Early Prediction of Postmeningitic Hearing Loss in Children Using Magnetic Resonance Imaging

Jonathan C. Kopelovich, MD; John A. Germiller, MD, PhD; Adrienne M. Laury, MD; Samir S. Shah, MD, MSCE; Avrum N. Pollock, MD, FRCPC

Objective: To determine whether early gadolinium-enhanced magnetic resonance imaging (GdMRI) can reliably detect meningitic labyrinthitis and thereby predict which children are at high risk for hearing loss. Permanent sensorineural hearing loss (SNHL) remains a common sequela of bacterial meningitis, and early diagnosis of the associated suppurative labyrinthitis can be difficult, especially in critically ill, sedated patients and young children.

Design: Retrospective cohort study.

Setting: Tertiary pediatric hospital.

Participants: Twenty-three survivors of bacterial meningitis (median age, 15 months [range, 3 months–14 years]) who had undergone brain GdMRI during the acute disease and had subsequent ear-specific audiometric data.

Main Outcome Measure: Blinded to disease and outcome, a neuroradiologist rated the relative enhancement of each cochlea on T1-weighted images using a 4-point scale. Scores were then correlated with the degree of hearing loss on subsequent testing.

Results: Sensorineural hearing loss occurred in 15 of 46 ears (8 of 23 patients). Enhancement on GdMRI was detected in 13 of the 15 ears that later developed SNHL but was absent in all 31 unaffected ears. Thus, GdMRI was 87% sensitive and 100% specific for predicting which ears would develop permanent SNHL. In the subgroup with pneumococcal meningitis (n=15), GdMRI was 100% sensitive and 100% specific. Labyrinthine enhancement was detectable as early as 1 day after diagnosis.

Conclusion: Gadolinium-enhanced MRI detected meningitic labyrinthitis at early stages and accurately predicted which patients would later develop hearing loss.


SENSORINEURAL HEARING LOSS (SNHL) is one of the most frequent and devastating sequelae of bacterial meningitis. Between 7% and 35% of survivors are afflicted and can experience significant linguistic and educational delays.1-4 Inner ear injury occurs via supplicative labyrinthitis, a consequence of either direct or hematogenous spread of infection.5 Labyrinthine ossification, occurring in up to one-third of affected ears,6 can considerably complicate cochlear implantation in survivors.7 Acute symptoms of supplicative labyrinthitis, including abrupt, severe hearing loss, roaring tinnitus, and vertigo, may be difficult to detect early in the disease course, particularly in critically ill patients and in pre-lingual or cognitively impaired children, who cannot verbalize such symptoms. This can delay diagnosis of this complication until well after irreversible cochlear damage has occurred.

Earlier detection of meningitic labyrinthitis during a patient’s hospitalization would have multiple benefits for management and rehabilitation. First, it would facilitate earlier audiological consultation. This would help identify patients most in need of further audiologic testing, provide additional time for families to accept the diagnosis and the importance of follow-up, and facilitate early intervention with amplification (hearing aids). The latter has been shown to have important benefits for subsequent speech development, especially in children younger than 2 years.8,9 Second, it would facilitate early referral to otolaryngology for cochlear implantation, a procedure that may need to be performed urgently, before the onset of cochlear ossification. Finally, if very early detection of labyrinthitis were possible, i.e., within the first 2 days of illness, it might even influence immediate management decisions, in particular, whether to use corticosteroids. Corticosteroids may mitigate...
hearing loss, if administered very early in the disease,\textsuperscript{10} and may reduce the severity of labyrinthine ossification.\textsuperscript{11} Nevertheless, their use remains controversial because a survival benefit has not been demonstrated in children.\textsuperscript{12}

Gadolinium-enhanced magnetic resonance imaging (GdMRI) has the ability to detect the inflammation associated with acute labyrinthitis, though prior studies included only small numbers of adults.\textsuperscript{13,14} To our knowledge, its role in children has not been explored. Our hypothesis is that early GdMRI will detect labyrinthitis, and thus accurately predict which patients will subsequently develop permanent hearing loss. To test this hypothesis, we retrospectively reviewed survivors of bacterial meningitis, who had undergone brain GdMRI for reasons unrelated to hearing loss. We postulated that if the subgroup of children who developed hearing loss, in hindsight, showed enhancement in their inner ear, this would support our hypothesis that GdMRI may be useful in the future for identifying children most at risk for this complication.

