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It is 2015: What are the best diagnostic and treatment options for Ménière's disease?

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Abstract

Ménière's disease (MD) is a common cause of recurrent vertigo. Its pathophysiology is still unclear and controversial. The most common histological finding in postmortem temporal bone studies of patients is endolymphatic hydrops (EH). However, not all cases of hydrops are associated with MD and it may represent the end point of various etiologies. The diagnostic criteria for MD have undergone changes during the past few decades. A recent collaboration among specialty societies in United States, Europe and Japan has given rise to a new set of guidelines for the diagnosis and classification of MD. The aim is to develop international consensus criteria for MD that would help improve the quality of data collected from patients. The diagnosis of MD can be difficult in some cases as there is no gold standard for testing. Previous use of audiometric data and electrocochleography are poorly sensitive as screening tools. Recently magnetic resonance imaging as a diagnostic tool for identifying EH has gained popularity in Asia and Europe. Vestibular evoked myogenic potentials are also used but lack specificity. Finally, the treatment for MD has improved with the introduction of intratympanic treatments with steroids and gentamicin as well as less invasive treatment with the Meniett device.

Key words: Ménière's disease; Review; Pathophysiology; Diagnosis; Treatment

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Core tip: The pathophysiology of Ménière's disease (MD) is still unclear and controversial. The most common histological finding in postmortem temporal bone studies of patients is endolymphatic hydrops. This finding is utilized in the newest method of diagnosis

using magnetic resonance imaging with intratympanic or intravenous gadolinium. Changes to the diagnostic criteria have been proposed with collaboration from various international societies. This will help in communication and improve quality of published data. Finally, the use of intratympanic steroids and Meniett pressure treatments offers less invasive and destructive treatments for patients with MD.

Shah S, Ignatius A, Ahsan S. It is 2015: What are the best diagnostic and treatment options for Ménière's disease? *World J Otorhinolaryngol* 2016; 6(1): 1-12 Available from: URL: <http://www.wjgnet.com/2218-6247/full/v6/i1/1.htm> DOI: <http://dx.doi.org/10.5319/wjo.v6.i1.1>

INTRODUCTION

Ménière's disease (MD) is an inner ear disorder that is characterized by episodic vertigo, low-pitched tinnitus and fluctuating hearing loss lasting for a minimum of 20 min. In the United States, 190 people per 100000 are affected, with a 2:1 female to male ratio^[1]. MD was named after the French physician Prosper Ménière, who in 1861 first argued that MD was an inner ear disorder and not a neurological one^[2]. Much time after his death, the most common finding in postmortem human temporal bone studies of MD patients was endolymphatic hydrops (EH), which is the dilation of the membranous labyrinth of the inner ear^[3]. It should be noted however that not all cases of EH are associated with MD^[4]. The lack of certainty in understanding the pathophysiology of MD makes it difficult to properly diagnose and treat. Most treatments are aimed at reducing endolymphatic size and pressure after which non-responders go on to ablative treatments.

PATHOPHYSIOLOGY

MD is an idiopathic disorder wherein the mechanism underlying its pathophysiology is still unclear and controversial. Affected individuals differ in terms of etiology and thus many studies propose various explanations for the manifestation of symptoms. However, it is generally agreed upon that EH is a consistent histological hallmark of the disease, a phenomenon seen in numerous temporal bone studies^[4-7]. EH can be described as a pathologic finding in which the structures bounding the endolymphatic space are distended by an enlargement of endolymphatic volume^[8]. The consequent hydropic state leads to various mechanical and chemical perturbations that ultimately give rise to the classic symptoms of MD.

In the cochlea, distension of the scala media causes the endolymphatic space to impinge on the bordering perilymphatic compartments. According to Wit *et al*^[9] the degree of distension is related to the mechanical compliance of the membrane involved. This explains why

EH is more prevalent in the cochlea and saccule, which are relatively more compliant than other structures such as the utricle or semicircular canals. Long-term distension may eventually lead to rupture of inner ear membranes. For example, rupture of Reissner's membrane has been reported in patients with MD, although Paparella *et al*^[10] note the absence of rupture in two thirds of patients. Nonetheless, it has been theorized that membrane rupture leads to an electrolyte imbalance, causing acute vertigo and hearing loss^[4,5,8,10,11]. Chemically, the hydropic state also creates a neurotoxic environment that leads to apoptosis of spiral ganglion cells^[5]. Excitotoxicity may therefore contribute to the auditory symptoms of MD.

Previous research has shown that almost all patients diagnosed with MD present with EH in the affected ear. However, this consistent finding does not imply that EH is the direct underlying cause of MD. Several studies involving histopathological examinations of human temporal bones have revealed that not every patient with EH presents with symptoms of MD^[4,12,13]. This makes it difficult to infer a simple cause-and-effect relationship. Instead, EH may be the result of various etiologies that disrupt normal endolymphatic fluid homeostasis. Semaan *et al*^[5] separate these etiopathogenic factors into intrinsic or extrinsic. Intrinsic factors may include hypoplasia of labyrinthine structures, anteriorly and medially displaced sigmoid sinus, genetic factors, and other causes attributable to the inner ear itself. Extrinsic factors include autoimmune disease, allergy, otosclerosis, viral infection and trauma^[5].

Genetics

Genetically, MD follows an autosomal dominant pattern with 60% penetrance^[14]. Koyama *et al*^[15] (1993) found relatively higher levels of histocompatibility antigens in affected patients, with HLA-DR, DQ, DP, A2 and B44 being particularly noteworthy^[16]. Furthermore, a missense mutation of the *COCH* gene in the DFNA9 locus has been shown to produce MD-like symptoms such as progressive sensorineural hearing loss and vestibular dysfunction^[17]. However, Morrison and Johnson propose that the *COCH* gene is an unlikely candidate for MD^[18]. Lastly, an animal model of postnatal EH in mice suggests that genetics may play a role in posttranscriptional modification of the gene product, which also explains phenotypic differences between patients^[5]. Overall, investigations into the genetic basis of MD suggest that multiple genes may be involved, and in combination they render certain individuals more susceptible to developing the disease.

Autoimmunity

It is believed that the immunological basis of the pathogenesis of MD may involve reactions between antibodies and tissue antigens, or IgG- and IgM-mediated circulating immune complexes (CICs)^[19]. While larger CICs are cleared from circulation, smaller complexes can

Table 1 1995 American Academy of Otolaryngology-Head and Neck Surgery diagnostic criteria for Ménière's disease

Certain	Definite Ménière's + histological confirmation
Definite	≥ 2 definitive spontaneous vertigo episodes ≥ 20 min + all criteria in Probable Ménière's disease
Probable	1 definite episode of vertigo audiometric hearing loss on ≥ 1 occasion Aural fullness or tinnitus in the affected ear Other causes exclude
Possible	Episodic vertigo of Ménière's type with no documented hearing loss or Fluctuating or fixed SNHL with disequilibrium without definitive vertigo episodes Other causes excluded

SNHL: Sensorineural hearing loss.

continue to circulate and accumulate in inner ear tissues, causing a local inflammatory response^[19]. Deposition within the stria vascularis and endolymphatic sac may even lead to increased vascular permeability, and the sudden efflux of fluid induces EH and even rupture of Reissner's membrane^[20]. Success with steroid-based treatments, which act as an anti-inflammatory agent, also bolsters the argument for an immunologic mechanism in the development of MD^[5]. Furthermore, other studies note the presence of intraluminal eosinophilic material within the endolymphatic duct, and conclude that it is evidence of an immunodefensive system in the inner ear as this material contains the macrophages that trap antigen^[21,22].

Endolymphatic duct and sac

The longitudinal flow theory states that the unidirectional flow of endolymph begins in the stria vascularis where it is produced, travels through the endolymphatic duct, and is eventually absorbed by the endolymphatic sac^[5]. Thus, it follows that narrowing of the endolymphatic duct could impair endolymph absorption at the sac, and consequently result in a hydropic state. In fact, numerous guinea pig models show the development of hydrops following surgical obstruction of the endolymphatic duct^[4]. However, Salt and colleagues found that the hydropic state could not be a result of the blockage of longitudinal flow because the rate of endolymph flow was too small. Instead, they believe that endolymphatic homeostasis is not volume-dependent; rather, it is dominated by ion transport and water equilibration *via* osmotic gradients^[23,24]. Shinomori *et al.*^[25] (2001) further this idea by proposing a cytochemical mechanism for the development of hydrops. After blocking the endolymphatic duct in 22 guinea pigs, changes were noted in the cytochemistry of type I and II fibrocytes as well as nonsensory epithelial cells before the development of hydrops. Blocking the endolymphatic duct changed the composition of perilymph, thus placing osmotic stress on fibrocytes, which are important in maintaining fluid homeostasis. Merchant *et al.*^[4] hypothesizes that the dysfunction of fibrocytes interferes with K⁺ recycling,

leading to osmotic imbalance and expansion of the endolymphatic compartment.

