Pneumococcal meningitis post cochlear implantation Wei et al.

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Pneumococcal meningitis post cochlear implantation: potential routes of infection and pathophysiology

Short running head: Pneumococcal meningitis post cochlear implantation

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Running Heads:

Pneumococcal meningitis post cochlear implantation

Abstract:

Objectives

This review describes the current concept of pneumococcal meningitis in cochlear implant recipients based on recent laboratory studies. It examines possible routes of *S. pneumoniae* infection to the meninges in cochlear implant recipients. It also provides insights into fundamental questions concerning the pathophysiology of pneumococcal meningitis in implant recipients.

Data Sources Medline search on topics related to pneumococcal meningitis post cochlear implantation

Review Methods Comprehensive analysis of the published clinical and scientific laboratory research data

Results The incidence of pneumococcal meningitis in cochlear implant recipients is greater than that of an age-matched cohort in the general population. Based on the current clinical literature, it is difficult to determine whether cochlear implantation *per se* increases the risk of meningitis in subjects with no existing risk factors for acquiring the disease. As this question cannot be answered in humans, the study of implant-related infection must involve the use of laboratory animals in order for the research findings to be applicable to a clinical situation. The laboratory research demonstrated the routes of infection and the effects of the cochlear implant in lowering the threshold for pneumococcal meningitis.

Conclusion The laboratory data complements the existing clinical data on the risk of pneumococcal meningitis post cochlear implantation.

Introduction

There has been an increase in the number of reported cases of cochlear implant-related meningitis, including a number of deaths since 2002¹. This led to investigations by a number of governmental agencies in several European countries, the U.S. Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC) and Health Canada. Based on the clinical studies of patients with cochlear implants, meningitis has been found to be more common than previously thought. The most common organism identified was *Streptococcus pneumoniae*¹⁻³. The incidence of pneumococcal meningitis was found to be greater than that of an age matched cohort in the general population². The exact mechanism of how a cochlear implant contributes to the risk of acquiring meningitis cannot be ascertained from the clinical data. This review describes the most recent development by examining the scientific literature which provides insights into fundamental questions concerning the pathophysiology of pneumococcal meningitis in patients with cochlear implants.

Meningitis post implantation- extent of the problem

Ninety-one cases of post implantation meningitis, including a total of 17 deaths, were reported to the FDA in 2002¹. By September 2003, the total number of reported cases worldwide had increased to 118 (55 cases in the United States and 63 cases from other parts of the world)¹. The age of patients with cochlear implant related meningitis ranged between 13 months and 81 years. The majority of US patients were less than 5 years of age; non-US patients were equally distributed amongst adults and children. The onset of meningitis ranged from less than 24 hours to more than 6 years after implantation. More than 60% of US patients developed meningitis within the first year of implantation, many within the first weeks following surgery¹.

Bacteria isolated from CSF specimens were only documented in 69 patients¹. By far the most common organism identified was *Streptococcus pneumoniae* (pneumococcus, diplococcus) accounting for 46 cases, or 67% of the total. Other bacteria cultured from patients' CSF included *Haemophilus influenzae* (both types B and non-B) (9 cases); *Escherichia coli* (4 cases); *Streptococcus viridians* (3 cases); *staphylococcus* (4 cases); and non-specific bacteria (4 cases).

However, many of the 118 patients in the FDA report had pre-existing risk factors for meningitis before cochlear implantation. These included age (less than 5 years), immunodeficiency, a history of pre-implant meningitis, congenital inner ear deformity, and basilar skull fracture. In addition, the presence of a middle ear infection may predispose patients with an implant to acquire bacterial meningitis: some of the reported cases of meningitis in cochlear implant recipients may have had overt or subclinical otitis media prior to surgery or before the meningitis developed¹. Therefore, the true aetiology of meningitis in these cochlear implant recipients could not be established from the FDA data.

