



Morbus Menière: Were the last 50 years of molecular biological research fruitless for Menière's disease?

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Abstract

After discovering an inner ear hemorrhage, Prosper Menière ascribed disease to the inner ear for the first time. Since that time, a lot of efforts have been made to determine the pathophysiologic causes of the classical symptoms sensorineural hearing loss, vertigo attacks, tinnitus and ear fullness. According to its express pattern Menière's disease may appear as classical and

atypical disease. In the last decades, huge advances have taken place in biochemical and physiological research and in pathophysiological understanding of the inner ear and its diseases. This encloses stimulus perception and conduction, regulation of inner-ear fluid homeostasis and inner ear diseases with underlying genetics. Menière's disease pathophysiologic correlate is an endolymphatic hydrops which is characterized by changes of inner ear homeostasis with its parameters volume, concentration, osmolality and pressure of the endolymph. Hormones, autonomous system and the immunsystem together with purinergic, adrenergic and muscarinic receptors, steroids, vasopressin, atrial natriuretic peptide and aquaporin channels regulate inner ear homeostasis. Consequently, general diagnostics comprise a magnetic resonance imaging with gadolinium, vestibular diagnostics and tone audiometry. Standard therapy for acute inner ear symptoms is limited to cortisone infusions together with a rheologic agent or a radical scavenger. For acute vertigo attacks and for the mainstay therapy antivertiginous pharmaceuticals are given. In severe cases destruction of the vestibular hair cells by ototoxic antibiotics, endolymphatic sac surgery or neurectomy of the vestibular nerve might be necessary. Certainly, in research there is a move from simple pharmaceutical therapy forward to nanoparticle-based, genetic-based and stem cell therapy.

Key words: Menière; Hearing loss; Vertigo; Tinnitus; Endolymphatic hydrops; Stem cell; Genetic-therapy; Nanoparticles

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Core tip: Morbus Menière has become the reference type of inner ear disease. It may express all kind of inner ear symptoms at once, but appears as atypical disease as well. There have been immense achievements in physiologic and biochemical understanding for the inner ear, various inner ear diseases in general and Menière's disease specifically. Pathophysiologic

understanding, ongoing research and therapeutic options for Menière's disease are described and discussed.

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Not holding the answer back, the response has to be "Yes" from a therapeutic understanding. But the last decades of molecular biological research involved immense achievements in pathophysiologic understanding for various inner ear diseases and underlied biochemical mechanisms that are valuable points of attachments for future nanoparticle-based and stem cell therapy.

Prosper Menière's description of an inner ear disease after performed dissection in a haemorrhagic ear in 1861^[1], was the first ascription of disease to the inner ear and since then Morbus Menière has become the reference type of inner ear disease. It may express all kind of inner ear symptoms at once, but appears as atypical disease just as often. The classic express pattern is only found in 7%-30% initially, in 40%-50% cochlear precede vestibular symptoms and in 20%-50% the disease manifests *vice versa*^[2]. Correlations with migraine and psychiatric patterns like anxiety and depression are typical, all the more than course and progress can't be foreseen. In addition, Menière's-like symptoms can be caused by various diseases like high jugular bulb, displacement of the venous sinus, and irregularities in the labyrinth system and its draining veins^[3] occur as well as affection of the efferent system^[4].

Endolymphatic hydrops as pathophysiologic correlate was described by Hallpike *et al*^[5] and Yamakawa^[6] simultaneously in 1938. It is characterised by changes of inner-ear homeostasis and its parameters volume, concentration, osmolarity and pressure of the endolymph. Potassium, as the major charge carrier for sensory transduction, and endolymph volume increase, followed by loss of stereociliary cross-links, with concomitant disarray of the outer hair cell stereociliary bundles and possible membrane rupture of the endolymphatic spaces, mixing perilymph with endolymph^[7]. Hormones, autonomous system and the immunsystem together with purinergic, adrenergic and muscarinic receptors, steroids, vasopressin, atrial natriuretic peptide and aquaporin channels regulate the inner ear homeostasis^[8-10]. Besides, cranial venous insufficiency might play an additive role as it correlates with Menière's disease and venous obstruction serves as an animal model for endolymphatic hydrops. Other animal models comprise an obstruction of the endolymphatic system, an obliteration of the endolymphatic sac that shows fibrosis in later disease stages of Menière disease, or immunmodulation by antigen challenge to

the endolymphatic sac. In recent years, endolymphatic hydrops in animal models triggered by vasopressin or its derivatives (ADH = antidiuretic hormone, AVP = arginine vasopressin, DDAVP = one trade name of desmopressin) have become more popular. They block the fluid absorption and increase the potassium secretion and its gradient along the length of the cochlea. Consequently, hormones responsible for inner ear homeostasis, aquaporin channels and ion channels represent the first therapeutic options for nanoparticle-based or genetic-based therapy.

Specific and comprised diagnostics may be necessary in the individual case, but the general test battery can be reduced to vestibular diagnostics like calorics and vestibular evoked myogenic potentials and to tone audiometry with the Klockhoff test (glycerol, furosemide), which results in an potassium increase in the endolymphatic spaces, and an improved hearing perception during the state of fluctuating hearing loss. A magnetic resonance imaging (MRI) with gadolinium should be performed to depict the endolymphatic hydrops and for exclusion. Imaging protocols were developed by Naganawa *et al*^[11]. The degree of endolymphatic hydrops in an MRI is correlated with cochlear and vestibular symptoms. It seems that all patients with classical symptoms have an endolymphatic hydrops, but not vice versa, as not all patients with hydrops show symptoms.

Currently, the preventive therapeutic options are limited to antivertiginous pharmaceuticals like cinnarizine and betahistine as mainstay therapy for vertigo control, which reduce number and intensity of vertigo episodes. Standard therapy for acute inner ear symptoms are cortisone infusions together with a rheologic agent, and radical savengers can be added to the therapy regimen what shows improved hearing outcome. In severe cases destruction of the vestibular hair cells by ototoxic antibiotics might be necessary showing in a metaanalysis a complete vertigo control in about 75% and substantial vertigo control in about 90%^[12]. Endolymphatic sac surgery or neurectomy of the vestibular nerve are used when chemical ablation of the vestibular organ fails. As the vestibular organ is four times more vulnerable to gentamicin than the cochlea, transtympanic application of gentamicin has become the most used intervention. Every diagnostic and therapeutic intervention has to be accompanied by a detailed counseling as the patients are disturbed and anxious by the dramatic kind of attacks.

Certainly, in research there is a move from simple pharmaceutical therapy for inner ear disease forward to nanoparticle-based, genetic-based and stem cell therapy. It is now already 10 years, when the first gene-therapy-mediated recovery of hearing loss in animals was reported in 2005^[13]. Due to the anatomical characteristics of the inner ear with bony isolation and the blood-inner ear barrier better understanding and therapeutic options in Menière's disease will go hand in hand with inner ear therapy in general.

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