Viral Etiology For Inner Diseases: Proven, Unproven, Unlike.

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Abstract: This is a revision article that deals with the broad field of inner ear disease caused by viral infections. Some of these entities have been proven to have a viral etiology. Others have strong evidence in favor of a viral causation but still can not be considered as a viral disease. Finally others have some published articles pointing to a viral etiology but when the whole body of evidence is considered one concludes that a viral etiology is indeed unlike. We review the literature and added our own experience in this subject. The result is presented in this communication. Clearly the most important evidences we have about this subject came from the study of temporal bone histopathology. Certainly we can learn much more if we continue to collect and study temporal bone specimens histopathologically.

Key words: viral etiology, inner ear diseases, temporal bone histopathology.

Introduction

Schuknecht in 1993[1] stated that from a clinical and histopathological stand point many disorders of the inner ear characterized by sudden loss of hearing and balance fit much better on a viral etiology than in any other possible cause.

Peripheral auditory and vestibular dysfunction occur in connection with respiratory viral diseases[2] sometimes associated with central nervous system disease[3]. Viral encephalopathies may also cause inner ear disease[4].

Van Dishoek and Bierman[5] reported 100 cases of sudden sensorineural hearing loss and found elevated viral antibody titles in many of these cases. Westmore et al in 1979[6] isolated mumps virus from the inner ear of a patient with sudden sensorineural hearing loss.

On the basis of clinical and pathological evidences some viral etiologies of inner ear diseases have been clearly established (herpes zoster oticus, measles, rubeola, cytomegalovirus infection). Others are not definitely demonstrated but are a very likely possibility (sudden deafness, Bell´s palsy, vestibular neuronitis, delayed endolymphatic hydrops). On the other hand viral etiology has been proposed for some other inner ear affections but this hypothesis seem to be quite unlike at this point (otosclerosis, benign paroxysmal positional vertigo, Menière´s disease).

We will review the pertinent literature on this topic and comment on our personal experience with viral etiology in relation to profound sensorineural hearing loss in infancy and early childhood[7].

1- Proven viral etiologies for inner ear disease

Herpes zoster oticus

Korner in 1904[8] called herpes zoster oticus the syndrome consisting of vesicles around the auricle, facial nerve palsy and hearing loss. Later in 1907 Ramsay Hunt[9]

described this disease and provided a classification for it. Since then herpes zoster oticus and Ramsay Hunt syndrome are common designations for this affection.

While there is no doubt about the etiology of this syndrome the pathology reports from autopsies of patients with the syndrome and of temporal bone studies have shown varied characteritics.

The varicella-zoster virus that also causes chicken pox is the etiologic agent of herpes zoster oticus. As it happens with herpes simplex virus this agent is latent in the central nervous system and is activated by systemic diseases, aging or immunodeficient states. Hunt[9] thought that the facial paralysis was caused by a viral geniculate ganglionitis. However pathological reports have failed to substantiate this hypothesis[10]. Indeed autopsy reports of patients with herpes zoster oticus and facial palsy[11, 12] have shown lymphocitic infiltration and degeneration of the facial nerve but no clear changes in the geniculate ganglion. It is possible that this affection is a form of encephalomeningo myelitis which later spreads to the motor and sensory nerve roots[11].

In conclusion even though the pathophysiology of the Ramsay Hunts syndrome is still in debate there are no doubts about the viral etiology.

Cytomegalovirus inclusion disease

Cells infected with this virus are usually large and have intranuclear inclusions. The virus is related to the herpes group and has the ability to remain latent in infected humans.

Congenital infections vary from simple viruria to abortion or extensive liver and brain injury. Forty eight percent of congenitally infected symptomatic children have sensorineural hearing loss as opposed to 6.9% of asymptomatic serologically positive patients[13]. Some have considered cytomegalovirus inclusion disease a leading cause of human congenital viral infection and hearing loss[14].

Temporal bone histopathology have been reported in patients with cytomegalic inclusion disease. Straus in 1990[15] found in six of nine temporal bones pathologic changes compatible with viral labyrinthitis. Two also had cochlear neurons involvement. Of the nine bones two showed no evidence of infection and cytomegalovirus was isolated from culture of inner ear fluids in one. In the bones with pathological evidence of infection the inclusions were seen in the epithelial lining cells of the cochlear duct not involving directly the organ of Corti.

