Clinical Subtyping of Ménière’s Disease

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract
Fundamentally, Ménière’s disease is a constellation of symptoms and, as such, may represent the final common pathway for a number of disease processes, as opposed to being the consequence of a single isolated pathology. Within this type of consideration, much can be learned regarding the etiology, presentation, prognosis, and treatment of these individual conditions by applying subtyping techniques currently employed to better understand similar disease processes that are encountered in other allied fields of medicine. This commentary proposes the principles, required processes, and benefits of subtyping for Ménière’s disease.

Keywords
Ménière’s disease, clinical subtyping, genetics, big data

Received March 11, 2018; revised April 3, 2018; accepted April 5, 2018.

Ménière’s disease is a condition with a variety of proposed etiologies and observed clinical presentations, as reflected by the progressive and varied development of diagnostic criteria over the last few decades. It is in the context of these observations that Ménière’s disease is likely to represent a heterogeneous clinical condition defined only by small groups of common but not always mandatory symptoms. Understanding how Ménière’s disease may exist as a spectrum of clinical subtypes is key to directing further research into its underlying pathophysiologic mechanisms, to the targeting of specific treatment strategies, and to permitting a better understanding of the physiology of the inner ear microenvironment.

Clinical subtyping has offered greater understanding of many other disease processes¹; Parkinson’s disease is a good example.² Like Ménière’s disease, Parkinson’s disease presents in a variable manner, and ongoing work to define clinical subtypes has been proposed to be important in identifying homogeneous groups with strong clinical, pathologic, and genetic coherence,³ leading to a better understanding of the involved biological pathways and ultimately to tailored treatment strategies and prognostic information. To achieve this goal, a data-driven approach has been utilized.³

Etiology
Since the beginning of the 20th century, endolymphatic hydrops has been upheld as the underlying histologic feature of Ménière’s disease.⁴ However, more recently, there has been an increasingly reported disconnect between the presence of endolymphatic hydrops and the presence of Ménière’s disease,³-⁵ suggesting to many that endolymphatic hydrops may merely represent an epiphenomenon.² In the 1990s, Schuknecht identified multiple sites within the endolymphatic sac that demonstrated evidence of fibrosis, only for this finding to be later disputed due to its presence being seen in the temporal bones of patients with and without Ménière’s disease.⁶ In addition, many factors have been proposed as leading to the development of endolymphatic hydrops, including excessive endolymph production, decreased endolymph absorption, ionic imbalance, genetic abnormalities, viral infection, autoimmune disease, dietary factors, and vascular irregularities.

Presentation
One of the first formal diagnostic definitions of Ménière’s disease arose from the American Academy of Ophthalmology and Otolaryngology Committee on Equilibrium in 1972. The academy recognized 2 major variants: vestibular Ménière’s disease (vestibular hydrops) and cochlear Ménière’s disease (cochlear hydrops). Two further variants were also recognized: Lermoyez syndrome and the otolithic crisis of Tumarkin. Patients with Ménière’s disease can demonstrate a wide spectrum of presentations—including hearing loss, which may be relatively static or even regress or frequently fluctuate; hearing loss that is

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acute, progressive, unilateral, or bilateral; tinnitus of a variety of forms; aural fullness, pressure, or pain or an absence of these features altogether; and vertigo, which often varies significantly with respect to onset, severity, frequency, and time course.

Genetics

A genetic theory for Ménière’s disease is supported by geographic clustering as well as increased incidence within affected families. While most cases of Ménière’s disease are sporadic, affected family members have been found in 10% of cases. Although Ménière’s disease presents in a variety of ways, it is not uncommonly seen in conjunction with migraine. The genetics of migraine are better established with numerous loci identified that result in ion dysfunction, and it has been suggested that these could be extrapolated to Ménière’s disease.

Many studies have examined the genetics of Ménière’s disease, and as of yet, there is no definitive evidence to point to single genes. FAM136A and DTNA were found in a single family with incomplete penetrance, and a recent study started to define 2 candidate genes associated with familial Ménière’s disease—namely, SEMA3D and DPT. While many genes have been investigated, including aquaporin, antiquitin, and adducin, no firm association has been found. It is possible that the phenotypic variation in Ménière’s disease results not from a single gene but rather from multiple individual genes.

Implications for Therapy

In view of the great heterogeneity of Ménière’s disease, it is unlikely that a single treatment will be effective for all individuals. Great promise has been reported from the application of corticosteroids; however, corticosteroids play a diverse role within the inner ear, influencing mechanisms of labyrinthine blood flow, fluid regulation, and ion regulation, to name a few.

Implications for Prognosis

The long-term outcome for Ménière’s disease is variable. The effect of the condition with respect to employment, driving, and other important everyday activities and responsibilities can be considerable. At present, the huge variability in possible outcomes creates specific difficulties for patients and their carers. To date, there are no known factors to enable accurate prognostication for patients with Ménière’s disease.

Proposed Solution

One approach to gaining greater insight into Ménière’s disease would be to obtain prospective clinical and laboratory data from individuals with the disease to subtype different groups of cases stored in a data platform. Based on specialist statistical techniques, such as cluster analysis, the knowledge acquired from such an endeavor would have a significant impact on the diagnosis of Ménière’s disease, the counseling and treatment of patients, the development of targeted drug therapies, the planning and delivery of services and suitable research, and our understanding of the fundamental workings of the inner ear. This data platform would make a significant difference to the lives of individuals with Ménière’s disease—alleviating the symptom burden and addressing the unpredictability of clinical course in the short and longer term—and so have significant positive implications for work, social, and other activities.
