrops and clinical MD. The endolymphatic flow may be usually obstructed in the endolymphatic duct, ductus reunions, and utriculo-endolymphatic valve.\[5\] Another study has revealed the endolymphatic duct blockage in five (23%) of 21 temporal bones from patients with MD, but in none of the 21 normal temporal bones (p=0.016). The aforementioned small percentile proposes that a physical developmental blockage only answers for a low ratio of these subject studies, and likely in the MD patients in general. It has been demonstrated that the number of fistulae between the cochlear duct and perilymphatic space is significantly higher in the ears influenced by MD, and approximately entire fistulae are found in the RM.\[7\]

**Degenerated intraskeletal channels in the otic capsule and vestibular aqueduct**

The mature otic capsule is comprised of three levels of bone: outer layer of periosteal bone, a central layer of bone made of cartilage, and an inner endosteal layer. The outer layer of the otic capsule and the vestibular arch are formed in the membrane (internal layer of the vestibular aqueduct). The remaining parts of the otic capsule, involving the outer layer of the vestibular aqueduct, are formed from the embryonic cartilaginous model. A different form of bony channel, occurred in relation to the origin of lamellar bone, is the Volkmann’s canal, which is structurally likened to that of the Haversian canal of long bones; however, not like the latter one, branching out in large numbers and to all directions alongside the whole otic capsule.\[8\] Following its primary development in the woven bone, vestibular arch developed a basis of lamellar bone, similar to the remaining parts of the otic capsule. During its development that is observed to be complete by the age of two, its characteristics are listed below: heavy infiltration with osteoblasts alongside the entire length of the vestibular arch; proof of existence of an programmed cell death at a smaller level based on the existence of degenerative alterations in certain osteoblast nuclei; the existence of many Volkmann’s canals, with varying sizes, and many including blood vessels within their lumina; the presence of high number of microcanals, particularly nearby the Volkmann’s canals, quite close to the endolymphatic duct. The inner layer of the bony vestibular aqueduct was defined by Michaels et al.\[9\] The cylindrical lining expanding toward the posteromedial portion of the vestibule in an arch-like form was titled as the vestibular arch by the researchers. This vestibular arch is a slim, osteal structure including many little skeletal cells. These researchers showed a drastic loss of those cells in 20 cases of MD, as well as an obvious new development of wide intraskeletal channels. The study demonstrated that osteoblasts were remarkably decreased or missing in MD, whereas they were naturally existing in vast numbers in the vestibular arch where they are accompanied by the Volkmann’s canals and microcanals.\[9\]

**Thickness of the round window**

The only soft tissue barrier between the middle and inner ear is the round window membrane. It is comprised of three basic layers and it is semipermeable. The round window membrane is able to transport substances in vastly different sizes.\[10\] Recently, the intratympanic injection (steroid or gentamicin) care for MD has drawn great attention and considered to have benefits. However, intratympanic injection treatments did not create an adequate difference in 5 to 20% of MD patients.\[11,12\] In a study conducted by Yoda et al., it was shown that there was a significant difference in the mean thickness of
round window membrane in temporal bones with MD vis-à-vis normal temporal bones. The mean thickness of the round window membrane of normal temporal bones was 67.430 µm and the thickness of the membrane of the temporal bones of the participants with MD was 93.988 µm.\[10\] Probably, this thickened membrane could explain the inadequacy of the intratympanic treatment.

