



Meniere's Disease - A Comprehensive New Theory

Jeremy Hornibrook*

Department of Otolaryngology-Head and Neck Surgery, University of Canterbury and University of Otago, New Zealand

Editorial

Meniere's disease is an inner ear disorder characterized by vertigo attacks with combinations of fluctuating hearing; tinnitus and aural fullness in the affected ear, named after Prosper Meniere. In the nineteenth century common notions of the function of the inner ear organs were that the cochlea was responsible for mediating the nature and pitch of sound, the otolith organs for the perception of loudness, and the semicircular canals for sound direction [1]. In 1824 Marie Jean Pierre Flourens, professor of physiology in Paris, lesioned pigeon semicircular canals causing violent head movements in the plane of each canal [2]. Although not his interpretation he is credited with the first observation that the semicircular canals are involved in balance function. Prosper Meniere, medical director of the Institute for deaf mutes in Paris, was aware of Flourens' experiments. In a lecture to the imperial academy of medicine in 1861 he stated: "An auditory apparatus, until then perfectly healthy, can become, all of a sudden, the seat of functional troubles, repeated cerebrovascular such as giddiness, uncertain walking, spinning and falling, nausea, vomiting, soon followed by profound deafness there is every reason to believe that the material lesion which is the cause of functional troubles lies in the semicircular canals" [3]. Ironically, in some respects, he may have been correct. After 156 years the true cause of Meniere's disease remains unproven. PUBMED list 7783 publications on Meniere's disease since 1883. In the nineteenth century vertigo as now recognized was classified as "apoplexy" along with stroke, epilepsy and believed to be due to impaired blood supply to the brain. The earliest PUBMED article on Meniere's disease by Edward Woakes extended this notion as a defect of blood supply to the inner ear [4]. Subsequent etiologic theories are too numerous to discuss in detail but include a variation in the size or position of the endolymphatic sac and duct [5-7], an autoimmune cause [8-10], allergy [11,12], a viral infection [13-15] or (assuming a provable family history) a genetically determined abnormality of endolymph control [16]. The advent of cadaver temporal bone pathology allowed an internal view of the inner ear. In 1938 almost simultaneous publications by Yamakawa [17] and Hallpike and Cairns [18] noted that the characteristic feature of Meniere's disease is an excess of endolymph called endolymphatic hydrops. At the time endolymph was presumed to be produced in the cochlea and absorbed in the endolymph by longitudinal flow [19]. Schuknecht established the largest and one of the few surviving human temporal bone laboratories in Boston. Experiments blocking the endolymphatic duct or destroying the endolymphatic sac in guinea pigs, cats and rabbits consistently result in endolymphatic hydrops and degenerative changes in the organs of Corti and cochlear neurons, but never vertigo attacks. This led Schuknecht to state that "the most plausible explanation is that Meniere's disease is caused by a functional failure of the of the endolymphatic sac [20]. In Meniere's ears he had frequently observed ruptures of Reissner's membrane [21] and stated that "the episodes of vertigo and fluctuating hearing could be accounted for by the toxic effect of potassium on the sensory and neural structures which are normally bathed in endolymph" [22]. This did not explain why in non-human animal vertigo attacks do not occur, but the rupture and potassium intoxication theory has been the predominant theory for Meniere's vertigo attacks since the 1960s. There are many arguments against the rupture theory. The strongest is the question of how a rupture in the cochlea could cause vertigo generated by distant vestibular organs. Another is why hearing losses do not occur at discrete frequency sites (rather than the characteristic initial low frequency fluctuation) or a total loss of hearing. Observations on nystagmus direction during an attack have been used both to support and disprove the potassium intoxication theory. Dohlman theorized that an initial ipsilateral nystagmus during an attack would be consistent with an increased potassium concentration surround afferent nerves [23]. McClure [24] performed ENG's on 8 patients at differing times during Meniere's attacks. In all cases the initial observed nystagmus direction was contralateral to the assumed Meniere's ear, often reversing to ipsilateral, and in some cases alternating (in one case over seconds) over hours. Others have observed the opposite pattern (initial ipsilateral) at the onset of attacks [25-27]. McClure, et al. also perfused the peri lymphatic space in guinea pigs with a high potassium solution

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*Correspondence:

Jeremy Hornibrook, Department of Otolaryngology-Head and Neck Surgery, University of Canterbury and University of Otago, 2 Riccarton Avenue, Christchurch 8011, New Zealand, Tel: 64-3-3640-125; Fax: 64-3-3640-125;

