Fluctuating Sensorineural Hearing Loss

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Keywords

Fluctuating hearing loss · Ménière's disease ·
Endolymphatic hydrops · Autoimmune inner ear disease ·
Enlarged vestibular aqueduct

Abstract

Background: Several otologic conditions can present with fluctuating sensorineural hearing loss, including Ménière's disease, autoimmune inner ear disease, and enlarged vestibular aqueduct. Although these 3 etiologies vary greatly, distinguishing between these conditions at initial presentation can be challenging. Furthermore, initial treatment of these conditions is often similar. In this review, we discuss historical and current perspectives on diagnosis and treatment of these conditions. **Summary:** A literature search was performed regarding fluctuating hearing loss, and current treatment of these etiologies of fluctuating hearing loss was summarized. Immediate measures at the onset of acute hearing loss include corticosteroid therapy, while preventative and chronic therapies, which can limit disease severity and frequency, vary based on the specific condition treated. **Key Messages:** Fluctuating hearing loss can represent a range of pathologies, but the precise etiology may not be clear at initial presentation. Timely treatment and long-term follow-up, along with appropriate diagnostics, are necessary to optimize long-term hearing.

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Introduction

Sensorineural hearing loss (SNHL) is a common clinical disorder characterized by elevated bone conduction thresholds on formal audiometric testing. Various classifications for SNHL have been proposed, and Schucknecht's [1993] classic description includes sensory, neural, stria, and cochlear conductive types. This classification notably omits fluctuating SNHL, which is often encountered clinically. Fluctuating SNHL presents as a single episode of SNHL, which is often acute in nature, followed by objective changes in hearing thresholds. The presence of these changes suggests a diagnosis of fluctuating SNHL.

More broadly, fluctuating hearing loss in both the pediatric and the adult population can result from a variety of etiologies. A perilymphatic fistula, which can be present congenitally or arise following trauma, often causes fluctuations in hearing [Grundfast and Bluestone, 1978]. An additional congenital etiology is the enlarged vestibular aqueduct syndrome (EVA). Infectious etiologies include cytomegalovirus infection and syphilis [Fowler et al., 1997]. Ménière's syndrome is deemed to be an idiopathic etiology, although inflammation likely plays a significant role in its pathogenesis. Other inflammatory etiologies include autoimmune inner ear disease (AIED) and Cogan's syndrome [Migliori et al., 2009]. Toxic etiologies include ototoxicity from systemic medications

[Yorgason et al., 2006]. Neoplastic etiologies include endolymphatic sac tumor and even vestibular schwannoma, although the latter is typically associated only with hearing decline and not hearing fluctuations [Cmejrek and Megerian, 2004]. This review will focus on 3 specific etiologies: Ménière's disease (MD), AIED, and EVA.

The most common cause of fluctuating SNHL is MD, which is idiopathic in nature [Shea and Bowers, 1975]. An immune-mediated phenomenon is AIED. Genetic causes have also been implicated; EVA, for example, is associated with mutations in *SLC26A4*, resulting in the Pendred syndrome, which can present with progressive and/or fluctuating hearing loss [Everett et al., 2001]. In EVA, fluctuating SNHL is associated with pathological changes in the membranous labyrinth and dysfunction of the microcirculation [Okumura et al., 1995].

The clinical diagnoses underlying fluctuating hearing loss can demonstrate significant overlap, particularly in the early stages of presentation. In some patients with fluctuating hearing loss, hearing loss may improve spontaneously. However, intervention, either medical, surgical, or both, may be warranted. In this review, we present the potential etiologies of fluctuating hearing loss and discuss options for treatment.

Methods

PubMed, Europe PMC, and Google Scholar searches were conducted using the following search terms: "Ménière's disease," "fluctuating hearing loss," "enlarged vestibular aqueduct," "large vestibular aqueduct," and "autoimmune hearing loss." Articles discussing treatment of these conditions were selected for full-text review, which was performed by all authors. Due to the heterogeneity of data presented, a meta-analysis was not performed. Rather, findings were summarized in qualitative format.

Results

MD and Cochlear Hydrops

The most common diagnosis in patients [Lopez-Escamez et al., 2015] with fluctuating SNHL is MD [Shea and Bowers, 1975], which was first described by Prosper Ménière in 1861. It is characterized by episodes of vertigo, hearing loss, and tinnitus and/or aural fullness, and diagnosis relies on the exclusion of other causes [Committee on Hearing and Equilibrium, 1995; Lopez-Escamez et al., 2015]. Temporal bone histopathology has demonstrated a pathognomonic distension of the endolymphatic space termed endolymphatic hydrops [Hallpike and Cairns,

1938]. When vertigo is absent, the clinical presentation is termed cochlear hydrops [Glasscock and Miller, 1977].