From the exposed it is safe to say that cytomegalovirus is a proven etiologic agent of inner ear disease.

Measles

A highly contagious paramixovirus is the cause of measles. Since 1928 measles is known to cause sensorineural hearing loss in incidences which varied from 6.7% of the cases to 10%[16, 17, 18, 19, 20]. It was also known that the involvement was bilateral with moderate to profound loss of auditory and vestibular function.

Temporal bone histopathology descriptions of measles labyrinthitis also started as early as 1937[21]. These descriptions are important because they established the pattern of histopathological changes in viral labyrinthitis which later would help to establish a viral etiology for other affections.

The organ of Corti is usually shrunken and without hair cells or it may simply be missing. These changes are more severe in the basal turn. Nager in 1907[22] described atrophy of the stria vascularis. Lindsay and Hemenway in 1954[23] described the pathology of the tectorial membrane wich was missing or detached, spherically deformed and sometimes encapsulated by a layer of flattened cells. Cochlear neurons may be severely depleted. Reissner membrane may be displaced toward the basilar membrane when there is severe atrophy of the stria vascularis. The sensori epithelium of the cristas and maculas are severely atrophied leading to loss of caloric sensitivity.

Measles encephalitis occurs much less frequently than measles labyrinthitis (once in 600 to 1000 cases) and therefore has no direct association with the inner ear disease. Subacute sclerosing panencephlitis occurs infrequently months to years after the measles infection and is usually fatal. It also is unrelated to measles labyrinthitis[1].

At this point there is abundant evidence to consider measles labyrinthitis as a proven cause of inner ear disease.

Mumps

Mumps is caused by a paramyxovirus and spreads by droplet infection[1]. Orchitis, pancreatitis, prostatitis, nephritis, myocarditis and meningoencephalitis may occur. The development of mumps meningoencephalitis apparently does not predispose the patient to have hearing loss[24].

The labyrinthine involvement in mumps cases is usually unilateral for unknown reasons. Bilateral hearing loss caused by mumps labyrinthitis is rare. The hearing loss varies from mild high frequencies loss to profound deafness. Even though most patients have vestibular symptoms they are often overlooked in young children[25].

Van Dishoek and Bierman in 1957[5] performed serologic tests and viral cultures of blood and stools of 66 sudden deafness patients and 14 were positive for mumps. Other evidences for mumps etiology of inner ear disease include the following: mumps antibody titers were high in four of nine patients with sudden unilateral sensorineural hearing loss and another two were borderline. Each patient clearly remembered having mumps in childhood[26]. Degenerative changes were produced in the cochleas and stria vascularis in monkeys and guinea pigs by injecting mumps virus into the labyrinth[27], hystopathological study of the temporal bones of a six year old child bilaterally deafened after mumps infection at age two showed severe atrophy of the organ of Corti and stria vascularis, collapse of Reissner´membrane, detachment of the tectorial membrane from the limbus in

the basal and middle turns and encapsulation of this membrane, there was moderate loss of cochlear neurons in the basal turn and the vestibular labyrinth was intact [28].

Vaccination against mumps has been effective in reducing cases of unilateral sensorineural hearing loss in childhood and adolescence.

It seems reasonable to say that mumps virus is an etiologic agent of viral labyrinthitis and sensorineural hearing loss usually unilateral (not allways)

Rubella

Hearing loss from maternal rubella was first described in 1943[29]. In 1945 116 children were found to have profound sensorineural hearing loss among 147 infants dysplaying other congenital defects following maternal rubella[30].

Studies in Sweden determined that the pattern of hearing loss after maternal rubella was a flat audiogram and that the degree of hearing loss could vary from one ear to the other[31]. In 1966 it was determined that rubella virus can cause defects atributable to the first trimester of development as well as in the second trimester and the rubella virus was isolated from affected fetuses[32].

Cochleo-saccular dysplasia has been established as the hallmark of rubella virus in the inner ear[32, 33, 34, 35, 36, 37]. One temporal bone report[38] described an anomalous stapes with cartilaginous fixation of the footplate and thickened cruras and capitulum.

Immunization against the rubella virus can prevent the outbreak of epidemics in young children that would spread to women in childbearing age.

Maternal rubella is certainly a proven viral etiology for inner ear disease.

