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Hearing disorders

Mechanisms of bacterial meningitis-related deafness

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Bacterial meningitis is the most common cause of acquired postlingual profound sensorineural hearing loss and labyrinthitis ossificans. This article reviews the underlying mechanisms including bacterial etiology responsible for bacterial meningitis-related hearing loss, time course of hearing impairment, sites of histological damage, routes of infection from meninges to labyrinth, suppurative labyrinthitis and ossification, pathophysiological processes, roles of cytokines, and finally, roles of reactive oxygen species and reactive nitrogen species.

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Introduction: Bacterial etiology responsible for bacterial meningitis-related hearing loss

Bacterial meningitis is the most common cause of acquired sensorineural hearing loss (SNHL) and labyrinthitis ossificans by spreading infection to the labyrinth. It accounts for approximately 60–90% of all acquired cases of postlingual (late onset) SNHL cases [1,2]. In spite of the improved antibiotic therapy, bacterial meningitis results in significant long-term neurological damages to the auditory system [3–7]. During the prevaccination period, the three most common organisms in the bacterial etiology responsible for bacterial meningitis are *Hemophilus influenza* (64%), *Streptococcus pneumoniae* (16%) and *Neisseria meningitides* (10%). With the advent of the *H. influenza* vaccines, *S. pneumoniae* has emerged as the major organism inducing bacterial meningitis in developed countries [5], whereas *H. influenza* remains the leading cause in developing countries. *S. pneumoniae* has lead to the highest mortality rate and hearing loss incidence [5–9].

Time course of hearing impairment

It has been generally believed that hearing loss occurs at the early stage of bacterial meningitis and progresses rapidly with the peak within 48 h after the onset of the disease [2,5,10]. In an animal model of pneumococcal meningitis, rats start to suffer from hearing loss approximately 12–15 h after inoculation and become completely deaf by 24 h (in 17 of 18 animals) [11]. Similarly, hearing loss in rabbits starts 12 h after infection and progressively becomes complete deafness within 36 h [8]. The animal studies suggest that bacterial meningitis-induced hearing loss appears to be progressive and related to the duration of untreated infection. Thus, early diagnosis and rapid antibiotic treatment would be useful for reducing the risk of hearing impairment. However, in humans, a marked correlation between the duration of symptoms of bacterial meningitis before treatment and the development of hearing deficits have not been confirmed [5,9,12,13], even though early and appropriate therapy is important to reduce the mortality of bacterial meningitis. Most meningitis-associated SNHLs emerge in the acute stage of meningitis and remain stable after recovery, but spontaneous regressions, fluctuations, or progressions in hearing loss have been observed after recovery from meningitis [14,15].

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Sites of histological damage

The sites of histological damage associated with meningitis-related deafness have long been investigated. The cochlea, auditory nerve, auditory brainstem and even auditory cortex have been proposed [2,3,5,8,10,15–24]. Both studies in humans and in animals have demonstrated that the cochlea is the primary locus of meningogenic lesions, including damages to hair cells, supporting cells, stria vascularis and spiral ligament. It has been reported that otoacoustic emissions (OAEs) are abolished in children with SNHL following newly diagnosed bacterial meningitis, suggesting outer hair cell damage [2]. A histopathologic study of human temporal bone by Merchant and Gopen [20] has shown that in bone from patients who died of acute bacterial meningitis, the cochleae were affected. Bones with suppurative labyrinthitis were found in 20 (41%) of the 41 bones. However, sensory and neural elements of the auditory and vestibular systems were intact in the 20 bones. Although biochemical alteration

IL-1ß, IL-6, IL-8, platelet-activating factor and TNF-α. These cytokines initiate an accelerating cascade of events, resulting in alteration of the blood–brain barrier (BBB), polymorphonuclear leukocyte and serum protein infiltration, meningeal inflammation, increased intracranial pressure and decreased cerebral vascular perfusion [31,32]. The spread of inflammation to the inner ear causes significant end-organ damage because of the lack of regenerative capacity at this site. Numerous anti-inflammatory agents have been found to be potential to reduce the host inflammatory response to bacterial meningitis. For example, steroids have the effect of reducing the bacterial meningitis-associated hearing loss [37]. Barkdull *et al.* [38] used cochlear microperfusion to facilitate removal of inflammatory cells and their byproducts in perilymph during the acute phase of inflammation between the onset of hair cell dysfunction and cell death, and substantially diminished the amount of cochlear damage and subsequent hearing loss.

