ORL

Review Article

ORL 2021;83:144–150
DOI: 10.1159/000511113

Received: February 13, 2020
Accepted: August 21, 2020
Published online: February 17, 2021

On the Nature of Hearing Loss in Ménière's Disease

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Keywords
Ménière's disease · Hearing loss · Antiviral drugs

Abstract
Objective: To explain the pathophysiology of the hearing loss in Ménière's disease (MD). ***Background:*** In a previous report, we described a dramatic recovery of hearing in 12/31 patients with MD using antiviral (AV) drugs. The hearing loss in the remaining 19 patients with a longer history of MD remained unchanged or else worsened. Vertigo control was complete in the group with improved hearing but poorer in the group with greater hearing loss (and a longer MD history). Since achieving the recovery of hearing and control of the vertigo using AV drugs in these patients with a shorter history (≤2 years) of MD, we have continued to record dramatic hearing recovery in MD when patients have a shorter history of symptoms. We describe this here in 5 representative MD patients. We feel that the most likely explanation for the outcome is the removal of viral nucleic acids (NA) from the organ of Corti. ***Summary:*** A likely explanation for the sensorineural hearing loss in MD is paralysis of the cochlear amplifier function of the outer hair cells due to the toxicity ofNA. These NA are released from neurotropic viruses located in the vestibular nerve ganglion. ***Key Messages:*** (1) Viruses (*Herpes* family) are the cause of the symptoms in MD. (2) Hearing loss is the result of viral NA in the organ of Corti. (3) A short history of MD symptoms (<2 years) favors hearing recovery.

Introduction

In a previous report, we described the recovery of hearing loss in Ménières disease (MD) after the use of antiviral (AV) drugs [1]. This improvement far exceeded the criteria set by the Academy of Otolaryngology-Head and Neck Surgery for signifying change following treatment [2]. The improvement in 12/31 patients with MD exceeded threshold and word discrimination scores to reach normal levels in almost all 12. We know of no other medical or surgical treatment that has been shown to produce such dramatic results in hearing improvement and vertigo control in MD.

In 1957, Schuknecht [3] noted a similar dramatic recovery of hearing in 5/8 patients with MD who were treated with streptomycin sulfate to ablate vestibular function. A logical explanation for this dramatic result could not be offered at that time. Significant improvement in hearing was noted in 20–30% of MD patients after selective vestibular nerve section or excision [4–9]. The common

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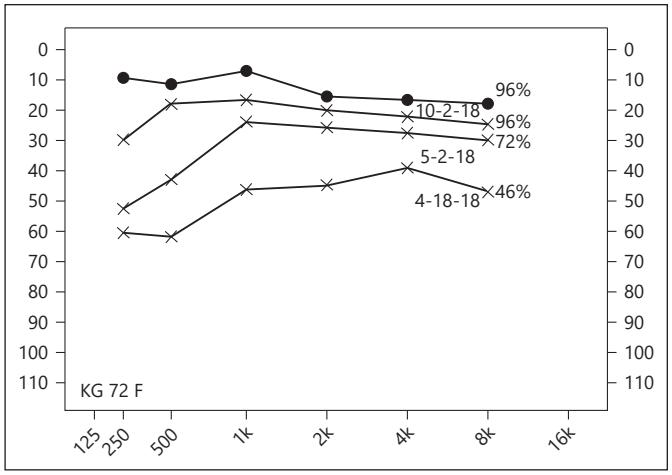

Fig. 1. Patient K.G. (73-year-old female).

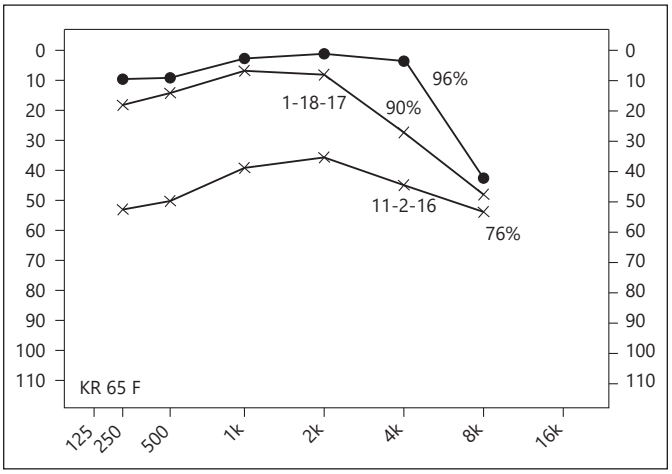

Fig. 2. Patient K.R. (65-year-old female).

theme in these reports is that the sensorineural hearing loss in MD can be improved following vestibular ablation.

