Predicting Parameters for Audiological Complications in Pediatric Patients Affected by Meningitis

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Abstract

Objective Meningitis is one of the most common causes of acquired sensorineural hearing loss in childhood. The aim of this study was to identify parameters predicting long-term audiological complications in meningitis.

Methods Patients under 18 years admitted to the Bambino Gesù Pediatric Hospital between March 2001 and February 2019 with a diagnosis of meningitis entered the study. Audiological complications had been investigated during hospitalization and at follow-up.

Results During the study period, 425 patients were enrolled. Sensorineural hearing loss was observed in 48 patients (11.3%). Multivariate analysis has shown that female gender predisposes to the development of permanent hearing loss after meningitis. Hearing impairment was associated with pneumococcal etiology ($p < 0.001$), lethargy ($p = 0.027$), reduced cerebrospinal fluid glucose level ($26.18$ mg/dL, $p = 0.004$), increase in both C-reactive protein ($17.77$ mg/dL, $p = 0.001$), and erythrocyte sedimentation rate ($106.3$ mm/h, $p = 0.004$). At follow-up, 19 patients had a persisting hearing damage, 7 recovered their hearing capacity and 20 were lost to follow-up. Among patients with permanent hearing damage, treatment was necessary in 16 patients. In details, 6 patients required external hearing aids and 10 patients required a cochlear implant.

Conclusions Female gender, lethargy at onset, reduced cerebrospinal fluid glucose level, increased inflammation index, and pneumococcal etiology are correlated with sensorineural hearing damage in meningitis patients.

Keywords► meningitis► children► hearing loss/impairment► audiological sequelae

Introduction

Meningitis is one of the most common causes of acquired sensorineural hearing loss in childhood, occurring in 5 to 18% of the survivors.1–3 The variability of reported incidence of hearing loss depends mainly on differences between hearing testing methods, interpretation of results, and parameters used to define hearing impairment. Hearing loss can be defined as conductive or sensorineural. Moreover, depending on severity, it is classified as mild (hearing threshold 20–40 dB), moderate (40–70 dB), severe (70–90 dB), and deep (>90 dB). Of note, postmeningitis forms are usually bilateral and deep.4 In the pediatric population, meningitis and
cerebral infections are linked to neurological and psycho-pathological sequelae.\textsuperscript{5} Hearing loss due to meningitis may onset as a silent impairment but it can seriously compromise the development of language and communication skills affecting children’s education and social growth.\textsuperscript{6} Indeed, to provide a prompt diagnosis of meningitis hearing impairment, a specialist evaluation is required.\textsuperscript{6} The onset of hearing loss is mainly observed in the first days of illness, usually within the first 48 hours.\textsuperscript{7,8} Hearing impairment after meningitis may be related to several causes. In many cases, the underlying mechanism is a suppurative labyrinthitis, spreading from the subarachnoid space through the cochlear aqueduct.\textsuperscript{9–11} In other cases, there is a direct damage of the cochlear nerve\textsuperscript{12} or a vascular damage, due to septic emboli or thrombotic occlusions of the cochlear artery/vein.\textsuperscript{12,13} Hearing loss pathogenesis includes different stages: a first acute phase, in the first days after onset, followed by a purulent phase, between the first and second week when both noninvasive or surgical treatment is possible and effective. Then it moves to a fibrous stage, between the second and third week from the onset, with granulation tissue and angiogenesis processes.\textsuperscript{8,14,15} At this time, the damage can be irreversible, but surgery is still possible. After at least 2 months from the onset, an ossifying stage occurs, with mineralization and obliteration of the structures of the inner ear.\textsuperscript{8,14,15} At this stage, hearing damage is irreversible and there is no possibility of effective surgical intervention.\textsuperscript{8,14,15}

The aim of the study was to identify epidemiological, etiological, clinical, and laboratory parameters predicting long-term audiological sequelae in patients with meningitis, to recognize patients who may require a different therapeutic strategy and/or more detailed clinical and instrumental monitoring.

