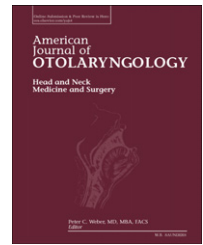


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Original contributions

Recovery of Hearing in Meniere's Disease after Antiviral Treatment



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ABSTRACT

Objective: Determine the outcome of hearing in Meniere's Disease (MD) after antiviral treatment.

Study design: Prospective study.

Setting: University Hospital.

Methods: Thirty one new patients with a diagnosis of MD were treated with antiviral drugs during 2012. Acyclovir or valacyclovir was used depending on insurance coverage and cost. A standard dose of 800 mg (acyclovir) or 1 g (valacyclovir) 3 times a day for 3 weeks was used. The dose was decreased to twice daily for three weeks, and finally once daily for a year or longer. Hearing test including pure tone average (PTA) and speech discrimination (SD) was performed prior to treatment and 1–2 months, 6 months and 1 year after the initiation of treatment. Effect on dizziness was recorded at each evaluation, hearing was judged to be improved if PTA was lowered by at least 15 db and/or an increase in SD of 20% or greater.

Results: Hearing was improved in twelve and not improved in nineteen patients. Complete control of vertigo was achieved in those patients with improved hearing. The nineteen patients with no improvement in hearing were divided into 2 groups based on the level of hearing at diagnosis. Nine patients presenting with a PTA of 50 db and SD of 50% or better experienced good control of vertigo (6 out of 7; 2 with no follow-up). Ten patients with PTA of 60 db or more and SD below 50% exhibited poor control of vertigo with antivirals (3 out of 10). The duration of MD in the group with hearing improvement was shorter (2.4 years) than the group with no improvement (5.5 years).

Conclusion: Significant hearing and balance control in patients with MD can be achieved with orally administered antiviral drugs.

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1. Introduction

Sensorineural hearing loss, tinnitus and recurrent vertigo constitute the hallmark symptoms of Meniere's Disease (MD) [1]. Fluctuation of a predominantly low frequency or flat threshold elevation for all frequencies and reduced word

discrimination are the usual audiometric patterns recorded in this inner ear disorder which has been assumed to be idiopathic. Occasionally a predominantly high frequency loss is recorded with early MD. Usually MD is clinically manifest in one ear with the chance of becoming bilateral ranging from 15% to 50% [2].

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Endolymphatic hydrops (EH) has been described as the responsible pathology in MD [3,4]. Since that description the medical and surgical treatment of MD has been directed at reducing the volume of endolymph [5,6]. Unfortunately, these approaches have had equivocal success in the control of vertigo and recovery of hearing [7-9]. The additional hypothesis that the release of neurophysiologically toxic potassium ion into the perilymphatic space following ruptures of a distended membranous labyrinth [10] is responsible for vestibular and cochlear deficits does not adequately account for some histopathologic findings in the temporal bones (TB) from patients with MD. These include fibrosis under the stapes footplate [7,11] (Fig. 1) and a significant loss of vestibular neurons [12-14]. Careful assessment of the TB in MD indicates that EH is not responsible for the clinical presentation in MD [15]. This long established histopathologic finding can be regarded as a marker for the underlying pathologic process in MD.

Furthermore, the pattern of vestibular nerve degeneration is not consistent with an effect caused by diffuse contamination of the perilymphatic space surrounding the sense organs. Potassium toxicity to the vestibular sense organs would induce a diffuse pattern of neural degeneration because the dendrites of vestibular ganglion cells are scattered in a haphazard fashion. However, the focal axonal degeneration observed in MD can only be produced by loss of a tight cluster of ganglion cells [16,17] because of the organization of vestibular axons and their ganglion cells (Fig. 2). Such a cluster of adjacent ganglion cells is characteristic of viral neuropathies where virus is spread between adjacent neurons over contact of their cell membranes [18] (Fig. 3).

This neural pattern of focal axonal degeneration has been observed in TB from patients with MD [14,17] and with vestibular neuronitis (VN) [16]. The subsequent demonstration by transmission electron microscopy (TEM) of fully formed viral particles in the cytoplasm of vestibular ganglion cells excised from patients with MD provides direct evidence [14,19] to support the indirect evidence of HSV DNA in MD (Fig. 4). This evidence has formed the basis for an antiviral treatment approach in patients with MD and VN [20]. Over the past 10 years this approach demonstrated control of vertigo in 90% of

