

## Chapter 155: Infections of the Labyrinth

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Infectious agents, particularly viruses and bacteria, are thought to play a direct or indirect role in causing a number of different inner ear disorders (Davis and Johnsson, 1983). Each year several thousand infants are born deaf or with impaired hearing. At least 18% of these are proven to be caused by a congenital viral infection, and a greater percentage are suspected of having an infectious etiology (Pappas, 1983). Each year over 4000 persons are stricken by so-called sudden deafness, which appears as unilateral or bilateral sensorineural hearing loss of varying degrees (Jaffe, 1973). Again, infectious agents are often suspected as the cause. Bacterial labyrinthitis with profound hearing loss occurs in about 10% of individuals with bacterial meningitis (Dodge et al, 1984). Thousands of children and adults each year suffer from vestibular neuritis. This acute deficit in vestibular function is accompanied by a period of intense vertigo that many think has an infectious origin (Schuknecht and Kitamura, 1981).

Despite the fact that many infectious agents are thought to play important etiologic roles in labyrinthine disorders, much of the evidence has so far been circumstantial (Davis and Johnsson, 1983). The reasons for the difficulty are several fold. Otologic examinations usually demonstrate the degree of functional deficit of the inner ear but seldom reveal the cause. Radiographic examinations of the temporal bone reveal the shape of the bony labyrinth but provide little information about the state of the membranous labyrinth. Serologic studies may demonstrate that a given virus or bacterium infected a patient but do not prove that the infectious agent caused the inner ear damage. Similarly, isolation of an infectious agent from the nasopharynx or from tissues other than the labyrinth does not necessarily indicate that it is the cause of the inner ear disease. For example, both herpes simplex and adenovirus are commonly latent in humans and are intermittently shed in the oropharynx (Fox and Hall, 1980). Other viruses, such as ECHO virus or coxsackievirus, can be isolated from the throats or stools of asymptomatic individuals, particularly when the virus is prevalent in the community (Fox and Hall, 1980). Although postmortem studies of the temporal bone may yield valuable histologic information, postmortem autolysis often makes evaluation of the organ of Corti and vestibular sensory cells difficult.

Establishing whether a given infectious agent is the cause of the patient's deafness or vertigo is difficult; one must demonstrate that the infectious agent not only is associated with the disease but also actually causes it.

For labyrinthine infections, optimal proof of causality involved fulfillment of three criteria (see box on p. 2796). First, there should be an association of the suspected infectious agent with a specific clinical syndrome of deafness or vertigo. Second, the infectious agent should be isolated from or identified in diseased labyrinthine tissues. Third, the infectious agent should be capable of causing a similar disease in experimental animals.

There are several methods to identify viruses within the inner ear. Viruses can be isolated from perilymphatic fluid, endolymphatic fluid, or inner ear tissue at surgery or autopsy. Viral antigens or viral nucleic acid can be identified within inner ear tissue. Viral antigens may be detected by immunohistochemical methods, and viral nucleic acid can be

detected by in situ nucleic acid hybridization or by the polymerase chain reaction (Eisenstein, 1990; Falser et al, 1986). Some infectious agents, such as bacteria or fungi, can be identified within the inner ear by light or electron microscopy. Finally, viral-specific cellular changes occasionally can be identified within the inner ear. Viral inclusion bodies and multinucleated giant cells are the most common cellular changes characteristic of viruses.

**Box: Optimal proof for infectious agent as cause of inner ear disease**

*Clinical association of specific inner ear disease with infectious agent*

Epidemiologic studies

Clinical studies of a specific inner ear disease with isolation of the infectious agent at sites other than the labyrinth and/or with serologic antibody titer rise.

*Regular isolation of infectious agent or detection of the infectious agent, its antigens, or nucleic acid from inner ear fluid or tissue.*

Isolation of infectious agent by in vitro or in vivo methods

Detection of infectious agent nucleic acid by in situ hybridization or polymerase chain reaction

Identification of infectious agent antigens by immunohistochemistry

Demonstration of the infectious agent by light or electron microscopy coupled with isolation of same infectious agent from other body tissues

Recognition of viral-specific cellular changes by light microscopy along with isolation of the virus from other body sites.

*Demonstration that infectious agent can cause similar auditory loss, vestibular signs, and inner ear pathologic conditions in experimental animals.*

To date only a limited number of infectious agents have been recovered from or identified within human labyrinthine tissues. Cytomegalovirus (Davis et al, 1979) and mumps virus (Westmore et al, 1979) have been isolated from perilymph. Cytomegalovirus antigen has been detected by immunohistochemistry within inner ear tissues (Davis et al, 1979; Stagno et al, 1977a). Morphologic identification of infectious agents within the labyrinth has been accomplished for several bacteria (Nadol, 1978; Paparella and Sugiura, 1967), fungi (Gussen and Canalis, 1982; Nadol, 1978), and *Treponema pallidum* (Mack et al, 1969). A multinucleated giant cell, typical of rubeola (measles) virus infection, has been seen within the scala vestibuli (Lindsay and Hemenway, 1954).

Although rubella virus has been closely associated epidemiologically with congenital deafness and has been isolated from many sites in congenitally deaf infants, the virus has never been isolated from viral antigens identified within inner ear tissues, and histopathologic changes of the temporal bone are not specific for rubella. Nevertheless, the weight of

available evidence strongly argues that rubella virus can cause congenital deafness.