**Cellular changes in endothelial structures**

**Damage in the otolithic membrane**

Endolympathic hydrops indicates distension of the endolympathic structures within the inner ear found on histopathology, and is usually connected to MD. Mechanical stimulation of the otoliths in the utricle and/or saccule could activate vestibulospinal pathways, causing a fall.\[7\] In a study conducted by Calzada et al.,\[13\] utricular membrane degeneration was manifested in the MD specimens compared to normal specimens with significantly decreased thickness of the otolithic membrane. These data indicate that an injury occurs in the otolithic organs in relation with the underlying pathophysiology of MD. In the aforementioned study, the mean thickness of the otolithic membrane of five archival temporal bone MD specimens was 11.45 µm versus 38 µm in five healthy specimens (p=0.001).\[13\]

**Reissner’s membrane**

The epithelial and mesothelial cells of the RM include pinocytic vesicles which indicate fluid transport throughout the membrane. Any alterations in the RM cellularity may influence the ion-fluid transportation system, producing the marks of MD. Therefore, the significance of structural alterations in RM that cause the symptoms of MD is a matter of speculation. Cureoglu et al.\[14\] demonstrated that the cellular densities of epithelial cells in the basal and middle turns of RM were significantly higher in the MD groups compared to the regular cases. Additionally, the researchers reported a decline concerning the figure of mesothelial cells of RM in basal and middle turn of MD participants compared to the control groups.

**Spiral ganglion cells and cochlear hair cells**

In their study, Kariya et al.\[15\] reported that cochlear hair cells in the contralateral ears in patients with unilateral MD were seriously influenced. Additionally, the loss percentile of hair cells was found to be more severe, compared to the rate of decline in the spiral ganglion cells, even in the contralateral side of the unilateral MD patients.

**Alterations in the cochlear lateral wall**

In a newly conducted study, Ishiyama et al.\[16\] demonstrated that the patients with a previous MD problem had stria vascularis, whose volume was 0.367 mm\(^3\) and it was significantly lower compared to those of normal participants within the same age group (0.479 mm\(^3\), \(p=0.01\)). The mean spiral ligament volume of the participants with MD was 6.86 mm\(^3\), and this figure was significantly lower compared to that of regular participants within the same age group (8.42 mm\(^3\), \(p=0.01\)). Kariya et al.\[17\] also showed that the total figure of the contralateral stria vascularis vessels in unilateral MD was significantly reduced compared to that of the control ears, and that vascularity of the stria vascularis manifested a predisposition to have a relation to the cross-sectional area of the stria vascularis in the contralateral ears of unilateral MD.

**The pathology of basal membrane**

In a previous study conducted by McCall et al.\[18\] a systematic analysis of the ultrastructural and cytological histopathology of vestibular endorgans was obtained from labyrinthectomy in MD. The study revealed neuroepithelial degeneration in various levels, whereas the semicircular canal cristaæ ampullares and saccular maculae had more serious degeneration, compared to the utricular maculae, which was highly related to an accompanying BM thickening. A significant correlation was determined between the existence of neuroepithelial monolayer degenerative alterations and the existing of thickening of the rudimentary BM (\(p>0.0001\)). Other vestibular epithelial alterations were not specific, taking place comparatively in equal terms in all of the vestibular endorgans. Those contained loss of hair cell stereocilia (ranging between 75 and 100%), vacuolization of the hair cells and supporting cells (ranging between 69 and 82%)
and increased intercellular stromal spaces (ranging between 50 and 80%). What remarkable was that, despite the gaps in the ages of the participants (ranging between 29 and 83) and the duration of the timespan with symptoms of MD prior to surgery (ranging between 1 and 20 years), among all participants, a noteworthy similarity was observed concerning the endorgan histopathology. This is suggestive that there may be a final common pathophysiological pathway for intractable Stage 4 MD.\[18\]

**Genetic and autoimmune origins**

An attracting technique for supporting a given theory of MD pathogenesis is employed through the genetic examination. Describing a gene mutation that decides sensitivity would apparently corroborate a given theory and refocus curing attempts on a particular molecular pathway. The quest for a genetic contribution to any illness includes a prudent epidemiological research of the target audience. Clinical observations concerning the prevalence, starting age, gender, race, socio-economic status, familial predisposition, and comorbidities assist for the creation of a hypothesis of disease sensitivity. Impartial data that can be utilized to corroborate the diagnosing process improve the ability to describe the affected individuals.\[19\]