Our experience treating MD patients with AV medication over the past 15 years has produced similar results with recovery of hearing to normal levels within a short period of time. Insight into the nature of the hearing loss in MD is offered in this report.

Review

Background

Our previous study involved 31 patients with MD seen during 2012 who were treated with AV drugs after the failure to control their symptoms with diuretics and a low-salt diet [1]. Twelve (40%) of these patients experienced significantly improved hearing (to almost-normal levels) and complete control of their vertigo. Nine patients (30%) with decreased but serviceable hearing (pure-tone average [PTA] <50 db; word discrimination >50%) had no change in hearing but excellent control of their vertigo (6/7 and 2 "no show"). Ten patients (30%) with worse hearing levels (PTA >60 db; word discrimination <50%) had poor control of their vertigo (3/10, with 7 requiring medical or surgical ablation). All 3 of these groups had a history of MD of a mean 2.4, 4.5, and 7 years, respectively. These results suggest that the longer the pathology exists (labyrinthitis), the poorer response to AV therapy.

Case Presentation

Several recent cases of MD are presented here to illustrate the timing and quality of hearing recovery following AV therapy.

K.G. was a 73-year-old female who noted left-sided hearing loss and tinnitus over 4–6 weeks. During this period, she had 1 episode of rotatory vertigo lasting 30 min to 1 h. She had a history of benign paroxysmal positional vertigo intermittently in the past 2 years. She had also experienced vocal-cord paralysis which had recovered after 3–6 months without treatment. She was started on 1 g of valacyclovir 3× daily for 3 weeks, reduced to 2× daily for 3 weeks, and then 1× daily. Her audiogram in Figure 1 demonstrates a prompt and complete recovery of hearing in the left ear.

K.R. was a 65-year-old female who experienced left-sided hearing loss with tinnitus for 1.5 years. She had 2 episodes of dizziness lasting 1–2 h. Because she worked as a security guard, she was sent to us after a traditional therapy of diuretics and a low-salt diet failed to improve her hearing. She noted a complete recovery of hearing and no dizziness after 6 weeks of the AV drug protocol with valacyclovir. Her audiogram is shown in Figure 2.

M.F. was a 35-year-old male with left-sided hearing loss and recurrent vertigo for 2 years. He had had profound hearing loss in the right ear since birth. He had been treated with diuretics and meclizine for 1 year without relief. He had 1 intratympanic injection of 10 mg of dexamethasone 4 months prior to being seen. He was started on 1 g of valacyclovir 3× daily and noted no change in his symptoms. He was switched to famcyclovir, 500 mg 3× daily. He noticed an improvement after 8 weeks of famcyclovir treatment. The dose was tapered to 500 mg daily and recovery of his hearing was tested (Fig. 3).

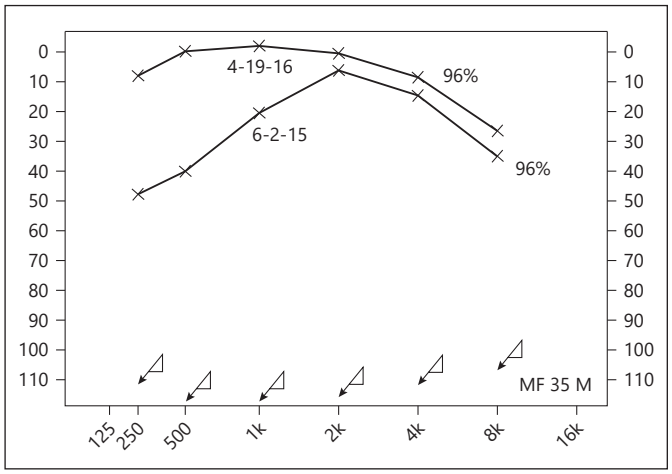

Fig. 3. Patient M.F. (35-year-old male).