**METHODS**

**STUDY DESIGN AND SETTING**

This retrospective cohort study was performed at the Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, an urban, tertiary care children's hospital. The Committees for the Protection of Human Subjects at our institution approved this study with a waiver of informed consent.

**PARTICIPANTS**

Children aged 3 months to 18 years with bacterial meningitis were eligible if they met all of the following criteria: (1) admission between January 1, 2000, and December 31, 2004; (2) performance of GdMRI imaging during the index hospital admission; and (3) availability of ear-specific audiometric data since the time of diagnosis. Patients with pre-existing SNHL and risk factors for SNHL (eg, exposure to ototoxic chemotherapeutic agents, temporal bone fractures, or extreme prematurity and/or severe neonatal illness) were excluded.

**STUDY DEFINITIONS**

Bacterial meningitis was diagnosed if 1 or more of the following criteria were met: (1) growth of a bacterial pathogen from cerebrospinal fluid (CSF); or (2) CSF pleocytosis (>7 white blood cells/µL) combined either with a positive blood culture or with CSF latex agglutination test result positive for *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, or *Streptococcus agalactiae*. Patients whose CSF culture only revealed skin commensals (eg, *Staphylococcus epidermidis* or *Propionibacterium acnes* in previously healthy patients) were excluded.\textsuperscript{13,16}

**DATA COLLECTION AND STUDY PROTOCOL**

**Data Collection**

Basic data collected from hospital records included details of medical history, symptoms and their onset, admission and discharge diagnoses, intensive care unit (ICU) records, radiology reports, inpatient audiologic test results, CSF and blood culture results, and medication lists. Follow-up data were collected from postdischarge outpatient otolaryngology and audiology records.

**Audiometric Data**

Audiological data included auditory brainstem responses (ABRs), otoacoustic emissions (OAEs), and audiograms. Patients were included only if one of the following ear-specific assessments of hearing status could be made: ear-specific audiogram, ear-specific ABR, or soundfield audiogram coupled with ear-specific OAE measurement. Data were not used if obtained in the presence of flat tympanograms. All patients underwent initial testing during the acute episode, at a mean 8.5 days after diagnosis (range, 1-14 days). Follow-up data were available after discharge in 10 patients, including all 8 with hearing loss. Median follow-up in these 10 patients was 2.6 months (range, 4 days to 1.2 years).

Each ear was divided into 1 of 3 hearing outcome categories, based on its most recent ear-specific data. The latter consisted of ear-specific audiogram in 10 patients (2 of whom had additional ABR testing); ear-specific screening ABR alone in 6 patients (all normal); ear-specific diagnostic ABR in 4 patients, and soundfield audiometry coupled with ear-specific OAE measurement in 3 patients. Normal hearing was defined as a pure tone average or speech threshold of 20 dB or below on audiograms. For purposes of this study, the normal hearing designation was also given to both ears in the following circumstances: (1) patients who had normal soundfield audiograms and either had normal ear-specific OAEs or passed ear-specific ABR screening as inpatients and (2) patients who passed ear-specific ABR screening as inpatients but failed to return for follow-up testing. Mild or moderate hearing loss was defined as pure tone average or speech threshold of 21 to 60 dB and as severe or profound if 61 dB or higher. All analysis of hearing outcome was done blind to radiologic findings.

**Radiological Review**

All patients underwent at least 1 GdMRI of the brain during their initial hospitalization. Notably, MRI was not used at the time to detect labyrinthitis but rather for other indications, for example, to define extent of intracranial infection, presence of abscess, and vascular compromise. For this study, MRIs were included only if both cochleas could be visualized. This criterion resulted in exclusion of only 1 patient, a 15-month-old child with severe brain atrophy due to a congenital demyelinating syndrome, in whom neither cochlea could be seen on brain MRI. This patient had pneumococcal meningitis that did not result in hearing loss. If multiple MRIs were performed, the earliest MRI allowing visualization of both cochleas was selected. Studies were performed at a median 3 days after diagnosis (range, 0-15 days; interquartile range, 1-5 days). In all cases, GdMRI and initial hearing evaluation occurred within the same 14-day period (median interval, 5 days).