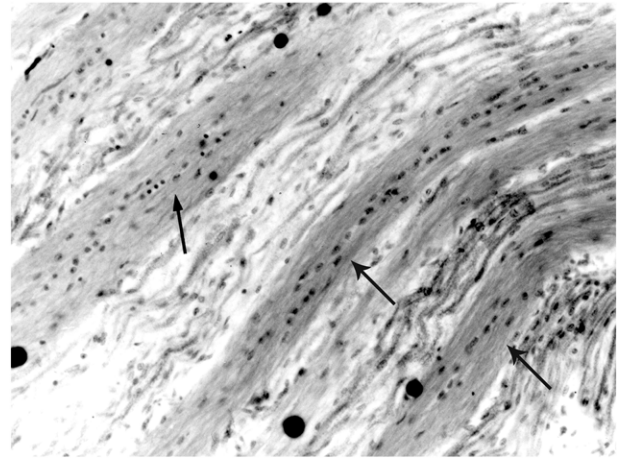


Fig. 2 – Photo of focal axonal degeneration in the vestibular nerve trunk of patient with MD. Mag = 350x.

patients [14]. The effect on hearing loss in MD has not been described. The purpose of this report is to demonstrate recovery of the sensorineural hearing loss in patients with MD treated with antiviral drugs.

2. Materials and Methods

Thirty one new patients who satisfied the requirements for a diagnosis of MD were seen from January 1st, 2012 to December 31st, 2012. The requirements included: Recurrent vertigo with duration of one-half to several hours; sensorineural hearing loss in one or both ears; tinnitus and aural fullness in the involved ear. All patients had magnetic resonance imaging with contrast enhancement of the brain which was reported as negative for neoplastic or vascular lesions. These patients had been treated previously by outside otolaryngologists and had failed to relieve vertigo and hearing loss by the use of low salt diet and diuretics. Some had received anti allergy medication and one (no. 6 in Table 1) had undergone bilateral sequential endolymphatic sac decompression.

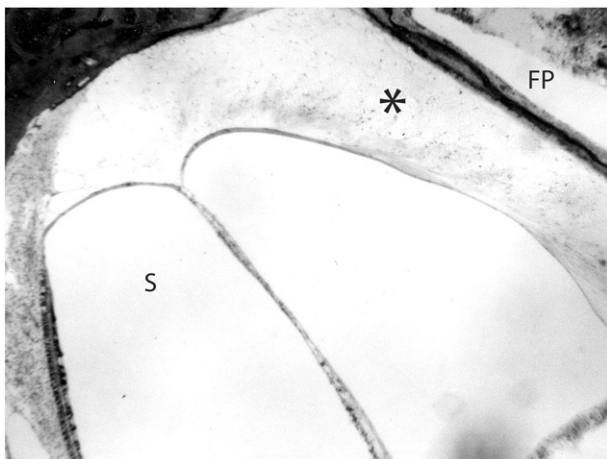


Fig. 1 – Photo micrograph of fibrosis under stapes footplate (FP) producing distention of saccular membrane (S). Mag = 80x.

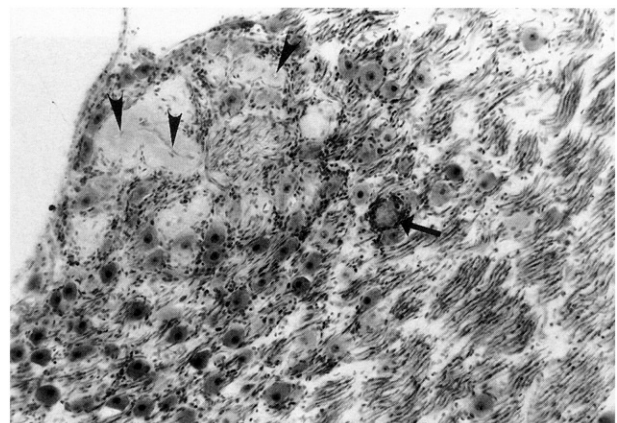


Fig. 3 – Cluster of ganglion cells undergoing degeneration with collagen replacement (arrow heads). Mag = 130x.