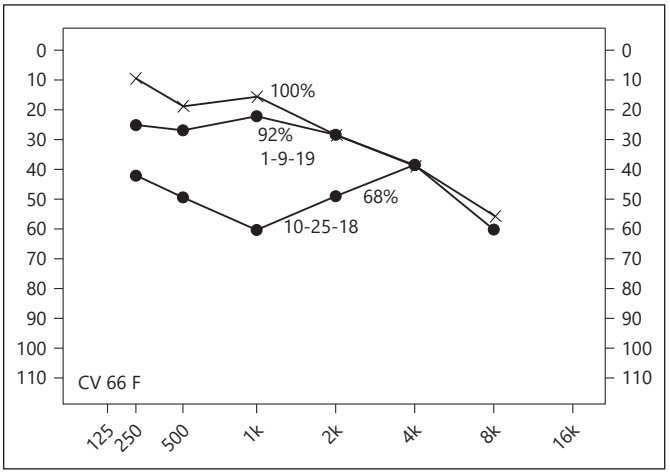

Fig. 4. Patient C.V. (66-year-old female).

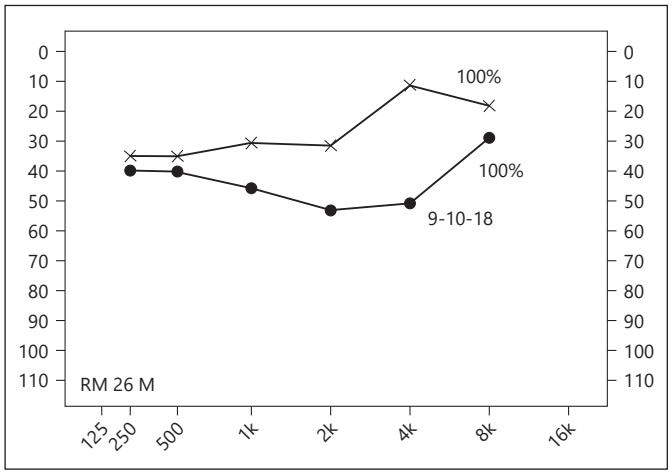

Fig. 5. Patient R.M. (26-year-old male).

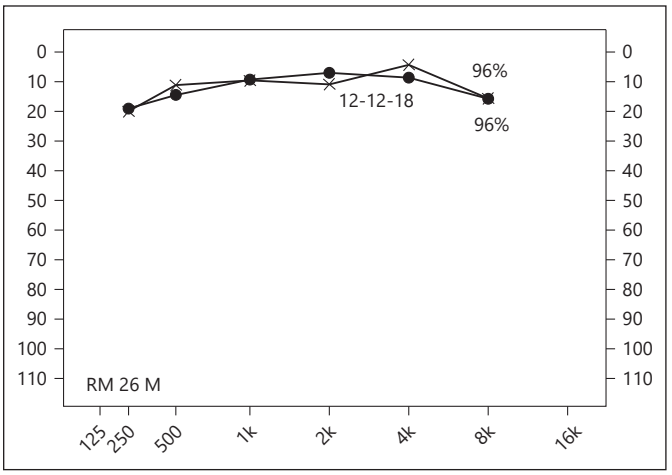

Fig. 6. Patient R.M. (26-year-old male).

C.V. was a 66-year-old female with fluctuating hearing loss in the right ear over 1 year. She had 1 episode of vertigo lasting 30 min to 1 h. After the AV (valacyclovir) protocol was completed down to 1 g daily, her audiogram showed complete recovery of hearing (Fig. 4).

R.M. was a 26-year-old male who noted bilateral hearing loss for 2 months. He had 1 episode of vertigo lasting 20–30 min. A hearing test at that time showed bilateral hearing loss, predominantly in the lower frequencies, with good discrimination scores (Fig. 5). He was placed on valacyclovir 3 g daily for 4 weeks, 2 g daily for 4 weeks, and then 1 g daily. Three months later, a hearing test revealed normal hearing in both ears (Fig. 6).

