

Editors-in-Chief

Toren Finkel – National Heart, Lung and Blood Institute, National Institutes of Health, USA

Charles Lowenstein – The John Hopkins School of Medicine, Baltimore, USA

Hearing disorders

# Mechanisms of bacterial meningitis-related deafness

Yi Du<sup>1</sup>, Xihong Wu<sup>1</sup>, Liang Li<sup>1,2,\*</sup>

<sup>1</sup>Department of Psychology, Speech and Hearing Research Center, National Key Laboratory on Machine Perception Peking University, Beijing 100871, China

<sup>2</sup>Centre for Research on Biological Communication Systems, Department of Psychology, University of Toronto at Mississauga, Mississauga, Ont., Canada L5L 1C6

**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.**

## 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 meningitidis* (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*

## Section Editor:

Richard Smith – University of Iowa, Iowa City, USA

remains the leading cause in developing countries. *S. pneumoniae* has led 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].

\*Corresponding author: L. Li (lliangli@pku.edu.cn)

### 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 of the inner ear liliu and ultrastructural pathology in sensory structures were not known, these findings definitely raise the possibility of preventing or reversing the hearing loss by appropriate therapeutic intervention. In addition, Merchant and Gopen observed that severe loss of spiral ganglion cells occurred in 12% of the 41 bones, suggesting that a subset of patients with postbacterial meningitis deafness might perform poorly even after cochlear implantation. In rabbits and guinea pigs with experimental meningogenic bacterial labyrinthitis, hearing loss is closely associated with damage to the organ of Corti (involving the hair cells, supporting cells and nerve terminals) and the stria vascularis [8,21,22,24].

In addition to the cochlea, a strong correlation between long-term hearing impairment and spiral ganglion neuronal loss has been reported [23]. Spiral ganglion cells, which are the cell bodies of the auditory nerve fibers and lie close to the hair cells, would also be susceptible to bacterial infection. Bacteria enter either along the nerve from the cerebrospinal fluid or from the fluid spaces of the inner ear. By contrast, hair cells loss might also induce neuronal death of the spiral ganglion due to inactivity [25,26]. Lesions of central neural pathways with disturbed auditory processing following bacterial meningitis have also been suggested [10,15,19].

### Routes of infection from meninges to labyrinth

The cochlear aqueduct, which links the subarachnoid space to the basal turn of the tympanic scale, is generally proposed as the most probable conduit of meningogenic labyrinthitis [3,5,8–11,16,20–22]. This might explain why the concentration of bacteria and inflammatory cells is high and the ossification more frequently occurs in the basal turn of scala tympani [8,11,20,21], and high-frequency hearing loss associated to the basal turn of the cochlea is more pronounced than low-frequency hearing loss associated to the apex of the cochlea. The short and patent cochlear aqueduct in children is more likely

to be affected than the mature one in adults, suggesting a potential explanation of the higher incidence of postmeningitic hearing loss in children [27]. However, in humans when the cochlear aqueduct is occluded by bone or loose connective tissue, or even absent, bacteria can still spread along the cochlear nerve and the modiolus by the perineural and perivascular channels. Merchant and Gopen [20] reported that the presence of labyrinthitis was uncorrelated with aqueduct patency but highly associated with modiolar inflammation. It would be important to know whether the modiolus in children is more vulnerable to infection than those of adults.

### Suppurative labyrinthitis and ossification

Histopathologic studies of temporal bone have suggested that a probable cause of SNHL is serous or suppurative labyrinthitis [20,28]. It has been traditionally assumed that suppurative labyrinthitis results in irreversible SNHL, whereas serous labyrinthitis results in reversible SNHL. However, Merchant and Gopen [20] reported that the differences of so-called serous and suppurative labyrinthitis were not so clear. Ossification in humans has been noted to occur within a year after meningitis and is a major problem in survivors, because it worsens the prognosis of cochlear implants [29,30].