CLASSIFICATION

The criteria for diagnosis of MD have undergone various changes within the past few decades. In 1974, the Japanese Society for Equilibrium Research proposed a set of conditions that classified the disorder into either definite or suspicious/uncertain MD. Lopez-Escamez *et al.*^[26] briefly outlined those conditions as the following: (1) repeated attack of whirling vertigo; (2) fluctuating cochlear symptoms; and (3) exclusion of central nervous system involvement, CN VIII tumor and other cochleovestibular diseases. A diagnosis of definite MD required fulfillment of all three conditions while suspicious/uncertain MD involved two of the conditions with the third being necessarily included^[26].

The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) also developed a set of guidelines in 1972, which were revised in 1985 and again in 1995. Nearly all studies since then have been based on the 1995 criteria, which classified MD into possible, probable, definite and certain^[27] (Table 1). A recent collaboration among the Equilibrium Committee of the AAO-HNS, the Japan Society for Equilibrium Research, the European Academy of Otolaryngology and Neuro-Otology, the Korean Balance Society and the Bárány Society gave rise to a new set of guidelines for the diagnosis and classification of MD (Table 2). The aim was to develop international consensus criteria for MD to improve the quality of data collected from patients. Furthermore, clarification was needed with regards to the nature of auditory symptoms^[26].

DIAGNOSIS

Audiogram

Traditionally, the most common audiometric configuration for patients with MD involved a "rising" pattern during the early stages, indicating low frequency hearing loss, followed by a flat audiogram in later stages of the disease^[28-30]. However, Opheim and Flottorp began to notice a pattern involving a "peak" audiogram in many of their patients with MD^[31]. Further investigations have been conducted in order to assess the usefulness of the peak audiogram as a diagnostic tool. In one study, 363 hearing impaired ears with MD were assessed for evidence of a peak audiogram. Paparella *et al.*^[28] (1982) noted the presence of a peak audiogram "if the air conduction threshold for one test frequency was at least 10 dB better than both hearing thresholds for the two adjacent octave frequencies". The reported sensitivity of the peak audiogram in detecting MD was 41.7%, while the specificity was 93.4%^[28]. Therefore, the audiogram appears to be useful in ruling out the possibility of MD in patients without a peak configuration. However, its low sensitivity makes it a poor diagnostic tool on its own. Perhaps the peak audiogram may best be used as an

Table 2 New proposed diagnostic criteria for Ménière's disease**Definite MD**

Two or more spontaneous episodes of vertigo, each lasting 20 min to 12 h

Audiometrically documented low- to medium-frequency sensorineural hearing loss in one ear, defining the affected ear on at least one occasion before, during or after one of the episodes of vertigo

Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear

Not better accounted for by another vestibular diagnosis

Probable MD

Two or more episodes of vertigo or dizziness, each lasting 20 min to 24 h

Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear

Not better accounted for by another vestibular diagnosis

MD: Ménière's disease.

adjunctive test to more advanced imaging techniques.

In a separate study by Lee *et al.*^[29], other audiometric patterns were considered in addition to the peak configuration. These included flat, rising, falling and dip configurations. The results once again supported a relatively higher proportion of the peak audiogram (50.65%), followed by the falling audiogram (26.26%), the dip audiogram (9.24%), and other types accounting for the remaining portion^[29]. Again, the low sensitivity of the peak audiogram makes it an unreliable diagnostic test for MD, and this study along with others show the involvement of a wider variety of configurations.

Paparella *et al.*^[28] also found that those with severe or profound hearing loss were just as likely to have a 2000 Hz peak audiogram as those with mild or moderate hearing loss. This implies that the prevalence of the peak audiogram is unrelated to the degree of hearing loss. Instead, prevalence of the peak audiogram appears to be affected by bilaterality and duration: Bilateral peak configurations are more likely to result in patients with bilateral diseased ears of longer duration^[28].

Magnetic resonance imaging

The use of magnetic resonance imaging (MRI) as a diagnostic tool for identifying EH gained popularity in 2007. Nakashima *et al.*^[32] (2007) used 3-T MRI following transtympanic (TT) gadolinium injection to visualize the endolymphatic space of patients diagnosed with MD, and since then it has been regarded as a possible gold standard test. It is also worth noting that a modified method involves intravenous (iv) administration of gadolinium.

The main outcome measure in using MRI as a diagnostic tool is perilymphatic enhancement in various portions of the labyrinth. Perilymphatic enhancement is an indirect measure of EH with progressively lower enhancement representing growing occupation of the perilymphatic space by the hydrops^[33]. For example, in the cochlea, decreased visualization of the scala vestibuli indirectly infers increased displacement of Reissner's membrane brought about by EH^[34]. Though perilymphatic enhancement is a reliable tool for inferring the presence of hydrops, the possibility of false positive findings cannot be ruled out. This could be due to impaired filtration of gadolinium into the perilymphatic

compartment as a result of degenerative changes in the inner ear^[33].

Gadolinium injection followed by MRI appears to be a well-tolerated test with good image quality, and relatively few, if any, complications have been reported^[35,36]. Furthermore, numerous studies support a high sensitivity of the test for identifying EH in symptomatic ears, whether the contrast is administered intravenously or using the TT method. Recent studies investigating the use of MRI as a diagnostic test report a relatively consistent sensitivity as high as 90%-100%^[33,36,37]. These results are comparable with previous investigations and bolster the usefulness of MRI as a diagnostic tool for the presence of EH in symptomatic ears. It is worth noting a recent study that compared MRI with tone burst electrocochleography (ECoG) in the diagnosis of MD. The sensitivity results with MRI differed significantly from previous studies, reporting 47%, 29%, and 8% for definite, probable and possible MD respectively^[35].

While gadolinium-enhanced MRI shows promise as a reliable tool for positively identifying hydrops in patients with MD, its specificity requires further investigation. Few studies have been conducted on this measure and the results are variable. For example, Pyykkö *et al.*^[37] found that MRI visualized EH in 65% of asymptomatic ears (35% specificity). In contrast, other studies yield better results in terms of correctly not identifying hydrops on MRI in asymptomatic ears. Baráth *et al.*^[34] used IV Gadolinium injection followed by MRI to look for hydrops in 53 patients with MD, reporting a specificity of 78%. Fiorino *et al.*^[33] had even better results with TTGad injection, noting no perilymphatic enhancement defects in all unaffected contralateral ears of patients with MD (100% specificity).

Generally, TTGad injection is preferred over the IV route because it provides a higher perilymphatic signal and thus a better visualization of the compartment^[38]. However, the advantages of IV injection should not be ignored and perhaps could be used in special cases. Of particular importance is its less invasive nature, the ability to simultaneously examine both ears for comparison and the fact that perilymphatic enhancement is independent of the status of the round window membrane^[34,39].

ECoG

ECoG is a technique that measures the electric poten-

tials generated in the cochlea in response to an auditory signal. The usual ECoG response consists of a cochlear microphonic (CM), the summing potential (SP) and the cochlear nerve compound action potential (AP). The CM is mainly generated by the outer hair cells closest to the recording electrode. Due to its proximity, the CM closely resembles the waveform of the stimuli and vibrations of the basilar membrane. If the polarity of the stimulus is reversed, the polarity of the CM will also reverse. The alternate polarity stimuli are used to cancel the amplitude of the CM so that SP and AP can be measured. The SP consists of a shift in the baseline of a CM in response to click stimuli and a deflection before the AP in response to tone-burst stimuli. Finally, the AP is the sum of the individual APs from the auditory nerve fibers^[40]. Two methods of obtaining ECoG differ by where the electrode is placed: TT has an electrode on the promontory wall of the middle ear and Extratympanic (ET) has one outside of the tympanic membrane. The ET method has a slightly lower sensitivity and specificity because of low signal amplitude, but is still the preferred method due to it being non-invasive and easy to implement. Using tone burst auditory stimuli is more reliable than the commonly used auditory clicks stimuli^[41].

The SP/AP ratio is commonly used to identify EH. The thresholds for the ratio vary with some authors suggesting 0.5 for ET with clicks and alternating polarity while others suggest 0.33 for TT. There is no universally agreed SP/AP ratio that we could find^[41]. It is thought that altered SP and AP is the result of mechanical asymmetry in the basilar membrane^[42].