Discussion

We contend that the 3 main vestibulopathies (vestibular neuritis, MD, and benign paroxysmal positional vertigo) presenting as recurrent vertigo are caused by a virus of the Alpha herpes virinae subfamily latent in the vestibular ganglion [10]. These are from the family of the herpes class of neurotropic (NT) viruses. The main members of this subgroup are *Herpes simplex 1/2* (HSV-1/2), *Herpes zoster*, *Cytomegalovirus*, and *Pseudorabies virus*. The virus enters the oral cavity by airborne transmission and is carried by anterograde axonal transport to the sensory ganglion (meatal) of the facial nerve early and throughout life. It spreads to the adjacent vestibular gan-

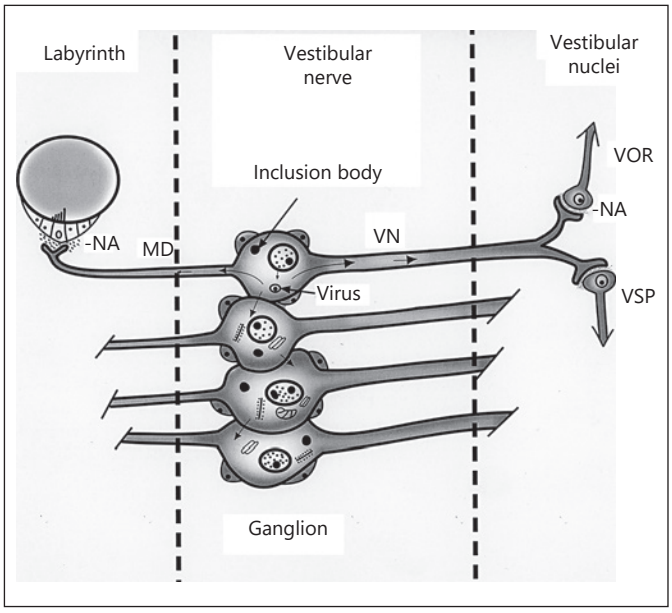

Fig. 7. A drawing of the bipolar vestibular ganglion (VG) cell illustrates how the anatomy favors the spread of the virus to the adjacent neurons, forming tight clusters of VG containing the virus. When reactivated, the nucleic acids (NA) may be released into the ear causing vertigo and hearing loss (MD), while release of NA toward the brain causes vertigo without hearing loss (VN). VN, vestibular neuritis; VOR, vestibulocular reflex; VSP, vestibulospinal reflex.

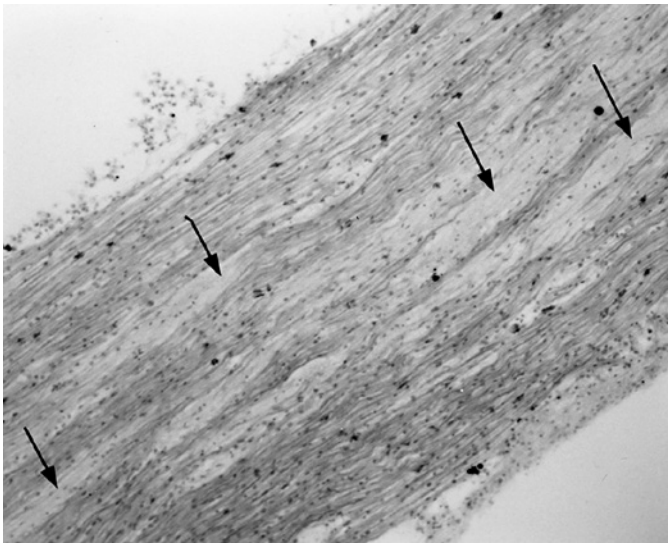

Fig. 8. Vestibular nerve in MD has many bundles of degenerated axons reflecting degenerated clusters of VG. ×80.

glion within the internal auditory canal over a lifetime. This spread is controlled by the host's immune system. Over decades, the virus genome accumulates, to the point where clinical symptoms may appear due to a weakened immune system and reactivation of the latent virus. This incidence rises with increased age. A study of 70 million patients in Germany showed a similar higher incidence rate of all 3 syndromes with increased age [11]. These features support a pathology located in the vestibular nerve early in life, that enters latency in the ganglionic mass and exhibits outbreaks when reactivation is permitted by a weakened immune system.