All MRI studies during this period were performed on a 1.5 Tesla system (Siemens, Erlangen, Germany). All sequences included multiplanar T1-weighted images, T2-weighted images, and postgadolinium T1 images. All had at least 2 planes with each sequence. Section thickness ranged from 3 to 7 mm, with an intersection gap ranging from 0 to 2.5 mm. In 100 of the 253 sequences, a magnetization transfer pulse was applied after administration of contrast, and 37 had fat saturation.

Blinded to all patient and audiologic data and outcome, a board-certified pediatric neuroradiologist (A.N.P.) reviewed all images and classified each ear according to degree of contrast enhancement. Signal intensity in the membranous labyrinth on
postgadolinium axial T1-weighted images was directly compared with that seen on equivalent anatomic regions on pre gadolinium images. Degree of enhancement was scored on a semi-quantitative, 4-point scale as follows: 0, no enhancement, ie, no difference in signal intensity between precontrast and post contrast images; 1, mild enhancement; 2, moderate enhancement; and 3, marked enhancement (Figure).

Statistical Analysis

All analyses were performed using Stata 10 software (Stata Corp, College Station, Texas). Continuous variables were summarized using mean, median, range, and interquartile range values. Categorical variables were summarized using frequencies and percentages and compared using the Fisher exact test. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of enhancement of the membranous labyrinth on GdMRI were calculated using the results of audiometric testing as previously described as the reference standard. Binomial exact 95% confidence intervals were calculated to provide an estimate of precision.

RESULTS

Twenty-three children met our study criteria; 12 (52%) were male. The median age at diagnosis was 15 months (range, 3 months –14 years). The median interval between symptom onset and diagnosis was 2 days (range, 0-22 days; interquartile range, 1-4 days). The median length of stay was 11 days (range, 6-34 days; interquartile range, 8-16 days). Causative pathogens, identified in 21 of 23 patients, included *S pneumoniae* (n=15), *N meningitidis* (n=2), and group B Streptococcus (n=2). There were no instances of *H influenzae* type b (Table 1).

Most patients (91%) spent a portion of their admission in the ICU, with median ICU stay of 5 days (range, 1-17 days) (Table 1). Eight patients (35%) required mechanical ventilation for a median 3.5 days (range, 1-9 days). Eleven patients had seizures and required prophylaxis with anticonvulsants. Two patients required ventriculostomy and intensive management of elevated intracranial pressure. Only 2 required vasopressor support (dopamine). Corticosteroids were given in only 3 cases (patients 2, 21, and 23; Table 1); however, only 1 patient (patient 23) received therapy at the outset of disease. The other 2 patients only had short courses for periextubation airway management (patient 2) or a single dose for stroke (patient 21). Twenty-two patients (96%) received vancomycin, but aminoglycoside antibiotics were administered in only 4 cases. Loop diuretics were not used in any patient. No patient had renal insufficiency (highest serum creatinine level was 0.6 mg/dL [1 to convert to micromoles per liter, multiply by 88.4]).

All patients had ear-specific audiometric data available. Eight of the 23 patients (35%) and 15 of the 46 ears (33%) ultimately developed SNHL (Table 1). Four ears were classified as mild or moderate SNHL, and the other 11 as severe or profound SNHL. Four patients developed bilateral profound hearing loss, and 2 of them ultimately received cochlear implants. In both, cochlear ossification was noted at surgery. Most (7 of 8) patients who developed hearing loss had pneumococcal meningitis; the other had *N meningitidis*. Almost half of the survivors of pneumococcal meningitis (7 of 15) developed hearing loss, and all were severe to profound in at least 1 ear.