E-mail: jeremy@jhornibrook.com

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producing an initial ipsilateral nystagmus followed by reversal in all animals, but rejected his patient observations as not supporting the potassium intoxication theory, but rather as supporting the alternative theory of raised endolymphatic pressure [28]. Tonndorf [29] had argued that raised endolymphatic pressure could explain the aural symptoms of Meniere's disease. McClure, et al. speculated that such a sudden rise in endolymphatic pressure could result in mechanical distortion of the semicircular canal ampulla, which for the horizontal canal would rotate the crest of the crista and turn the base of the cupula towards the utricle (utriclefugal displacement), causing a contralateral nystagmus [24]. The limitations of conventional animal and human post-mortem histology and the differing observations of nystagmus during attacks have been advanced by newer approaches. Gibson performed transtympanic electrocochleography recordings in Meniere's ears and normal ears with a tone burst stimuli [30]. In Meniere's ears a 1 kHz tone burst produces a measurable large negative Summating Potential (SP), reflecting basilar membrane distortion from endolymphatic hydrops. From hundreds of recordings 87 patients could be identified as having an attack during the test, 1 to 24 hr before the attack and up to 72 hr after the attack. All had an abnormally enlarged SP which was greatest 1 hr to 24 hr prior, dramatically decreasing during the attack, then increasing over the next 72 hr. This implies that prior to the attack the hydrops increases suddenly and then decreases over 72 hr, and that the Action Potential (AP) measuring cochlear nerve function, which might be expected to be reduced or lost from a rupture, is preserved. McNeill and Gibson [31] allowed Meniere's patients to test their own hearing daily with a programmable hearing aid. In 6 who measured their own hearing during an attack 5 had no change of hearing before, during or after an attack, and 1 had a probable change in threshold prior to but not during the attack. These observations make a rupture and potassium intoxication unlikely. Brown and colleagues [32,33] injected 3 to 4 microlitres of artificial endolymph into guinea pig inner ears and measured vestibular-evoked short latency potentials which are assumed to be from articular neurons. Recovery of cochlear function was often followed by a transient increase or decrease in articular sensitivity (similarly if injected directly into the utricle) suggesting there may be a sudden opening of the articulo-sacculus duct to alleviate hydrostatic pressure, resulting in a change of articular function due to an increase in its volume. Micro CT on these ears did not show ruptures. Vestibular-Evoked Myogenic Potentials (oVEMPs) have been studied as to their ability to diagnose hydrops in the vestibule. In static studies on ears between attacks there appears to be no single reliable VEMP measure [34]. Manzari and colleagues, in a unique dynamic study on 15 patients during an attack, found a significant increase of the 10 of the contralateral ocular VEMP and a significant decrease in the ipsilateral cervical VEMP (cVEMP) [35]. This implies a decrease in saccular function followed by an increase in articular function, consistent with a surge of endolymph towards the utricle. Although often not appreciated, isolated otolith stimulation or paralysis can elicit nystagmus and vertigo [36-38]. The video Head Impulse Test (vHIT) is a new technique to objectively measure semicircular canal function both statically and dynamically. In a dynamic vHIT study on horizontal canal function Manzari and colleagues found that in 6 Meniere's ears. Eye velocity (gain) was enhanced at quiescence and during an attack and reduced after the attack, likely due to mechanical changes in the horizontal canal ampulla [39]. Yacovino, et al. [40] report similar changes in the horizontal VOR in one Meniere's patient during an attack, but they attribute it to perilymph potassium intoxication. Experiments by Salt