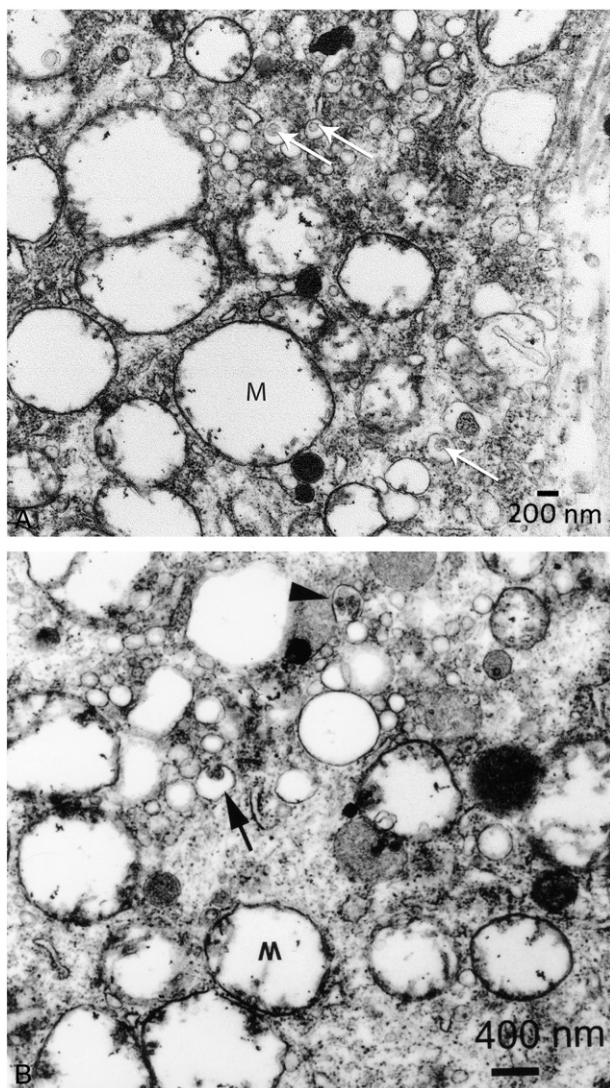


Fig. 4 – (A) EM of ganglion cell from same patient. Arrows point to virus particles enclosed in transport vesicles. Mag = 13,000 \times . (B) Electron micrograph (EM) of vestibular ganglion cell excised from patient with MD. Arrow points to a virus particle being enclosed in a transport vesicle M = Mitochondrion. Mag = 13,000 \times .

Two forms of acyclovir were used. Acyclovir or valacyclovir (Valtrex) was used based on expense and insurance coverage. Hepatic and renal functions were cleared as normal. Complete Otolaryngological examination was normal.

Hearing test including air and bone frequency thresholds and word discrimination scores were recorded. Tympanograms were normal. The hearing test was repeated after 1–2 months of treatment; then at 5–6 months, 1 year and 2 years. Antiviral therapy was initiated only if the patient complained of recurring episodes of vertigo that had an impact on their home or work activities. Hearing was judged to be improved if there was a decrease in the original pure tone average (PTA) for 0.5, 1, 2 and 3 kHz of 15 db or more and/or an increase in the speech discrimination (SD) of 20% or more. These criteria are more demanding than those required by the committee on hearing and equilibrium for Meniere's disease (PTA: 10 db; SD: 15%) [1].

The schedule for administration of antiviral was as follows: Acyclovir: 800 mg Tab TID for 3 weeks and re-examined. If there is improvement in vertigo, reduce to 800 mg BID/3 weeks, then 800 mg daily. Valacyclovir: 1 g tab. TID for 3 weeks and re-examined. If there are improvements in vertigo reduce to 1 g BID/3 weeks, then 1 g daily. Patients remain on 1 tab/daily for one year. Then a discussion with patient is held to determine continuation. All patients elected to remain on the daily dose of 1 tablet.

3. Results

Thirty-one patients with MD comprised this group of patients. There was improvement of hearing in twelve and no improvement in nineteen patients. Hearing was judged to be improved if the PTA was lowered by at least 15 db and/or an increase in word discrimination of 20% or greater. The ages of patients ranged from 20 to 81 years. Most [24] were in the fifth, sixth and seventh decades. The female to male ratio was 21 to 10 and the side involved was approximately equal (18:14). A description of the twelve patients who experienced improvement in hearing after antiviral therapy is shown in Table 1. Two of these patients had bilateral MD and experienced hearing improvement in one ear. The average duration of MD was shorter in the improved group (2.4 years) than in the group with no improvement (5.5 years).

All patients in the group with improved hearing experienced complete control of vertigo and the hearing improvement within 1–2 months of treatment. Occasionally patients noted this in the third week. The graphs in Figs. 5 and 6 demonstrate the change in PTA and in word discrimination in this group with improved hearing. Only three patients had a pre-treatment PTA more than 55 db and two with SD of less than 50%. Improvement of PTA to 20 db or less was experienced in nine of fourteen ears while SD was 84% or better in twelve out of thirteen ears. A predominant low frequency or a flat threshold pattern of hearing was present in the same number [7] of ears. The final assessment of hearing and control of vertigo was made at 12 months or longer after treatment.

Table 2 summarizes the nineteen patients who failed to experience hearing improvement following antiviral treatment. These patients are divided into two subsets based on the PTA in their presenting hearing test. Subgroup I had PTA of 50 db or less while subgroup II had PTA greater than 50 db. The pattern of threshold elevation in the first group was almost equally divided between flat and low frequency while in the second group the flat pattern was predominant. In general the SD in subgroup I was greater than in subgroup II. These features and the duration of symptoms all indicate a greater degree of pathology in subgroup II.

