Ménière's Disease Is a Viral Neuropathy

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Key Words
Ménière's disease • Viral neuropathy

Abstract
Morphological and clinical evidence supports a viral neuropathy in Ménière's disease (MD). Quantitative examination of 11 sectioned temporal bones (TBs) from 8 patients with a history of MD revealed a significant loss of vestibular ganglion cells in both the endolymph hydropic (EH) and non-EH ears. Transmission electron microscopy of vestibular ganglion cells excised from a patient with MD revealed viral particles enclosed in transport vesicles. Antiviral treatment controlled vertigo in 73 of 86 patients with vestibular neuronitis (85%) and 32 of 35 patients with MD (91%).

Introduction
Endolymphatic hydrops (EH) of the membranous labyrinth, especially the pars inferior, has been recognized as the pathological correlate for Ménière's disease (MD) for over 70 years [1, 2]. Although obstruction of the longitudinal flow and absorption of the endolymph has been implicated as the cause of EH [3–5], significant questions to this proposed pathophysiological mechanism persist. First, although EH is readily produced by surgical obliteration of the endolymphatic sac in lower forms (guinea pig, chinchilla, gerbil) [3, 5], comparable EH does not occur in higher mammals (cat, monkey) [4] following sac obliteration even after long (years) survival periods [6]. Second, imbalance (vertigo) has not been observed in these animal models. Third, the temporal bones (TBs) of animal models with successful experimentally induced EH do not contain fibrous tissue adjacent to the stapes footplate with attachment to the saccular wall. Such vestibular fibrosis has been observed in 35% of human TBs from MD patients [7, 8].

Since EH has been demonstrated as a pathological response of the labyrinth to an inflammatory process in the perilymphatic compartment (labyrinthitis) [9], it is reasonable to consider the role of injury in the EH observed in MD. Fibrous tissue within the perilymphatic space can only be explained on the basis of a tissue reaction to injury. In human TB material, the cellular phase of the response to injury would be expected to be resolved, leaving the reparative phase (fibrosis).

A recent human TB study [10] has suggested that the EH in MD is a marker for a disordered homeostasis of the labyrinth in which some factor (as yet unknown) produces both the clinical symptoms of Ménière's syndrome and endolymphatic hydrops. A possible source of the chemical injury to the labyrinth could be the release of infectious nucleic acids from vestibular nerve terminals following virus reactivation in the vestibular ganglion.
Such nucleic acids have a level of infectivity unlike that of live virus, but neutralized by nuclease enzyme release by blood components [11].

Traditionally, to prove that a clinical syndrome is caused by an organism, Koch's postulates must be satisfied. While such an approach is possible for bacterial and some viral organisms, the neurotropic (NT) viruses belonging to the herpes viridae family do not lend themselves to this approach because the virus exists in an incomplete latent form within the ganglion cell nucleus with brief periods of recrudescence when the virion is formed [12, 13]. This makes detection difficult.

Therefore, attempts to document NT virus presence have been indirect. The presence of HSV-1 antibodies in the perilymph of MD patients [14] and HSV-I DNA in the VG excised from MD patients [15, 16] have been discounted as a mere reflection of the ubiquitous nature of these viruses in the worldwide population. Direct evidence of a viral neuropathy in MD must come in the form of virus presence in the vestibular nerve.

The present report offers light and electron microscopic evidence of virus presence in the vestibular nerve in MD and the results of antiviral therapy of MD patients over a 34-month period.

**Material and Methods**

Eleven TBs from 8 patients with a documented history of MD were prepared by standard techniques used for histopathologic examination of human TB. These TBs were stained with hematoxylin and eosin and examined qualitatively and quantitatively under a light microscope.

**Qualitative**

The membranous epithelial and neural structures of the 7th and 8th nerves in the TB were evaluated for EH, vestibular cistern fibrosis, and neural degeneration.

**Quantitative**

VG and spiral ganglion cells were counted under 400× magnification according to previously described techniques for estimating ganglion cells in sectioned TB [17, 18]. These estimates were compared to normative values established for TB [7, 18].

**Case Report**

The vestibular nerve and ganglion excised from a 45-year-old female with a history of MD were examined by transmission electron microscopy (TEM).