A few nominee genes were suggested for MD, most of them organizing the ionic composition or water transport of the inner ear. There was a great concern for the aquaporin water channel genes aquaporin 1-4,\[20\] in the potassium channel genes KCNE1 and KCNE3,\[21\] and Na-K pump activity regulator ADD1.\[22\] In addition, mutations in the coagulation factor C homolog (COCH)\[23\] and a connection was revealed concerning the host cell factor C1 (HCFC1) gene.\[24\] Meniere’s disease was linked to the single nucleotide polymorphisms (SNP) of the heat-shock protein 70 gene (HSPA1A)\[25\] and to a polymorphism of PTPN22, encoding a lymphoid protein phosphatase.\[26\] In a recent work, interleukin-1 gene (IL-1) polymorphism was linked to not only MD, but also sudden sensorineural hearing loss.\[27\]

Meniere’s disease was linked with HLA-B*27, HLA-B*44, HLA-B*13, HLA-Cw*07, HLA-DBR1*1602, and HLA-DBR1*1101 in various populaces.\[28\] These multiple genetic changes leading MD in a patient might interpret the formerly monitored multifactorial inheritance pattern in clinical MD. In a previous study, Gazquez et al.\[29\] found a growth in systemic autoimmune disease in individuals with MD (rheumatoid arthritis [RA], systemic lupus erythematosus [SLE], and ankylosing spondylitis [AS]). Concerning RA and AS, the evaluated frequency in patients with MD was two or three times more regular; however, the prevalence of SLE was eight times more frequent.\[29\]

**Aquaporins**

Aquaporins control the amount and internal osmotic pressure of cells and, therefore, they are significant for the life of any living organism. They are found in all life forms including bacteria, plants, and animals, as well as humans.\[30\] Up to now, 13 isoforms of aquaporins (0-12) were determined in mammals, and RT-PCR revealed messenger ribonucleic acid (mRNA) of Aquaporins 1-9, except for Aquaporin 8, in the mammalian inner ear.\[31\] It has been suggested that MD is a dysregulation of the aquaporin-vasopressin system in the inner ear.\[32\] Aquaporin 2 is vital concerning MD. Aquaporin 2 is expressed in the endolymphatic sac of guinea pig and humans, and recently Aquaporin 2 protein is immunolocalized to rat stria vascularis and Aquaporin 2 mRNA expression is down regulated by lithium.\[33\] Aquaporin 2 expression in the collecting duct is controlled by vasopressin via the type-2 vasopressin receptor. It has been recently suggested that hormones such as vasopressin, aldosterone, and natriuretic peptide may be included in the homeostatic mechanisms of the inner ear. In a previous study, Sawada et al. reported that the vasopressin concentration in the blood of MD patients increased, implementation of vasopressin caused endolymphatic hydrops in guinea pigs, and type-2 vasopressin receptor mRNA was expressed in the rat inner ear. These discoveries propose that vasopressin may have a vital influence in endolymph homeostasis. The outcomes of this study demonstrate that the expression of Aquaporin 2 mRNA in the cochlea and the endolymphatic sac is upregulated by arginine-vasopressin, similar
to that of in the kidney. Aquaporin 3, along with Aquaporins 2 and 4, is co-expressed in the endolymphatic sac, in an identical way to the expression as in the principal cells lining the collecting duct in the kidney. The co-expression of these aquaporins may take place in cells, leading to water absorption. Aquaporin 4, the main aquaporin in the central nervous system, is expressed in astrocyte foot processes in large numbers, and it has the highest level of water permeability. In the inner ear, Aquaporin 4 protein and mRNA are highly expressed in the corroborating cells, including Hensen’s cells and inner sulcus cells, Claudius cells, in the corroborating cells of the vestibular endorgans, and in the central portion of the cochlear and vestibular nerves of rat and mouse. Aquaporin 5 is known as an exocrine-type water channel. Certain influences in transmitting a high degree of membrane water permeability, as well as other impacts were proposed, involving the control of paracellular permeability, cell proliferation, or cell migration. Aquaporin 5 is expressed in the external sulcus cells at the spiral prominence of the scala media in the upper turns of the rat cochlea. In a new study, the relationship between the MD risk and Aquaporin 5 polymorphisms was examined. Nishio et al. found a significant correlation between Aquaporin 5 polymorphism and the MD risk. Aquaporin may be changed by steroids, maybe interpreting a different instrument of steroid cure for MD. Kitahara et al. found that an adverse feedback scheme between plasma vasopressin and its receptor in the endolymphatic sac in normal participants would assure inner ear fluid homeostasis.