Hearing in subgroup I was not improved but maintained without significant change. Control of vertigo with the antiviral was achieved promptly in six patients and failed in one (No. 14). Two patients (No. 15 and 16.) did not have recurrent vertigo at presentation and did not return for follow-up. Hearing in subgroup II was worse than in subgroup I and control of vertigo was also poor with the antiviral drug. Three patients (No. 26, 28, 30) experienced control of vertigo with the antiviral drug alone.

Table 1 – Hearing Improved.

Patient		Side	PTA db		SD %		Change		Vertigo Control	Duration Meniere's Disease (YR)
			PRE	POST	PRE	POST	SRT db	SD %		
1.	68 F	L	LF 40	15	CNT	CNT	25	-	+	0.5
2.	62 M	L	FL 73	61	32%	74%	12	42	+	1
3.	31 F	L	LF 50	11	64%	96%	39	32	+	1
4.	50 F	L	FL 53	27	64%	96%	26	32	+	2
5.	36 F	L	LF 25	8	96%	96%	17	4	+	5
6.	61 M	R	FL 58	20	66%	94%	38	28	+	10
		L	FL 40	40	82%	86%	0	4		
7.	34 F	L	LF 45	15	100%	100%	30	0	+	0.5
8.	47 F	L	LF 35	10	88%	92%	25	4	+	1
9.	58 M	L	LF 53	30	52%	84%	23	32	+	0.5
10.	65 M	R	LF 21	10	68%	92%	11	24	+	0.5
11.	59 F	R	FL 18	11	96%	96%	7	0	+	5
		L	FL 53	40	54%	92%	13	38		
12.	66 F	L	FL 68	15	20%	96%	53	76	+	0.1
										AVG = 2.4

F = female.
M = male.
R = right.
L = left.
PTA = pure tone average.
SD = speech discrimination.
CNT = could not test because of language.
LF = low frequency.
FL = flat.

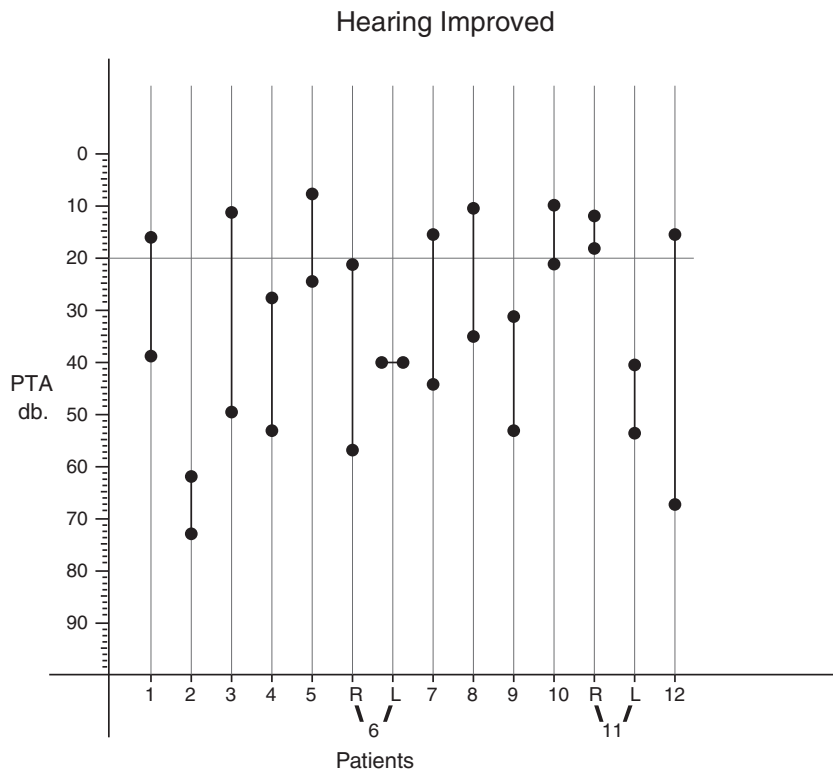


Fig. 5 – Bar graph summarizes the improvement of pure tone average in twelve patients with improvement in hearing. Pretreatment values are at the bottom. Post treatment values are at top.