The episodic symptomatology of MD has classically been explained by periodic ruptures in the already distended endolymphatic membranes. This results in disturbances in ion concentration in the endolymphatic and perilymphatic spaces, loss of the membrane potential, and resultant alterations in hearing and vestibular function, resulting in hearing loss and vertigo [Schuknecht et al., 1990]. More recently, however, it has been proposed that the histopathological changes observed with endolymphatic hydrops may not be directly responsible for the symptoms of MD but are rather a histological marker. This was suggested by a series of cases where histopathological findings and patient symptoms demonstrated little correlation [Merchant et al., 2005].

MD remains an idiopathic process, but potential etiologies, including viral infection or reactivation, autoimmune disorders, and changes in microvascular circulation, have been proposed [Mancini et al., 2002]. Histologically, MD is characterized by thickening of the basement membrane of the vestibular end organs; monolayer degeneration; and varying degrees of hair cell vacuolization, loss of stereocilia, formation of microvesicles in supporting cells, and stromal perivascular basement membrane thickening [McCall et al., 2009]. These changes may be secondary to cochlear ischemia, particularly in the stria vascularis, with resultant basement membrane thickening, fibrosis, and hair cell degeneration.

Edema in the cochlear duct may precede edema in the vestibular end organs, and fluctuations in edema in the cochlea as well as the vestibular end organs lead to fluctuating symptoms. Aquaporin dysfunction, which has been shown to cause impaired hearing in the setting of a morphologically normal cochlea in a mouse model, can cause basement membrane swelling, hair cell dysfunction, and hearing loss, and may also play a role in MD [Li and Verkman, 2001].

The glycerol or mannitol dehydration test, electrocochleography, and videonystagmography have all been utilized in the diagnosis of MD. In the dehydration test, administration of glycerol or mannitol causes a decrease in intralabyrinthine pressure and a transient improvement in hearing [Klockhoff and Lindblom, 1966]. Electrocochleography may reveal an elevated summing potential/action potential ratio in MD, deemed secondary to the presence of endolymphatic hydrops [Gibson et al., 1977]. Videonystagmography reveals diminished peripheral vestibular function in the ear affected by MD, although testing during an acute episode of vertigo may

reveal an excitatory response [Sajjadi and Paparella, 2008]. More recent improvements in imaging technology, particularly of magnetic resonance imaging (MRI), have led to MRI emerging as a valuable diagnostic tool in MD. The relationship between MD symptomatology and membranous labyrinth edema as seen on MRI has recently been elucidated [Nakashima et al., 2007; Liu et al., 2008]. Using gadolinium-enhanced MRI and a 3-dimensional analysis protocol, labyrinthine edema and increased fluid was correlated with the degree of hearing impairment [Sepahdari et al., 2015].

Enlarged Vestibular Aqueduct

Another cause of fluctuating hearing loss is EVA, which commonly occurs in conjunction with the Pendred syndrome [Reardon et al., 2000]. Hearing loss is variable and most commonly affects high frequencies at initial presentation; later, hearing loss across all frequencies is commonly seen [Levenson et al., 1989]. Hearing loss is typically diagnosed in childhood, and worsening hearing thresholds have been associated with closed head trauma, strenuous exercise, and upper respiratory infections. A recent meta-analysis revealed that decreased hearing after minor head trauma was reported in roughly one-third of patients with EVA [Noordman et al., 2015]. The classic radiographic description, by Valvassori and Clemis [1978], is an enlargement of the vestibular aqueduct >1.5 mm in diameter. The newer Cincinnati criteria define EVA as a diameter ≥ 1.0 mm at the midpoint or 2.0 mm at the operculum [Boston et al., 2007]. Cross-sectional imaging, including computed tomography and MRI, is the gold standard for diagnosis [Hirsch et al., 1992; Okamoto et al., 1997].

EVA commonly presents with stepwise, progressive hearing loss, but hearing fluctuations can also occur [Ito et al., 2014]. The mechanism of these hearing fluctuations in EVA is not clear. Proposed etiologies have included changes in intracranial pressure causing pressure changes within the inner ear. Similar to MD, this can cause microruptures in the membranous labyrinth, leading to disruption in the endolymphatic and the perilymphatic composition and the electrochemical gradient [Jackler and De La Cruz, 1989].