\section*{Materials and Methods}

Patients under 18 years, admitted to Bambino Gesù Children Hospital (Rome, Italy) for meningitis were included. All subjects had no hearing loss before suffering from meningitis. The study period ranged from March 1, 2001 to February 28, 2019. Children’s parents sign an authorization to have their children undergo the exams related to their disease. The diagnosis of meningitis was obtained by chemical-physical, cultural, and biomolecular tests performed on a cerebral spinal fluid (CSF) sample from lumbar puncture or by the association of clinical evidence of central nervous system infection confirmed by positive inflammation indexes on blood samples. Patients with ventricular–peritoneal shunt and patients affected by congenital malformation involving skull bones were excluded.

The following data were collected from medical records of hospitalization and follow-up:

- Personal data (sex, age at onset, length of hospitalization);
- Underlying medical conditions;
- Presenting symptoms;
- Laboratory tests from blood samples and CSF, including complete blood count, C-reactive protein (CRP), erythrocyte sediment rate (ESR), CSF glucose and protein levels, CSF white blood cell count.

Visual, neurological, and hearing impairment information studied both at discharge and during follow-up was collected. Patients’ neurological status at onset was evaluated using the AVPU scale, giving an A score if the patient was Alert, V if responsive to Verbal stimulus, P if responsive to Painful stimulus, and U if Unresponsive. Lethargy was defined if the patient received “P” or “U” at the AVPU scale.\textsuperscript{16} Audiological complications were analyzed: all patients underwent hearing assessment according to the audiological management protocol currently in use at Bambino Gesù Children’s Hospital. It provides first level of functional tests (TEOAE or AEP or pure tone audiometry), both during hospitalization and at discharge. In case of unilateral sensorineural hearing loss, patients entered audiological follow-up, with half-yearly or annual checks. If bilateral sensorineural hearing loss was found, high-resolution temporal computed tomography (CT) scans and magnetic resonance imaging (MRI) with gadolinium for the study of the inner ear and 3D reconstructions of the membranous labyrinth were urgently performed. The imagine may identify signs of labyrinthine fibrosis or ossification, with a sensitivity of 94% and specificity of 88%.\textsuperscript{6,17} In cases of severe or profound sensorineural hearing loss, if ossification was detected, urgent bilateral simultaneous cochlear implantation was prescribed. Otherwise, a 15 days follow-up was required with imaging and audiological evaluation. In case of no improvement, cochlear implantation or hearing aid fitting was prescribed within 6 weeks of onset, according to the degree of hearing impairment. According to Italian guidelines, cochlear implantation surgery is recommended in children from 1 year age affected by severe or profound bilateral deafness (hearing threshold >75 dB HL) and in cases of no improvement of hearing and communication skills after 3 to 6 months of treatment with hearing aids and speech therapy.\textsuperscript{5,18} However, in profound sensorineural hearing loss cases due to meningitis, bilateral simultaneous cochlear implantation surgery is mandatory even under 12 months.\textsuperscript{5,17}

The study population was characterized using descriptive statistics: mean value ± standard deviation for continuous variables and proportions for categorical variables. The reported data were compared with the Mann–Whitney U test (for continuous variables with nonnormal distribution) and chi-squared test for categorical variables; a value of $p < 0.05$ was considered statistically significant. Multivariate analysis was performed via binary logistic regression, adopting “hearing loss” as the dependent variable and the significant results of the univariate analysis as the independent variables.

\section*{Results}

A total of 425 patients entered the study. Out of them, 261 were male (M) and 164 females (F) (M: F ratio of 1.6: 1). The median age was 1.83 years (range: 0.01–17.44). The highest frequency of disease cases was in infants younger than 1 year...
old (181 patients). As for the others, 109 patients were aged 1 year and over but less than 5 years, 83 patients were aged 5 years and over but less than 10 years, and 52 patients were aged 10 years and over but less than 18 years. Preexisting comorbidities were found in 21 cases. In detail, three patients suffered from a severe heart disease, five had immunoglobulin deficiency, one had hypocomplementemia, one was affected by autoimmune lymphoproliferative disease, two had brain neoplasms, four had nonderivative hydrocephalus, two were affected by Arnold Chiari type I syndrome, and three had kidney transplantations.