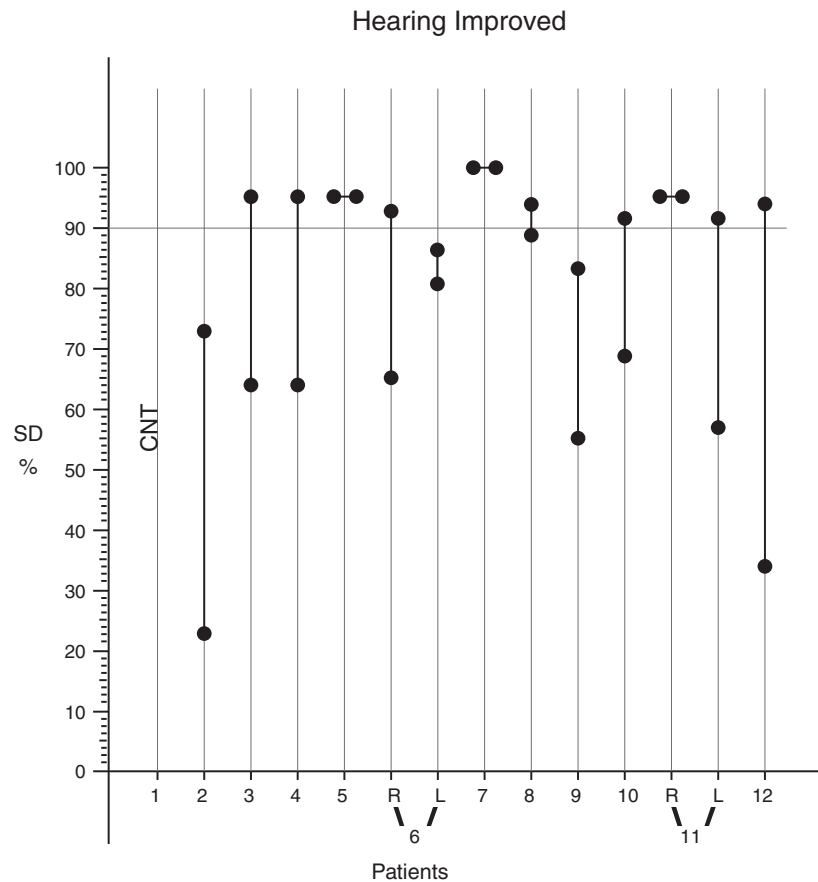


Fig. 6 – Bar graph for improved speech discrimination in twelve patients receiving antiviral treatment. Pre and post treatment scores are plotted as in Fig. 5.

Two patients (No. 24, 31) required intratympanic labyrinthotomy with gentamycin to achieve control while one patient (No. 25) failed to return for follow-up. Four patients required surgical labyrinthectomy to control symptoms.

4. Discussion

Meniere's disease has been regarded as idiopathic since the TB demonstration of EH by Hallpike [3] and Yamakawa [4]. Based on the EH deformation of the membranous labyrinth and strengthened by the experimental demonstration of EH following Endolymphatic sac obstruction in lower animals [21], medical [22–24] and surgical [8,25] treatments designed to reduce endolymph volume were widely employed to relieve the vestibular and auditory manifestations of MD. These approaches have not proved to be effective in this regard but are still routinely recommended by otologists. The most recently espoused concept of the pathophysiology in MD [7] has been that EH induced by some abnormality in endolymphatic sac function increases to a point where ruptures occur in the distended membranous wall, releasing neurotoxic potassium ion into the perilymphatic space causing a sudden disruption in the neurophysiology of vestibular and auditory neurons.

Reports of a loss in vestibular and auditory neurons in TB of MD patients would seem to support this widely held view [12–14]. We have earlier discussed the incompatibility of a scattered pattern of neural degeneration from a chemical source of injury in the perilymphatic space with the focal axonal degeneration in bundles which is characteristic of MD [17].

It is well established that the axonal transport of viral proteins in sensory neurons is strain specific. Some strains of HSV-I (McIntyre) transport nucleic acids peripherally (toward the labyrinth) (Fig. 7) while other strains (HS 129) transport centrally (toward the brain) [26,27] (Fig. 8). Therefore activation of retrograde transport virus in the vestibular ganglion can release infectious nucleic acids [28] into perilymph from vestibular nerve branches. On the other hand those viruses which send their nucleic acids centrally will present as recurrent vertigo without hearing loss (vestibular neuronitis). These nucleic acids can reach the base of hair cells in the vestibular and auditory sense organs where nerve terminals are separated by a synaptic cleft from the HC membrane. Vestibular and auditory manifestations of this chemical labyrinthitis are then produced. Fluctuation in symptoms reflects the decrease and increase in neural discharge caused by the intermittent release of toxins by vestibular neurons containing the virus genome. Repeated inflammation in these critical areas may result in fibrous tissue proliferation around

Table 2 – Hearing not improved.