**Oxidative stress**

Increasing evidence propose that oxidative stress is included in the formation of endolymphatic hydrops and cellular damage and apoptotic cell death may promote to the sensorineural deafness observed in further phases of MD. The excess reactive oxygen species (ROS) are toxic; however, regulated ROS have a significant influence on cellular signaling. Capacity of a cell to weaken stressful conditions, known as cellular stress response, necessitates activating pro-survival footpaths and the producing molecules with antioxidant, anti-apoptotic or pro-apoptotic activities. Include heat shock proteins (HSPs) and the thioredoxin/thioredoxin reductase system, vitagenes, has a vital influence by conferring guard against oxidative stress amongst the cellular pathways. In a recent study, Calabrese et al. examined systemic oxidative stress and cellular stress response including participants with MD and healthy participants with matching ages. It was found that participants influenced by MD were under systemic oxidative stress and the induction of vitagenes HSP70 was a continued reaction for counterbalancing the intracellular pro-oxidant status originated from declined glutathione ingredient and thioredoxin expression.

Nitrile oxide (NO), a product of a NO synthase (NOS)-catalyzed reaction which converts L-arginine to citrulline, is critical in contributing to neuronal survival and plasticity and in dominating mitochondrial oxygen consumption. The genes NOS1 (nNOS) and NOS2A (iNOS) code for two isoforms of NOS (neuronal and induced) expressed in spiral ganglion neurons (SGNs). The NOS1 is a low-output, Ca^{2+}-calmodulin constitutive form that is activated by the influx of Ca^{2+} via the N-methyl-D-aspartate (NMDA) receptor through postsynaptic density protein (PSD) 95. The NOS2A is a high-output, Ca^{2+}-independent enzyme, whose expression in human cells is induced by cytokines such as interferon gamma (IFN-γ), IL-1β, and tumor necrosis factor-alpha (TNF-α).

After iNOS induction, NO is generated constantly until the enzyme is degraded. This relation may be correlated to transformation of NO to NO-, a highly reactive free radical that can conjugate with other free radicals to become cytotoxic at high concentrations or under oxidative conditions. Surprisingly, not only NOS1, but also NOS2A are upregulated in SGNs in a model of endolymphatic hydrops, suggesting that alternatives of these genes may be related to the neurotoxicity and programmed cell death of SGNs in MD.

Incremented NO-synthesis is related to the development of ROS-like lipid peroxides, hydroxyl radicals or peroxynitrite (ONOO•). As it is well-known, oxidative stress by ROS
may damage mitochondria complexes, deoxyribonucleic acid, lipid membranes, and proteins. The result is apoptosis characterized by cell shrinkage, chromatins condensation, and fragmentation of the nucleus. Conversely, NO may use cytoprotective effects, probably by scavenging ROS or by the activation of rescuing footways. The toxic or protective effect of NO depends on the rate of NO synthesis and the degree of ONOO· development.\(^{[42]}\)

In conclusion, many morphological and pathophysiological research studies concerning MD were conducted on human archival temporal bones. This review reveals that it may promote a better comprehension of the pathogenesis. The point of view of the pathological alterations defined herein would provide an insight for further research studies. The newly conducted research would enlighten the improvement of diagnosis and cure interventions for MD.

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