Following traumatic sinus surgery, this 45-year-old female experienced episodic vertigo followed by fluctuating hearing loss in her right ear for 10 years. The episodes of vertigo lasting more than 1 h occurred almost daily and the sensorineural hearing loss in the right ear was profound. There was an episode of truncal herpes zoster during the 10-year period.

**Ménière’s Disease**

Since the vertigo was not relieved by a 3-week course of acyclovir (800 mg t.i.d.) and two intratympanic applications of gentamicin (40 mg/ml), a transcanal labyrinthectomy was performed. After 7 months of complete relief, episodes of vertigo following exercise occurred. Excision of the right vestibular nerve and ganglion was performed via a transmastoid approach with complete relief of vertigo. The nerve specimen was placed in buffered glutaraldehyde and processed for TEM.

**Clinical Series**

One hundred and forty-seven consecutive patients with MD or vestibular neuritis (VN) were treated with oral acyclovir from April 2004 to February 2007 (34 months).

These patients were referred by primary care physicians, otolaryngologists, and neurologists. Almost all had imaging studies (contrast CT or MRI) of the brain prior to treatment. These patients had failed vertigo control while on standard medical treatment including diuretics, low salt diet, anti-allergy medication, meclizine, and diazepam. Patients were instructed to discontinue all previous medications given for vertigo relief. Oral acyclovir (800 mg t.i.d.) was administered for 3 weeks and the patient was reexamined to determine the response. If the patient experienced complete or almost complete (no additional medication needed) relief of vertigo, the dose was reduced to 800 mg b.i.d. for 3 weeks. If continued control of vertigo was present at 30 days, the antiviral was further reduced to one daily.

** Definitions**

**Ménière’s disease (MD).** A history of recurrent vertigo (duration 0.5 to several hours) associated with a low-frequency or flat

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**Table 1. Temporal bone pathology in Ménière’s disease**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/No. sex</th>
<th>EH VF MG FA</th>
<th>Vestibular ganglion counts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ménière’s disease normal [18]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SVG IVG</td>
<td>SVG IVG</td>
</tr>
<tr>
<td>1R</td>
<td>53/F</td>
<td>+ + + +</td>
<td>5,958 2,772 10,882 7,880</td>
</tr>
<tr>
<td>2R</td>
<td>58/M</td>
<td>+ + + +</td>
<td>4,628 1,848 10,882 7,880</td>
</tr>
<tr>
<td>2L1</td>
<td>58/M 0 0 + + +</td>
<td>4,694 2,684 10,882 7,880</td>
<td></td>
</tr>
<tr>
<td>3R</td>
<td>65/F</td>
<td>+ + + +</td>
<td>4,030 2,870 10,201 7,661</td>
</tr>
<tr>
<td>4R</td>
<td>71/F</td>
<td>+ + + +</td>
<td>4,479 4,866 10,167 6,762</td>
</tr>
<tr>
<td>5R</td>
<td>76/F</td>
<td>+ + + +</td>
<td>7,928 3,308 10,167 6,762</td>
</tr>
<tr>
<td>6L</td>
<td>78/M + 0 + +</td>
<td>9,882 4,497 10,167 6,762</td>
<td></td>
</tr>
<tr>
<td>6R</td>
<td>78/M + 0 + +</td>
<td>7,260 5,218 10,167 6,762</td>
<td></td>
</tr>
<tr>
<td>7L</td>
<td>83/F + 0 + +</td>
<td>5,667 3,106 10,136 6,468</td>
<td></td>
</tr>
<tr>
<td>7R1</td>
<td>83/F 0 0 + +</td>
<td>6,336 3,846 10,136 6,468</td>
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<tr>
<td>8L</td>
<td>83/F + + + +</td>
<td>7,146 2,702 10,136 6,468</td>
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</tr>
</tbody>
</table>

EH = Endolymphatic hydrops; SVG = superior vestibular ganglion; VF = vestibular fibrosis; IVG = inferior vestibular ganglion; MG = meatal ganglion degeneration; FA = focal axon degeneration.
1 Contralateral ear in unilateral MD.
sensorineural hearing loss in one or both ears. Tinnitus is usually present in the affected ear.