Electrovestibulography (EVestG) is similar to ECoG except that it measures saccule function instead of cochlear function. Instead of acoustic stimuli, the patient experiences passive whole body tilts in a hydraulically controlled chair located in an electrically and acoustically shielded chamber. The test has shown encouraging results in other neurological diagnostic applications such as Parkinson's disease, depression, and schizophrenia disorder by other studies. It is possible that with more research, EVestG could be used to identify neural firing patterns that are diagnostic in patients with MD^[43].

Sensitivity of ECoG ranges from 57% to 71% and specificity ranges from 94% to 96%^[41]. A study found 1 kHz tone-burst stimuli to be the most reliable stimuli with a sensitivity of 86% and specificity of 80.5%^[44]. ECoG interpretation is complicated by the fluctuating behavior of MD. Sensitivity can go from 60% to 92% when ECoG is used during a symptomatic period^[41]. Additionally, sensitivity is found to increase with duration and severity of the disease. A study found 71% sensitivity in stage 1 MD compared to 90% in stage 4, and 43% in MD for less than 1 year duration compared to 100% in 30 years duration^[45]. However, ECoG is not a useful tool in differentiating between definite and probable MD^[41].

Vestibular evoked myogenic potentials

Vestibular evoked myogenic potentials (VEMPs) are

becoming a popular tool to assess inner ear function. Cervical VEMPs utilize the vestibulocolic reflex by measuring the inhibitory potentials of the ipsilateral sternocleidomastoid muscle in response to loud auditory signals. Signals from the acoustically responsive sensory cells and neurons of the saccule are conducted centrally *via* the inferior vestibular nerve^[46]. Studies have shown that altered motion mechanics of the distended saccule can lead to an altered VEMP response in MD patients^[46]. A cVEMP curve is made by plotting the dB SPL as a function of frequency for tone bursts at 250, 500, 750 and 1000 Hz. Healthy patients are most sensitive at 500 Hz and patients with MD showed a sensitivity shift to 1000 Hz^[47]. Thirty percent of unaffected ears in patients with unilateral MD also show a sensitivity shift, but to a lesser degree. This could be because the unaffected ear has a minor form of MD. It was found that normal adults above the age of 60 show a sensitivity shift. In some cases they showed flattening of the threshold response curve. A high proportion of patients with caloric asymmetry $\geq 25\%$ did not show any VEMP response^[47].

Another version of VEMP called ocular VEMP records excitatory potentials from the superior vestibular nerve going to the inferior oblique and inferior rectus muscles of the opposite side^[48,49]. It is thought that utricular afferents and some saccular afferents travel through the superior nerve division and most saccular afferents travel through the inferior division. With more research, VEMPs could be used to differentiate dysfunction in the otolith and saccule^[50]. VEMP measurement has been found to be a more reliable test for saccule function compared to a calorics^[51]. It has been suggested that a negative VEMP test does not rule out MD, however a positive test result suggests that MD is probable^[47].

MIGRAINE AND MÉNIÈRE'S

Since the term MD was first coined, the prevalence of migraine among MD patients and MD among migraine patients has suggested a possible link between these two diseases^[52]. What was once called Vestibular Ménière's is no longer recognized by the current guidelines for MD^[53]. Others suggest that most likely this variant of MD was actually undiagnosed vestibular migraine (VM)^[54,55].

Recently, the Migraine Classification Subcommittee of the International Headache Society has proposed diagnostic criteria for VM which have been included in the International Classification of Headache Disorders (ICHD) 3rd beta edition. It should be noted that the term VM could be used interchangeably in other papers with migraine-associated dizziness/vertigo and migrainous vertigo. According to the ICHD, VM is characterized by vestibular symptoms such as vertigo and head motion-induced dizziness lasting between 5 min and 72 h. Common symptoms in MD such as tinnitus, aural pressure and fluctuating hearing loss other than profound can occur in VM. Likewise, migraine headaches, photophobia and even migraine auras are

common in MD^[56]. A pathophysiological relationship between MD and VM remains uncertain however some theories have been proposed. The prevalence of allergy among MD and migraine patients compared to the general population may suggest an immunological link^[57]. There is some evidence of increased IgE levels in MD patients that could lead to EH in MD and meningeal vasculature changes in migraines^[57,58]. However, more work needs to be done in this area to support this claim.

Early MD can present with early episodic vertigo only and can be difficult to separate from VM. Differentiating MD from VM can be done through the patient's history or by means of vestibular function tests^[56]. In VM the spells of vertigo can be anywhere from few minutes to over 24 h. Migraine is more likely the source of vertigo if there are associated features like photophobia, paresthesia, visual disturbances (scintillating lights, visual hallucinations). Meanwhile, patients with MD will eventually develop a progressive hearing loss. In VM while audiometric and vestibular test findings can be found, they are typically mild and do not fluctuate over time^[52]. A recent study using VEMP separated MD from VM with a sensitivity of 90% and specificity of 70%^[59]. Shepard suggests that if VM is likely, even though MD has not been ruled out, it is better to treat for migraine. Even in cases where both migraine and MD coexist, it is better to treat migraine first^[52].

TREATMENTS

Dietary/salt restrictions

The typical first treatment option for an MD patient is a low salt diet consisting of sodium in the range of 1000 mg to 2000 mg per day^[60,61]. Some patients with MD report that a salt binge seems to precede an acute episode of MD^[61]. The purpose of the diet is to reduce endolymphatic pressure, due to the idea that a high-salt diet can influence the osmotic gradients in the inner ear to develop hydrops^[61]. Some however have challenged the idea that a salt diet could affect the plasma sodium level or fluid dynamics in the inner ear. Sodium levels in endolymph have been found to be normal in animals with induced EH and patients from which endolymph were sampled. Thai-Van *et al*^[62] suggests the alternative theory that a low sodium intake influences aldosterone secretion that may affect endolymph regulation.

There have been some reports that a low sodium diet associated with diuretics brings positive result^[63,64]. However, the evidence in the literature to support low sodium diet as an effective treatment for MD has been lacking. A low salt diet can limit the patient's lifestyle and quality of life. This can often make it difficult to remain on the diet in the long-term^[61].

Diuretics

Diuretics are relatively inexpensive and commonly used to treat MD^[60]. The purposes of diuretics are to alter ion concentrations in order to reduce endolymphatic

volume and pressure. Some have argued against the use of diuretics suggesting that there are too many active mechanisms and buffer systems in the inner ear for diuretics to be useful^[65]. As previously noted, smaller studies have found that the use of diuretics with a low salt diet can be beneficial^[63,64]. A recent Cochrane review found no evidence in support for or against the use of diuretics because of the lack of articles that meet accepted review standards^[66]. Common side effects are weakness, dizziness and headache. Serious side effects are cardiac arrhythmias, hyperkalemia, renal failure and hypersensitivity^[67]. Side effects are much more prevalent in the elderly population^[68]. It is important to avoid drugs that increase serum potassium concentration and antiarrhythmic drugs because Dyazide can potentiate toxicity. In addition, Dyazide interacts with methotrexate, lithium, cyclophosphamide, pixantrone, and others^[67]. Pirodda *et al*^[65] suggests diuretics lower blood pressure, which can exaggerate a vasomotor response inducing local ischemia, which can lead to damage.

Betahistine

Betahistine is one of the most widely used drugs to treat MD, with 94% of surgeons prescribing it in the Europe and United Kingdom^[60]. In addition to being an H1 agonist and an H3 antagonist, it is thought to promote blood flow into the cochlea through the stria vascularis by its suspected vasodilatory effects^[69]. Several clinical trials have shown that Betahistine may in some way improve vertigo, nausea and vomiting^[70-74]. However, long term, longitudinal, uncontrolled trials have failed to show a benefit on hearing loss^[75,76]. A Cochrane review looking at 243 patients concluded that there is insufficient evidence for the effectiveness of betahistine^[77]. Some suggest that it should not be considered the gold standard therapy for MD^[78]. However, others suggest that Betahistine is a cheap drug with limited side effects and that if there is no improvement it should be withdrawn^[68]. Common side effects are bronchospasms, asthma, drowsiness, lethargy, nausea, headache, eye and skin irritation, peptic ulcers due to its histamine-like activity, mild stomach discomfort^[79-81]. However, systematic reviews still tend to underreport the side effects^[82].

TT steroid

Steroids have been used to treat an autoimmune response, ischemia and sudden sensorineural hearing loss, all of which have made it a likely candidate for the treatment of MD^[61,67,83]. Studies show that steroids can also have mineralocorticoid effects. Dexamethasone increases the principal epithelial sodium transporter of semicircular canals by threefold, possibly influencing the sodium and fluid dynamics in the inner ear^[84].