Criterion two assumes that infectious agents are not normally present in the human membranous labyrinth or adjacent ganglia; therefore isolation of an infectious agent from the inner ear carries considerable etiologic significance. However, this assumption is not based on comprehensive bacteriologic or virologic studies. Of interest is that healthy guinea pigs may harbor viruses in the spiral ganglia neurons (Craft et al, 1973; Lohle et al, 1982). As a consequence the third criterion, the establishment of an appropriate animal model, becomes more important (Davis, 1991).

Many infectious agents have been reported to be associated with deafness or vertigo. For some infectious agents the association has been based on case reports that describe acute deafness or vertigo that developed during a systemic infection. For other infectious agents, for example, rubella virus, there has been a strong epidemiologic association between systemic infection of the individual or mother and subsequent deafness or vertigo. The following infectious agents have been associated with deafness or vertigo, but have yet to fulfill the three criteria for optimal proof of causality.

Rubella	Lymphocytic choriomeningitis
Varicell-zoster	Yellow fever
Herpes simplex	Western equine encephalitis
Epstein-Barr	Tick-borne encephalitis
Variola (smallpox)	St. Louis encephalitis
Hepatitis virus	Encephalomyocarditis
Adenovirus	Lassa fever.
Influenza	
Parainfluenza	
Coxsackievirus	

More details regarding the viral associations are presented in the review by Davis and Johnsson (1983).

This chapter reviews the clinical and pathologic features of human labyrinthine infections in which a specific infectious agent has been identified or is highly suspected. The chapter discusses both congenital infections and postnatal acquired infections.

### **Congenital Cytomegalovirus Infections**

Cytomegalovirus (CMV) is the most common congenital infection in the USA. In the USA alone, congenital cytomegalovirus annually accounts for over 4000 cases of sensorineural hearing loss (Stagno et al, 1977b). The incidence of cytometalovirus infection is about one or two cases per 100 live births (Reynolds et al, 1974). Approximately 90% of congenital infections are "silent", with infants showing no overt signs of disease in the neonatal period. However, 1% to 5% of newborn infants are symptomatic and develop cytomegalic inclusion disease (CID) with damage to many organs, including the liver, spleen, brain, eye, and inner ear (Hanshaw, 1976).

A number of studies have suggested that congenital cytomegalovirus infections may occur in children of mothers who were immune to this virus before they conceived (Stagno et al, 1977b). Having consecutive pregnancies with congenital cytomegalovirus infections is therefore possible. Cytomegalovirus isolates from consecutively infected infants have been shown to be identical, suggesting that the latent virus in an immune mother can be reactive during pregnancy and cross the placenta. This virus therefore differs from other viruses (such as rubella) in which only non-immune mothers are at risk.

### **Clinical features**

The incidence of sensorineural hearing loss in children with CID is as high as 50% in infants who survive the neonatal period (Alford et al, 1990). Hearing loss in these infants, when evaluated years later, is usually relatively symmetric and often severe (Pass et al, 1980). The loss of high frequencies appears to be greater than at low frequencies. A marked asymmetric or unilateral form of hearing loss only occasionally has been found (Pass et al, 1980). In some children born with moderate hearing loss, the auditory deficit may progress during the first 10 years of life (Stagno et al, 1977b). The explanation for this progression of hearing loss is still unknown.

In infants with silent infections, follow-up examinations have shown that 5% to 15% of these children develop a mild to moderate bilateral hearing loss (Hanshaw et al, 1976; Reynolds et al, 1974; Saigal et al, 1982). Occasionally these children have a profound hearing loss in one or both ears.

### **Diagnosis**

The diagnosis of congenital cytomegalovirus is made in both symptomatic and asymptomatic infants by isolation of cytomegalovirus from fresh urine during the first 1 to 2 weeks of life. About 60% to 75% of congenitally infected infants have detectable IgM antibodies to cytomegalovirus in the umbilical cord or infant serum. Antibodies of the IgM class imply fetal synthesis, since maternal IgM antibody normally does not cross the placenta. This serologic test is difficult to perform and should be done only in qualified laboratories. Cytomegalovirus has been isolated from the amniotic fluid of mothers with a congenitally infected fetus (Davis et al, 1971). After 1 year of life, establishing a diagnosis of congenital cytomegalovirus infection is very difficult. Normal infants may acquire the virus infection asymptotically, shedding the virus in their urine, as well as developing antibody titers. Since most maternal infections are asymptomatic, no reliable history can be obtained retrospectively from the mother.

### **Management**

Acyclovir has been given to infants with symptomatic congenital CMV infections (Plotkin et al, 1982). There was a transitory decrease in urinary shedding of CMV but no obvious clinical improvement. A newer, but related drug, ganciclovir, appears to be 25- to 100-fold more active than acyclovir against clinical isolates of CMV (Balfour, 1990). Ganciclovir appears to function both as an inhibitor of and as a faulty substrate for CMV DNA polymerase. Clinical trials of ganciclovir in the treatment of CMV retinitis, CMV pneumonia, and gastrointestinal CMV disease have been favorable, suggesting it may be

beneficial in congenital CMV infections. However, to date no studies have been published on the efficacy of ganciclovir in congenital CMV infection or CMV hearing loss. Foscarnet is another new drug that appears to possess antiviral activity against CMV (Balfour, 1990). Clinical studies of this drug are in progress.