To investigate the extent of the problem, the CDC, the FDA, and state and local health departments in the US conducted a study which focused on young children with cochlear implants, as they constitute the majority of known meningitis cases and represent the population that will receive most cochlear implants in the future². It consisted of a cohort study and a nested case-control investigation of 4,264 children receiving a cochlear implant in the US between January 1, 1997 and August 6, 2002 under the age of 6 at the time of implantation. Twenty-nine episodes of bacterial meningitis were reported before September 15, 2002 in 26 children with implants. Nine of the 29 cases occurred within less than a month (peri-operative) of the patient receiving the implant and the remaining 20 occurred 1 month after implantation. The incidence of all cases of meningitis in the cohort was 239.3 per 100,000 person-years which is significantly higher than the incidence in the age matched cohort of general population of the same time period (2 to 5 per 100,000 person-years)². *Streptococcus pneumoniae* was the most common cause of meningitis and accounted for 15 of the 24 episodes of bacterial meningitis with a known cause (63% of the reported cases). Four episodes occurred within the first month and 11 episodes occurred between 1.5 to 19 months post implantation. Three children acquired pneumococcal meningitis despite immunization with 7-valent pneumococcal conjugate vaccine (PCV 7). The serotypes of the bacteria causing the disease were unknown in 2 of these children. However, the third child acquired meningitis caused by serotype 10A *S. pneumoniae* not included in PCV 7. The incidence of post implant meningitis caused by *S. pneumoniae* was 138.2 cases per 100,000 person-years which was 30 times greater than that of an age matched cohort in the general population in 2000. A number of specific risk factors associated with post implant meningitis were also identified in this study: implants with a positioner; inner ear malformation with CSF leak; CSF leak alone; incomplete insertion of the electrode; history of a ventricular peritoneal shunt; a history of otitis media before meningitis².

To quantify continuing risk of meningitis, the authors conducted an additional follow up of these children from September 16, 2002 through December 1, 2004⁴. Twelve new episodes of meningitis were ascertained in 12 children, 11 of whom received a cochlear implant with a positioner. The incidence rate during this additional follow up period (> 24 months) for children with a positioner implant was 450 cases per 100,000 person-years (versus 0 for children without a positioner). *S. pneumoniae* was isolated in 9 of the 12 episodes of meningitis (75%). Six episodes occurred between 24 and 95 months post-implantation⁴. Based on these results the FDA issued a web notification to emphasize the importance of continued monitoring and prompt treatment of bacterial infections in children with cochlear implants beyond 2 years post-implantation, particularly among children whose implants have a positioner⁵.

Based on these clinical data, it remains to be determined whether cochlear implantation *per se* increases the risk of meningitis in subjects with no existing risk factors for acquiring the disease.

The routes of pneumococcal infection

The pathogenesis of pneumococcal meningitis is complex. There may be differences in the pathogenesis of pneumococcal meningitis among subjects with a cochlear implant depending upon the route of bacterial infection. This is because 40% of subjects with post implant meningitis were found to have concurrent acute otitis media and 80% were found to have bacteraemia². Therefore, an understanding of the routes by which *S. pneumoniae* reaches the meninges is an important first step in examining whether the presence of a cochlear implant in the inner ear increases the risk of pneumococcal meningitis and in determining improved surgical techniques and implant designs in order to reduce the risk.

A review of the literature for patients who acquired pneumococcal meningitis and have not received a cochlear implant suggests that *S. pneumoniae* can spread to the meninges either directly from the middle ear or from the haematogenous seeding of bacteria (Figure 1). The otogenic spread of infection can be further sub-classified into either a direct invasion of the meninges by the bacteria^{6,7} or indirect invasion via the inner ear. The spread of bacteria from the middle ear to the meninges via the inner ear in patients with cochlear implants is the most commonly accepted view and has been the main focus of the study of infection prevention strategies in implant related meningitis⁸. This view is supported by the fact that the bony, soft tissue and mucosal barriers between the middle ear and inner ear are potentially compromised in the presence of a cochlear implant and this may allow easier access for bacteria to enter the inner ear from the middle ear. The presence of peri-implant fibrous tissue seal has been considered to be an important way to resist the spread of infection from the middle ear to the inner ear. Moreover, pneumococcal meningitis is considerably more frequent following skull fractures abutting the respiratory tract (including middle ear, mastoid cavity and paranasal sinuses), with direct spread of the bacteria from the respiratory mucosa to the meninges being the probable mechanism. There is also experimental evidence of direct spread of infection from the nasopharynx through the cribriform plate to the meninges, as a *galU* mutant of *S. pneumoniae* - without the ability to sustain bacteraemia- has been shown to invade the central nervous system (CNS) following intranasal instillation⁹.