The bipolar vestibular ganglion cell is the virus location for these syndromes (Fig. 7). Located in the nucleus of a bipolar neuron, the virus is reconstituted from latency and released into the cytoplasm, sending its nucleic acids (NA) in either an anterograde (toward the brain) or retrograde (toward the ear) direction. Retrograde transmission of the NA causes an inflammatory process in the labyrinth (labyrinthitis). The major determinant of this retrograde flow of NA to the labyrinth is the virus strain itself [12]. The MacIntyre strain of HSV-1 has been shown to send its NA in a retrograde direction while the H-129 strain of HSV-1 sends its NA in an anterograde direction.

After the retrograde direction of NA flow, an inflammatory response in the labyrinth is reflected in the distension of the yielding membranes of the labyrinth (endolymphatic hydrops) [13]. Anterograde NA flow will cause vertigo without hearing loss. As the inflammatory effect is repeated, there is a weakening and outpouching of the more rigid membranous portions of the labyrinth and semicircular canals. In 40–50% of MD temporal bones, fibrous tissue formation may be seen in the vestibular cistern and is claimed to be responsible for a history of vertigo on pneumatic otoscopy.

Although disequilibrium or vertigo will occur from the effect NA toxicity has on neural activity in the nerve fibers, severe vertigo and falling actually occur because of abrupt vestibular ganglion cell degeneration. Episodes of vertigo and falling are produced by viral damage to a cluster of vestibular ganglion cells. The morphologic correlate of this event is focal bundles of degenerated axons in the vestibular nerve trunk (Fig. 8). A hearing deficit occurs because of NA toxicity in the perilymphatic compartment [14].

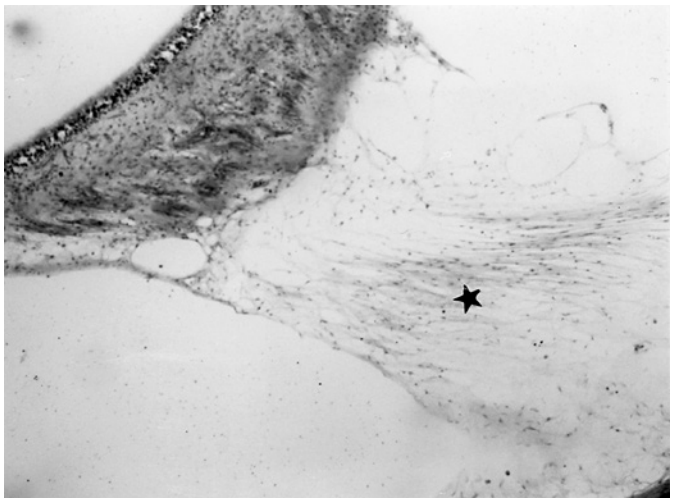

Fig. 9. View of vestibular cistern in MD shows early fibrosis stretching from the utricular nerve to the perilymph. ×80.

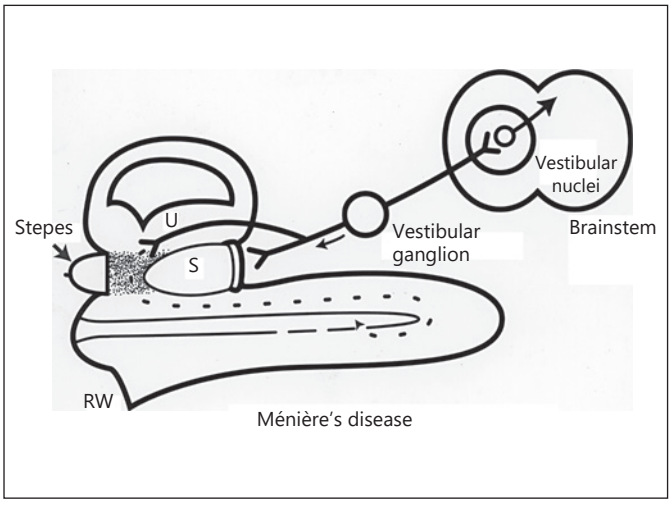

Fig. 10. The path of the nucleic acids (NA) from the vestibular cistern up the scala vestibuli to the helicotrema, where they first enter the organ of Corti in the scala tympani. RW, round window; S, saccule; U, utricular nerve.