2. Unproven viral etiologies for inner ear diseases

Infantile cochleosaccular degeneration

This pathological entity when appearing in children and with the vestibular labyrinth intact is "almost certainly caused by a viral attack to the inner ear"[1]. This assumption was based on the fact that the cochlea and saccule (pars inferior) is phylogenetically younger than the vestibular labyrinths (pars superior) and could have enzymatic processes more vulnerable to a viral attack and on the fact that the rubella virus causes cochleosaccular degeneration as it´s hallmark in the inner ear[33, 35, 37].

Cochleo saccular dysplasia does not dysplay the fibro-osseous proliferative reaction seen in meningogenic suppurative labyrinthitis, it is almost exclusively a disease of infancy, may be unilateral or bilateral and the hearing loss is usually profound.

We will further comment on this condition when we discuss the pathology of profound sensorineural hearing loss in infancy and early childhood[7].

Sudden deafness

A viral etiology for sudden idiophatic sensorineural hearing loss has been advocated by Schuknecht[39] and Schuknecht and Donovan[2]. This was done by comparing the temporal bone hystopathology of known cases of viral labyrinthitis (rubella, mumps, measles) with the histopathological findings in 12 cases of sudden idiopathic sensorineural hearing loss from the temporal bone collection of the Massachusetts Eye and Ear Infirmary. Studying the pathology of these bones they could not find any evidence favoring a vascular etiology (absence of fibrous reaction known to occur after vascular inner ear injury). Some membrane breaks were found but they argued that a segmental, localized membrane break does not cause a sudden generalized hearing loss according to previous experimental evidence[40].

Yoon et al in 1990[41] studied 11 temporal bones from 8 patients with a history of sudden sensorineural hearing loss. They stated that the origin of sudden sensorineural hearing loss was obscure in seven bones from 5 patients but the causes seemed to be multiple. Atrophy of the organ of Corti and loss of cochlear neurons were common findings

and the latter was the main finding in patients with viral infections. Labyrinthine fibrosis and new bone formation were seen in two ears associated with vascular insult and in two others associated with autoimmune disease. They therefore advocated multiple causes for sudden sensorineural hearing loss.

Khetarpal and Nadol in 1990[42] studied 22 temporal bone speciments from 18 patients with a history of sudden sensorineural hearing loss from the temporal bone collection of the Massachusetts Eye and Ear Infirmary. They divided these patients in three groups: one with history of upper respiratory tract infection preceding or occurring concurrently with the hearing loss (six ears, six patients); one with no hystory of upper respiratory infection in relation to the hearing loss (seven ears, six patients); and one with presumptive postnatal viral labyrinthitis (hearing loss following attacks of mumps, measles or herpes zoster oticus) comprising nine ears, six patients. Because of dissimilarities in ganglion cells count between the groups without history of upper respiratory infection and the group of presumptive viral labyrinthitis they casted doubt on the theory of viral infection for sudden idiophatic sensorineural hearing loss.

Berrocal and Camacho in 2002[43] reviewed the possible causes for sudden sensorineural hearing loss and tried to establishs autoimmunity as a distinctive cause for this syndrome on the basis of clinical, pathologic and immunologic findings. They also mention the possibility of a viral infection of the inner ear start an immunologic reaction that leads to sudden deafness.

Merchant et al in 2005[44] described the temporal bone histopathology in 17 ears aged 45 to 94 years with idiopathic sudden sensorineural hearing loss from the Massachusetts Eye and Ear Infirmary collection. One temporal bone acquired during idiopathic sudden sensorineural hearing loss did not show any feature compatible with an acute viral cochleitis. The finding in the other cases did not strongly support viral cochleitis as a cause of sudden idiopathic sensoryneural hearing loss.

At this point it seems clear that sudden deafness has many possible causes and viral labyrinthitis may certainly be one of them but the latter etiology remains presumptive. A large multicentric prospective study would help to determine the prevalence of viral infections as a cause of sudden deafness.