The round window niche can also be another route for otogenic spread of infection from the middle ear to the inner ear. Bacterial toxins, antibiotics, antiseptics, arachidonic acid metabolites, local anesthetics, albumin and tracers, when placed in the middle ear transverse the round window membrane¹⁰. However, the permeability of the round window membrane in humans to *S. pneumoniae* with and without cochlear implantation is unknown. In animal models, *S. pneumoniae* were observed to pass through an intact round window membrane (Figure 2) to enter the inner ear and then into the modiolus through the small pores in the osseous spiral laminae^{11,12}. Grafting the round window membrane with gelatin sponge increases the thickness of the membrane and reduces the incidence of labyrinthitis¹². Thus, the round window membrane can be a potential site for bacteria to enter the inner ear despite a perfect fibrous seal around the electrode

array. However, the thickness of the round window membrane varies across species and is an important factor to consider when designing experiments to study the permeability of the round window membrane to bacteria. The round window membrane in humans is reportedly thicker (40-70µm) than the laboratory animals¹³.

On the other hand, in the absence of head trauma, pneumococcal meningitis via bacteraemia, with a subsequent invasion of the central nervous system, is thought to be a major route of infection^{14,15}. This has been supported by animal studies which show a rapid transit of pneumococci via the bloodstream to the brain after the direct inoculation of the bacteria in either the nasopharynx or middle ear cavity^{9,16-19}. Hence, the role of haematogenous spread of the bacteria to the meninges in patients with cochlear implants should be considered when investigating pneumococcal meningitis post cochlear implantation. Furthermore, in human cochlear implantation, surgery directly adjacent to the dura within the mastoid or deep to the temporal squamosa in providing a bed for the receiver-stimulator, may affect the blood-brain barrier. Any change may affect both the threshold for direct and haematogenous routes of infection.

Temporal bone studies in patients with pneumococcal meningitis

The routes by which *S. pneumoniae* reaches the meninges have also been examined in a number of temporal bone studies. Some studies of individual subject's temporal bones with pneumococcal meningitis have provided evidence to support the direct association between otitis media and meningitis and the direct spread of the infection to the meninges via the inner ear²⁰⁻²³. However, a haematogenous spread of bacteria from the middle ear or nasopharynx to the meninges with subsequent labyrinthitis (retrograde spread of infection) is difficult to distinguish from the direct spread of infection from the middle ear to the inner ear and then to the meninges (anterograde spread of infection). When examining the temporal bones of individuals who have died from meningitis, the disease is at the terminal stage and there may have been retrograde spread from the meninges to the inner ear via the cochlear aqueduct²²⁻²⁴. Moreover, otitis media can occur in meningitic labyrinthitis as a result of the destruction of the round window^{25,26}. Therefore it can be difficult to determine whether the labyrinthitis was a result of a complication of the otitis media or as a result of the meningitis. Thus, temporal bone studies have not provided convincing evidence of the exact route(s) of the spread of the infection.

In summary, when meningitis occurs in the presence of acute otitis media, there is insufficient evidence to suggest a direct spread of *S. pneumoniae* from the middle ear to the inner ear then to the meninges as the only means of infection. The role of the haematogenous spread of the bacteria from the middle ear to the meninges should also be considered. Furthermore in patients with meningitis following cochlear implantation and concurrent acute otitis media, the exact routes by which the bacteria reach the meninges from the middle ear are not known. Therefore, all potential routes of infection should be considered when examining the pathophysiology of pneumococcal meningitis post cochlear implantation.