### **Temporal bone pathologic changes**

There are several reports of histologic changes in temporal bones of infants dying from symptomatic cytomegalovirus infection (Davis, 1969; Davis et al, 1981). Signs of labyrinthitis of the endolymphatic system include the presence of inclusion-bearing cells in both the auditory and the vestibular portions of the inner ear (Fig. 155-1). Within the cochlea pathologic changes tend to be most severe in the basal turn. Judging the condition of the organ of Corti has been difficult because of postmortem autolysis. It appears, however, that major hair cell degeneration does not occur and that the tectorial membrane remains normal. The eighth cranial nerve (CN VIII) with its spiral ganglion neurons also appears to be spared major pathologic damage. Hydrops of the cochlea and saccule and collapse of Reissner's membrane have been observed. In one case a thick layer of these inclusion-bearing cells was found inside the membranous walls of the utricle in the regions where "dark" cells are located (Davis et al, 1981). Immunofluorescent staining has identified cytomegalovirus antigen within cells lining the membranous labyrinth (Davis et al, 1981). Virus particles belonging to the herpes virus family have been seen within cells of the membranous labyrinth by electron microscopy (Davis, 1969; Davis et al, 1981). Cytomegalovirus has also been cultured from the perilymph obtained at autopsy from a congenitally infected infant (Davis et al, 1981). However, CMV was not isolated from inner ear fluid of a child who died 15 years after a severe congenital CMV infection (Davis).

The temporal bones from a 5-month-old infant who died with asymptomatic congenital CMV infection have been studied (Davis et al, 1987). Morphologic examination of the cochlea was normal. However, CMV was isolated from the perilymph/endolymph fluid.

In guinea pigs, guinea pig CMV can be inoculated directly into the basal turn of the cochlea. Inflammation and cytomegalic cells developed in the perilymphatic duct along with variable secondary degeneration of the organ of Corti (Keithley et al, 1988, 1989). Cochlear microphonic thresholds for all frequencies and the thresholds for the compound nerve potential increased. Guinea pig CMV can also cross the placenta to reach the fetal cochlea (Woolf et al, 1989).

### **Congenital Rubella Deafness**

During the Australian rubella epidemic of 1939 to 1941, rubella infections of pregnant women were first associated with congenital deafness (Swan et al, 1943). Since then, many reports have described profound hearing loss in infants born with congenital rubella. In the USA more than 12,000 infants were born with hearing loss and congenital rubella during the 1964 to 1965 rubella epidemic (Trybus et al, 1980). With the introduction of the rubella vaccine, the incidence of rubella has dramatically decreased in the USA and so, correspondingly, have the cases of congenital rubella. A maternal rubella infection during the first trimester of pregnancy places the fetus at the highest risk for congenital infection and subsequent hearing loss. In addition to the hearing loss, infants are often born with cardiac

malformations, vision loss, and mental retardation (Fig. 155-2) (Horstmann, 1982). About 50% of infants born with symptomatic congenital rubella have hearing loss. Infants infected with rubella virus during the second and third trimesters often are born with silent rubella infection and appear normal at birth. Of these children, however, 10% to 20% are subsequently found to have hearing impairment (Karmody, 1968). Rubella vaccine has been shown to cross the placenta and can infect the fetus if the vaccine is administered to nonimmune pregnant women. Fortunately, the risk of subsequent hearing loss appears to be minimal. Although hearing loss from congenital rubella is rare in countries that widely administer rubella vaccine, rubella deafness is still a significant problem in developing countries.

### **Clinical features**

Congenital rubella infections of the inner ear usually result in bilateral hearing loss. The hearing loss may be somewhat asymmetric. In a series of 8168 children with hearing loss from congenital rubella, 55% had profound hearing loss (91 dB or more by ISO (International Standards Organization) criteria), 30% had severe hearing loss (71 to 90 dB), and 15% had mild to moderate hearing loss (less than 70 dB) (Trybus et al, 1980). The audiograms of these children were usually flat with hearing deficits occurring in all frequencies. Some children, however, had the greatest hearing loss in the middle-frequency range, between 500 and 2000 Hz (Bordley and Alford, 1970). Children with rubella deafness may have poor speech discrimination, and a few may experience progressive hearing loss. Some children have had delayed or impaired speech development but still have normal pure-tone hearing, which suggests central auditory imperception (Ames et al, 1970).

The vestibular system appears to be involved to a lesser extent than is the auditory system. Caloric stimulation with 1 mL of ice water has suggested that some children may have reduced or absent caloric responses in one or both ears (Frost and Millet, 1971). Older children with congenital rubella have shown clumsiness and incoordination, but most of these children have been mentally retarded or show signs of limb spasticity; determining if vestibular impairment plays a role in that clumsiness is therefore difficult. Children with hearing loss and minimal other CNS abnormalities do as well in school as other deaf children and show no striking vestibular impairments (Stuckless, 1980).