In 1981 Oliveira[45] embolized cochlear capillaries with polyestirene copolymer beads in chinchillas, demonstrated the beads in the cochlear capillaries in surface preparations after injection of Prussian blue solution through the aorta (Figure 1) and determined the ionic composition of endolymph and perilymph at various time intervals after embolization. The endolymph potassium drecreased fast and reached the lower level at two hours. This ion concentration slowly returned to normal but was still low two months after the vascular injury (Figure 2). The freezing technique[46] was employed to obtain endolymph and this technique was later found to have incorrections due to intracelular potassium being liberated by the freezing process. However there were clear changes in perilymph and endolymph ionic composition. These changes could not be due to the freezing process which was the same before and after embolization. This is a clear evidence of how a vascular phenomenon can cause sudden drop of hearing. Untill a similar pathiphysiologic mechanism is demonstrated in relation to an inner ear viral infection this etiology for sudden deafness must remain presumptive.

Delayed endolympathic hydrops

Schuknecht et al in 1990[47]described the temporal bone histopathologic findings in two cases of contralateral delayed endolymphatic hydrops. The pathology in the deaf ears was compatible with the ones found in mumps and measles labytinthitis. The ear with the delayed symptoms had findings compatible with Menière´s disease temporal bone pathology. They hypothesized based on these findings a viral etiology or Menière´s disease. This of course remains just an unproven hypothesis as well as the viral etiology for delayed endolymphatic hydrops.

Vestibular neuritis

Schuknecht and Kitamura in 1981[48] described the histopathology of four patients with clinical history compatible with vestibular neuronitis. The histopathology they found was a discrete atrophy of the vestibular nerve similar to the findings in one case of herpes zoster oticus. Based on this they recomended the disease to be called vestibular neuritis instead of neuronitis and a viral etiology was presumed. This entity has not been further described and it´s etiology is presumptive and unproven.

Vestibular neuronitis

Vestibular neuronitis is caractherized by recurrent vertigo attacks without hearing loss[50]. This affection is regarded as caused by a degeneration of vestibular ganglions cells problably caused by a viral infection. This assumption is based in epidemiologic[50], clinical[48] and histopathological[51] evidences. However the viral etiology for this syndrome remains presumptive up to now.

Bell´s palsy

In 1972 Mc Cormick[52] suggested that herpes simple virus I could be present in a latent state in the geniculate ganglion and be reactivated by upper respiratory tract infection, stress, cold. Reactivated the virus could travel down the axon and cause a neuropathy of the seventh nerve. Burgess et al[53] detected herpes simplex virus genomic sequences postmortem in a patient 6 weeks after he developed Bell´s palsy. Other studies of seroprevalence have added supportive evidence[54]. Other studies have presented evidences that varicela zoster virus is the etiologic agente in many cases of clinically diagnosed Bell´s palsy[55].

Adour et al[56] published a double blind study in which they treated patients with Bell´s palsy with acyclovir plus steroids and steroids alone. This antiviral drug has

documented efficacy against herpes simplex and varicela zoster viruses. They found the drug combination more effective. However a large evidence based review[57] stated that steroids are safe and probably effective while acyclovir is safe and possibly effective against Bell´s palsy.

Stjernquist-Desatinik et al[55] in 2002 found herpes simplex and varicella zoster DNA in CSF and post-auricular muscles using polymerase chain reaction in only 10% of patients with Bell´s palsy in the first 73 hours after onset.

It is safe to say that at this point a viral etiology for Bell´s palsy is only a possibility that must be further studied.

3. Unlike viral etiologies for inner ear diseases

Otosclerosis

Immunocompetent cells including macrophages, HLA-DR positive cells, cells expressing beta-2 microglobulin, T-supressor cells and complement C have been found in otosclerotic focuses[58, 59]. Because of this an inflamatory nature of this process has been hypothesized. The presence of autoantibodies to collagen II and IX in serologic specimens of otosclerosis patients has been detected[60]. Col IAI gene has been associated with a familial case of clinical otosclerosis[61]. Osteoblasts and preosteoblasts of otospongiotic focuses have filamentous structures similar to paramyxoviral nucleocapsid[62]. Immunohistochemical studies confirmed the expression of measles virus nucleocapsid (N) and fusion (F) proteins in chondrocytes, osteocytes, osteoblasts and connective tissue in otospongiotic focuses[63]. However attempts to culture measles virus from otosclerotic bones and to localize the virus by in situ hybridization have failed. Using the reverse polymerase chain reaction measles virus RNA have been amplified from otosclerotic focuses in frozen or archival temporal bones[62, 63, 64, 65].