Early in this release of NA into the vestibular cistern only, fullness may be experienced by the patient (Fig. 9). However, with the continued release of NA, these toxic proteins (DNA or RNA) flow up towards the apical turn in the scala vestibuli, where they first have an opportunity to reach the scala tympani after passing through the helicotrema (Fig. 10). Once in the scala tympani, the NA can penetrate the osseous spiral lamina and enter the perilymph-derived fluid in the organ of Corti and cochlear nerve fibers (Fig. 11).

The anatomy of the organ of Corti provides an insight into how this toxicity affects the structures essential to hearing (Fig. 12). Since the outer hair cells (OHC) are freely surrounded by perilymph, their walls and nerve terminals are also bathed in this fluid. The few type-II spiral ganglion cells in contact with the OHC are unlikely to play a significant role in hearing loss because of their low numbers and the lack of a known connection to the central auditory pathway. On the other hand, the primary auditory projections are provided by inner hair cells (IHC), which are tightly enclosed by supporting cells with no free space surrounding them. Contacted by the terminals of type-I spiral ganglion cells, these provide the major input of auditory signals to the central auditory system.

The major innervation of OHC is from the efferent olivo cochlear bundle, which provides the cochlear amplifier function by overcoming the viscous damping of the basilar membrane caused by the fluid-filled nature of the cochlea [15, 16]. Activation of this efferent system is responsible for the contraction and elongation of OHC to counteract the damping effect of these fluids. The function of reducing this damping effect is most prominent in the apical turn, with a lesser effect in the lower turns of the cochlea. Loss of the cochlear amplifier is mainly responsible for low-frequency loss as well as some higher-frequency loss of threshold, eventually giving a flat loss of 50–60 db and normal or reduced word discrimination. A loss of threshold >60 db and word discrimination worse than 50% indicate a loss of function of the IHC and of their innervation.

Recovery of the auditory threshold follows cessation of NA toxicity by AV drugs. These drugs prevent the reactivation of the virus by competing for the enzymes necessary for their reconstitution. Medical (streptomycin) and surgical (vestibular-nerve section) methods cause degeneration of type-I vestibular ganglion cells which carry the virus genome. Hearing improvement follows the removal of the source of the toxic NA.

After the NA have been blocked, nuclease enzymes released by the host's white blood cells will eventually neutralize the effects of the NA. This permits recovery of the cochlear amplifier by the reversal of changes in the walls of the OHC and the return of efferent neural control to counteract the damping effect on the motion mechanics of the organ of Corti. The initial return of function is usually noted at higher frequencies (Fig. 1) because of a lower concentration of the NA in the lower turns of the cochlea. If there is greater (longer) exposure to NA, perma-

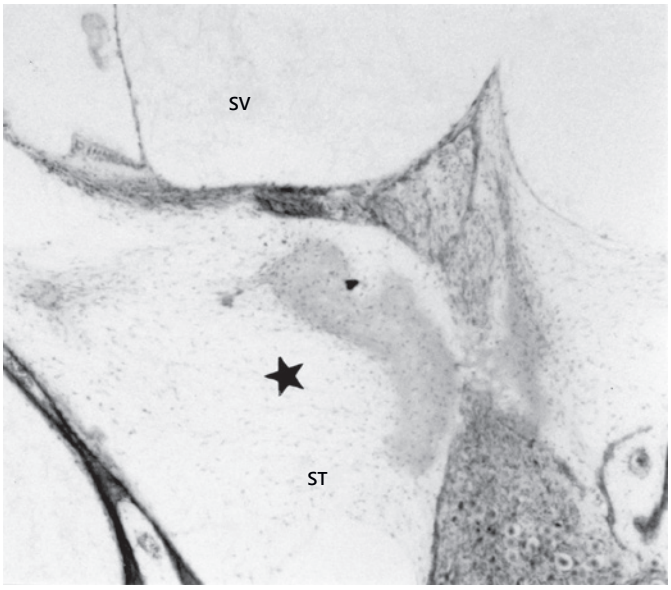

Fig. 11. Fibrosis in the apical scala tympani (ST) indicates the presence of inflammation. ×80. SV, scala vestibuli.