### **Diagnosis**

The diagnosis of congenital rubella may be made by (1) isolation of rubella from urine or throat cultures during the first weeks of life, (2) identification of IgM antibodies against rubella in serum from the neonate, or (3) increased antibody titer to rubella virus in an infant during the first few months of life. The identification of IgM antibodies against rubella virus is difficult and should be performed only in qualified laboratories. After the child is 1 year old the diagnosis of congenital rubella is difficult to establish, since many children may have received the rubella vaccine. A maternal history of rash during pregnancy is not reliable for either establishing or ruling out the diagnosis. Congenital rubella has been diagnosed in utero by isolation of rubella virus from amniotic fluid. Unfortunately, no specific treatment for children exists, and management should be directed toward minimizing the consequences of the hearing loss.

### **Temporal bone pathologic changes**

The pathologic change of the temporal bones in congenital rubella deafness, although characteristic, is not specific for rubella virus infections. The predominant abnormality is cochleosaccular degeneration and stria atrophy of varying degrees (Brookhouser and Bordley, 1973; Lindsay et al, 1953). Reissner's membrane and the wall of the saccule may sag and in some patients collapse (Fig. 155-3). The tectorial membrane is frequently abnormal, often displaced from the organ of Corti toward the limbus. The stria vascularis shows varying degrees of atrophy. Inflammatory cells in the cochlea are seldom seen. Cells with inclusion bodies have not been seen. The vestibular neuroepithelia and their nerves are usually normal.

### **Acquired Mumps Virus Deafness**

Mumps was first recognized to be associated with deafness in 1860. Since then Everberg (1957) has estimated that mumps infections are associated with hearing loss in about 5 of every 10,000 cases of mumps. Children and young adults of both sexes are most commonly afflicted.

### **Clinical features**

The deafness associated with mumps usually develops toward the end of the parotitis; deafness occasionally occurs, however, in the absence of parotitis. The onset of the deafness is usually rapid, and it is unilateral 80% of the time. Hearing loss is often profound and usually permanent, but a prospective study by Vuori et al (1962) found it to be transient in some cases. The hearing loss is maximal in the high frequencies. Tinnitus and fullness in the involved ear are common, and some patients develop frank vertigo. Disequilibrium usually resolves over several weeks, but persons may be left with diminished or absent caloric responses in the involved ear. Absent caloric responses have also been found in persons with deafness associated with mumps who never had a history of dizziness.

### **Diagnosis**

The diagnosis of mumps can be made by (1) isolation of mumps virus from the throat or cerebrospinal fluid or (2) a fourfold or greater serologic rise in mumps antibodies between acute and convalescent serum samples. Mumps virus has been isolated from the perilymphatic fluid in one patient with acute unilateral deafness associated with parotitis (Westmore et al, 1979). Currently no specific treatment for mumps deafness exists. Administration of mumps vaccine in infancy, however, will effectively prevent subsequent mumps infections in childhood and adulthood.

### **Temporal bone pathologic changes**

Temporal bones from two patients with mumps-associated deafness have been examined (Lindsay et al, 1960; Smith and Gussen, 1976). In these, the cochlea showed severe atrophy of the organ of Corti and the stria vascularis, with partial collapse of Reissner's membrane in the basal turn (Fig. 155-4). The tectorial membrane in one case was folded, thickened, and displaced from the organ of Corti. The upper turns showed less damage, with occasional loss of hair cells. Cochlear ganglion neurons may be decreased in the area of the

basal turn. Minimal vestibular abnormalities were seen.

In experiments, mumps virus inoculated into the inner ear of hamsters, guinea pigs, and monkeys principally infected nonneuroepithelial cells of the membranous labyrinth (cells of Reissner's membrane, stria vascularis, and supporting cells of the organ of Corti) (Davis and Johnson, 19976; Tanaka et al, 1988a, 1988b). Degeneration of the basal turn of the organ of Corti and damage to the stria vascularis developed. Cells of the inner ear could be infected if the virus was inoculated directly into the inner ear or if it entered the perilymphatic fluid of the scala tympani via the cochlear aqueduct following intracerebral inoculation. Since the virus could reach the perilymph from the cerebrospinal fluid (CSF) in this model, the question arises as to whether this route of infection could occur in humans. Mumps viral meningitis occurs in up to one third of infected children. The cochlear aqueduct is more often patent in children than in adults. Since deafness usually develops toward the end of the first week of parotitis (Everberg, 1957), the clinical course of deafness is consistent with virus spread from cerebrospinal fluid to inner ear. CN VIII, along with its cuff of arachnoid that contains CSF, provides another possible route to the perilymphatic space. One study, however, found no correlation between sensorineural deafness and meningitis (Vuori et al, 1962).

### **Acquired Measles Deafness**

Rubeola virus is the cause of measles and is an important cause of acquired deafness. Before the introduction of rubeola vaccine, 3% to 10% of all cases of acquired deafness in children were thought to be secondary to measles. The incidence of deafness following rubeola, however, is less than 1 per 1000 cases of measles (Miller et al, 1956). Since the introduction of rubeola vaccine in the USA, hearing loss associated with this virus has been reduced dramatically.