*Vestibular neuronitis (VN).* History of recurrent vertigo (>5 h) without hearing loss. Vestibular function may be normal or decreased. Tinnitus may be present in one or both ears.

### Results

**TB Pathology (table 1)**

EH of the pars inferior (cochlea and saccule) was present in 9 of 11 TBs. The 2 TBs without EH were from the contralateral ears of 2 patients with unilateral MD. There was visible fibrosis in the vestibular cistern in 6 of the 9 TBs with EH. This fibrous tissue was seen to extend from the utricular nerve to the stapes footplate in several TBs (fig. 1). Degenerated ganglion cells in the facial nerve meatal ganglion [19, 20] (fig. 2) and focal axonal degeneration in the vestibular nerve trunk were observed in all 11 TBs (fig. 3).

There was a loss of VG cells in all 11 TBs (table 1). This loss was significant in the superior VG of all but 1 TB (6L) and in the inferior ganglion of all 11 TBs. The loss was 50% or greater in 7 TBs and 20–40% in 4 TBs. In the pairs of TBs from 2 patients with unilateral MD, the loss of cells in the contralateral VG was similar to the hydropic ear. These VG cell losses are shown graphically in figures 4 and 5. The vestibular sense organs were normal in all 11 TBs.

The loss in spiral ganglion cells in these TBs paralleled the degree of hearing loss experienced by the patients with MD (table 2). Figure 6 illustrates the magnitude of the sensorineural loss in terms of word discrimination scores which are most affected by pathology in the apical and middle turns of the cochlear duct. Noteworthy is the near normal number of hair cells and au-
Fig. 4. Bar graph of superior vestibular ganglion counts in 11 temporal bones from 8 patients with Ménière's disease. ■ = Unpaired temporal bone; □ = pairs of temporal bone from 3 patients.

Fig. 5. Bar graph of inferior vestibular ganglion counts in temporal bone of Ménière's disease patients. ■ = Unpaired temporal bone; □ = pairs of temporal bone from 3 patients.

Fig. 6. Bar graph of spiral ganglion cell counts in the same series of temporal bones from Ménière's disease patients. Speech discrimination scores (%) are located above the bars. ■ = Unpaired temporal bone; □ = pairs of temporal bone from 3 patients.

Auditory neurons associated with normal word discrimination scores in the contralateral ear of 2 pairs of TBs with unilateral MD (patients 2 and 7). However, the VG populations in these contralateral ears without EH were almost as severely degenerated as in the TB with EH. Together with the observation that there is widespread loss of cochlear inner and outer hair cells in the TB with EH, this suggests that the pathologic process that causes EH originates in the vestibular nerve and causes the auditory deficit by creating a sense organ lesion responsible for retrograde degeneration of type I spiral ganglion cells.
Fig. 7. Virion particles (arrows) were present in transport vesicles of vestibular ganglion cells excised from patient with Menière's disease. M = Mitochondria. Original magnification x13,000.

Fig. 8. Virus invaginating transport vesicle (arrow) in vestibular ganglion cell of the same patient as in figure 4. The arrowhead points to virus in a transport vesicle. M = Mitochondria. Original magnification x6,300.

Table 2. Spiral ganglion in Menière's disease

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/sex</th>
<th>Spiral ganglion</th>
<th>Normal [7]</th>
<th>Hearing</th>
</tr>
</thead>
<tbody>
<tr>
<td>1R</td>
<td>53/F</td>
<td>15,444</td>
<td>25,260</td>
<td>70 dB SRT; 8% SD</td>
</tr>
<tr>
<td>2R</td>
<td>58/M</td>
<td>15,012</td>
<td>25,260</td>
<td>60-70 dB SRT; 44% SD</td>
</tr>
<tr>
<td>2L¹</td>
<td>58/M</td>
<td>20,439</td>
<td>25,260</td>
<td>Normal; 100% SD</td>
</tr>
<tr>
<td>3R</td>
<td>65/F</td>
<td>11,988</td>
<td>25,270</td>
<td>80 dB SRT</td>
</tr>
<tr>
<td>4R</td>
<td>71/F</td>
<td>17,595</td>
<td>22,871</td>
<td>60-70 dB SRT; 72% SD</td>
</tr>
<tr>
<td>5R</td>
<td>76/F</td>
<td>12,900</td>
<td>22,871</td>
<td>60-90 dB SRT; 28% SD</td>
</tr>
<tr>
<td>6L</td>
<td>78/M</td>
<td>18,864</td>
<td>22,871</td>
<td>40 dB SRT; 88% SD</td>
</tr>
<tr>
<td>6R</td>
<td>78/M</td>
<td>19,557</td>
<td>22,871</td>
<td>Normal; 96% SD</td>
</tr>
<tr>
<td>7L</td>
<td>83/F</td>
<td>11,394</td>
<td>18,626</td>
<td>54 dB SRT; 60% SD</td>
</tr>
<tr>
<td>7L¹</td>
<td>83/F</td>
<td>17,290</td>
<td>18,626</td>
<td>50 dB SRT; 96% SD</td>
</tr>
<tr>
<td>8L</td>
<td>83/F</td>
<td>14,256</td>
<td>18,626</td>
<td>65 dB SRT; 48% SD</td>
</tr>
</tbody>
</table>