### Pathophysiological processes

The extension of meningeal infection and/or inflammation from the subarachnoid space via the cochlear aqueduct and/or internal auditory canal to the inner ear results in labyrinthitis and consequent end-organ lesions, therefore deafness [3–5,8–11,15,19–23,28]. Foreign pathogens, such as wall components of cytotoxic bacterial cells, stimulate the release of cytokines, including tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 (IL-1), triggering vigorous inflammatory responses and causing damage to the cochlea [31–34]. The inflammatory byproducts, such as nitric oxide (NO), superoxide and peroxy nitrite, might contribute to blood-labyrinth barrier (BLB) disruptions and induce cytotoxic effects on hair cells and spiral ganglion neurons [23,35,36]. Additional deficits include cochlear ischemia after septic emboli and thrombotic occlusion of small vascula supplying the inner ear, and neural damage after neuritis or hypoxia [14,16].

### Roles of cytokines

Vigorous inflammatory responses occur as a result of triggering local immune defenses by components of the bacterial cell wall. *S. pneumoniae* cell wall lipoteichoic acids have been found to be potent activators for the bacterial meningitis related morbidity and mortality [32]. The release of subcomponents of the cell wall and subsequent activation of the complement cascade result in an excessive degree of inflammation. Activated monocytes, leukocytes, cerebrovascular endothelial cells and astrocytes, in turn produce various proinflammatory cytokines such as interleukin (IL)-1 $\alpha$ ,

IL-1 $\beta$ , IL-6, IL-8, platelet-activating factor and TNF- $\alpha$ . 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- $\alpha$  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- $\alpha$  by TNF- $\alpha$  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- $\alpha$  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 neo-

ossification, 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- $\alpha$ , 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.

### References

- 1 Kulahi, I. *et al.* (1997) Evaluation of hearing loss with auditory brainstem responses in the early and late period of bacterial meningitis in children. *J. Laryngol. Otol.* 111, 223–227
- 2 Richardson, M.P. *et al.* (1998) Otoacoustic emissions as a screening test for hearing impairment in children recovering from acute bacterial meningitis. *Pediatrics* 102, 1364–1368