### **Clinical features**

Children with measles and labyrinthine involvement usually develop an abrupt bilateral hearing loss at the time of the rash. Some children, however, develop only unilateral deafness, retaining normal hearing in one ear. In one study, 45% of the patients were deaf, and 55% had a mild to moderate hearing loss (Shambaugh et al, 1928). The characteristic audiogram shows bilateral loss that may be asymmetric. Maximal hearing loss occurs at higher frequencies. The hearing loss is usually permanent and may be accompanied by tinnitus and vertigo. Up to 70% of patients may have absent or diminished caloric responses in one or both ears (Shambaugh et al, 1928).

### **Diagnosis**

The diagnosis of measles can be made by (1) isolation of rubeola virus from throat cultures; (2) identification of rubeola viral antigen by immunofluorescent staining of exfoliated epithelial cells obtained by swabbing the pharynx, conjunctiva, or buccal cavity; and (3) demonstration of a fourfold or greater serologic rise in measles antibody titer between acute and convalescent serum samples.



## **Temporal bone pathologic changes**

Only a few temporal bones have been examined from patients with deafness associated with measles (Lindsay and Hemenway, 1954; Schuknecht, 1974; Suboti, 1976). In these, sensorineural degeneration was seen both in the cochlea and in the vestibular organs. The cochlear degeneration was most severe in the basal turn. The tectorial membrane was often thickened and distorted. Atrophy of the stria vascularis excised, with maximal changes occurring in the basal turn. The saccule had collapsed, and the membranous wall adhered to the degenerated macular epithelium. The macula utriculi and the crista ampullaris frequently showed minimal changes. Interestingly, in one case a subacute inflammatory process with granulomas and a giant cell was seen in the endolymphatic fluid attached to the stria vascularis (Lindsay and Hemenway, 1954). The giant cell was similar to those commonly caused by rubeola virus infection.

Experimental rubeola virus infections in hamsters have been shown to cause an inner ear infection with viral antigen, demonstrated principally within sensory structures of the cochlea, utricle, saccule, and semicircular canals (Davis and Johnson, 1976). Both cochlea and vestibular ganglion cells were infected, and viral antigen could often be identified in their distal nerve processes. Giant cells, typical of measles virus, were seen within the organ of Corti and spiral ganglion cells.

## **Acquired Varicella-Zoster Virus Deafness**

Hearing loss occasionally occurs after chickenpox, but this is usually caused by secondary viral or bacterial otitis media producing a conductive hearing loss. Auditory and vestibular symptoms, however, develop in approximately 25% of patients with herpes oticus. Herpes zoster oticus, or the Ramsay Hunt syndrome, is caused by a varicella-zoster virus infection and occurs years after the primary infection that manifests as chickenpox.

## **Clinical features**

Painful vesicles usually develop on the skin of the pinna of the ear, behind the pinna, and along the external auditory canal (Fig. 155-5). This development is followed 1 to 2 days later by unilateral facial paralysis and deep ear pain (Aleksic et al, 1973). The facial weakness usually improves over weeks but is occasionally permanent. In 25% of these patients, hyperacusis, tinnitus, nystagmus, and disequilibrium develop along with facial paralysis. Severe vertigo that is associated with ear vesicles but not facial paralysis has occasionally occurred. Although patients may complain of auditory symptoms, sensorineural loss occurs in about 6% of patients. Audiograms have varied and may suggest primary cochlear involvement or cochlear nerve involvement (Harbert and Young, 1967). Caloric tests may show decreased to absent responses in the involved ear. The hearing loss and vertigo usually improve, along with the facial weakness, over the next several weeks. Occasionally patients may have permanent hearing loss, and some have permanently reduced caloric responses. The diagnosis of herpes zoster oticus can be suspected in a patient with acute facial weakness and vesicles on the auricle or in the external canal. A magnetic resonance image of the temporal bone following administration of intravenous gadolinium often demonstrates enhancement of the involved geniculate ganglion and nerve (Tien et al, 1990).

## **Diagnosis**

The presence of vesicles on the auricle or external canal allows a clinical diagnosis. The diagnosis can be confirmed by isolation of varicella-zoster virus from vesicle fluid.

## **Management**

Acyclovir therapy increases the rate of virus disappearance in skin lesions and decreases pain in acute zoster. The dosage of acyclovir is 15 mg/kg/day intravenously given in three divided doses for 5 to 10 days. Use of corticosteroids may help reduce the intensity of inflammation and edema in the facial canal and labyrinth. The dosage of prednisone is 40 to 80 mg/day in three divided doses by mouth for 5 days with tapering over the next 5 days. If a history of peptic ulcer is present, two 200 mg tablets of cimetidine at bedtime are often given along with antacid medications during the course of prednisone. One should also monitor blood glucose levels during treatment. Analgesics may be required to control ear pain, if present.

## **Temporal bone pathologic changes**

Herpes zoster oticus is believed to be caused by a reactivation of a latent varicella-zoster virus in the geniculate ganglion. The virus reactivation in the geniculate ganglion results in the development of vesicles over the sensory portion of the facial nerve, with ganglionitis and neuritis of the facial nerve (Aleksic et al, 1973). In patients with auditory and vestibular symptoms, the inflammation appears to spread to involve CN VIII and labyrinth (Blackley et al, 1967; Proctor et al, 1979). Temporal bones of patients with herpes zoster oticus have been examined histologically days to months after the acute illness. During the subacute phase the facial nerve demonstrates active neuritis within inflammatory cells throughout the facial nerve sheath but maximally near the geniculate ganglion. Edema, necrosis, and hemorrhages are also found in this area. The geniculate ganglion usually shows corresponding inflammation, edema, and neuronal degeneration. The facial nerve nucleus in the brain stem is not involved. In cases studied years after the acute facial palsy, loss of facial nerve axons was seen.