Information about vaccination status against *Haemophilus influenzae* type B (Hib) and *Streptococcus pneumoniae* was available for 167 patients: 99 patients were vaccinated against *S. pneumoniae* and Hib, 15 patients were vaccinated only against *S. pneumoniae*, 25 patients were vaccinated only against Hib, and the remaining patients were unvaccinated.

Most cases of meningitis had a bacterial etiology (218 cases). Among the others, in 50 cases a viral etiology was found, while in 157 cases, no pathogen could be identified. *Neisseria meningitidis* was the most common bacterium identified, accounting for 70 (16.5%) cases, followed by *S. pneumoniae*, isolated from 60 (14.1%) patients (Fig. 1). The most common symptom or sign was fever, occurring in 364 (85.6%) of patients, followed by vomiting (135, 31.8%) and nuchal rigidity (88, 20.7%); 86 (20.2%) patients presented in a lethargic state. CSF examination showed a mean glucose concentration of 37.8 mg/dL, a mean protein value of 180.5 mg/dL, and a mean white blood cell count of 1944.9/mmc.

Blood parameters mean values were hemoglobin 11.9 g/dL; white blood cell count 15,270 /mmc (with 68% of neutrophils and 48% of lymphocytes); total platelets 343.196/mmc, CRP 12.3 mg/dL (normal range: <0.5 mg / dL); and ESR 74.9 mm/h (normal range: 0–13 mm/h).

Patients’ clinical, etiological, and epidemiological data are outlined in Tables 1 and 2.

Four (1.6%) patients died during hospitalization (7/425). The onset of neurological, visual, and audiological sequelae was studied in the 419 surviving patients, which identified 157 (37.4%) complicated cases. Neurological complications were the most frequently observed (82 cases, 19.3%), followed by auditory complications (48 cases, 11.3%) and visual complications (27 cases, 6.4%). Data on auditory complications are reported in Tables 3 and 4. Hearing impairment was clinically evident in 44 of the 48 patients with abnormal audiometry. Nine patients had profound deafness, which was unilateral in four cases and bilateral in five cases. Thirty-six patients were classified as having sensorineural hearing loss, bilateral in 21 and unilateral in 15. Only one patient had mixed damage with bilateral hearing loss. Hearing impairment was associated with visual impairment in 5 cases and with neurological sequelae in 16.

The median ages of patients with (1.7 years) and without (1.87 years) hearing impairment were not significantly different. Male sex predominated in those with hearing impairment, with a ratio of 2.9:1 (p = 0.057). A significantly longer hospitalization was found in patients with hearing loss (26.37 vs. 24.9 days; p = 0.012). Only three patients with audiological complications had preexisting pathological conditions: one patient with severe heart disease, one patient had immunoglobulin deficiency, and one patient had Arnold Chiari type I syndrome.

Most cases of hearing loss were related to *S. pneumoniae* (40.4%, 19 cases), compared with 27.7% (13 cases) of *N. meningitidis* infection (p < 0.001). Meningococcal etiology showed a slightly higher prevalence in the group of patients with sensorineural hearing loss compared with the others (27.7 and 16.5%, respectively).

Clinically, the onset of meningitis was characterized by fever in 42 patients (91%), associated with the typical symptoms of acute meningitis: vomiting (11 cases, 23.4%), neck stiffness (11 cases, 23.9%) headache (8 cases, 17%), and lethargy (15 cases, 32.6%). Laboratory tests showed that the mean CSF glucose concentration was lower in patients with hearing impairment (26.18 mg/dL compared with 39.3 mg/dL, p = 0.004). The mean CSF protein concentration was little different between patients with and without hearing impairment (181.5 mg/dL vs. 180.12 mg/dL). Patients with hearing impairment tended to have higher white blood cell CSF counts (2,846/mmc and 1,830/mmc, respectively). Statistically significant higher blood inflammatory indexes were also seen in patients with hearing impairment. The mean CRP and ESR were 17.77 mg/dL and 106.3 mm/h, respectively. Patients with hearing impairment tended to have lower platelet counts (mean values: 280.337 and 350.714, respectively). At the follow-up evaluation, 7 patients showed improved auditory function and 19 a persistent deficit. Comparison of patients with transient hearing loss and those with a persistent deficit showed no significant results for any of the given variables. However, 12 patients with persistent hearing loss were younger than 1 year, while only 2 patients in the same group had a transient deficit; this difference only just failed to be statistically significant (p = 0.051). Follow-up data were not available for 20 patients. Patients with audiological impairment continued the follow-up evaluation with the execution of CT and MRI to highlight signs of ossification of the inner ear. Treatment was required in 16 patients: hearing aids in 6 cases and cochlear implant in 10. Unfortunately, in 4 out of 10 cases, cochlear fibrosis and/or ossification was observed, with a definitive hearing damage. All of them had a delay in audiological screening.