Threshold of *S. pneumoniae* required for meningitis

The occurrence of meningitis seems directly related to the duration and the intensity of the bacteraemia, because these variables determine how many bacteria reach the subarachnoid space ²⁷. It appears that a threshold of the bacteria with the required virulence factors must be reached in the blood and meninges of a healthy animal to establish meningitis, with any breach of the dura reducing the threshold of the bacteraemia required to produce meningitis ²⁸.

The quantification of the bacterial threshold(s) for pneumococcal meningitis is a prerequisite to test whether a cochlear implant increases the risk of meningitis. This was established in an animal model involving the rat ¹¹. In order to apply the animal research to clinical application, the particular strain of bacteria used in these experimental studies must be able to cause meningitis in both humans and the animal model under study ¹¹. Furthermore, the routes by which the pneumococci reach the CNS in the animal model must also resemble human infection. These two important criteria were achieved by using *Streptococcus pneumoniae* 447A, which carries the type 2 capsular antigen ¹¹. In the presence of a cochlear implant, the bacteria can reach the CNS from the upper respiratory tract mucosa either through the systemic circulation or via the inner ear. The bacteria can also reach the CNS via a combination of both routes. Three different methods of inoculation (haematogenous, middle ear and inner ear) were implemented in the laboratory study to cover all potential routes of infection ¹¹.

In the absence of a cochlear implant, the quantitative threshold model demonstrated that a minimal threshold of bacterial count was required to induce meningitis in healthy non-implanted animals (Figure 3) ²⁹. The threshold for pneumococcal meningitis differed between the three different routes of infection (haematogenous, middle and inner ear) ²⁹. The threshold required to induce meningitis was highest for the haematogenous route and lowest for the direct inner ear route ²⁹. A cochleostomy performed on the inner ear 4 weeks prior to bacterial inoculations did not alter threshold for the three routes of infection studied ²⁹.

Although it cannot be proven that threshold numbers of pneumococci are required to cause human meningitis, the experimental findings are consistent with some clinical observations. Patients with lower immune competence are known to be more susceptible to meningitis than the rest of the population ^{30,31}. This can be understood within the context of a threshold model as an effective increase in the bacterial load mediated by a reduced capacity of the host to kill the inoculated pneumococci; greater numbers of bacteria survive per inoculum and the bacterial count required to cause meningitis is more easily exceeded. The rarity of meningitis in the human population suggests that the bacterial thresholds for pneumococcal meningitis are not often reached, presumably because host immunity seldom fails even after infection with invasive serotypes of these bacteria. The threshold model gave us new insight as to how *S. pneumoniae* could potentially induce meningitis in human subjects. Extrapolating from this threshold model, whether a healthy human subject acquires pneumococcal meningitis may depend on the route of infection and the

bacterial load for each route. It is important to understand that a quantitative threshold model can be established in animals but not in humans due to ethical reasons. Therefore the animal model is an alternative means to study human disease¹¹ and is instrumental in that possible mechanisms behind pneumococcal meningitis in human subjects with or without a cochlear implant can be examined in a controlled laboratory environment¹¹.

The effect of cochlear implantation on the threshold

The quantitative threshold model was used to examine the fundamental question : does the presence of a cochlear implant increase the risk of pneumococcal meningitis in healthy subjects who have no existing risk factors ? Compared to non-implanted control cohorts, the presence of a cochlear implant in healthy animals was associated with a reduction in the threshold of bacteria required to induce pneumococcal meningitis, irrespective of the route of infection (Figure 4)³². This threshold shift was observed in healthy rats that were implanted with a scala tympani electrode 4 weeks prior to infection. It is the presence of the implant, and not the surgical entry into the inner ear that is associated with the increased meningitis risk; as noted above, the threshold developing pneumococcal meningitis was not altered in a group of control animals that underwent surgical entry (cochleostomy) but not electrode implantation³². This finding is significant as such an association cannot be answered by examining the current clinical data. Many cochlear implant recipients who acquire pneumococcal meningitis have pre-existing risk factors such as cochlear malformation and skull base fractures^{1,2,4}. A major advantage of this study was that in a controlled laboratory environment, animals did not have pre-existing risk factors for pneumococcal infection.