Pathologic changes in the auditory nerve and labyrinth have also been reported. In all cases the patients had vertigo and hearing loss associated with facial nerve paralysis. As long as several months after acute paralysis, inflammatory cells have been seen along CN VIII, particularly the vestibular branches. Inflammatory cells have also been seen in the macula of the utricle and saccule. In one case the branch of the vestibular nerve going to the lateral and superior semicircular canals was atrophic (Proctor et al, 1979). There was corresponding atrophy and loss of hair cells of the corresponding semicircular canals' cristae.

## **Bacterial and Fungal Labyrinthitis**

Bacteria and fungi can result in damage to the peripheral auditory and vestibular systems through (1) suppurative labyrinthitis, (2) toxic labyrinthine damage from bacterial or fungal toxins or inflammatory cell cytokines that reach the perilymph through the round window or modiolus, (3) purulent exudate enveloping the eighth cranial nerve with nerve infarction or entrapment, or (4) ototoxic antibiotics given to treat the infection whose

concentrations become elevated in blood. In most cases suppurative labyrinthitis appears to be the most important mechanism with bacteria or fungi reaching the cochlea from the subarachnoid space (meningitis), temporal bone (osteomyelitis), or middle ear (otitis media). In the case of meningitis, bacteria or fungi reach the scala tympani from the subarachnoid space via a patent cochlear aqueduct or up the internal auditory canal passing through perineural and perivascular spaces (Nadol, 1978).

### **Temporal bone pathologic changes**

When bacteria infect the labyrinth, a suppurative labyrinthitis ensues (Prado and Paparella, 1978). The acute bacterial infection elicits an acute inflammatory response of neutrophils that results in severe destruction of the membranous labyrinth (Igarashi et al, 1974)). Usually this results in severe hearing loss and acute vertigo. The hearing loss is usually permanent, whereas the vertigo slowly resolves over weeks to months. There is often permanent loss of caloric responses.

Following appropriate antibiotic treatment, the acute inflammation slowly resolves. Macrophages may invade from the bloodstream, giving rise to granulomas. Over months to years fibroblasts may invade the membranous labyrinth to cause permanent scarring of endolymphatic structures (Paparella and Sugiura, 1967). Primitive multipotential mesenchyme cells invade and proliferate from the adjacent modiolus, bony endosteum lining, and so on to become osteoblasts. The osteoblasts may form ectopic ossification sites with bony spicules in the perilymphatic space. Eventually the spicules and trabeculi become vascularized to become new ectopic bone that may partially obliterate the old membranous labyrinthine space (Paparella and Sugiura, 1967). When fungi such as mucormycosis (Gussen and Canalis, 1982) and coccidiomycosis (Nadol, 1978) infect the labyrinth, the pathologic changes are similar except ectopic bone formation appears to be less common.

### **Hearing Loss in Bacterial Meningitis**

It has been estimated that about one third of all hearing deficits acquired after birth are caused by complications of bacterial meningitis (Schildroth, 1982). Dodge et al (1984), in a careful prospective study of acute bacterial meningitis in children, found persistent sensorineural hearing loss in 10% of patients. The sensorineural hearing loss was bilateral in 5% and unilateral in 5%. A transient conductive hearing loss was found in 16%. The incidence of hearing loss varied by strain of bacteria isolated from the cerebrospinal fluid: *Streptococcus pneumoniae* in 31%, *Neisseria meningitidis* in 10.5%, and *Haemophilus influenzae* in 6%. The high incidence of hearing loss from pneumococcal meningitis has been noted by others (Ozdamar and Kraus, 1983).

### **Clinical features**

In general, the deafness occurs early in the course of the meningitis. If hearing loss is not present by the second day of antibiotic treatment, it rarely develops later. However, early diagnosis and treatment of the meningitis may not prevent deafness (Klein et al, 1986). All ages of children appear about equally susceptible to develop the deafness. The hearing loss may be either unilateral or bilateral. It usually involves all frequencies and is often profound. Although most patients with sensorineural hearing impairment after meningitis have

a permanent loss of hearing, clinical hearing improvement does occur in some patients, especially if the initial hearing loss was partial (Nadol, 1978). Evoked response audiometry is helpful in young uncooperative children and is sensitive in detecting sensorineural hearing loss (Dodge et al, 1984). Vertigo, nausea and vomiting, and ataxia are often present in children with bacterial meningitis regardless of whether hearing loss is present.

### **Management**

Treatment of the bacterial meningitis with appropriate antibiotics is essential. Initial treatment is usually with a broad-spectrum antibiotic that crosses the blood-brain barrier. The antibiotic should be given immediately after performing a lumbar puncture and obtaining blood cultures. Specific antibiotic sensitivities of the bacteria then are determined following isolation of the organism from cerebrospinal fluid or blood.