Fig. 1 Pathogens detected in meningitis patients by age group.
Patients who required surgical treatment had mostly a pneumococcal etiology (70%). No statistical relationship between corticosteroid treatment and audiological impairment was found (►Table 5).

Finally, we performed multivariate analysis focused on the significant results we previously obtained (►Table 6). When performing multivariate analysis of the variables sex, hospitalization, lethargy, CRP and ESR levels, CSF glucose concentration, and different etiologies, only female sex was associated with a significantly increased likelihood of hearing loss.

**Discussion**

Patients who experienced bacterial meningitis can have numerous sequelae, including neurological, audiological, and cognitive deficits.19,20 Sensorineural hearing impairment is one of the most frequent complications described.3,12,21 The impairment is permanent in ~10% of survivors of bacterial meningitis.3 In accordance with literature, we observed a sensorineural hearing loss in 11% of cases. In the literature, *S. pneumoniae* etiology, male gender, and intracranial hypertension and neck stiffness as presenting symptoms have been associated with audiological sequelae.22–27 The main factors associated with poor prognosis and neurological or audiological sequelae have been *S. pneumoniae* etiology, low glucose, and high protein levels in CSF.12,22,23 The number of bacteria in the CSF, as well as the severity of the infection, have also been reported as risk factors for hearing loss.25 As in previous studies, we found higher values of inflammatory parameters (CRP and ESR) in complicated patients.28 Also, hearing impairment was commoner in patients with *S. pneumoniae* infections. Following introduction of Hib vaccination, *S. pneumoniae* has become

| Table 1 Patients’ characteristics |
|----------------------------------|
| **n** | **Symptoms at onset—no (%)** | **n** |
| Total population—no. | 425 | Fever | 364 (85.6) |
| | | Vomiting | 135 (31.8) |
| Median age (range)—years | 1.83 (0.01–17.44) | Neck stiffness | 88 (20.7) |
| | | Lethargy | 86 (20.2) |
| Age distribution—no (%) | | Headache | 76 (17.9) |
| Less than 1 years | 181 (42.5) | Seizure | 58 (13.6) |
| 1 year and over but less than 5 years | 109 (25.6) | Anorexia | 42 (9.9) |
| 5 years and over but less than 10 years | 83 (19.5) | Agitation | 25 (5.9) |
| 10 years and over but less than 18 years | 52 (12.2) | Ataxia | 18 (4.2) |

| | | Visual disturbances | 15 (3.5) |
| | | Tremors | 8 (1.9) |
| | | Female | 164 (38.6) |
| | | Hypotonia | 5 (1.2) |
| | | Male | 261 (62.4) |
| | | Dysarthria | 4 (0.9) |
| Female to male ratio | 1:1.6 | Blood cell count—mean (SD) |
| | | Hemoglobin | 11.9 (4.8) |
| Preexisting conditions—no (%) | 21 (4.9) | Platelet count | 334196 (187713) |
| | | White blood cells | 15270 (8355) |
| Etiology—no (%) | | Neutrophils, % | 68 (18) |
| Bacterial | 218 (51.3) | Lymphocytes, % | 48 (15) |
| Viral | 50 (11.7) | CRP (mg/dL)—mean (SD) | 12.3 (17.9) |
| N/A | 157 (36.9) | ESR (mm/h)—mean (SD) | 74.9 (44.0) |

| Complications—no (%) |
| Neurological sequelae | 82 (19.3) | Lumbar puncture—mean (SD) |
| Auditory sequelae | 48 (11.3) | CSF white blood cells | 1944.9 (4513.4) |
| Visual sequelae | 27 (6.4) | CSF glucose | 37.8 (27.8) |
| Deaths | 7 (1.6) | CSF protein | 180.5 (268.2) |
| Hospitalization (days)—mean (SD) | 25.04 (27.14) | Follow-up (months)—mean (SD) | 36.21 (87.59) |