and colleagues [41] have challenged normal longitudinal flow of endolymph by injecting chemical markers into guinea pigs cochlea as without volume disturbance. In normal volumes marker diffusion was static (radial) and not longitudinal, suggesting that the latter occurs only when there is abnormal volume. The endolymphatic sac contains hydrophilic proteins [42]. It also contains natriuretic peptides which may have a role controlling cochlear endolymph [43,44]. In combination some of these findings have been the basis of the "drainage" theory by Gibson and Arenberg [45,46]. Mild hydrops is cleared by radial flow, but if there is excessive hydrops longitudinal flow it is initiated by the endolymphatic sac. It may clear it, but if the endolymphatic duct is dysfunctional or blocked, obstruction to flow results in an endolymph build-up in the sinus of the endolymphatic duct. Excessive endolymph then refluxes through the articular valve of Bast into the ampulla of the semicircular canals. In an MRI imaging inner ear study Gurkov and colleagues [47] found hydrops only in the horizontal canals of three patients, suggesting it may be the predominant canal affected. Overall there is strong evidence from non-histological studies that ruptures leading to potassium intoxication of the perilymph are not the cause of Meniere's vertigo attacks. Other evidence supports a hydrostatic process where an obstructed endolymphatic sac attempts to clear the hydrops. The variable nystagmus observed is most likely to be explained by endolymph moving in one direction and then in the opposite direction with (possibly alternating) displacement of the horizontal canal receptor and stimulation of the utricle. In vitro experiments on mouse otoconia in endolymph conclude that they usually dissolve in 20 hr [48] or more slowly if the calcium concentration is raised, so it is likely that the same occurs in human ears. It is now well accepted that Benign Paroxysmal Positional Vertigo (BPPV) is caused by detached non-dissolved utricularotoconia entering a semicircular canal [49]. However, it is seldom asked what is the fate of the detached saccular otoconia that do not dissolve? Most human histological studies on otoconia are confounded by their dissolution by the temporal bone decalcification process, but that is not a limitation for embryos. The endolymphatic sac has histological features suggesting a phagocytic role in removing endolymph debris, including otoconia [50-52]. Otoconia have been found in the endolymphatic sac of foetal guinea pigs [53]. Yamane and colleagues injected foetal and adult guinea pigs with streptomycin. Electron microscopy of endolymphatic sacs found otoconia in the sacs of 30-day old foetuses but none in the adult sacs, possibly a preparation effect [54]. Ohashi and Igarashi [55] studied dislodged otoconia from streptomycin and intense linear acceleration in squirrel monkeys and found phagocytised otoconia in the endolymphatic sac. Parnes, et al. [56] recently achieved a scanning electron microscopic analysis of material operatively removed from the endolymphatic compartment of the posterior canals of two patients with benign paroxysmal vertigo (BPPV), revealing broken fragments of articular macula membrane with attached and detached otoconia. In one patient there was similar particulate matter in the endolymphatic duct. Overall there is evidence that detached otoconia can reach the endolymphatic sac, and their most likely origin is the saccule. A multi-institutional temporal bone study concludes that in Meniere's disease always begins in the cochlea [57]. The cause of the initial cochlear hydrops is unknown. Kumara and Schuknecht [58] surgically blocked the reuniting duct in guinea pigs, with the majority of animals showing cochlear hydrops, saccule collapse and an abnormal utricle. Yamane and colleagues, using micro 3D CT scans, suggest that in Meniere's ears the reuniting duct may have become obstructed by detached saccular otoconia [59,60]. In a further study

[61] the vestibular aqueduct the vestibular aqueduct and proximal endolymphatic sac were not visible in 60% of Meniere's ears compared with 32% of opposite healthy ears and 4% of healthy control ears, suggesting that obliteration is a characteristic finding in Meniere's disease. A proposed comprehensive mechanism is the following. It appears that the likely fate of detached otoconia is to dissolve in endolymph. Detached articular otoconia that do not dissolve cause BPPV. The normal passage of non-dissolved saccular otoconia is to be phagocytised in the endolymphatic sac. However, if otoconia obstruct the reuniting duct they may initiate cochlear hydrops. The hydrops moves into the saccule. Otoconia from the damaged saccule move towards the endolymphatic duct and sac as the sac attempts to clear the hydrops and the otoconia. If the hydrops refluxes through the valve of Bast past the utricle the damaged utricle releases more otoconia [62]. The sac may eventually clear the otoconia and the hydrops as the endolymph moves in the opposite direction. As the sac becomes more dysfunctional and as more attacks occur the hydrops eventually involves the whole inner ear. The common association of Meniere's disease and BPPV has been recognized [63,64], and also the possibility of a common otoconial cause for Meniere's disease [65-67]. On this assumption Meniere's treatments by mastoid vibration and the micropressure device [68] might be explained by their massage effect on dislodged saccular otoconia [65,67]. Finally, new data on the age of onset of Meniere's disease shows a remarkable similarity to BPPV [69], based on two studies with identical criteria age of onset defined as age at the first vertigo attack, and clinical certainty with tone burst electrocochleography proof of endolymphatic hydrops [70]. Both conditions are rare in children, occasional in teenagers, increasing in incidence in the 20s, most between 30 and 60 years, and its onset over the age of sixty in approximately one third of patients. This raises the possibility that the two conditions have the same fundamental cause [71]. Progress on confirming the mechanism of Meniere's attacks and other inner disorders is likely to depend on significant advances in the resolution of CT inner ear imaging in human ears [72].

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