No.	PAT	PTA < 50 db	SD	Vertigo control	Duration of M.D. (year)
Sub Group I					
13.	47 F	LF 40	94%	+	1
14.	52 F	FL 50	68%	-	6
15.	60 F	FL 55	60%	0	1
16.	48 F	FL 50	48%	0	5
17.	67 M	LF 35	90%	+	0.5
18.	45 F	LF 48	48%	+	20
19.	20 F	LF 16	90%	+	0.5
20.	26 M	LF 50	90%	+	1
21.	45 F	FL 53	CNT	+	1
		FL = flat			AVG = 4.4
		LF = low frequency			
Sub group II					
22.	49 F	FL 60	16%	- LAB	5
23.	42 F	FL 63	0%	- LAB	3
24.	62 F	LF 60	16%	+G	1
25.	71 F	FL 65	12%	0 - NR.	2
26.	45 F	LF 60	36%	+	4
27.	59 M	FL 60	42%	- G/LAB	3
28.	65 M	FL 70	0%	+	10
29.	46 M	FL 70	45%	- LAB	3
30.	59 M	FL 66	32%	+	7
31.	81 F	FL 90	0%	+G	30
					AVG = 6.8

NR = no return.
LAB = surgical labyrinthectomy.
Gentamycin-intratympanic.
0 = effect on vertigo not known.

the base of hair cells, thus impeding excitatory activity in vestibular and auditory neurons. The vestibular nerve branch with the largest exposure to perilymph is the utricular nerve. The vestibular cistern is the location of fibrosis in 40% of MD TB [7]. The EH in MD can be regarded as the labyrinthine response to recurrent episodes of labyrinthitis caused by repeated release of toxic proteins into the perilymphatic space [29]. Fully formed viral structures enclosed in transport

vesicles in the cytoplasm of vestibular ganglion cells excised from three patients with refractory MD have been observed in transmission electron microscopy [14]. (Fig. 4).

Prior to formation of the virion, protein elements migrate toward the nuclear membrane where they acquire a primary envelop before release into transport vesicles formed by the Golgi apparatus [30,31] (Fig. 4). These stages in the re-activation of neurotropic viruses from the herpes viridae family demonstrate the difficulty in finding morphological evidence of the virus in the nucleus of a neuron. The formed virus particles are to be found in the cytoplasm. Infectious Nucleic acids released from ganglion cells containing these virus particles flow into the perilymph filled vestibular cistern. They are then carried up the scala vestibuli where they enter the apical part of the scala tympani after passing through the helicotrema (Fig. 7). Unaltered by antibodies, these toxic nucleic acids are able to penetrate Rosenthal's canal through the perforating canaliculi in the inferior osseous spiral lamina. After collecting in perilymph filled channels these toxins may then be carried along auditory nerve fibers to the habenula perforator. Entrance into the perilymph of the organ of Corti, (OC) occurs between the pillar cells and initially contaminates the perilymph surrounding outer hair cells (OHC) and their nerve terminals (Fig. 9). Interference with the function of OHC would be expressed clinically as a low frequency threshold elevation of about 50 db. The contaminants can also be carried longitudinally through the tunnel space and the OHC manifesting as a flat threshold elevation of about 50 db.

After repeated contamination of the OC, the toxic nucleic acids can then penetrate the tight surround between the inner hair cells (IHC) and supporting cells resulting in decreased afferent neural transmission at the IHC/neuron junction. As the apical turn spiral ganglion is important to word recognition, this would present clinically in a lowered SD in addition to the pure tone threshold elevation. As the duration and toxicity of the nucleic acid contamination of the OC continue, these deficits are likely to become permanent because of IHC and spiral ganglion cell loss.

Based on this concept of altered cochlear physiology, the results in this series of 31 patients with MD can be used to

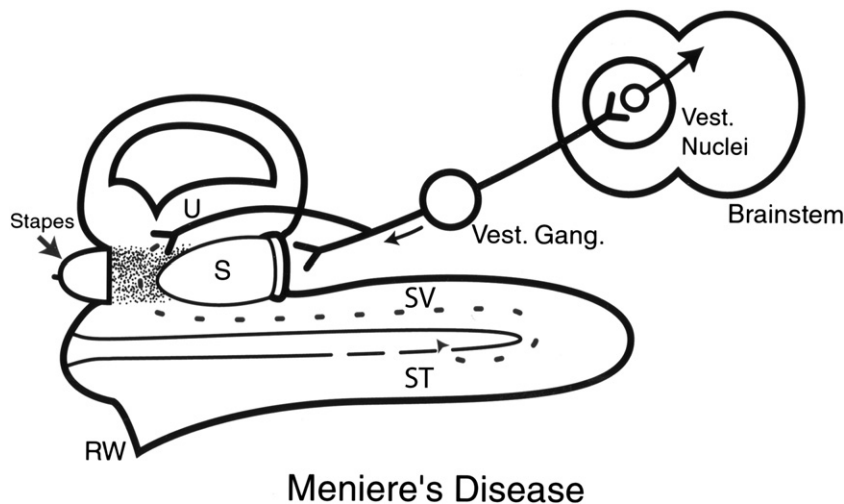


Fig. 7 – Schema describing flow of viral nucleic acids from vestibular cistern to apex of cochlea in Meniere's Disease.