There is currently some controversy as to whether the addition of corticosteroids reduces the incidence of hearing loss. The use of corticosteroids is based on the argument that the intense inflammation in or near the membranous labyrinth or CN VIII causes secondary damage to the cochlea or auditory nerve (Smith, 1988). Drugs such as corticosteroids should reduce the intensity of inflammation and hence lower the incidence of hearing loss. In a human trial of 200 children with acute bacterial meningitis, those individuals receiving dexamethasone (0.5 mg/kg/6 hours for 4 days) were less likely to develop moderate to severe sensorineural hearing loss than those receiving placebo (Lebel et al, 1988). In a second study of childhood bacterial meningitis, dexamethasone (0.15 mg/kg) was given intravenously 15 minutes before antibiotics. A significant reduction in audiologic sequelae was also found (Oodio et al, 1991). However, earlier studies failed to demonstrate any benefit from corticosteroids in bacterial meningitis (Belsey et al, 1969; de Lemos and Haggerty, 1969).

Once the hearing loss has developed, no treatment has been found to modify the severity of the hearing loss or its permanency. Because hearing deficits are common in patients with bacterial meningitis, a hearing evaluation of all patients during recovery is recommended. If the child is young or uncooperative, evoked response audiometry should be used (Klein et al, 1986).

### **Congenital and Acquired Syphilitic Deafness**

Sensorineural hearing loss can be a complication of both congenital and acquired syphilis. Congenital syphilis appears in two forms: early congenital (birth to 3 years) and late congenital (8 to 20 years). Acquired syphilis in both the secondary and tertiary stages may cause deafness. The recent increase of primary syphilis in the USA has led in turn to an increase in the incidence of congenital syphilis (Centers for Disease Control, 1989).

### **Clinical features**

Extensive multisystem damage from syphilitic infections of other organs usually accompanies early congenital syphilitic hearing loss. In these children the hearing loss is a bilateral, profound, symmetric, sensorineural hearing loss. Relatively few vestibular symptoms and signs are noted.

Patients with late congenital syphilitic hearing loss usually are between 8 and 20 years of age when symptoms first appear, but occasionally the hearing loss takes even longer to occur. These patients usually develop a progressive but fluctuating hearing loss that is asymmetrical. Audiograms show a flat sensorineural type of hearing loss. Frequently there are low speech discrimination scores that are out of proportion to the loss in pure-tone thresholds. Tinnitus may appear intermittently. In addition, these individuals may experience episodes of acute vertigo similar to those of Ménière's disease. Hennebert's sign (a positive fistula test with intact tympanic membranes) may be present. Frequently, decreased caloric responses are found. Patients with late congenital syphilis often demonstrate other signs of congenital syphilis, including Hutchinson's teeth (peg-shaped and notched permanent upper central incisors), mulberry molars (a first lower molar grinding surface with many tiny cusps), and interstitial keratitis.

Early acquired syphilitic deafness usually occurs during secondary syphilis (Saltiel et al, 1983). The hearing loss usually has an abrupt onset, tends to be bilateral, and is progressive. Usually minimal vestibular symptoms exist. Patients may have headaches, stiff necks, cranial nerve palsies, optic neuritis, secondary syphilitic rashes, and lymphadenopathy. The CSF shows lymphocytic pleocytosis, elevated protein, and normal glucose.

Late acquired syphilitic hearing loss usually occurs during the tertiary stage of syphilis (Nadol, 1975). Similar to the late congenital form, the hearing loss is progressive, fluctuating, asymmetrical, and sensorineural. Tinnitus may occur. Episodes of vertigo similar to that in Ménière's disease may be experienced. Loss of speech discrimination may be out of proportion to the pure-tone hearing loss. Decreased caloric responses and a positive fistula test with an intact tympanic membrane may exist. The CSF may show minimal pleocytosis and elevated or normal protein.

### **Diagnosis**

The diagnosis of all types of syphilitic hearing loss requires the presence of a positive fluorescent treponemal antibody-absorption (FTA-ABS) test in serum. The presence in CSF of a positive CSF - Venereal Disease Research Laboratory (CSF - VDRL) or CSF-FTA-ABS test is helpful. Spirochetes have been demonstrated by dark-field examination of perilymph obtained from a diagnostic stapes footplate labyrinthotomy.

### **Management**

The treatment of choice in syphilitic hearing loss is benzathine penicillin (Rothenberg, 1979). In older children and adults, long-acting benzathine penicillin (2.4 million units) may be given weekly for 6 weeks to 3 months. Alternately, aqueous procaine penicillin (600,000 units) may be given IM daily for 6 weeks to 3 months. In addition to penicillin, prednisone at 30 to 60 mg/day on alternate days should be given for 3 to 6 months with slow tapering. If hearing loss recurs after tapering, long-term maintenance of prednisone at a dose of 10 to 20 mg every other day may be necessary. This complication occurs most commonly in the late congenital and late acquired forms of the disease.

The prognosis following treatment is poor in the early congenital form; bilateral profound permanent hearing loss usually results. In the late congenital or acquired forms of syphilitic hearing loss the prognosis is better. Overall, 50% of patients show minor to considerable improvement after treatment.