Proinflammatory cytokines play a significant role in the morbidity associated with bacterial meningitis, including hearing loss and labyrinthitis ossificans [34]. Among them, TNF-α has been regarded as one of the primary and upstream mediators in the inflammatory response and a key factor causing hearing loss. Aminpour *et al.* [33] reported that blockade of TNF-α by TNF-α antibody resulted in a significant reduction of postmeningitic hearing loss and cochlear injury caused by *S. pneumoniae* meningitis, whereas exposure of noninfected animals to intrathecal flow of TNF-α resulted in hearing loss similar to that seen in bacterial meningitis.

Roles of reactive oxygen species and reactive nitrogen species

There is a substantial body of evidence that oxidants, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), are crucial mediators of brain damage associated with experimental bacterial meningitis [31,32]. Because of the similarity of BBB and blood–labyrinth barrier, oxidants might be involved in the disturbance of the BLB during meningogenic pneumococcal labyrinthitis. In a rat model of pneumococcal meningitis used by Kastenbauer *et al.* [35], suppurative labyrinthitis is accompanied by increased expression of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS), which produce nitric oxide, causing oxidative cochlear damage and BLB disruption. Although Klein *et al.* [23] investigated the role of antioxidants and found that they attenuated the morphological correlates of meningogenic hearing loss, including long-term BLB disruption, spiral ganglion neuronal loss and fibrous obliteration of the perilymphatic spaces. Similarly, Ge *et al.* [36] investigated the role of oxygen free radicals in the pathogenesis of sensorineural hearing loss following bacterial meningitis and found that after bacterial meningitis, intrathecal injection of superoxide dismutase (SOD), an oxygen radical scavenger, significantly reduced cochlear fibrosis and neoossification, the spiral ganglion cell loss, damage to the cochlea and consequently hearing loss.

The powerful ototoxic effect of the oxidants might be based on several potential mechanisms. First, RNS or ROS contributes to the breakdown of the BLB during the acute stage of bacterial meningitis. The integrity of the BLB is essential for maintaining the endocochlear potential which is crucial for the appropriate operation of the hair cells [39]. In addition, the influx of neurotoxic excitatory amino acids from the blood causes spiral ganglion neuronal damage during meningitis [31,32]. The leakage of plasma proteins into the cochlea might also accelerate the fibrous obliteration of the perilymphatic spaces which has been proved to correlate with long-term hearing loss. Moreover, the strong oxidant peroxynitrite results in direct cytotoxic effects on hair cells and spiral ganglion neurons. The unregenerative nature of these neurosensory structures leads to permanent hearing impairment and poor prognosis of cochlear implantation as the effectivity of electrodes depends on the number of residual spiral ganglion cells.

Conclusions

Hearing loss during bacterial meningitis emerges as early as 48 h after infection, and appears to be uncorrelated with the duration of symptoms before treatment. The major site of injury is the cochlea (including hair cells, supporting cells, stria vascularis and spiral ligament), and the spiral ganglion neurons are often involved. It has been well documented that deafness results from spread of infection from meninges to the labyrinth, and the cochlear aqueduct is the primary conduit of the infection extension, causing more pronounced injury in the basal turn of scala tympani and more serious hearing loss in high frequencies. In humans, the cochlear nerve in the modiolus is the secondary pathway for the spread of infection. Suppurative labyrinthitis accounts for end-organ damages in the inner ear, and labyrinthitis ossification leads to permanent deafness in a subset of patients. Vigorous inflammatory responses are triggered within the inner ear, and cytokines, such as TNF-α, play an important role in meningogenic hearing loss. Oxidants contribute to disruption of BLB and produce cytotoxic effects on hair cells and the spiral ganglion cells directly. Understanding the mechanisms underlying bacterial meningitis-associated deafness is useful for designing more effective adjunctive therapies, such as the modulation of cytokines and antioxidant, and guiding cochlear implantation in patients suffering from irreversible profound hearing loss.

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