Niedermeyer et al in 2001[66] studied bone and perilymph specimens from 40 patients with spontaneous otosclerosis and from control patients. They used reverse polymerase chain reaction, western blot techniques and cell cultures. Reverse polymerase chain reaction detected measles virus RNA in 32 patients but not in the control subjects. They found antibodies to N, F1 and M measles virus proteins in all cases. Antibodies against H protein were present in two cases. No measles virus could be amplified from otosclerotic bone chips. They concluded that in the vast majority of cases the spontaneous form of otosclerosis is a measles virus associated disease of the otic capsule.

Even though there are evidences associating the measles virus with otosclerosis there are no convincing evidence to establishs the virus as the cause of the disease. The familial occurrence of this disease, the differences in prevalence of otosclerosis in different geographical locations and in different ethnic groups make it very dificult to accept measles virus as the cause for this process. In Korea and Japan otosclerosis is virtually non-existent. How about measles? In Brasil the vaccination against measles is still not universal yet the prevalence of otosclerosis is much lower that in Sweden or the United States.

These epidemiological features of otosclerosis are much better explained if we consider the genetic factor. Our population in Brasil have strong indian ascendence and the brazilian indians do not have otosclerosis just like the Korean and Japanese people. Of course it is common knowledge the fact that black people have a much lower prevalence of otosclerosis than caucasian people. None of these variations is true for the measles virus.

Yet it is worth to know what the measles virus is doing in otosclerotic focuses.

Benign Paroxysmal positional vertigo, Menière´s disease

Vrabec in 2003[67] studied the vestibular ganglion of 35 patients undergoing vestibular neurectomy through the middle fossa or translabyrinthine approach using a nested polymerasse chain reaction designed to amplify the herpes simplex virus DNA and quantitative analysis to determine the number of viral copies per standard unit of ganglionic

DNA. All these patients had Menière´s disease according to the American Academy of Otolaryngology – Head and Neck Surgery criteria. Control specimens were obtained from willed body donors. They found viral DNA in 100% of parafin embeded ganglia from patients with Menière´s disease and in 81% o fresh frozen control ganglia. Fixation and parafin embedding substantially reduced recovery of viral DNA in selected control specimens. However quantitative analysis found no correlation between viral copy number in control ganglia processed frozen versus formalin fixed and parafin embeded. He concluded that herpes simplex virus is more commonly recovered from vestibular ganglia of Menière´s disease patients than from control patients. They considered this finding as supportive evidence for a viral etiology in Menière´s disease.

Gacek and Gacek in 2002[49] on the basis of clinical and temporal bone histopathologic evidence suggested that Menière´s disease, benign paroxysmal positional vertigo and vestibular neuronitis are all due to reactivation of latent neurotropic viruses in the vestibular and meatus ganglia.They presented three cases each having Menière´s disease, benign paroxysmal positional vertigo and vestibular neuronitis. The temporal bones of these three patients had histopathologic evidence of viral ganglionitis. They also reviewed 75 temporal bones. Fifty one bones were selected because of neuronal degeneration in the vestibular and facial ganglia. A history of reccurrent vertigo was present in 20 of these patients. Menière´s disease had been diagnosed in 5 of these patients, vestibular neuronitis in 5 and benign paroxysmal positional vertigo in 3 of these 20 patients. The other donors never had a precise diagnosis for their vertigo.

These are at the best circunstancial evidence for a viral etiology for these entities. On the other hand there are abundants evidences favoring cupulo and cannal lithiasis etiologies for benign paroxysmal positional vertigo. Menière´s syndrome has a number of possible etiologies . Viral might be one of them but on the basis of current evidences it seems indeed unlike that such and etiology for Menière´s disease exists.

4. The viral etiology in profound sensorineural hearing loss in infancy and early childhood

Oliveira and Schuknecht in 1990[7] found in the temporal bone collection of the Massachusetts Eye and Infirmary 9 cases with bilateral and 5 with unilateral profound deafness that were detected in infancy or early childhood. Six of the nine bilateral cases had unknown onset and 3 allegadly were caused by measles, 2 at age 4 and 1 at age 5. The age of onset was stated in their records. One of the 5 cases with unilateral profound deafness was believed to be due to mumps and another occurred after a febrile illness of unknown etiology. The remaining 3 cases of unilateral deafness had no records of onset or cause.