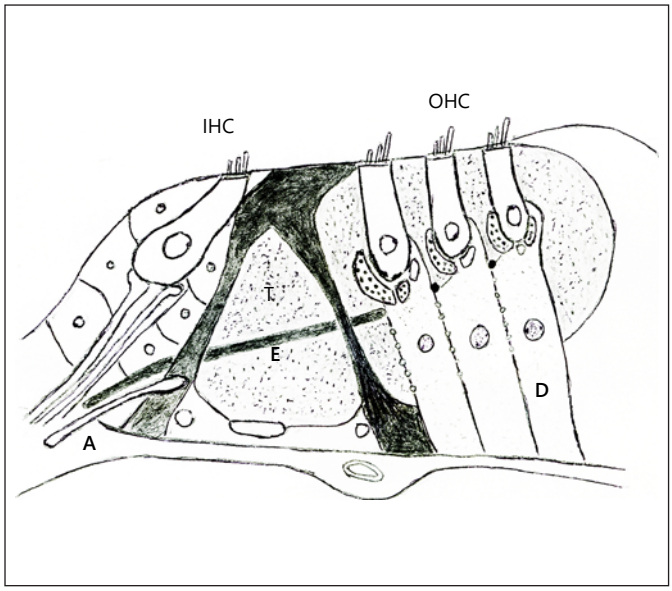

Fig. 12. A drawing of the organ of Corti demonstrates the pathway for NA in the perilymph to surround the outer hair cells (OHC) and the efferent fibers (E) crossing the tunnel space (T). The inner hair cells (IHC) are protected by support cells. A, afferent cochlear nerve; D, Deiter's cells.

nent effects on the units (OHC and IHC) may cause nonreversible changes that result in a permanent loss of threshold and of word discrimination.

Treatment

Since MD represents the clinical manifestation of recurrent viral labyrinthitis, a logical treatment plan can be formulated using the acyclovir class of drugs. These drugs are safe and have minimal side effects. They achieve their goal by preventing the reactivation of viral proteins by competing for the enzymes that the virus needs to complete this formation (thymidine kinase and DNA polymerase). These drugs are excreted via the renal system. Therefore, renal function must be demonstrated to be normal before their use. Crystallization in the kidney tubules can be a serious result if not cleared.

While acyclovir is an effective AV drug, its bioavailability is the lowest (20%) of the available acyclovir drugs effective for neurotropic viruses of the Herpes family. Other AV drugs (valacyclovir [55%] and famcyclovir [75%]) have better bioavailability, but some insurance plans do not cover them.

We recommend the drugs are administered (1) as soon as a diagnosis is made, because the damaging effects of labyrinthitis should be avoided, and (2) at a high enough dose for long enough to maximize efficacy. Our regime consisted of 1 g of AV drug 3× daily for 3 weeks, downsized to 2× daily for 3 weeks, and then 1× daily (maintenance dose) for 6 months to 1 year. (3) The drug is also given to prevent the risk of bilateral involvement of the inner ear. (4) If cytomegalovirus is suspected, use the AV drug ganciclovir.

Conclusion

The dramatic recovery of the sensorineural hearing loss in MD following the use of AV drugs can best be explained by a recovery of toxic paralysis of the cochlear amplifier caused by free viral NA. The relief of auditory and vestibular symptoms of MD confirm that its cause is located in the vestibular neurons. The earliest possible (AV) treatment of MD favors the recovery of hearing and the control of vertigo.

Conflict of Interest Statement

The author has no ethical conflicts of interest to declare as this is a review article.

Funding Sources

No form of financial support has been received in the previous three years.

Author Contributions

The writing of this manuscript has been the sole work of the author.

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