An older study showed promising results, with 82% of patients having improved vertigo when treated with steroids compared to 57% treated with saline injections^[85].

One trial showed that 91% of MD patients had adequate control with intratympanic dexamethasone injections and did not require more ablative treatments^[86]. A recent review looking at 5 RCT's found that there is enough evidence to support the effectiveness of intratympanic steroid for treating vertigo^[87]. There is a small risk of tympanic membrane perforation and middle ear inflammation^[67].

TT gentamicin

Gentamicin is an aminoglycoside antibiotic that is used as an ablative treatment for MD. Although both vestibulotoxic and cochleotoxic, the drug has a high affinity for type 1 vestibular hair cells and therefore results in more vestibular damage than hearing loss^[88]. Gentamicin is thought to operate by accumulating in hair cells and also interfering with calcium dependent receptors in the plasma membrane by competitive inhibition^[89,90]. Aminoglycosides can also interfere with hair cell secondary cell messengers and the integrity of the cell membrane^[91]. The drug is titrated to control vertigo symptoms, although some argue to titrate until there are signs of unilateral vestibular weakness. The main goal is to titrate just enough to get the most reduction of vertigo with the smallest reduction of hearing and balance. Titration of gentamicin until there is complete unilateral vestibular ablation is usually unnecessary and can result in worse hearing and balance outcomes^[67].

Gentamicin has been shown to be an effective treatment for vertigo with minimal vestibular loss compared to ablative surgeries^[87,92]. One RCT comparing intratympanic gentamicin to saline found a reduction of vertigo with an average reduction in hearing thresholds of only 8 dB^[93]. Another RCT comparing intratympanic gentamicin to dexamethasone found greater control of vertigo with gentamicin, with minimal hearing damage^[94]. Typically 54% of patients only require one injection and 96% do not need further ablative surgeries^[95]. Clinical evidence shows that anatomic factors such as adhesions or bone dust can prevent drug uptake by blocking the round window. Middle ear exploration with exposure of the round window membrane and direct application of gentamicin is effective at controlling vertigo in 75% of gentamicin non-responders^[96].

Resultant unilateral vestibular hypofunction can cause symptoms of imbalance with rapid ipsilateral head turns^[97]. Hearing loss can occur in 17% to 25% of patients^[98,99].

Meniett therapy

The Meniett device operates by adding positive pressure to the middle ear, which has shown to influence pressure in the inner ear^[100]. This is a noninvasive procedure that involves a short-term ventilation tube and consists of a repeated 0.6-sec. pulse at a range of 0 to 20 cm H₂O at 6 Hz applied to the middle ear. The treatment consists

of three to four cycles per day with each cycle lasting for 5 min^[101]. It is thought that the pulses vibrate the round window aiding in endolymphatic turnover^[67].

A 2014 meta-analysis looking at 12 studies including 2 RCTs found that the device improved short-term vertigo and some hearing^[101]. A recent Cochrane review from 2015 looked at 5 RCTs and found that only one showed an improvement in vertigo with positive pressure therapy^[102].

The Cochrane review found moderate quality evidence in two studies that hearing is worsened after use of the device^[102]. The Meniett device is minimally invasive other than the associated risks of inserting a ventilation tube.

Endolymphatic sac surgery

The endolymphatic sac is an outpouching of the endolymphatic membrane in contact with the dura of the temporal bone^[67]. It was originally thought to be involved in the resorption of endolymph but more recently was found to also have an immune function^[103]. Endolymphatic sac surgery is aimed at shunting, draining or decompressing the sac, which is thought to prevent hydrops by facilitating outflow of endolymph^[67]. Similar results have been noted in decompressing the sac vs shunting^[104]. The most common shunting technique is the endolymphatic mastoid shunt which involves draining endolymph from the sac into the mastoid cavity^[105]. A histological study looked at temporal bones after sac surgery and found that correct placement of the shunt had no relation to vertigo improvement^[106]. Ghossaini *et al*^[107] noted that in situations when the endolymphatic sac cannot be found, decompressing the surrounding dura gives positive results. Additionally, it is possible that removing the bone surrounding the endolymphatic sac could also lead to decompression^[107].

Endolymphatic sac surgery, although invasive, is considered a conservative approach because it leaves the vestibular neuroepithelium and innervation intact. Unilateral MD patients with intractable vertigo and especially bilateral MD patients that do not respond to medical treatments are considered for endolymphatic surgery in order to avoid possible hearing loss with ablative treatments^[107]. Some trials have found high rates of long-term improvement in vertigo with low risk of hearing loss^[108,109]. Some studies report 55% to 85% hearing stabilization or improvement^[110-112]. However, a Cochrane review in 2013 noted that 2 RCTs found no difference between treatment and placebo groups^[113]. It should be noted that the low number of patients considered for surgery out of the already low number of patients unresponsive to medical treatment makes it difficult to obtain high-level evidence. Patients who had good primary results from endolymphatic surgery but experience recurrence of symptoms after a period of time can be considered for revision sac surgery. The idea is that iatrogenic osteogenesis and perisacculus fibrosis reestablishes the pathogenic

state by compromising endolymphatic drainage^[114-116]. Huang^[117] found that perisaccular fibrosis is linked with recurrence of symptoms after surgery. It has been shown that correctional surgery will provide symptom relief^[114]. Some reports show that use of intraoperative mitomycin C to the endolymphatic sac area may prevent perisaccular fibrosis^[117]. Endolymphatic sac surgery has a small risk to residual hearing, up to 2%^[118]. Bleeding from the lateral sigmoid sinus and cerebrospinal fluid leak are other potential complications in endolymphatic sac surgery. Conductive hearing loss after endolymphatic sac surgery has been reported and is thought to be secondary to bone dust making its way to the middle ear^[118].

Vestibular nerve section

The purpose of vestibular nerve section (VNS) is to treat vertigo by selectively cutting the vestibular portion of CN VIII while preserving the cochlear portion. This surgery is usually the last option for clinicians when dealing with unilateral MD patients with hearing function that have exhausted all other medical and surgical treatments. Patients without hearing function would be considered for a labyrinthectomy. Patients with bilateral vestibular disease are not considered for a VNS because of the oscillopsia and permanent imbalance that can result from bilateral vestibular loss^[107]. VNS can be accomplished through either retrosigmoid or retrolabyrinthine approach. The retrosigmoid approach requires a suboccipital craniotomy and the retrolabyrinthine approach requires mastoidectomy. Both usually involve decompression of the internal auditory canal in order to identify and section the vestibular nerve. Care must be taken in order to avoid injuring the facial and cochlear nerve^[67]. VNS is the most effective treatment for vertigo in MD^[107]. Vertigo control rates between 78% and over 90% have been reported in the literature^[119-124]. Possible reasons for failure are incomplete sectioning of the vestibular nerve in order to avoid injury to the cochlear nerve and inability to identify the vestibulocochlear cleavage plane^[125]. Remaining or recurrent vertigo after surgery can be further treated by intratympanic gentamicin^[107]. About 4% of patients experience significant hearing loss^[124]. Other complications are facial nerve paralysis, cerebrospinal fluid leak, and headache^[107].

Labyrinthectomy

Labyrinthectomy is a destructive treatment involving the removal of the neuroepithelium from the five vestibular organs. The treatment is typically the last resort for unilateral MD patients with severe hearing loss that do not respond to medical and surgical treatments. As was the case for VNS, bilateral MD is a contraindication because of the oscillopsia and permanent imbalance that can result from bilateral vestibular loss^[107]. Several studies have shown excellent control of vertigo in up to 97% of patients^[16,126,127]. There is a 2% risk of facial nerve injury and a 3% risk of CSF leak^[128].

CONCLUSION

The pathophysiology of MD is still unclear and controversial, however EH represents the hallmark histological finding in postmortem temporal bone studies of patients. More than likely, it represents the end point of various causes. As we become more experienced with evaluating these patients it is necessary to fine tune the diagnostic criteria for improved communication and improve the reporting of research data across specialties. The new international consensus on diagnostic criteria is an important step towards this.

The diagnosis of MD can be difficult and many commonly used tests are poor screening tools. More specific diagnostic methods are needed to fine-tune the diagnosis and to help differentiate MD from Migraine associated vertigo. Recently MRI for identifying EH has gained popularity.

Finally, new and less invasive and destructive treatments of MD are available with the introduction of intratympanic treatments with steroids and gentamicin as well as the Meniett device.