This reduction in threshold demonstrated that the presence of a foreign body, such as a cochlear implant electrode array, in the inner ear could increase the risk of pneumococcal meningitis by reducing the number of bacteria required for CNS infection. The exact mechanisms associated with this reduction is not known. Nevertheless, previous studies have shown that foreign bodies, such as polytetrafluoroethylene, when implanted in subcutaneous tissue increased the apoptotic activity of polymorphonuclear leukocytes and impaired their ability to phagocytose bacteria^{33,34}. There are two possible aetiologies for a reduction in threshold for meningitis via both otologic and haematogenous routes. First, it is possible that the presence of an implant may reduce the local inner ear immunity and allow a direct invasion of CNS when bacteria are inoculated into the middle or the inner ear³². Second, the implant could possibly reduce the global CNS immunity to allow bacterial invasion of the blood-brain barrier from the systemic circulation. The histopathological appearance of the cochlear specimens supported both the aetiologies³². While these hypotheses require further examination, the findings indicate that human cochlear implant recipients may have an increased risk of meningitis due to a threshold shift.

Effects of inner trauma on the risk of pneumococcal meningitis

In addition to the presence of a cochlear implant, a severe surgical insertion trauma (fracture of osseous spiral laminae and modiolus) was found to be an independent factor for subsequent risk of pneumococcal meningitis³⁵. In these instances, the threshold for infection was reduced when bacteria were given via the middle or inner ear route but not the haematogenous route³⁵. Presumably, a more direct communication between the inner ear and the internal auditory meatus (IAM) was created by trauma to the modiolus and OSL. This provided an easier access route for the bacteria to reach the CNS once in the inner ear. As local inner ear trauma did not alter the haematogenous route of infection, one would expect the risk of pneumococcal meningitis to be unaltered when the bacteria were inoculated via the haematogenous routes³⁵.

Recurrent meningitis in patients with a cochlear malformation

Patients with abnormal cochlear morphology are at increased risk of spontaneous meningitis^{36,37}. It has been suggested that this increased risk may be due to more open communication between the inner ear and the CNS in these subjects³⁸⁻⁴². It is also possible that the cochlear aqueduct is more patent in patients with malformed cochleae, again providing more direct communication between the cochlea and the CNS. However, there are no published data reporting the size and patency of the cochlear aqueduct and vestibular aqueduct in patients with cochlear dysmorphism. Although the threshold model has not been applied to animals with malformed cochleae, this situation resembles, to some extent, the open communication between the cochlea and IAM created by a trauma model³⁵, suggesting that a more open communication between the inner ear and the CNS increases the risk of meningitis.

Histopathology and routes of infection based on the threshold model

The histopathological appearance of the cochlear specimens was very distinct and varied between different routes of inoculation^{11,29,32}. Animals that acquired meningitis following haematogenous inoculation showed a bilateral symmetrical distribution of bacteria and inflammatory cells within the cochleae (Figure 5)^{11,29,32}. In these animals, bacteria were found predominately in the modiolus and IAM during the early stage of meningitis and they were not observed in the scalae of the ipsilateral and contralateral cochlea. In contrast, in meningitic rats that received either a middle ear or inner ear inoculation, an asymmetrical distribution of bacteria and inflammatory cells was seen (Figure 6). In these instances, a severe labyrinthitis was observed in the ipsilateral ear compared to the contralateral ear^{11,29,32}. Bacterial organisms and inflammatory cells were found in all three scalae of the ipsilateral ear predominately in both the scala tympani and scala vestibuli. In the contralateral ear, bacteria and inflammatory cells were predominately located in the basal turn of the scala tympani. The histopathological appearances of the the ipsilateral and contralateral cochleae during early stage of meningitis can be used to determine the route of infection from the upper respiratory tract mucosa to the central nervous system.