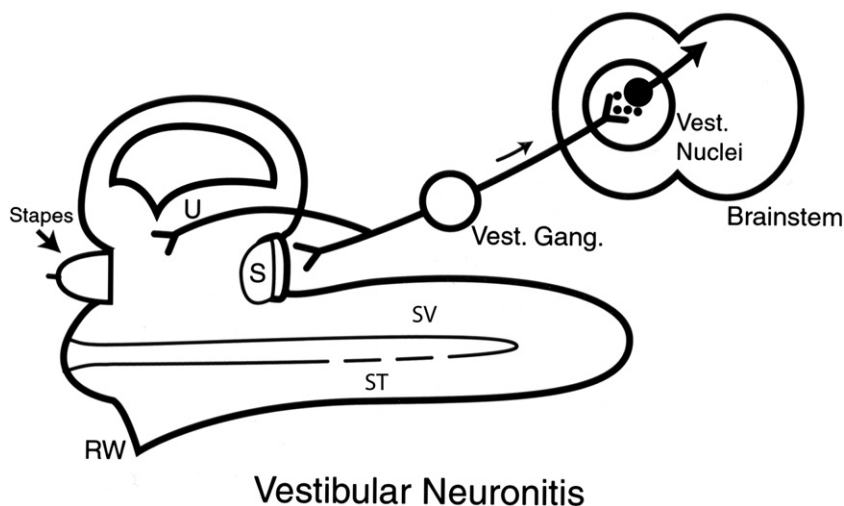


Fig. 8 – Schema of the viral nucleic acid flow in vestibular neuronitis. Hearing is unaffected but transynaptic spread to second order neurons is possible.

predict the reversibility of the hearing loss in MD. Except for one patient (No. 2) all these patients who recovered hearing after antiviral therapy presented with PTA of 50 db or lower and word discrimination scores of 50% or higher. Moreover, all except three (No. 2, 9 and 11) recovered normal hearing. All

twelve patients with recovered hearing experienced complete control of their recurrent vertigo with antiviral drugs. On the other hand those patients who did not experience hearing improvement recorded worse pre-treatment audiometric values. Eleven of the nineteen patients presented PTA of

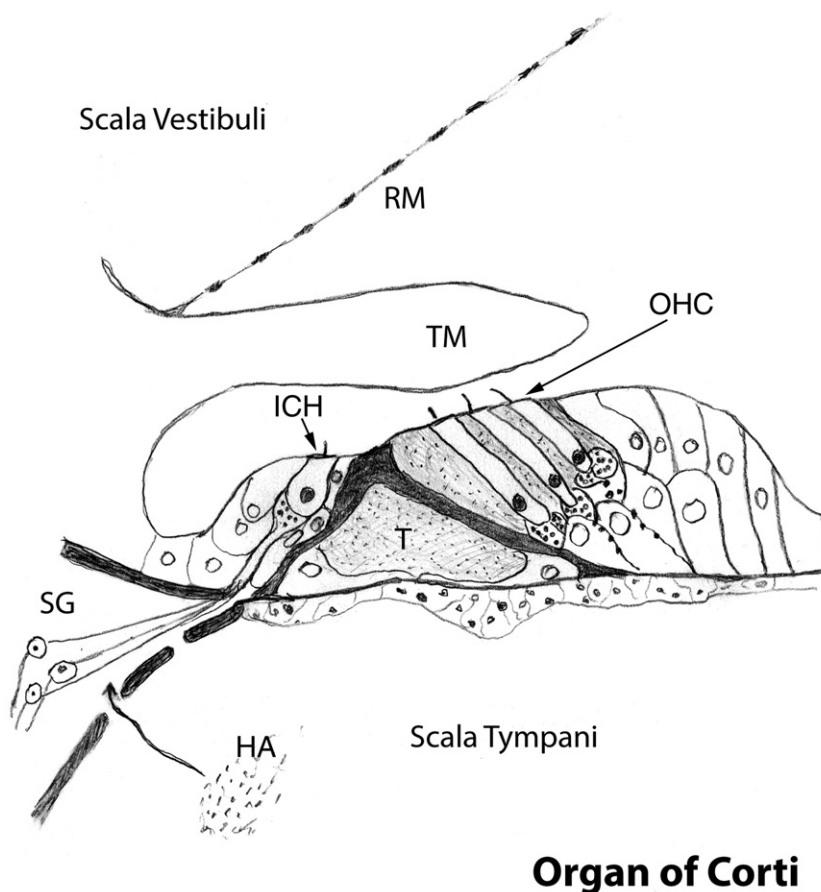


Fig. 9 – Drawing of the organ of Corti demonstrating the pathway for toxic nucleic acids (NA) in the perilymph space to reach inner (IHC) and outer hair cells (OHC) and their nerve terminals. T = Tunnel Space.

greater than 50 db and twelve had SD scores less than 50%. Twelve had flat audiometric patterns. Only six patients had SD better than 50%. These values suggest damage to more than just OHC. Degeneration of IHC and/or spiral ganglion cell is likely present in these failures. Degeneration of apical ganglion cells has been reported in the TB of patients with MD [7].