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Management of intratemporal facial nerve schwannomas: The evolution of treatment paradigms from 2000-2015

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Abstract

Intratemporal facial nerve schwannoma (FNS) are rare benign tumors of the skull base. Many of these tumors will be detected during evaluation for symptoms suggestive of vestibular schwannoma. However, there are several signs and symptoms which can suggest the facial nerve as the origin of the tumor. Intratemporal FNS can be multiple, like "beads on a string", or solitary lesions of the internal auditory canal. This variable tumor

morphology necessitates multiple treatment options to allow patients the best chance of preservation of facial nerve function. Historically FNS were managed with resection of the nerve with cable grafting. However this leaves the patient with permanent facial weakness and asymmetry. Currently most patients find this outcome unacceptable, especially when they present with good to normal facial nerve function. Facial paralysis has a significantly negative impact on quality life, so treatment regimens that spare facial nerve function have been used in patients who present with moderate to good facial nerve function. Nerve sparing options include tumor debulking, decompression of the bony facial canal, radiosurgery, and observation. The choice of management depends on the degree of facial nerve dysfunction at presentation, hearing status in the affected ear, medical comorbidities and patient preference. Each treatment option will be discussed in detail and suggestions for patient management will be presented.

Key words: Facial nerve schwannoma; Middle cranial fossa; Intratemporal; Translabrynthine; Stereotactic radiosurgery; Cable graft; Tumor stripping; Facial nerve decompression

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Core tip: The management of intratemporal facial nerve schwannoma (FNS) has changed over the past 15 years. Current management strategies involve tumor stripping, bony decompression, radiosurgery, and observation. Each of these treatment options are designed to minimize the risk of injury to a functional facial nerve. Complete surgical excision and cable grafting are reserved for tumors which have already resulted in severe facial weakness. Each management strategy will be discussed in detail with a management algorithm will be presented. Intratemporal FNS are unusual benign tumors affecting the facial nerve as it passes through the bony canal of the temporal bone. Previous management paradigms involved complete resection of

the tumor and nerve with simultaneous cable grafting; however, patients were left with long term facial paresis. Newer treatment strategies resulting in less facial nerve morbidity have become more popular in the last 15 years including: Surgical debulking, stereotactic radiosurgery, bony decompression and observation. Each of these strategies will be discussed with emphasis on facial nerve outcomes and tumor control rates.

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INTRODUCTION

Facial nerve schwannoma (FNS) are rare benign tumors which can affect any part of the facial nerve (FN). Classically these tumors were treated with complete tumor resection and cable grafting of the residual nerve. However within the last 15 years the emphasis on preservation of FN function has become paramount. Various treatment modalities are available to this end: Observation, radiosurgery, debulking/tumor stripping surgery, or decompression of the facial canal. Physicians who manage these patients must understand the risks and benefits of the different treatment approaches and to understand their efficacy in managing FNS patients.

ANATOMY

The FN, cranial nerve VII, has a complex anatomy and path. The FN can be divided into four segments: The brainstem nucleus and tracts, cisternal segment, intratemporal segment, and peripheral segment. The FN nucleus comprises the motor component whereas the nucleus ambiguus is the first order synapse for the sensory division of the nervus intermedius which runs with the main trunk of the FN. The cisternal segment begins as the nerve exits the brainstem and ends as the nerve enters the internal auditory canal (IAC). This segment has no epineurium. The intratemporal segment begins at the porus acusticus and travels through the bony facial canal to end at the stylomastoid foramen. The intratemporal nerve can be divided into 5 discrete segments: Fundal (IAC), labyrinthine, geniculate ganglion, tympanic and descending (mastoid) segments (Figure 1). The peripheral segment refers to the nerve as it exits the stylomastoid foramen and continues on to the face, where it innervates muscles of facial expression^[1].

DIAGNOSIS

Tumors involving the intratemporal FN can be challenging to identify preoperatively. These tumors may have

several symptoms in common with the more common vestibular schwannoma (VS) including sensorineural hearing loss, vertigo and imbalance, and tinnitus. While FN dysfunction is relatively uncommon in patients with VS (2%) this symptom is much more common in primary FN tumors. Symptoms suggesting possible FN origin also include lacrimal gland dysfunction and taste disturbance^[2,3]. The classic motor symptoms for a FN tumor are recurrent FN weakness (frequently misdiagnosed as bell palsy), hemifacial spasm or slowly progressive facial weakness. These symptoms are not specific to FNS but common to all FN tumors including hemangioma.

However, many FN tumors do not present with FN dysfunction at all. It is common for the diagnosis of FNS to be made intra-operatively; this is particularly true for tumors limited to the CPA/IAC (2) (Figure 2A). As imaging technology has improved over time, it has become much easier to diagnose a FNS before going into surgery. High-resolution computer tomography (HRCT), magnetic resonance imaging (MRI), audiometry and vestibular testing, electroneurography, and electromyography became tools to help make the diagnosis^[2,4]. Full discussion of the diagnostic modalities for the FNS is beyond the scope of this article and the reader is referred to other references for more in-depth discussions^[5].

FNSs are classically described as a contrast enhancing mass in the course of the FN, on MR. On T1-contrast enhanced MRI, FNSs present as smoothly circumscribed fusiform enhancing mass along the intratemporal FN. Usually, intratemporal FNSs involve multiple segments of the FN and appear as "beads on a string" on MR^[6] (Figure 2C).

Other distinct appearances of the FNS are seen along the various segments of the FN. Those limited to the cerebellopontine angle or IAC (CPA-IAC) are very hard to distinguish from VS. Occasionally a labyrinthine "tail", the schwannoma's extension into the labyrinthine segment of the FN canal, can be seen as an indication of a FNS rather than VS. A large CPA-IAC FNS may present with a "dumbbell" imaging appearance, due to the extension of the FNS from the IAC fundus to the labyrinthine segment and to the geniculate fossa^[3]. FNSs centered in the geniculate fossa or those that extend along the greater superficial petrosal nerve present with a mass in the middle cranial fossa (MCF)^[3] (Figure 2B). These lesions may enhance along the course of the nerve or be discrete, well-defined extradural lesions arising along the floor of the middle fossa. FNSs located in the tympanic segment often lobulate into the middle ear cavity^[3]. FNSs arising from the mastoid segment may spread into nearby mastoid air cells, demonstrating unusual, irregular tumor margins as the tumor expands through the air cells along the pathways of least resistance. HRCT images of these lesions reveal a widening or even erosion of the bony canal^[3] (Figure 2D).

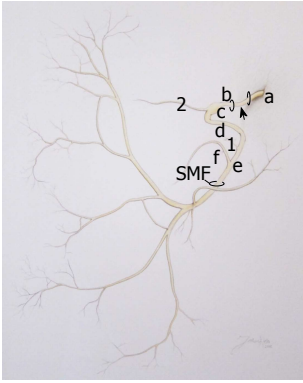


Figure 1 Line drawing of the facial nerve. The nerve takes a very tortuous course through the temporal bone within the Fallopian canal before exiting the skull base at the SMF. Any portion, intra or extratemporal, can be affected by a facial nerve schwannoma. a: Nerve as it exits the brainstem and crosses the cerebellopontine angle; b: Labyrinthine segment; c: Geniculate ganglion; d: Tympanic segment; e: Mastoid segment; f: Chorda tympani nerve; arrow: Intracanalicular segment. ¹Nerve to stapedius; ²Greater superficial petrosal nerve. (Joshua M Klein, MSM I artist). SMF: Stylomastoid foramen.

HISTORICAL PERSPECTIVES

As the approach to medicine has changed over time, the goals of treatment have evolved. For many benign pathologies, medicine now focuses on maximizing the patients' quality of life (QOL), in addition to treating the disorder. This changing pattern is evident in the treatment patterns for intratemporal FNSs.

Complete surgical resection and grafting were very popular up until the mid-1990s^[7]. Many physicians offer tumor resection with cable grafting if the patient presents with facial palsy and facial dysfunction, House-Brackmann (HB) Grade 4 or worse (Table 1)^[8]. Grafting provides the possibility that some degree of function will resume, however, full symmetric facial function is never achievable.

Depending on the location of the tumor and the degree of hearing loss at the time of presentation, the surgical approach will vary^[6,9]. For tumors involving the geniculate and more medially, the MCF or subtemporal approach is offered to the patients if the tumor does not extend significantly (less than 1.5 cm) into the CPA and the hearing is serviceable (hearing is defined as at least serviceable if it is either Class A or B on the AAO-HNS scale^[10]) (Figure 3).