SD = Speech discrimination; SRT = speech reception threshold.
¹ Contralateral ear in unilateral MD.

One of the TBs (No. 3R; table 1, 2) has been previously reported [21]. It represents a 65-year-old female who experienced episodic vertigo 27 years after severe bilateral sensorineural hearing loss which occurred at 32 years of age. The vertigo was present for several years before her death from intracerebral hemorrhage. In addition to severe EH of the cochlea and saccule, there was severe (>60%) loss of vestibular and cochlear neurons. The dark epithelial cells which covered the utricular nerve surface and filled the vestibular cistern contained a large intranuclear inclusion body surrounded by a halo in the nuclear sap. These features are characteristic of cytomegalovirus (CMV) labyrinthitis [22].

The excised VG of a patient with MD was examined in TEM. Several ganglion cells contained viral capsids enclosed within transport vesicles in the cytoplasm (fig. 7). Occasionally, a viral capsid was observed in the process of invaginating the wall of a transport vesicle in order to acquire a new envelope (fig. 8). The nucleus of these ganglion cells contained marginated chromatin which precedes the organization of protein elements before penetrating the nuclear membrane (fig. 9).

Clinical Series
There were 94 females and 53 males in this series. Their ages ranged from 23 to 87 (average 53) years. Twenty-six patients were lost to follow-up. Vertigo was completely controlled in 73 of 86 patients with VN (86%) and in 32 of 35 patients with MD (91%). Hearing loss was
The argument that this neural degeneration may be secondary to end-organ toxicity from increased potassium levels [7] rather than a primary neuropathy is not valid because it has been shown that labyrinthectomy results in a loss of only one third of the VG [25]. The loss of VG cells in many of these TBs was greater than 50%. In addition, a similar ganglion cell loss was found in the contralateral TBs of 2 patients with unilateral EH where potassium intoxication is not present in the ear without EH.

The similar VG loss in the contralateral ear of the 2 pairs of TBs with unilateral MD was unexpected. Although similar in degree and form (i.e. focal axonal degeneration), this VG loss in the non-involved ear of unilateral MD was slightly less than the loss in the symptomatic ear (table 1). The contralateral spiral ganglion count was almost normal and associated with normal word discrimination scores (patients 2 and 7; table 2). The 3rd pair of TB in this series (patient 6; table 1, 2) demonstrated bilateral EH and vestibular nerve degeneration that was less severe than in the remaining 9 TBs. The near normal hearing and spiral ganglion cell levels in these 2 TBs further illustrates the correlation between vestibular and spiral ganglion pathology in MD. One interpretation of these results is that the VG pathology precedes the development of an auditory deficit and EH. This interpretation is consistent with the notion that EH is not the cause of clinical MD, but probably the result of an underlying pathology in the labyrinth and its nerve supply [10]. The results of vestibular testing in delayed endolymphatic hydrops, a variant of MD described by Schuknecht [26, 27], supports this concept. He found evidence of decreased vestibular function, as revealed by caloric stimulation, in both the involved and non-involved ears of patients with contralateral delayed EH. Furthermore, the vestibular weakness was more severe in patients with contralateral delayed EH than those with ipsilateral delayed EH.