Histopathological findings from autopsy and temporal bones in the cases with unknown etiology ruled out: 1- vascular disease, 2- autoimmune disease (there was no involvement of other organs or systems at autopsy), 3- developmental defects because the pathological changes appeared to have occurred in fully developed structures, 4- meningogenic bacterial labyrinthitis because there was no hystory of meningitis in these cases.

On the other hand when they compared the histopathologic findings in patients with no viral etiology suspected (Figure 3) with the findings in cases of strongly suspected viral etiology (Figure 4) it became clear that the temporal bones had very similar findings. Indeed the temporal bone histopathology of all 14 cases were compatible with viral labyrinthitis.

They concluded that there are no significant differences in the inner ear pathology of profound deafness discovered in infancy and early childhood with no known initiating illness and those that by medical history were caused by measles or mumps. Therefore these findings support the contention that profound deafness in one or both ears that is discovered in infancy or early childhood is caused by subclinical viral labyrinthitis. Neuronal loss was present in all cases in varying degrees and whenever bone and fibrous tissue was present in the cochlea and labyrinth no more than 10% of cochlear neurons remain. Cochleo-saccular degeneration was the pathological pattern in all cases. There was

a positive correlation between preserved vestibular ganglion neurons and cochlear neuron population.

Later[1] Schuknecht talked about infantile cochleosaccular degeneration as being tipically caused by a viral attack to the inner ear in infancy. Vestibular function would be preserved and normal caloric tests would suggest good preservation of cochlear neurons.

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Legends for the figures

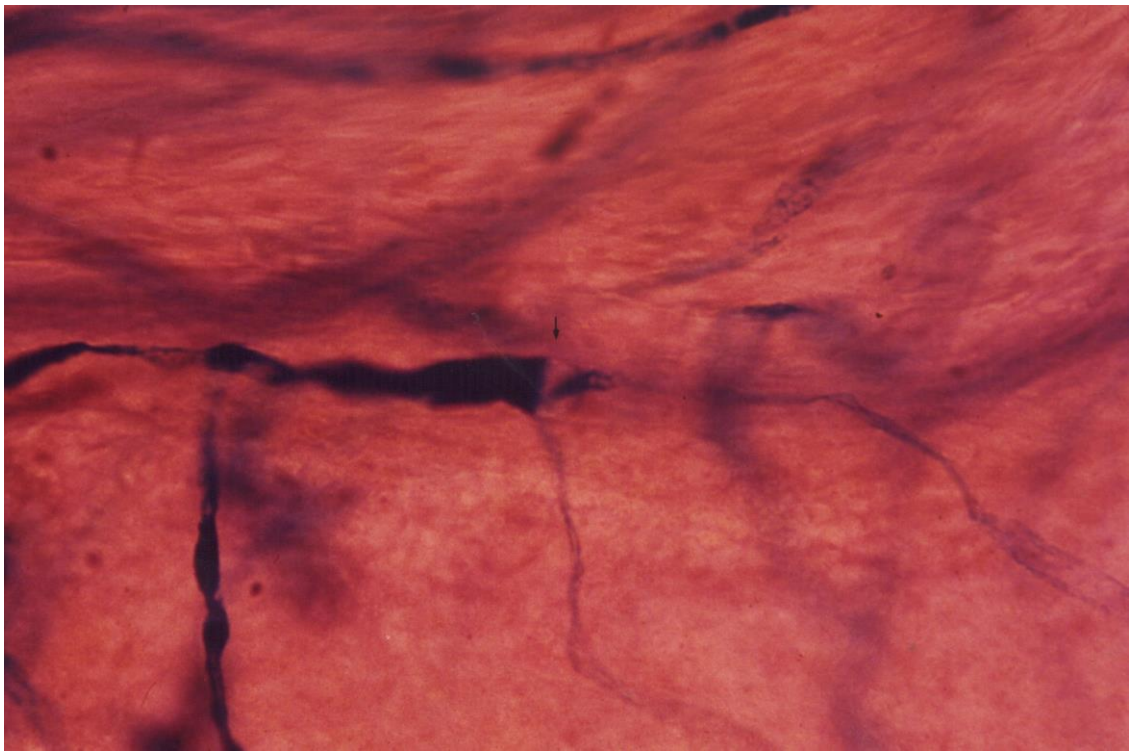

Figure 1- Polyestirene copolymer bead in the vessel of the tympanic lip of chinchilla. Methilene blue intravascular infusion and surface preparation of the basilar membran.