The MCF approach can be combined with a trans-mastoid approach for tumors involving larger portions of the nerve but with serviceable hearing. This combined approach allows for access to multiple segments of the nerve while maintaining the auditory apparatus. When hearing is non-serviceable a translabyrinthine approach is appropriate and can be used for any size or location of tumor^[6]. This can be carried out using a nerve graft (greater auricular nerve, sural nerve or cadaveric donor cable graft) or through direct anastomosis^[9,11]. Graft length has not been shown to correlate to the degree of facial function, but graft location has been shown to be a factor; the more proximal to the brainstem the first

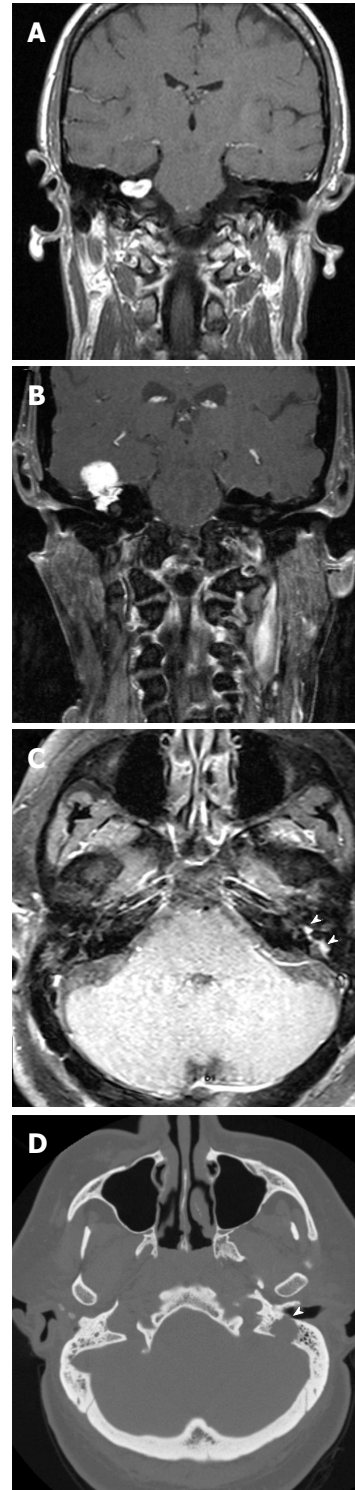


Figure 2 Radiographic images of facial nerve schwannoma. A: Contrasted coronal T1 weighted MRI of right intracanalicular FNS. The patient was presumed to have a vestibular schwannoma but the tumor arose from the FN. The patient underwent tumor debulking with HB grade 1 at follow-up; B: Contrasted T1 weighted coronal MRI of a large FNS arising from the geniculate ganglion with significant extension into the middle fossa and the middle ear. The patient underwent a translabyrinthine resection with cable grafting; C: Post contrast axial T1 weighted MRI demonstrating a FNS involving multiple levels of the facial nerve. This is a typical appearance of the "beads on a string" pattern of tumor growth (arrowheads); D: Axial bone window high resolution computer tomography of the temporal bone demonstrating a large FNS of the mastoid segment causing erosion of both the bony ear canal (arrowhead) and the posterior fossa plate. MRI: Magnetic resonance imaging; FNS: Facial nerve schwannoma; HB: House-Brackmann.

Table 1 The House-Brackmann Scale of facial nerve function (adapted from Ref. [8])

Grade	Description	Gross function	Resting appearance	Dynamic appearance
1	Normal	Normal	Normal	Normal
2	Mild dysfunction	Slight weakness with effort, may have mild synkinesis	Normal	Mild oral and forehead asymmetry; complete eye closure with minimal effort
3	Moderate dysfunction	Obvious asymmetry with movement, noticeable synkinesis or contracture	Normal	Mild oral asymmetry, complete eye closure with effort, slight forehead movement
4	Moderately severe dysfunction	Obvious asymmetry, disfiguring asymmetry	Normal	Asymmetrical mouth, incomplete eye closure, no forehead movement
5	Severe dysfunction	Barely perceptible movement	Asymmetric	Slight oral/nasal movement with effort, incomplete eye closure
6	Flaccid paralysis	None	Asymmetric	No movement

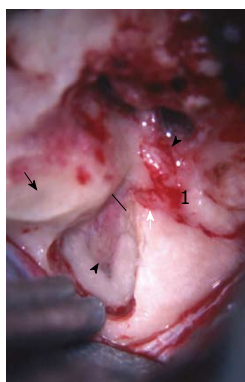


Figure 3 Intraoperative photograph of a left subtemporal/middle cranial fossa approach to the facial nerve. The middle fossa approach to the internal auditory canal is appropriate for decompression of the bony canal surrounding the nerve. Access to the upper tympanic segment (proximal to the cochleariform process) is achievable *via* this approach. ¹Geniculate ganglion. Solid line represents the entrance of the bony facial canal; Solid black arrow: Blue-line of superior semicircular canal; Black arrowhead: Fundus of the internal auditory canal decompressed; White arrow: Labyrinthine segment; White arrowhead: Tympanic segment.

neurotomy is placed, the worse the FN outcome^[6]. Pre-operative FN function is one predictor of ultimate FN function after grafting; those with better pre-operative function do better with grafting than those who present with poorer FN function and have a graft. In patients undergoing total tumor resection, tumor recurrence is not expected^[6].

Many studies have shown the negative effects of facial paralysis on psychosocial function and QOL using evaluation tools such as the Glasgow Benefit Inventory, the short-form 36, the Derriford Appearance, the FaCE Scale, and the Facial Disability Index^[12,13]. Facial paralysis affects QOL is by limiting the patient's ability to express emotion through facial motor movements, thus affecting their ability to form social relationships and have successful social interactions. This leads to feelings of social isolation^[14]. Facial paralysis alters self-perception of facial appearance. People with a disfigured facial appearance are often looked at differently by society and valued less because they do not look "normal", affecting their ability to form relationships and affecting their psychosocial well-being^[15]. Because

QOL factors are more heavily considered in current treatment algorithms, management techniques that preserve FN function while still successfully managing the tumor may be preferred^[7].

ALTERNATIVES TO TUMOR RESECTION

The main alternative management modalities for intratemporal FNSs are tumor debulking, bony decompression, stereotactic radiation, and observation.

Debulking

Debulking or stripping surgery refers to the removal of as much of the tumor as possible while leaving the main trunk of the FN intact^[6,16]. The goal of a tumor debulking is to remove as much of the tumor mass as possible while maintaining the anatomic and functional integrity of the nerve. This surgical method can achieve near-total tumor removal. However, by definition, some of the tumor is left on the FN, which can result in tumor regrowth. Debulking surgery is carried out under high magnification microdissection between nerve fibers and the actual tumor. In some cases however, the nerve fibers are scattered in the tumor and thus not suitable for debulking; this cannot be determined until the tumor-nerve interface is assessed intraoperatively^[6]. Continuous electromyographic FN monitoring is used during debulking. Short bursts of activity may be present but the microdissection is stopped if fibrillation potentials (trains) are produced^[6]. The percentage of tumor removal is then estimated by the end of the operation and can also be assessed *via* volumetric analysis of post-operative MRI scans. As in tumor resection, an MCF or a TL approach can be used, taking into consideration the hearing factors previously mentioned.

Debulking surgery is generally a choice of treatment in patients that do not present with facial dysfunction^[16]. This surgical technique can be very useful for tumors of the CPA/IAC, which are generally presumed to be VSs preoperatively. If a FNS is found intra-operatively instead of a VS, the physician may choose to debulk the FNS until fibrillation potentials are encountered, at which point they will leave the rest of the tumor on the nerve. Post-operative FN function is expected to be maintained

(a Grade 1 or 2 HB). In one study, the immediate and long-term postoperative FN function after debulking was evaluated. Out of 11 patients who underwent debulking, only 2 patients had worse than a HB score of 3 upon immediate post-operative evaluation. Results for the long-term follow-up were even better. Only one patient had a score of HB 3; all other patients scored HB 1 or 2^[6]. However, patients should be informed of the risk of FN damage and functional decline. There is also a risk of regrowth, because a portion of the tumor is left on the nerve. Therefore, it is imperative to continue following the tumor with serial MRI imaging^[6].

Surgical decompression

Bony decompression refers to the removal of the bony facial canal along the course of the FN to relieve the intrafascicular pressure created by the tumor^[17-19]. Bony decompression should be considered as a first-line option in patients that are pre-operatively diagnosed with a facial schwannoma and present with normal facial function (HB 1 or 2) and small tumors^[6,7,17]. Decompression is beneficial in that it preserves facial function, and may even improve facial function, while also preserving hearing ability^[2,6,17-19]. However, because decompression does not treat the underlying tumor, risk of tumor growth does exist^[13,17]. Therefore, it is important to continually monitor the tumor post-op using a serial MRI imaging^[17]. Wilkinson *et al*^[7] reported that in 78.9% of patients undergoing decompression, FN function either remained the same or improved. Furthermore, three patients (15.8%) in the decompression group showed improvement whereas only one patient (11.1%) in the observation group showed improvement. No patients had hearing loss^[7].