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; ESR, erythrocyte sediment rate; N/A, not available. SD, standard deviation.
the leading cause of meningitis in children.\textsuperscript{30,31} We also found a statistically significant association between presentation with leghathy and audiological sequelae, indicating that more serious neurological clinical features at presentation are a predictive factor of audiological complications.

When assessing for transient and persistent hearing loss at the follow-up evaluation, no significant difference was found according to age group. However, the \( p \)-value was only just above 0.05, suggesting that larger studies might show that children aged under 1 year are at greater risk of permanent hearing loss.

Finally, in the multivariate analysis only female sex was predictive of hearing loss. In our study, dexamethasone did not appear to decrease the risk of deafness. The role of dexamethasone in pediatric meningitis is still controversial.\textsuperscript{28,32} Some researchers found that early use of corticosteroids reduced the incidence of hearing loss in \textit{H. influenzae B} meningitis and labyrinthitis ossificans occurrence that is connected to a limit of full cochlear implant insertion and a worsening of outcomes.\textsuperscript{30,31,33} Even if literature showed a protective role of glucocorticoid treatment for hearing impairment in case of \textit{H. influenzae B} infection, our study did not show any statistically significant differences (\textsuperscript{\textendash}Table 6).\textsuperscript{34} As well as reported in previous studies, the clinical outcome was not influenced by the prescribed therapy.\textsuperscript{35} A potential limit of our study is the poor patients’ adherence to follow-up evaluation.

\begin{table}[h]
\centering
\caption{Patients’ characteristics (etiology)}
\begin{tabular}{|l|c|}
\hline
Condition & \( n (%) \) \\
\hline
Corynebacterium striatum & 1 (0.2) \\
Coxsackievirus & 2 (0.4) \\
Escherichia coli & 7 (1.6) \\
Epstein–Barr virus & 2 (0.5) \\
Enterovirus & 29 (6.8) \\
Streptococcus agalactiae & 33 (7.8) \\
Haemophilus influenzae type B & 14 (3.3) \\
HHV-6 & 6 (1.4) \\
Herpes simplex virus & 8 (1.9) \\
Klebsiella pneumoniae & 4 (0.9) \\
Listeria monocytogenes & 1 (0.2) \\
Mycobacterium tuberculosis & 23 (5.4) \\
Neisseria meningitidis & 70 (16.5) \\
Parvovirus & 1 (0.2) \\
Streptococcus pneumoniae & 60 (14.1) \\
Staphylococcus aureus & 2 (0.4) \\
Varicella zoster virus & 2 (0.5) \\
N/A & 157 (36.9) \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Comparison between patients with or without hearing loss}
\begin{tabular}{|l|c|c|c|}
\hline
 & Hearing loss & No hearing loss & \( p \)-Value \\
\hline
Total population—no\textsuperscript{a} & 48 & 338 & – \\
Median age (range)—years & 1.7 (0.01–15.53) & 1.87 (0.01–17.44) & 0.901 \\
Female to male ratio & 1:2.9 & 1:1.5 & 0.057 \\
Hospitalization—mean (SD) & 26.37 (14.0) & 24.90 (28.3) & 0.012 \\
\hline
Symptoms at onset—no (\%) & & & \\
Fever & 42 (91.3) & 322 (84.7) & 0.246 \\
Lethargy & 15 (32.6) & 71 (18.7) & 0.027 \\
Neck stiffness & 11 (23.9) & 78 (20.5) & 0.599 \\
Vomiting & 11 (23.4) & 115 (34.0) & 0.179 \\
Headache & 8 (17.0) & 66 (19.5) & 0.69 \\
Seizure & 5 (10.9) & 53 (15.9) & 0.561 \\
Anorexia & 2 (4.3) & 35 (10.4) & 0.185 \\
\hline
Blood cell count & & & \\
Hemoglobin—mean (SD) & 11.0 (1.86) & 11.8 (2.04) & 0.051 \\
Platelet count—mean (SD) & 280337 (167675) & 350714 (188821) & 0.745 \\
White blood cells—mean (SD) & 19523 (40282) & 14738 (17053) & 0.152 \\
C-reactive protein (mg/dL)—mean (SD) & 17.77 (12.4) & 11.76 (18.4) & 0.001 \\
Erythrocyte sedimentation rate (mm/h)—mean (SD) & 106.3 (33.8) & 70.5 (43.6) & 0.004 \\
\hline
Lumbar puncture & & & \\
Cerebral spinal fluid white blood cells—mean (SD) & 2846 (5518) & 1830.3 (4373) & 1.001 \\
Cerebral spinal fluid glucose—mean (SD) & 26.18 (19.9) & 39.3 (28.3) & 0.004 \\
Cerebral spinal fluid protein—mean (SD) & 181.5 (150.1) & 180.12 (279.4) & 0.109 \\
\hline
Complications & & & \\
Neurological sequelae—no (\%) & 12 (28.5) & 61 (20.6) & 0.241 \\
Visual sequelae—no (\%) & 4 (8.9) & 22 (6.9) & 0.543\textsuperscript{b} \\
Deaths—no (\%) & 1 (2.1) & 4 (1.2) & 0.477\textsuperscript{b} \\
Corticosteroid administration & 24 (77.4) & 86 (71.6) & 0.521 \\
\hline
\end{tabular}
\end{table}