Since reactivation of the latent NT virus is dependent on viral load in a sensory ganglion [28], VG loss in the contralateral nerve may represent the potential to develop bilateral MD. Bilaterality has been reported to occur in 15–50% of patients with MD [29–31]. Therefore, when the virus load reaches a critical level, reactivation from latency overcomes the host immune response with the release of viral nucleic acids. Release of such toxic by products in the labyrinth causes a labyrinthitis which eventually leads to fibrosis in the vestibular cistern and EH. This toxic effect on the hair cells of the cochlea is responsible for retrograde degeneration of the spiral ganglion. Since the flow of perilymph carrying such toxins

Discussion

The hypothesis that MD is a viral neuropathy is supported by significant loss of VG cells compared to age-matched TBs. This loss was present in both the ear with EH as well as the ear without EH in two pairs of TBs from donors who expressed unilateral MD. A pattern of neural degeneration which affects tightly grouped ganglion cells shown as focal axonal degeneration in the vestibular nerve trunk is typical of a viral neuropathy [23, 24].

Fig. 9. Nucleus of vestibular ganglion cell in same patient shows margination of nuclear chromatin (arrows) adjacent to the double-layer nuclear membrane. The asterisk indicates a collection of ribosomes used for virion assembly. Original magnification ×6,300.

not changed positively or negatively in patients with MD. Tinnitus was improved in approximately 50% of patients.
first reaches the organ of Corti of the apical turn, the initial auditory deficit is low frequency sensorineural hearing loss. The presence of a near normal number of spiral ganglion cells in the uninvolved contralateral ear of unilateral MD indicates that reactivation of latent virus in that VG has not reached a level that is toxic to the labyrinth (no EH or hearing loss).

Similar morphological changes represent the neuropathological correlate in VN [23, 32]. VN has long been assumed to be a viral neuropathy manifest clinically as either a solitary episode of vertigo or recurring episodes without demonstrable sensorineural hearing loss. Therefore, it is reasonable to assume that a similar viral neuropathy is responsible for vestibular symptoms in MD. The absence of an auditory deficit in VN can be explained by a difference in viral strain. It is well known that reactivation of virus from latency may transport viral products either toward (anterograde) or away from the central nervous system (retrograde) [33–36]. Such directionality of axoplasmic flow is strain-dependent. Therefore, depending on the strain of HSV-1 virus present in a given VG, toxic viral nucleic acids may flow toward the labyrinth, where they cause a serous labyrinthitis, or flow toward the brainstem, avoiding any deleterious effects on the labyrinth including sensorineural hearing loss. It is possible that the anterograde flow of virus may travel transsynaptically to second order neurons in the vestibular pathway. Signs of central nervous system involvement are often demonstrated by vestibular tests in VN.

Of all the vestibular nerve branches, the utricular nerve has the greatest exposure to perilymph in the vestibular cistern. Therefore, morphologic evidence of viral nucleic acid release would be most visible in the vestibule. Direct evidence of viral particles is beyond the resolution power of light microscopy. However, fibrous tissue in the vestibular cistern may be indirect evidence of an inflammatory response. Nucleic acids have been noted to elicit an inflammatory response less destructive than that following bacterial insult [11]. Vestibular fibrosis was seen in 6 of the 9 TBs with EH. A fibrous connection between the stapes footplate and the utricular nerve is responsible for the ocular response to pneumatic otoscopy (Hennebert's sign) seen in MD [8].

Light microscopic evidence of viral release from vestibular nerve terminals is provided by the TB with histologic features of CMV intranuclear inclusion bodies in epithelial cells covering the utricular nerve surface. The CMV is the only herpes subfamily member with an inclusion body large enough to be recognized in light microscopy. The fact that this patient's history is one of delayed EH suggests that variations in the clinical picture of MD may be manifestations of a difference in virus type and strain.