The genetic etiology of EVA has been identified as *SLC26A4*, which encodes pendrin, an anion exchange protein [Everett et al., 2001]. In a rat model, loss of expression led to enlargement of the endolymphatic sac, with consequences on hearing and vestibular function. Associated abnormalities include blood vessel degeneration and pigmentary abnormalities [Wangemann et al., 2004; Albert et al., 2006].

Autoimmune Inner Ear Disease

A third condition presenting with fluctuating hearing loss is AIED [McCabe, 1979; Harris and Sharp, 1990]. AIED has been associated with systemic autoimmune conditions and viral infections, yet a significant proportion of patients lack systemic manifestations [Hughes et al., 1988]. Antigen-antibody interactions in the inner ear have long since been described [Lehnhardt, 1958]. These can lead to the development of bilateral hearing loss, and AIED is characterized by rapid progression of the hearing loss. Bilateral involvement is estimated to exceed 80% of cases [Girasoli et al., 2018]. This can fluctuate both early and late in the disease; spontaneous regression has also been described [Moscicki et al., 1994]. Viral etiologies, including associations with cytomegalovirus, herpes zoster, herpes simplex type I, influenza type B, and mumps, have been implicated [Merchant et al., 2008]. A seminal paper investigating the antibody profile of both human subjects and an animal model of experimental autoimmune SNHL demonstrated an autoantibody reactive to a 68-kD inner ear antigen [Harris and Sharp, 1990].

On a related note, the immune system has been implicated in hearing loss separate from AIED. For example, patients with sudden low-frequency hearing loss demonstrate low serum concentrations of CD4- and CD8-positive lymphocytes compared to normal controls [Garcia-Berrocal et al., 2006]. Monocytes and macrophages are the primary actors, and the inflammatory cascade causes an immune response resulting in potential tissue damage [Wynn et al., 2013]. Human immunodeficiency virus infection in young adults (age 18–35 years) has been associated with an increased risk of sudden hearing loss, an observation that hints at the potential effects of the immune system on hearing [Assuiti et al., 2013; Burdo et al., 2013; Lin et al., 2013].

Treatment of MD

Although treatment of fluctuating hearing loss varies based on the specific etiology, strategies and medications demonstrate significant overlap. Initial treatment of MD includes medical measures such as a low-salt diet, diuretics, and betahistidine. Ultimately, however, the natural history of MD is progressive stabilization of hearing [Herraiz et al., 2006], and, therefore, the consequence of any active MD treatment on the final hearing outcome is controversial [Grant and Welling, 1997; Kinney et al., 1997; Fisher et al., 2012]. Just the same, some research suggests that timely MD therapy can lead to better long-term hearing [Tokumasu et al., 1995; Wu and Minor, 2003]. This is likely secondary to the observation that patients with MD

demonstrate pathological, structural changes not only in the cochlea (e.g., cochlear edema) but also in the auditory nerve. Because of this, early pharmacologic therapy may be beneficial for long-term hearing outcomes [Paparella et al., 1982; Megerian, 2005].

Treatment of MD can be stratified into medical and surgical therapies as well as nonablative versus ablative therapies. Medical nonablative therapies include lifestyle modification with a low-salt diet, diuretic therapy, corticosteroid therapy (including intratympanic administration), and betahistine. Medical ablative therapies include intratympanic gentamicin injection. Surgical nonablative therapies include endolymphatic sac decompression and the endolymphatic-mastoid shunt, while surgical ablative therapies include vestibular nerve section and labyrinthectomy.

Diuretic therapy in MD is aimed at reducing intralabyrinthine pressure, analogous to the effects of the glycerol test [Klockhoff et al., 1974]. Various regimens have been proposed, including acetazolamide, hydrochlorothiazide, and the combination of triamterene and hydrochlorothiazide. Acetazolamide likely has central effects that may ameliorate symptoms further [Foster, 2015].