Abbreviations: HHV-6, human herpesvirus 6; N/A, not available.

In conclusion, the identification of risk factors for audiological impairment, such as female sex, \textit{S. pneumoniae} etiology, lethargy onset, higher values of inflammatory indexes, and lower CSF...
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Table 4 Comparison between patients with or without hearing loss (etiology)

| Staphylococcus aureus—no (%) | Hearing loss | No hearing loss | p-Value |
|-----------------------------|-------------|----------------|---------|
| Enterovirus                 | 1 (2.1)     | 23 (6.8)       | 0.454   |
| Haemophilus influenzae type B | 2 (4.3)     | 11 (3.4)       | 0.993   |
| HHV-6                       | 1 (2.1)     | 5 (1.5)        | 0.973   |
| Neisseria meningitidis      | 13 (27.7)   | 56 (16.5)      | 0.048   |
| Streptococcus pneumoniae    | 19 (40.4)   | 37 (10.9)      | <0.001  |
| Mycobacterium tuberculosis  | 1 (2.1)     | 19 (5.6)       | <0.001  |
| N/A                         | 10 (21.2)   | 140 (41.4)     |         |

Abbreviations: HHV-6, human herpesvirus 6; N/A, not available.
Note: Percentages were calculated accounting for missing data when needed.

Table 5 Corticosteroid therapy and hearing loss in bacterial meningitis

| Staphylococcus pneumoniae—no (%) | Hearing loss | No hearing loss | p-Value |
|----------------------------------|-------------|----------------|---------|
| CT                               | 12 (19)     | 6 (9)          | 0.144   |
| NT                               | 2 (3)       | 4 (5)          |         |
| NA                               | 6 (9)       | 43 (61)        |         |
| Neisseria meningitidis—no (%)    | 7 (10)      | 0 (0)          | 0.231   |
| CT                               | 4 (5)       | 9 (12)         |         |
| NT                               | 43 (61)     | 7 (10)         |         |
| HA                               | 1 (2.1)     | 1 (7)          |         |
| CT                               | 8 (57)      | 2 (14)         | 0.621   |
| NT                               | 1 (7)       | 2 (14)         |         |

Abbreviations: CT, corticosteroid therapy; NT, no corticosteroids.

Consent to Participate
At hospital admission, parents signed an authorization to get their children underwent exams related to the diagnostic and therapeutic program.

Authors’ Contributions
E.B. planned the study, G.S. and C.M. collected the data, P.M. and A.S. performed audiological investigations, M.R. performed statistical analysis, M.S. revised the literature, and A.V. supervised the research. All authors read and approved the manuscript.

Funding
None.

Conflict of Interest
None declared.

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