Stereotactic radiosurgery

Stereotactic radiosurgery (SRS) is a less invasive approach in which external beam radiation is directed at the tumor while minimizing damage to surrounding tissue^[20,21]. Ionizing radiation acts at the cellular level to causing DNA damage to the rapidly dividing cells. In rapidly dividing malignant cells, this results in apoptosis and tumor resolution. In benign, slowly growing tumors (such as FNS), SRS does not result in resolution of the tumor; however, tumor growth is controlled and the volume of the tumor may even be reduced over time^[21]. Recent evidence suggests that schwannoma cells are relatively radioresistant and tumor control may be more related to radiation induced fibrosis of the tumor vasculature^[22].

SRS is typically used for benign tumors less than 3.5 cm in size^[20]. A major benefit of SRS is that pre-treatment FN function is preserved and in rare cases, may be improved^[23-29]. SRS should only be used in tumors that are demonstrating growth on serial MRI. This may include residual tumors that remain after debulking surgery or partial resection^[23,25,27,29].

Large series of FNSs alone are lacking due to the rarity of this lesion^[23,27]. Some inferences about

effectiveness and long-term effects of SRS for FNS can be taken from the body of literature for VS; however these VS data must be used with caution when counseling FNS patients. Hearing ability in patients undergoing SRS for VS seems to be maintained up to about 5 years post-treatment. However, evidence suggests that beginning 6 years after VS SRS, patients may experience hearing loss, especially in tumors limited to the IAC^[23,27,28]. Another risk is potential damage to the FN resulting in worse FN function than pre-treatment levels^[23,27,28].

Observation

Observation with serial imaging techniques is now becoming a popular first-line management choice for FNSs. Patients presenting with small FNSs and without facial dysfunction (present with HB 1 or 2) or other neurologic deficit can be followed with MRI, audiograms, and other imaging techniques^[2,25,26,30]. This conservative approach may allow the patient to maintain their functional FN for a long period of time, up to 10 years, without having to intervene with a more destructive or invasive approach^[25,26,30,31]. It is possible to take a conservative approach because of the slow-growing characteristic of these tumors, allowing the patient to avoid intervention for many years^[4,25]. Observation with imaging should be maintained until facial function deteriorates (HB Grade 3 or worse), or the tumor grows significantly in size^[2,4,25,26]. At this point, the physician should consider a more aggressive approach^[2,4,25,26]. It has been shown that observation for a period of time before doing surgery does not result in worse outcomes, when compared to cases in which surgery was the initial treatment of choice^[4]. Observation is especially recommended in elderly patients or those patients who have significant comorbidities^[27]. Observation is not an appropriate choice for tumors causing significant brainstem deformation or compression^[26].

TREATMENT RECOMMENDATIONS

Poor FN function (HB IV-VI) and poor hearing (AAO-HNS class C-D) at presentation a translabyrinthine resection with cable grafting is recommended; Poor FN function (HB IV-VI) and serviceable hearing (AAO-HNS class A-B) consider middle fossa ± transmastoid resection; Moderate facial function (HB III) and serviceable hearing consider FN decompression *via* MCF and mastoid or consider observation; Good facial function (HB I - II) and serviceable hearing consider observation or FN decompression *via* MCF and mastoid; Poor surgical candidate or refuses surgery consider radiosurgery if growth demonstrated or observation.

CONCLUSION

In summary, there are currently many options for management of intratemporal facial schwannomas, and the modern practitioner should be familiar with these

various treatment options when counseling patients. A high index of suspicion for FNS will allow appropriate diagnosis and treatment when these patients do present. Non-surgical options are also appropriate management choices for a select group of patients. Good facial function and hearing preservation are possible with a number these surgical techniques.

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X-linked deafness: A review of clinical and radiological findings and current management strategies

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Abstract

X-linked deafness is a rare genetic disorder causing a severe mixed hearing loss. This is due to an abnormal connection between the internal auditory meatus (IAM) and the basal turn of the cochlear leading to a "3rd window effect" and cochlear conductive hearing loss. Patients are traditionally treated with conventional

hearing aids however these are often unsatisfactory. Cochlear implantation is a high-risk procedure in such cases due to the risk of inadvertent electrode placement in the IAM. We present three paediatric cases where the hearing loss was managed with a combination of a bone anchored hearing aid in combination with a conventional behind the ear hearing aid. We also present a review of the current literature regarding the management of X-linked deafness.

Key words: X-linked deafness; Bone anchored hearing aid; 3rd window; Cochlear implantation; Paediatric; Conductive hearing loss; Sensori-neural hearing loss

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Core tip: X-linked deafness is a rare genetic disorder causing a severe mixed hearing loss. This is due to an abnormal connection between the internal auditory meatus (IAM) and the basal turn of the cochlear leading to a "3rd window effect" and cochlear conductive hearing loss. Patients are traditionally treated with conventional hearing aids however these are often unsatisfactory. Cochlear implantation is a high-risk procedure in such cases due to the risk of inadvertent electrode placement in the IAM.

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INTRODUCTION

X linked deafness (DFXN3) is a rare genetic disorder associated with a mutation on the *POU3F4* gene on the

Xq21 chromosome. Due to its X-linked recessive pattern of inheritance, male patients present with a severe hearing loss whilst female patients may present with normal to mild hearing loss^[1]. Patient's present with a mixed progressive hearing loss at a young age, delayed speech and subsequent educational difficulties. They are traditionally treated with conventional hearing aids.

The hearing loss associated with X-linked deafness can be explained by the well-recognised inner ear abnormalities identified. Most notably there is widening of the fundus of the internal auditory meatus (IAM) bilaterally with dilatation of the internal auditory canal. This was first described in the early 1990s across seven pedigrees of patients^[2]. In addition there is also an absence of the bony partition between the fundus of the IAM and the basal turn of the cochlear. Abnormalities of the bony modiolus, vestibular aqueduct and facial nerve canals have also been described with female patients displaying milder abnormalities compared with the males.

The abnormal connection between the IAM and the basal turn of cochlear acts as a 3rd window and therefore causes both a cochlear conductive loss as well as a progressive profound sensorineural hearing loss. Clinically there is also an association with stapes fixation adding to the conductive component of the hearing loss^[1].

The abnormal connection between the CSF filled subarachnoid spaces and the perilymphatic space of the cochlear represents a high risk for surgery such as stapedectomy. This abnormal communication leads to an increased perilymphatic pressure which in turn leads to perilymph gushing or a "stapes gusher" which is well documented during mobilization of the stapedial footplate^[3]. It was suggested therefore that X-linked deafness was an absolute contraindication to stapes surgery due to the risk of gushing^[4]. The increased perilymphatic pressure also causes progressive cochlear damage and therefore a progressive sensorineural hearing loss.

Cochlear implantation is a recognized treatment for patients with profound X-linked sensorineural deafness. However there is a risk in such patients of inadvertent electrode placement within the IAM due to the abnormal connection between the basal turn and the IAM. There are several reports of CSF leak during cochleostomy and in some cases minimal auditory benefit^[5]. Repeat implantation following wrongful electrode insertion, although possible, is a difficult procedure with many risks including injury to the labyrinthine artery^[6] and image guided insertion may be useful tool in the future^[7].

CASE REPORT

Case 1

An 11-year-old boy from Bulgaria was referred for a cochlear implant assessment when he moved to the United Kingdom. He became deaf as a baby shortly after gentamicin treatment for meningitis at the age of 1. His parents declined a cochlear implant aged 3 and he

subsequently learnt to sign, attended mainstream school and wore bilateral behind-the-ear (BTE) hearing aids. As he grew older his communication became more limited and he was only able to repeat 9% of the AB word list when he used both hearing aids. His audiogram is presented below (Figure 1). His air conduction threshold demonstrated a severe to profound loss whilst his bone conduction threshold confirmed a moderate hearing loss. A CT scan showed a wide connection between the IAM and the basal turn of the cochlear and genetic testing confirmed a mutation in the *POU3F4* gene. The patient was fitted with a right bone anchored hearing aid (BAHA), which he wears alongside his BTE hearing aids.