### **Temporal bone pathologic changes**

The pathologic changes seen in cases of early congenital syphilitic hearing loss are primarily those of a labyrinthitis with lymphocytic infiltration and destruction of the labyrinth and CN VIII. Spirochetes have been demonstrated in temporal bones obtained at autopsy and stained with a silver stain (Mack et al, 1969). In late congenital syphilis, an osteitis of the otic capsule exists with secondary involvement of the membranous labyrinth (Mayer and Fraser, 1936). This may give rise to endolymphatic hydrops.

In early acquired syphilis the predominant finding is a basilar meningitis affecting CN VIII, particularly its auditory branch. In late acquired syphilitic deafness, temporal bone osteitis again is seen, resulting in secondary degeneration of the cochlear end organ (Nadol, 1975). Damage to the membranous labyrinth may occur, giving rise to endolymphatic hydrops.

### **Vestibular Neuritis**

Vestibular neuritis has been referred to as epidemic vertigo, acute labyrinthitis, vestibular paralysis, and vestibular neuropathy. The name *vestibular neuritis* is currently preferred because the available pathologic findings suggest that the vestibular nerve is the site of damage (Schuknecht and Kitamura, 1981). Infectious illnesses, especially sinusitis and other respiratory tract infections, precede or occur with vestibular neuritis in about 50% of the cases (Clemis and Becker, 1973); however, no viruses have yet been proven to cause vestibular neuritis.

### **Clinical features**

The peak onset of vestibular neuritis is between 30 and 60 years of age. Most patients experience an abrupt onset with a single, severe attack of prolonged vertigo (Clemis and Becker, 1973; Coats, 1969; Hart, 1965). Patients occasionally experience several attacks over the next several weeks to months (Coats, 1969). Occasionally the patient requires hospitalization because the nausea and vomiting are severe enough to result in clinical dehydration. Usually only one ear is involved. Compared with the symptoms of Ménière's disease, the vertigo lasts much longer and has no auditory symptoms. Other neurologic abnormalities are usually absent (Clemis and Becker, 1973). Patients have vigorous spontaneous nystagmus toward the uninvolved side, usually of a horizontal or horizontal-rotary type. Caloric responses are diminished or absent in the involved ear. Cerebrospinal fluid examination and electroencephalogram are normal.

The acute vertigo usually lasts for days to weeks, with gradual recovery occurring over weeks to months (Greisen, 1974). By 6 months most patients have fully recovered but may still experience vertigo from sudden head movements. The spontaneous nystagmus usually lasts 1 to 3 weeks. At clinical recovery the caloric response often returns to normal but

may remain diminished or even absent.

### **Temporal bone pathologic changes**

Studies of temporal bones have been reported from only a few patients with vestibular neuritis (Hart, 1965; Schuknecht and Kitamura, 1981). No patient who died during the acute phase of the illness has been studied. Pathologic findings from subacute cases, however, suggest primary damage to the vestibular nerve (Schuknecht and Kitamura, 1981). A partial to total loss of branches of the vestibular nerve, especially in the superior division supplying the horizontal and superior ampullae, has been seen (Fig. 155-6). Associated degeneration of hair cells has occurred in the corresponding sense organs.

In experimental animals, several viruses have been shown to infect the vestibular portion of the labyrinth and the vestibular ganglion cells (Davis and Johnson, 1976). These include rubeola, herpes simplex, mumps, and reoviruses.

### **Ménière's Disease**

The cause of Ménière's disease is still unknown. Syphilis has been found to be the cause in about 7% of patients with Ménière's-like syndromes (Nadol, 1975). Viral infections have also been postulated as one possible cause of endolymphatic hydrops (Adour et al, 1980; Schuknecht, 1982; Williams et al, 1987), but to date no specific viruses have been associated with the disease, and pathologic studies have not found histologic changes suggestive of viral infections. Herpes simplex virus has been considered on theoretic grounds since it is known to cause recurrent infections and is commonly latent in neurons of the adjacent trigeminal ganglia. In spite of theoretic considerations, viral cultures and ultrastructural studies of vestibular ganglion tissue obtained at surgery from six patients with Ménière's disease failed to demonstrate any viruses in this surgical tissue (Palva et al, 1978).

Experimentally, guinea pig cytomegalovirus when inoculated directly into the endolymphatic sac of seronegative or seropositive adult guinea pigs, has produced the histologic picture of endolymphatic hydrops (Fukuda et al, 1988). Endolymphatic hydrops is a common histologic finding in patients with Ménière's disease.

### **Summary**

Both RNA and DNA viruses as well as bacteria and fungi have been shown to cause infections of the human labyrinth. Studies of human temporal bones have discovered differing pathologic findings in the labyrinth. Experimental studies have demonstrated that several viruses can infect the labyrinth with differing sites of inner ear infection (Davis, 1991). These observations suggest that cells in the labyrinth have differing selective vulnerability to different viruses. Some infectious agents appear primarily to destroy sensorineural endothelium, making the recovery of hearing after infection unlikely; however, other infections, such as cytomegalovirus, cause relatively little direct damage to cochlear sensorineural structures, suggesting a different pathogenesis of the hearing loss (Davis et al, 1981).

Currently the best treatment of hearing loss from infectious agents is prevention. The widespread use of rubeola, rubella, and mumps vaccines has been associated with a dramatic fall in the number of individuals with hearing loss attributed to these viruses.