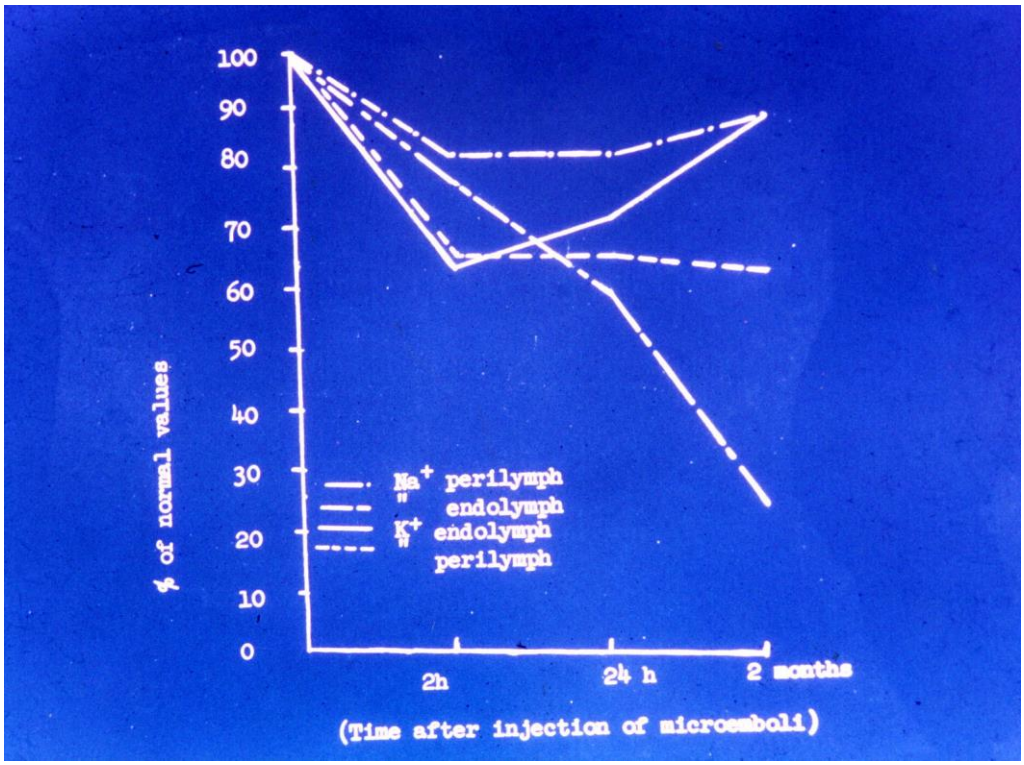

Figure 2- The time course of eletrolytes (Na+ and K+) in endolymph and perilymph after microembolization of cochlear capillaries.