In nine of these patients with no hearing improvement vertigo was controlled with the antiviral medication alone. Four failed to be relieved with the antiviral and were so disabled that a labyrinthectomy was performed to allow them to return to work. Two patients (No. 15 & 16) did not have vertigo at the time of examination and one (No. 25) failed to return for follow-up. Two patients (No. 24 & 31) required intratympanic gentamycin in addition to the antiviral for relief of vertigo. One patient (No. 14) chose to remain on meclizine for vertigo control. Although it is possible that virus resistance may be responsible for failure of the antiviral drug to be more effective in control of vertigo in this last group of patients, the increased duration of MD may suggest another explanation. Increased fibroblast activity surrounding vestibular ganglion cells and obliteration of the synaptic cleft in both the auditory and vestibular sense organs may represent an increase in the blood brain barrier for the antiviral drug to cross before reaching the virus containing neuron. Therefore, early medical treatment of virus activity may be effective in controlling the number of failures. The question of control group of patients is difficult to answer. Having been on the standard medical treatment of MD for 6 months to several years, these patients were referred for a specifically different treatment program (antiviral) to control their symptoms.

Support for the concept that the pathologic process responsible for MD is located in the vestibular ganglion comes in reports of hearing improvement following vestibular neurectomy or nerve transection (Table 3). Approximately half of these report a 26% to 36% of patients experienced hearing improvement [34,35,37] and half with a 10% to 16% rate of improvement [32,34,39,38]. Most of these were based on improvement in the pure tone thresholds in the affected ear and word discrimination scores were not recorded. Both excision of the vestibular ganglion via a middle cranial fossa approach and proximal nerve transection in the cerebello

pontine angle result in loss of vestibular ganglion cells where the causative virus is located. This neural deficit removes the source of recurrent serous labyrinthitis responsible for EH and a sensorineural hearing loss. Using the antiviral approach the incidence of recovery in hearing was 40% in this series.

The variety of percentages in hearing improvement associated with selective surgical ablation may be related to completeness of vestibular ganglion cell loss. Difficulty in retraction and excision of the inferior division ganglion in the middle fossa approach and variability in the interface between cochlear and vestibular axons in the retro labyrinthine procedure are impediments to complete selective vestibular ablation. On the other hand, antiviral therapy reaches all ganglion cells with the virus genome. The outcome in pure tone and word discrimination after antiviral treatment is superior to surgical ablation. The results in this small series support this concept.

Since type I neurons in the vestibular ganglion degenerate following loss of the trophic effect of type I hair cells in the sense organs [40], the use of intratympanic gentamycin may also have some effect in reducing the virus load responsible for the inflammatory insult to the labyrinth. Therefore, the use of this ototoxic agent locally may add an antiviral effect to its ablation effect on vestibular symptoms.

Hearing improvement following standard diuretic medical treatment of MD has been reported [24,25]. These reports claim 20% to 40% of patients experience hearing improvement in pure tone thresholds of 10 db or more. Description of changes in threshold sensitivity as well as some relief of dizziness (40% to 50%) could be explained by a dilution of toxic nucleic acids in the perilymph of the OC and around vestibular sense organs caused by changes in labyrinthine fluid volume and ion levels. Therefore, the earlier the antiviral treatment in MD, the better chance for recovery of hearing. Since there is morphological and functional evidence of virus presence in the contra lateral or asymptomatic ear in MD [14,17], the prophylactic use of antiviral drugs is a worthy consideration. The risk of development of bilateral MD has been shown to increase with the length of symptoms [2]. As a final note on the pathophysiology of hearing loss in MD, this concept may be used to understand the mechanism of the hearing loss in other otopathologies causing serous labyrinthitis. Examples include post-stapedectomy granuloma, perilymphatic fistula and chronic otitis media with footplate erosion.

Table 3 – Hearing improved after vestibular neurectomy in Meniere's disease.

Surgeon	Technique	PTS. with improved hearing
Glasscock [30]	MF	13%
Fisch [32]	MF	16%
Silverstein [33]	MF	26%
Garcia-Ibanez [34]	MF	31%
Gacek [35]	MF	13%
Wazen [36]	RL	27%
Silverstein [33]	RL	23%
	RS/RL	36%
Kemink [37]	RL	10%
Teixido + Wiet [38]	RL	36%

MF = middle cranial fossa.

RL = retro labyrinthine.

RS = retro-sigmoid.

5. Conclusion

The sensorineural hearing loss in MD can be reversed in almost half of patients treated with acyclovir or valacyclovir. This outcome is similar to that seen after vestibular neurectomy and supports morphological evidence of viral presence in the vestibular ganglion.

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