Case 2

TB was referred to the cochlear implant clinic aged 2 years and 10 mo. His hearing loss was identified through the newborn hearing screen and he had been managed with hearing aids. However his thresholds had deteriorated significantly over the last few months. His speech was significantly delayed. There was no family history of hearing loss. His audiogram demonstrated a down-sloping mild to moderate sensorineural loss and an up-sloping conductive loss (Figure 1). The CT scan showed an outpouching in the area of the vestibular aqueduct and a wide connection between the IAM and the basal turn of the cochlear. There was also evidence of fixation of the malleus hear to the anterior attic wall bilaterally. An examination under anaesthetic of the right ear revealed mobile ossicles and therefore TB was fitted with a left BAHA. The BAHA in combination with bilateral BTE hearing aids allowed TB's speech and conversational language to progress.

Case 3

AP is a 7-year-old boy whose hearing loss was identified aged 2 when he lived in India. He was initially treated with conventional hearing aids and a diagnosis of Mondinis malformation of the cochlear was made. Over time he was noted to have a mixed hearing loss and a drop in his low frequency air conduction thresholds (Figure 1). A review of the imaging he underwent in India as a baby has shown the typical appearances of X-linked deafness and he is currently undergoing genetic testing confirmed mutations in *POU3F4* gene alongside his younger brother who also has a hearing loss. He was fitted with a BAHA to use with his conventional hearing aids.

DISCUSSION

In our three cases we have successfully managed the hearing in these patients with a combination of a BAHA alongside a conventional BTE avoiding the complications of implant surgery (Figure 2). Our series of patients all demonstrated a progressive drop in low frequency air conduction thresholds. BAHAs have the advantage of aiding the low frequency thresholds where conventional air conduction aids may fail. In conjunction

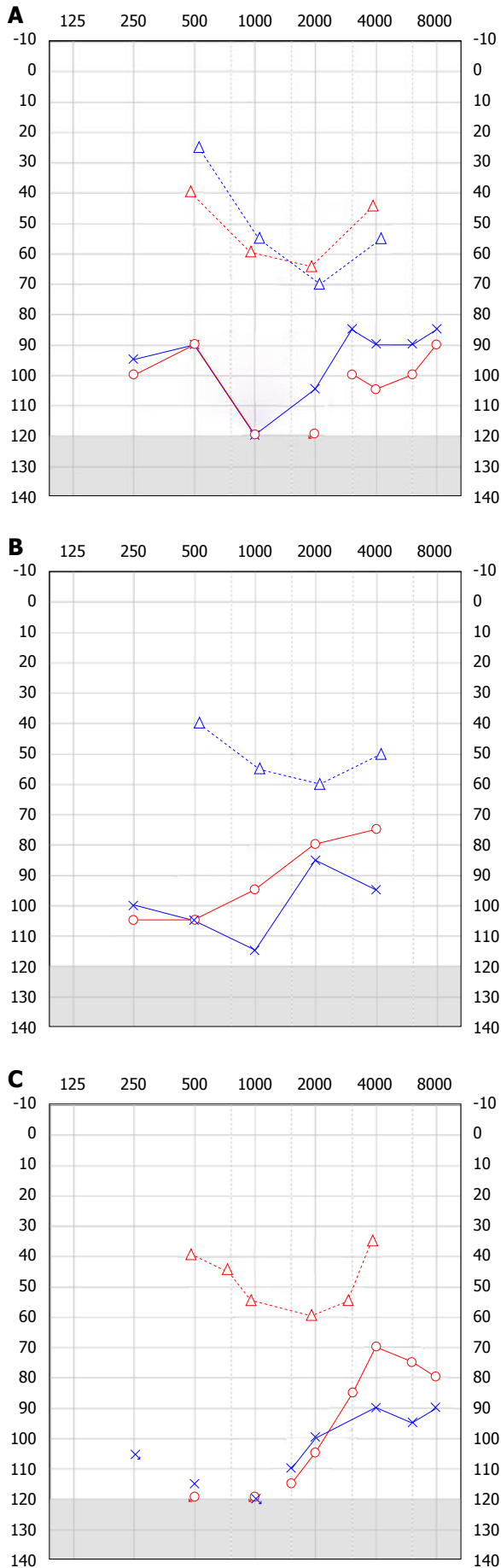


Figure 1 Pure tone audiograms of patients with X-linked deafness pre-operatively.

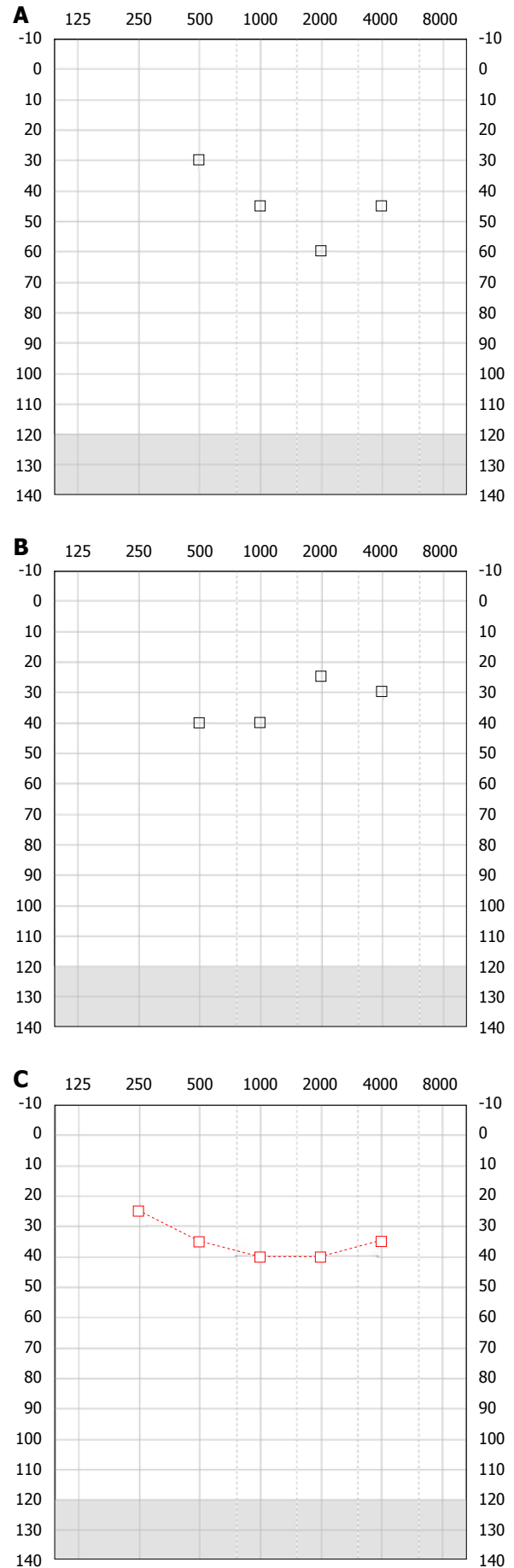


Figure 2 Aided audiograms of patients (bone anchored hearing aid and behind the ear hearing aids in combination).

with a conventional aid for the high frequency loss our patients have reported good outcomes as stated by parents and school. The bone conduction thresholds in our patients were within the limits at which a BAHA is considered beneficial and even our third patients, AP, whose threshold were borderline, had some perceived auditory benefit. BAHA is a safe, quick and well-tolerated procedure and is licensed in the United Kingdom in children aged 5 and over. Those patients that are younger may use the device on a softband.

COMMENTS

Case characteristics

An 11-year-old boy from Bulgaria was referred for a cochlear implant assessment when he moved to the United Kingdom; AP is a 7-year-old boy whose hearing loss was identified aged 2 when he lived in India.

Clinical diagnosis

As he grew older his communication became more limited and he was only able to repeat 9% of the AB word list when he used both hearing aids; over time he was noted to have a mixed hearing loss and a drop in his low frequency air conduction thresholds.

Differential diagnosis

The hearing loss associated with X-linked deafness can be explained by the well-recognised inner ear abnormalities identified.

Laboratory diagnosis

All labs were within normal limits.

Imaging diagnosis

The computed tomography scan showed an outpouching in the area of the vestibular aqueduct and a wide connection between the internal auditory meatus and the basal turn of the cochlear.

Pathological diagnosis

Bone anchored hearing aids have the advantage of aiding the low frequency thresholds where conventional air conduction aids may fail. In conjunction with a conventional aid for the high frequency loss the patients have reported good outcomes as stated by parents and school.

Treatment

Cochlear implantation is a recognized treatment for patients with profound

X-linked sensorineural deafness.

Related reports

There are several reports of CSF leak during cochleostomy^[5] and in some cases minimal auditory benefit^[5].

Experiences and lessons

Repeat implantation following wrongful electrode insertion, although possible, is a difficult procedure with many risks including injury to the labarynthine artery^[6] and image guided insertion may be useful tool in the future^[7].

Peer-review

The paper is well written.

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