As a group, patients who developed hearing loss had similar hospital course as patients who did not (Table 1). Admission to ICU occurred in most in both groups. Mechanical ventilation was somewhat more common in the SNHL group (4 of 8, compared with 4 of 15 in the normal hearing group). However, seizures occurred less often (3 of 8 in the SNHL group compared with 8 of 15 in the normal hearing group). One patient in each group required ventriculostomy with intensive intracranial pressure management. Stroke occurred in 2 patients in the SNHL group and 1 in the normal hearing group. Aminoglycoside use was uncommon overall (2 patients per group) (Table 1).

Gadolinium-enhanced brain MRIs, obtained during the meningitis episode were evaluated by the senior author (A.N.P.), a neuroradiologist, blinded to all clinical information including hearing outcome. The degree of enhancement of each cochlea was rated on our 4-point semi-quantitative scale (Figure). Imaging occurred between 0 and 15 days after diagnosis (median, 3 days). Most ears (n=33) did not enhance (score “0”). Four were scored as mild (“1”), and 6 each were scored as moderate (“2”) or marked (“3”) enhancement. Notably, this enhancement was seen as early as 1 day after diagnosis (Table 1). Every patient with enhancement had pneumococcal men-
ingitis. Three patients received a second MRI during the same admission. In all 3, enhancement score in each ear on subsequent MRI was identical to the first. In 2 of these patients (3 ears), enhancement was evident on both scans, and its relative intensity remained unchanged at 12 and 19 days after initial diagnosis.

Correlation of hearing outcome with MRI findings is given in Table 2 and Table 3. A strong association was found between MRI enhancement and degree of hearing loss. Hearing loss developed in only 2 of 33 ears (6%) without enhancement, but developed in all 13 ears that had any degree of enhancement on MRI (P < .001, Fisher exact test). The calculated sensitivity of GdMRI in predicting hearing outcome in our cohort was thus 87%, with a specificity of 100% (Table 4). The PPV was 100% and the NPV, 94%. Both ears that were falsely negative for
enhancement were from the same patient, who had meningococcal meningitis. Finally, if analysis is limited to only those 15 subjects with pneumococcal disease, the sensitivity, specificity, PPV, and NPV of GdMRI in predicting hearing outcome were all 100%.

Sensorineural hearing loss is a common sequela of bacterial meningitis. It results from suppurative labyrinthitis, a direct bacterial invasion of the inner ear’s membranous labyrinth. Bacteria may enter the inner ear through direct extension from the meninges or via hematogenous spread. Permanent destruction of the inner ear’s delicate sensory apparatus occurs due to the intense inflammatory reaction.

There are currently no reliable criteria to predict which patients will sustain postmeningitic hearing loss. Known risk factors include pneumococcal disease, decreased CSF glucose levels, length of hospitalization, development of seizures, and elevated CSF protein levels. Though helpful, these features lack specificity. For example, CSF glucose was only predictive in the presence of 4 other criteria (symptom duration over 2 days, absence of petechiae, Streptococcus pneumoniae, and ataxia). Applying such criteria would place 62% of all meningitis children in the “at risk” group for hearing loss.

Detecting the onset of suppurative labyrinthitis itself can also be difficult, particularly in critically ill and very young children, who would not be able to report the auditory or vestibular symptoms of this complication. At present, the labyrinthitis is only inferred from its consequences (ie, permanent hearing loss), and then only after cochlear damage has occurred. At our institution and many others, routine audiological consultation is made during the latter part of the hospital stay to detect hearing loss prior to discharge. Unfortunately, this may not be the case at all centers. Riordan et al found that only 78% of children were referred for audiological evaluation following meningitis. Even with universal referral, 25% of patients failed to follow-up, and evaluations were delayed over 6 weeks in another 14%. Improved rates of follow-up and earlier rehabilitation of hearing loss might be expected if an additional technique were available to accurately identify children at highest risk, especially if this were possible earlier in the disease. The goal of this study was to determine if GdMRI might serve this role.