Direct evidence of viral neuropathy in MD is provided by the TEM observation of viral structures in VG cells excised from a patient with MD. The formation of viral capsids takes place in the nucleus of an affected cell. The process of virus formation is incompletely known, but involves several viral genes which direct the organization of immediate early, early and late proteins in the nucleus [13]. Margination of chromatin near the nuclear membrane is an early sign of this formation before the nucleocapsid is released through the nuclear membrane. The temporary envelope acquired from the nuclear membrane is lost after the capsid travels within the cisterna of the rough endoplasmic reticulum and is released into the cytoplasmic compartment. The nucleocapsids then acquire the tegument and final envelope with its glycoproteins by invagination into the wall of transport vesicles provided by the Golgi network, where glycoproteins are assembled. The full virus is then ready to be released through the cell wall into the extracellular space where it is capable of infecting other living host cells. When the virus breaks through the ganglion cell membrane, the ionic gradient between the inside and outside of the cell is disturbed and action potentials are drastically lowered. Death of the cell ensues followed by axonal degeneration. Virus release from ganglion cells promotes infection of adjacent cell bodies forming a cluster. Degeneration of the clustered ganglion cells is reflected in focal axonal degeneration in the nerve trunk.

The clinical response to antiviral medication indicated that patients with recurrent vertigo from MD and VN are relieved in 85–90% of cases. It is important to note that patients with a history of MD or VN, but not actively experiencing vertigo, are not candidates for antiviral therapy because the latent virus is not replicating. Admittedly, the reported series is not a double-blind randomized clinical trial, but such practice-based research has been recognized as a worthwhile approach to determine the effectiveness of new or novel treatments for disorders of unknown etiology [37, 38]. The fact that all these patients were symptomatic while on standard medical treatment may be regarded as a control group for comparison. The issue of placebo is not addressed, however. Such an antiviral approach has several advantages over current treatment strategies for MD or VN. First, it preserves vestibular function by targeting the specific agent responsible. By avoiding ablation methods (chemical or surgical), the central nervous system changes that follow ablation [25] are also avoided. Second, the prevention of
bilateral involvement by MD or VN may be accomplished by either the repetition or maintenance of the antiviral regimen.

The fact that so many patients with recurrent vertigo are referred because of the ineffectiveness of diuretics, low salt diets, and vestibular suppressants (meclizine, diazepam) indicates that the currently employed medical management of recurrent dizziness needs to be changed. The antiviral approach described in this report should be made available for patients with these disabling symptoms.

This antiviral approach to the very common disabling balance symptoms experienced by patients with MD or VN has virtually eliminated the employment of various surgical methods used in the past. These include labyrinthectomy, endolymphatic sac decompression and vestibular nerve transection. Side effects of acyclovir administration are minimal and usually involve gastrointestinal tract hyperactivity which is eased by decreasing the dosage or changing the antiviral preparation. Acyclovir is used based on expense; Valtrix or Famvir have better bioavailability, but are significantly higher in cost. Rare side effects such as skin rash, headache or tremors may require other options to control vertigo. These include the intratympanic instillation of gentamycin, steroids or antivirals (ganciclovir). No increase in side effects or resistance of the virus to the long-term (decades) use of maintenance dose (acyclovir 800 mg or Valtrix 1 g daily) has been reported [39].

It is not surprising that control of vertigo was not greater than 85 or 90%. Mutant strains of the herpes virus group which do not encode genes for thymidine kinase or DNA polymerase would be resistant to the acyclovir class of antivirals which compete for those enzymes. Therefore, until newer antivirals are developed, approximately 10% of MD patients with vertigo will not be controlled. This is similar to the reported resistance of HSV-2 isolates to acyclovir in immunocompromised patients [39]. The auditory symptoms of MD are less effectively treated by the antiviral approach. Sensorineural hearing loss is generally not improved in patients with complete control of vertigo because loss of hair cells and spiral ganglion cells secondary to the toxicity of viral proteins in the perilymph is not reversible.

**Conclusion**

Morphological and clinical evidence supports the concept that viral vestibular neuropathy is responsible for the symptoms of MD. The viral nature of this neuropathy is based on the magnitude and pattern of vestibular nerve degeneration and inflammatory changes associated with EH in TBs from patients with clinical symptoms of MD. These histopathologic observations are enhanced by TEM demonstration of viral particles in VG cells excised from a patient with MD. The high (90%) rate of vertigo control with orally administered antivirals provides clinical experience that should be considered as a frontline of treatment for recurrent vertigo that can be employed by the medical specialties. Only those patients (approximately 10%) who fail to respond to orally administered antivirals require consultation by an otologist. The advantages in cost and convenience are obvious.

**References**