Bethahistine is a histamine receptor agonist that has been proven beneficial in the treatment of MD not only by limiting vertigo but also by improving hearing and stabilizing fluctuations. It acts as a vasodilator, causing increased blood flow to the cochlea, but its beneficial effects have also been attributed to inhibition of vestibular nuclei. It has been shown to be more effective than placebo [Lacour et al., 2007], and it is typically given at a dosage of 16 mg twice or three times daily. Dosages up to 480 mg/day have even been reported [Lezius et al., 2011]. In a more recent investigation, both low- and high-dose bethahistines were noted to be no better than placebo at improving the symptoms of MD [Adrion et al., 2016].

Pressure equalization tube (PET) placement has been reported as MD treatment. The mechanism of benefit is unclear, but patients may undergo PET placement in preparation for the Meniett device (Medtronic Xomed, Jacksonville, Florida, USA). The Meniett device introduces low-pressure pulses through the tympanic membrane (via PET or, if present, an existing tympanic membrane perforation). In a recent study, both PET placement alone and PET placement with the Meniett device improved patient symptoms [Russo et al., 2017]. Recent meta-analyses of the Meniett device have reached differing conclusions, with 2 reviews supporting the use of the device [Ahsan et al., 2015; Zhang et al., 2016] and 1 review noting that the device had no benefit [Syed et al., 2015].

Ablative medical therapy in the treatment of MD notably consists of intratympanic gentamicin injection. Gentamicin is directly toxic to vestibular hair cells, dark cells of the stria vascularis, and the cristae ampullaris, and causes a decrease in endolymph production. In a meta-analysis, gentamicin therapy was found to be 96% effective in controlling vertigo when administered in a titrated fashion, with 82% achieving complete control of vertigo. Hearing loss was noted in 13–35% of patients who underwent injection, with multiple doses daily associated with a greater degree of hearing loss [Chia et al., 2004]. However, some patients remain refractory to intratympanic gentamicin injections, and this has been hypothesized to be secondary to the robustness of the utricular macula to gentamicin toxicity in select patients [Ishiyama et al., 2007].

Surgical treatment in MD is reserved for patients with more severe symptoms. Surgical management may be divided into 2 main categories: first, nonablative operations aimed at changing the physiology of the disease, and, second, ablative operations aimed at removing the inner ear function and/or the nerve connection to the brain [Wiet et al., 1981; Konrad, 1986].

Nonablative surgical options most prominently include endolymphatic sac decompression/shunt in addition to the less-frequently performed semicircular canal plugging [Charpiot et al., 2010]. Endolymphatic sac decompression has been associated with postoperative improvement of hearing, which generally remains stable after surgery [Bretlau et al., 1989]. At the time of sac decompression, a silicone shunt may be inserted into the mastoid, the so-called endolymphatic mastoid shunt. In a contrasting report, however, endolymphatic sac surgery demonstrated no significant hearing difference between MD patients who underwent surgery compared to a control group [Thomsen et al., 1981], which has been supported by additional research [Welling and Nagaraja, 2000]. Endolymphatic sac surgery may be more efficacious in treating vertigo symptoms, and decompression and shunt placement are generally regarded as being equally efficacious [Sood et al., 2014]. An argument for decompression over shunting is the theoretically decreased risk of meningitis with decompression and the possibility of worse hearing outcomes associated with shunt placement [Sood et al., 2014].

Destructive surgical options for MD include labyrinthectomy, which can be performed in either transmastoid or transcanal fashion [Cawthorne, 1957; Kemink et al., 1989]. Lateral semicircular canal plugging has also been described and can be effective at controlling rotatory ver-

tigo [Charpiot et al., 2010]. Vestibular nerve section may also be performed, and surgical approaches include the middle fossa, retrolabyrinthine, retrosigmoid, and trans-labyrinthine approaches [Glasscock et al., 1980]. These can lead to durable resolution of vertigo, although profound hearing loss may be an unavoidable consequence depending on the approach used [Kemink et al., 1989; Teufert and Doherty, 2010].

Bilateral MD is estimated to occur in 10–25% of patients [House et al., 2006]. In patients with bilateral disease, nonablative therapies are preferred, as removal of bilateral peripheral function via ablative treatments, either medical or surgical, can lead to oscillopsia and permanent instability [Pykkö et al., 1994].

Treatment of EVA

Medical management of patients with EVA is primarily aimed at treating any sudden loss of hearing regardless of any association with trauma. Treatment with corticosteroids is generally accepted as beneficial. In one study, 80% of EVA patients treated with corticosteroids experienced hearing improvement, while only 20% of EVA patients not treated with corticosteroids improved spontaneously [Grimmer and Hedlund, 2007]. Other reports have suggested that steroid therapy does not change the natural course of the disease and does not decrease the volatility of patients' hearing.