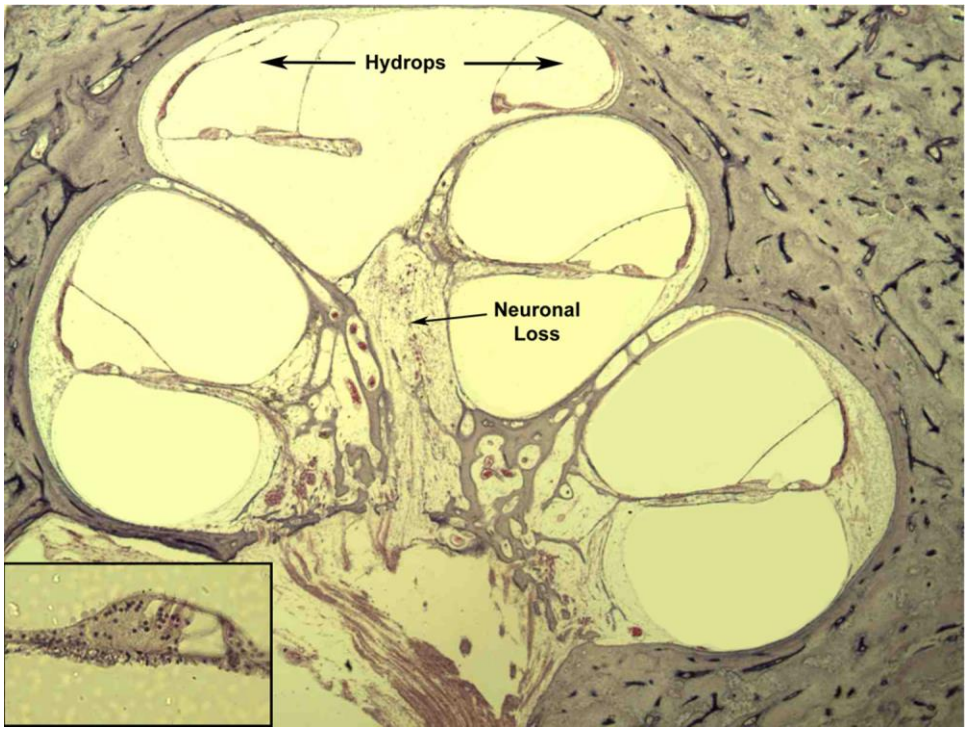

Figure 3- Midmodiolar section of a patient who was found to be profoundly deaf in his left ear after a febrile illness in early childhood. Cochlear neuronal population is 48% of normal for his age at death (58 yo). There is mild scattered loss of outer hair cells. The neuronal loss is greater in the apical third of the cochlae. Endolymphatic hydrops is present in the apical region. Inset shows organ of Corti which is normal in the 12mm region. These findings are compatible with acute cochlear neuritis of viral etiology. (Compare with figure 2).

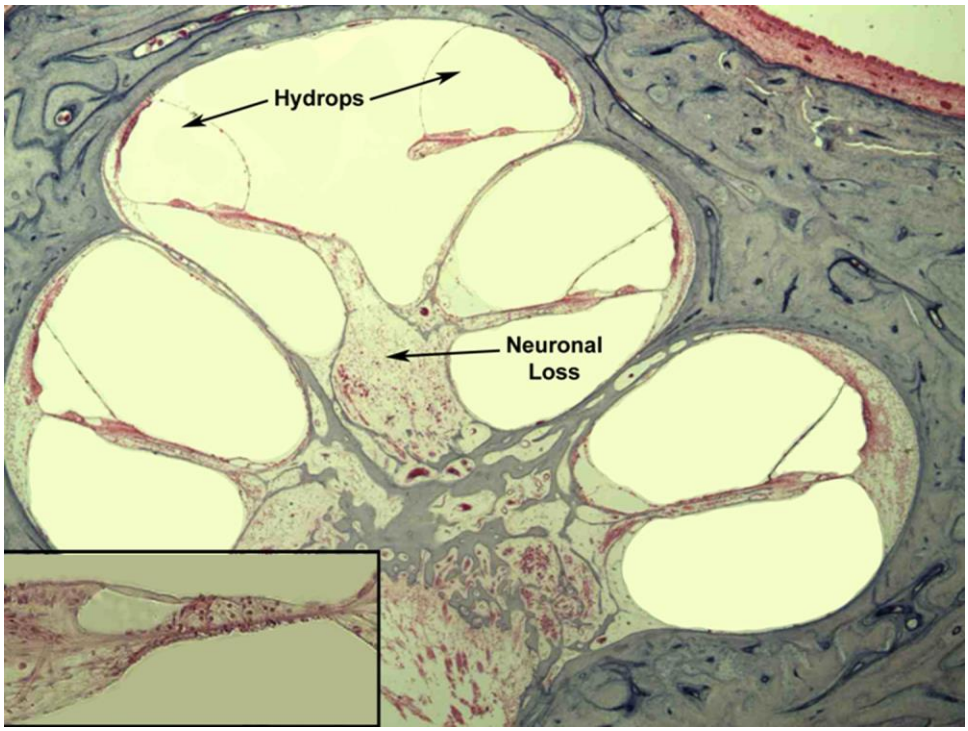

Figure 4. Similar section as in figure 3. This patient was profoundly deaf in both ears and there was no record of any initiating illness. He was found to be deaf in early infancy. The pathologic findings are nearly identical to the ones in figure 1. Sixty percent of the neuronal population normal for the age at death remained. The neuronal loss was greatest in the apical regions, endolymphatic hydrops is present in the apical region. There is atrophy of the organ of Corti with nearly total hair cells loss. At the 10mm region the organ of Corti is normal (inset). These findings are consistent with bilateral viral cochleitis.