- 3 Nadol, J.B., Jr (1978) Hearing loss as a sequela of meningitis. *Laryngoscope* 68, 739–755
- 4 Berlow, S.J. *et al.* (1980) Bacterial meningitis and sensorineural hearing loss: a prospective investigation. *Laryngoscope* 90, 1445–1452
- 5 Dodge, P.R. *et al.* (1984) Prospective evaluation of hearing impairment as a sequelae of acute bacterial meningitis. *N. Engl. J. Med.* 311, 869–874
- 6 Baraff, L.J. *et al.* (1993) Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr. Infect. Dis. J.* 12, 389–394
- 7 Bedford, H. *et al.* (2001) Meningitis in infancy in England and Wales: follow up at age 5 years. *Br. Med. J.* 323, 533–536
- 8 Bhatt, S.M. *et al.* (1993) Progression of hearing loss in experimental pneumococcal meningitis: correlation with cerebrospinal fluid cytochemistry. *J. Infect. Dis.* 167, 675–683
- 9 Wellman, M.B. *et al.* (2003) Sensorineural hearing loss in postmeningitic children. *Otol. Neurotol.* 24, 907–912
- 10 Dodds, A. *et al.* (1997) Cochlear implantation after bacterial meningitis: the dangers of delay. *Arch. Dis. Child.* 76, 139–140
- 11 Kesser, B.W. *et al.* (1999) Time course of hearing loss in an animal model of pneumococcal meningitis. *Otolaryngol. Head Neck Surg.* 120, 628–637
- 12 Radetsky, M. (1992) Duration of symptoms and outcome in bacterial meningitis: an analysis of causation and the implications of a delay in diagnosis. *Pediatr. Infect. Dis. J.* 11, 694–698
- 13 Wright, T. (1999) Bacterial meningitis and deafness. *Clin. Otolaryngol.* 24, 274–276
- 14 Brookhouser, P.E. *et al.* (1988) The pattern and stability of postmeningitic hearing loss in children. *Laryngoscope* 98, 940–948
- 15 Hugosson, S. *et al.* (1997) Audiovestibular and neuropsychological outcome of adults who had recovered from childhood bacterial meningitis. *Int. J. Pediatr. Otorhinolaryngol.* 42, 149–167
- 16 Fortnum, H.M. (1992) Hearing impairment after bacterial meningitis: a review. *Arch. Dis. Child.* 67, 1128–1133
- 17 Kotagal, S. *et al.* (1981) Auditory evoked potentials in bacterial meningitis. *Arch. Neurol.* 38, 693–695
- 18 Özdamar, Ö. *et al.* (1983) Auditory brainstem responses in infants recovering from bacterial meningitis. *Arch. Otolaryngol.* 109, 13–18
- 19 Jiang, Z.D. *et al.* (1990) Long-term impairments of brain and auditory functions of children recovered from purulent meningitis. *Dev. Med. Child. Neurol.* 32, 473–480
- 20 Merchant, S.N. and Gopen, Q. (1996) A human temporal bone study of acute bacterial meningogenic labyrinthitis. *Am. J. Otol.* 17, 375–385
- 21 Osborne, M.P. *et al.* (1995) The cochlear lesion in experimental bacterial meningitis of the rabbit. *Int. J. Exp. Pathol.* 76, 317–330
- 22 Tarlow, M.J. *et al.* (1991) Endotoxin induced damage to the cochlea in guinea pigs. *Arch. Dis. Child.* 66, 181–184
- 23 Klein, M. *et al.* (2003) Meningitis-associated hearing loss: protection by adjunctive antioxidant therapy. *Ann. Neurol.* 54, 451–458
- 24 Winter, A.J. *et al.* (1996) Ultrastructural damage to the organ of corti during acute experimental *Escherichia coli* and pneumococcal meningitis in guinea pigs. *Acta Otolaryngol.* 116, 401–407
- 25 Takeno, S. *et al.* (1998) Degeneration of spiral ganglion cells in the chinchilla after inner hair cell loss induced by carboplatin. *Audiol. Neurootol.* 3, 281–290
- 26 Webster, M. and Webster, D.B. (1981) Spiral ganglion neuron loss following organ of Corti loss: a quantitative study. *Brain Res.* 212, 17–30
- 27 Palva, T. (1970) Cochlear aqueduct in infants. *Acta Otolaryngol.* 70, 83–94
- 28 Rappaport, J.M. *et al.* (1999) Electron microscopic temporal bone histopathology in experimental pneumococcal meningitis. *Ann. Otol. Rhinol. Laryngol.* 108, 537–547
- 29 Brodie, H.A. *et al.* (1998) Induction of labyrinthitis ossificans after pneumococcal meningitis: an animal model. *Otolaryngol. Head Neck Surg.* 118, 15–27
- 30 Axon, P.R. *et al.* (1998) Cochlear ossification after meningitis. *Am. J. Otol.* 19, 724–729
- 31 Saez-Llorens, X. *et al.* (1990) Molecular pathophysiology of bacterial meningitis: current concepts and therapeutic implications. *J. Pediatrics* 116, 671–684
- 32 Tuomanen, E. (1997) Molecular and cellular mechanisms of pneumococcal meningitis. *Ann. N. Y. Acad. Sci.* 797, 42–52
- 33 Aminpour, S. *et al.* (2005) Role of tumor necrosis factor-[alpha] in sensorineural hearing loss after bacterial meningitis. *Otol. Neurotol.* 26, 602–609
- 34 Adams, J.C. (2002) Clinical implications of inflammatory cytokines in the cochlea: a technical note. *Otol. Neurotol.* 23, 316–322
- 35 Kastenbauer, S. *et al.* (2001) Reactive nitrogen species contribute to blood-labyrinth barrier disruption in suppurative labyrinthitis complicating experimental pneumococcal meningitis in the rat. *Brain Res.* 904, 208–217
- 36 Ge, N.N. *et al.* (2004) The effects of superoxide dismutase in gerbils with bacterial meningitis. *Otolaryngol. Head Neck Surg.* 131, 563–572
- 37 Rappaport, J.M. *et al.* (1999) Prevention of hearing loss in experimental pneumococcal meningitis by administration of dexamethasone and ketorolac. *J. Infect. Dis.* 179, 264–268
- 38 Barkdull, G.C. *et al.* (2005) Cochlear microperfusion: experimental evaluation of a potential new therapy for severe hearing loss caused by inflammation. *Otol. Neurotol.* 26, 19–26
- 39 Anniko, M. and Wroblewski, R. (1986) Ionic environment of cochlear hair cells. *Hear Res.* 22, 279–293