As noted above, *Streptococcus pneumoniae* were found to enter the pores within the osseous spiral laminae and track along the peri-vascular and peri-neural space within the modiolus to reach the internal acoustic meatus and central nervous system^{11,29,32}. The bacteria can also enter the central nervous system via the cochlear aqueduct. Conversely, bacteria in the central nervous system can reach the contralateral cochlea via one of these routes^{11,29,32}.

There is a great variation in published descriptions of the patency, shape and size of the human cochlear aqueduct^{43,44}. Some studies described patency of the cochlear aqueduct to be age dependent^{45,46}; in newborns it is reportedly short and patent⁴³. However, another study found no statistical correlation between age and patency of the cochlear aqueduct⁴⁴. To date little is known about the patency and size of aqueduct in patients with cochlear malformation.

Conclusion:

The most common organism identified in post implantation meningitis is *S. pneumoniae*. All potential routes of spread of *S. pneumoniae* from the middle ear to the meninges should be considered when examining post implant meningitis. A quantitative pneumococcal meningitis threshold model in rodents was established and demonstrated that the presence of a foreign body, such as an electrode array in the inner ear increased the risk of pneumococcal meningitis in healthy animals. The threshold shift was significant for all three different routes of infection from the upper respiratory tract to the CNS. Furthermore, the histological examination of the cochleae in the implanted and non-implanted animals showed differing patterns depending on whether the meningitis was acquired via the haematogenous or via the otogenic route. The association between meningitis and inner ear structural damage secondary to insertion of the cochlear implant array was also demonstrated in the animal model.

Figure legends:

Figure 1 *Streptococcus pneumoniae* can reach the central nervous system via the haematogenous route or the otogenic route. The Otogenic route can be divided into either the direct or the indirect (via the inner ear) route.

Figure 2 Lower power H & E photomicrographs taken at the level of the round window niche of the unimplanted cochlea following middle ear inoculation of *S. pneumoniae*. The inflammatory cells and the bacteria infiltrating the round window membrane (rwm). Higher power of the round window niche (b) was taken from region (b) in the lower power micrograph (a). Scale bar: (a) 200 µm; (b) 50 µm.

Figure 3 The relationship between the amount of bacterial inoculum and the rate of meningitis. The different threshold curves have been observed and this depends on the route by which the pneumococci reach the CNS from the upper respiratory tract [haematogenous (H), middle ear (M) or inner ear (I)]. CFU: colony forming unit.

Figure 4 The effect of cochlear implant on the infectious threshold. A threshold of bacteria is required to induce meningitis is significantly reduced in the presence of a cochlear implant. The threshold curve is shifted from (M) to (M''). CFU: colony forming unit

Figure 5 The implanted (a) and contralateral control (b) cochleae of a rat developed meningitis following IP inoculation. The scalae of both cochleae were devoid of gross infection. Higher power photomicrograph of Gram stain from basal turn of the contralateral cochlea (c), the lateral wall of the scala media of the contralateral cochlea (d), the modiolus of the ipsilateral cochlea (e) and the internal acoustic meatus of the contralateral cochlea (f), illustrates the presence of bacteria (arrows). The approximate location of the higher power micrographs (e,f) are illustrated in (a) and (b). sv: stria vascularis. Scale bar: (a) & (b) 200 µm; (c) 100 µm; (d-f) 10 µm.

Figure 6 The implanted (a) and contralateral control (b) cochleae of a rat developed meningitis following inner ear inoculation of *S. pneumoniae*. Extensive labyrinthitis of the inoculated left ear involved all three scalae. In contrast, the contralateral cochlea exhibited a less severe labyrinthitis with infection predominantly localized to the scala tympani. Higher power photomicrograph of Gram stain from the modiolus (c) and the internal acoustic meatus (d) implanted left cochlea illustrates the presence of bacteria (arrows). The approximate location of the higher power micrographs (c,d) are illustrated in (a) and (b). bn: bone. Scale bar: (a) & (b) 200 µm; (c) & (d) 10 µm.

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Figure 1 Routes of infection to the meninges

Figure 3
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Figure 3 Threshold Model

Figure 4 The effect of cochlear implant on the threshold for meningitis

Figure 5
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