Gadolinium-enhanced MRI proved remarkably effective at predicting later onset of SNHL. It predicted hearing outcome with 87% sensitivity and 100% specificity in our cohort of 46 ears and did so despite important technical limitations (ie, all were brain protocols not designed to finely resolve the inner ear). It appeared even more effective in the large subgroup with pneumococcal meningitis, where it was 100% sensitive and specific. Importantly, enhancement was detectable as early as 1 day after diagnosis and appeared to persist, unchanged, for as long as 19 days. The long persistence of enhancement on follow-up MRIs suggests ongoing cochlear inflammation, which may underlie the process of labyrinthine ossification. This suggests GdMRI may also have utility in monitoring disease course and identifying patients who require expedient cochlear implantation. Finally, we found that few children need to receive MRI to identify meaningful abnormalities. The number needed to diagnose, calculated as 1/(sensitivity – (1 – specificity)), was 1.15, which means that fewer than 2 MRIs are needed to diagnose 1 case of labyrinthitis. Together, these data strongly support further exploration of GdMRI as a technique for early detection of meningitic labyrinthitis.

An important, unresolved question is whether MRI can detect labyrinthitis early enough to affect immediate management, particularly the decision to use corticoste-
In our series, MRI diagnosis was possible as early as 1 day after admission, but we emphasize that such early data were available in only 1 patient. However, the only falsely negative MRI in our series was performed 3 days after diagnosis in a patient (patient 16) who had hearing loss due to meningococcal meningitis. No enhancement was seen in her inner ears, suggesting either that her MRI lacked sensitivity for labyrinthitis early in the disease course or simply that her labyrinthitis was delayed in its onset. Future studies will be needed to better define the sensitivity of MRI very early in the disease course and in the setting of different pathogens.

The role of dexamethasone in pediatric meningitis remains controversial, though it is generally accepted that if it is to be used, it must be given very early. Early initiation of corticosteroids reduces incidence of hearing loss in childhood meningitis caused by *H influenzae* type b, and in animal models, dexamethasone reduced hearing loss in meningitis caused by *S pneumoniae*.10,23 Dexamethasone also reduces occurrence of labyrinthitis ossificans, a progressive ossification of the lumen of the cochlea that can begin as early as 3 days after meningococcal infection.13,23 Such ossification can severely hinder treatment options because it may limit the full insertion and optimal performance of a cochlear implant.7 Nevertheless, the use of corticosteroids in children remains controversial because a clear survival benefit has not been demonstrated in this age group.12 At this time, the decision remains individualized, after weighing potential benefits and risks for each child.24,25 Toward that end, any technique that can predict, early enough, which children will have hearing loss deserves further study, since it has the potential to have a significant impact on patient care.

This study had several limitations. First, there is spectrum bias because brain MRI is more likely to be performed in severe cases than mild ones. However, though such a bias would lead to a higher prevalence of hearing loss in this study, it should not affect the interpretation of the data, since the correlation between cochlear enhancement and hearing status should remain independent of meningitis severity (i.e., the test characteristics of sensitivity and specificity are independent of disease prevalence, in this case, hearing loss), and in fact all levels of hearing outcome were well represented. Second, our study may have overlooked a few cases of mild hearing loss, since it included 6 patients who underwent only ear-specific screening ABR but no further testing. Because such screens are conducted at 30 to 35 dB, it is conceivable that 1 or more of them had undetected mild hearing loss in the 20- to 30-dB range. If so, this would have caused a slight upward bias of the apparent sensitivity of GdMRI but would not have affected its specificity. Finally, the images were brain MRIs with relatively large slice thicknesses. While this did not allow resolution of fine inner ear detail, an assessment of its MRI enhancement was in fact possible in nearly all ears. Only 1 patient was excluded owing to inadequate visualization of both inner ears. This did not bias our results, since even in the worst case of a false-positive MRI result (the patient had normal hearing), specificity would only drop to 97% and PPV to 93%.

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Correspondence: John A. Germiller, MD, PhD, Division of Pediatric Otolaryngology, The Children’s Hospital of Philadelphia, Wood Center, First Floor, 34th Street and Civic Center Boulevard, Philadelphia, PA 19104 (germiller@email.chop.edu).

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