The role of surgery in EVA is less clear. Endolymphatic sac surgery has been suggested as a technique to ameliorate hearing loss with variable success, including worse postoperative hearing in select cases [Jackler and De La Cruz, 1989; Welling et al., 1999].

Cochlear implantation (CI) may be entertained in patients with EVA who demonstrate profound hearing loss, particularly bilaterally. EVA patients demonstrate acceptable performance after CI [Au and Gibson, 1999; Miyamoto et al., 2002]. Curiously enough, however, fluctuating hearing in EVA patients following CI has also been described, with an incidence approximating 75% [Lai and Shiao, 2004; Wu et al., 2008]. Potential causes include changes in endolymphatic fluid pressure leading to fluctuations in electrode impedance [Powell and Birman, 2015]. Given the potential for spontaneous improvement in hearing in EVA, the timing of implantation following progressive hearing loss is also a matter of debate. Only after stabilization of hearing should CI be considered [Chen et al., 2011]. Long-term data regarding CI in EVA suggest that a majority of patients achieve good hearing and speech recognition 5 years post-CI [Ko et al., 2013].

Treatment of AIED

Corticosteroids are commonly used for hearing fluctuations in patients with AIED. The standard dosage is 1 mg/kg/day or 60 mg/day for at least 1 week, or until the hearing improves, followed by a taper [Rauch, 1997]. When treating AIED, corticosteroid therapy may last for weeks, if not longer [Niparko et al., 2005], although an average treatment duration of 4 weeks has been proposed [Loveman et al., 2004]. High-dose steroid pulse therapy has also been noted to be effective, although steroid side effects may limit long-term high-dose therapy in AIED [Alexander et al., 2009]. Common considerations with steroid therapy include exacerbation of preexisting diabetes or tuberculosis as well as gastrointestinal and neurological side effects. Avascular necrosis of the femoral head has also been described [Alexander et al., 2009].

Intratympanic injections for AIED may also be considered; these are typically performed on a weekly basis [Garcia-Berrocal et al., 2006]. Intratympanic injections have the benefit of minimizing systemic side effects of corticosteroid therapy, although their additional efficacy over oral steroids has not been proven. More targeted therapies for AIED include low-dose methotrexate, which has been associated with hearing improvement [Matteson et al., 2001]. However, in a randomized, double-blind, placebo-controlled trial, methotrexate was not found to maintain the hearing improvement achieved with prednisone therapy [Harris et al., 2003]. Azathioprine has also been suggested [Lasak et al., 2001]. Adalimumab and rituximab were studied in the treatment of AIED and demonstrated significant improvements in vertigo, tinnitus, and aural fullness, but not in hearing loss [Matsuo-ka and Harris, 2013]. The use of immune modulators in AIED remains a subject of active research [Derebery et al., 2014].

Discussion

Fluctuating SNHL, defined as SNHL that fluctuates on serial audiometry and/or by subjective patient complaint, can represent a spectrum of conditions that may present similarly. A patient may first present with a single episode of sudden SNHL. On follow-up, hearing levels may improve and worsen; if this is the case, then fluctuating SNHL is diagnosed. Meanwhile, initial treatment of any sudden SNHL with corticosteroids is reasonable, and asymmetric sensorineural function should be evaluated with MRI. MRI can diagnose EVA, while MD and AIED are diagnosed primarily via history.

Medical and surgical treatments depend on the severity of the disease and the specific pathophysiological process involved. Treatment of additional hearing loss subsequent to the initial episode includes further corticosteroid therapy, administered in either oral or intratympanic fashion. Surgical treatment may be considered for MD and includes nonablative and ablative procedures.

Over the course of follow-up, patients may progress to profound hearing loss in one or both ears in all 3 conditions: EVA, MD, and AIED. When this is the case, CI may provide significant benefit in hearing rehabilitation. Ultimately, a low threshold of suspicion for fluctuating SNHL is essential to ensure timely diagnosis and appropriate treatment.

Statement of Ethics

The authors have no ethical conflicts to disclose.

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Author Contributions

Drs. Liu and Zhou provided substantial contributions to the conception or design of the work. Drs. Zhang and Peng provided acquisition, analysis, and interpretation of the data for the work. Drs. Liu, Zhou, Zhang, and Peng drafted the work and revised it critically for important intellectual content, provided final approval of the version to be published, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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