The Journal of International Advanced Otology

J Int Adv Otol 2024; 20(2): 135–141 • DOI: 10.5152/iao.2024.231373

Original Article

Magnetic Resonance Imaging in Prediction of Sensorineural Hearing Loss in Patients with Neuroinfections

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Cite this article as: Vilhelmsen FJ, Skovgaard Jensen E, Damgaard B, Cayé-Thomasen P, Brandt CT, Kirchmann M. Magnetic resonance imaging in prediction of sensorineural hearing loss in patients with neuroinfections. *J Int Adv Otol.* 2024;20(2):135-141.

BACKGROUND: Magnetic resonance imaging (MRI) may be useful in detecting labyrinthitis and thereby predicting the development of sensorineural hearing loss (SNHL) in adults with central nervous system (CNS) infections. We therefore investigated the coherence between brain MRI and SNHL among adults with CNS infections.

METHODS: Twenty-eight patients with bacterial or viral meningitis, viral encephalitis, or Lyme neuroborreliosis, who had a brain MRI during the acute disease and pure-tone audiometry at follow-up, were included. Neuroradiologists were blinded to the audiometric outcome when rating each inner ear for MRI cochlear gadolinium enhancement using a postcontrast T1-weighted (T1W) sequence and signal intensity using a fluid-attenuated inversion recovery (FLAIR) sequence. Scores were compared to the degree of SNHL.

RESULTS: Sensorineural hearing loss was observed in all types of infection, affecting 14 patients (26 of 56 ears). Enhancement on T1W was detected in 1 ear with normal hearing. Fluid-attenuated inversion recovery signal intensity was detected in 26 of 50 ears, of which 12 developed SNHL. The sensitivity of T1W could not be calculated. Fluid-attenuated inversion recovery had a sensitivity of 50% and specificity of 46%.

CONCLUSION: Standard brain MRI protocols are not sufficient for the detection of labyrinthitis leading to SNHL following infection of the CNS.

KEYWORDS: Magnetic resonance imaging, hearing loss, sensorineural hearing loss, meningitis, lyme neuroborreliosis

INTRODUCTION

Bacterial meningitis and viral encephalitis remain devastating diseases despite advances in diagnosis, therapy, and supportive care. Other neuroinfections such as viral meningitis and Lyme neuroborreliosis (LNB) are rarely fatal but may cause sequelae. A frequent and severe sequela of bacterial meningitis is permanent or reversible sensorineural hearing loss (SNHL) occurring in up to 69% of surviving adults.[1] Sensorineural hearing loss is presumably caused by injury to the inner ear due to suppurative labyrinthitis, caused by direct spread of infection through the cochlear aqueduct, or by hematogenous spread, and poses a notable risk of inflammation progressing to fibrosis and ultimately ossification of cochlea.[2,3] Ossification may complicate cochlear implantation, the treatment for profound SNHL, considerably if not exclude the procedure entirely. Therefore, early detection of SNHL in the setting of neuroinfection is of utmost importance.

In studies of bacterial meningitis, magnetic resonance imaging (MRI) has been suggested to improve the detection of labyrinthitis in early stages before the onset of cochlear fibrosis and ossification. Studies investigating cochlear enhancement on brain MRI in patients with bacterial meningitis found that radiologists were able to predict SNHL with a sensitivity of 58%-87% and a

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Received: December 3, 2023 • **Revision requested:** January 9, 2024 • **Last revision received:** January 29, 2024 • **Accepted:** February 7, 2024 • **Publication Date:** March 27, 2024
Available online at www.advancedotology.org

specificity of 84%-100% using postcontrast T1-weighted (T1W) and T2-weighted sequences.[2-6] One study also evaluated hyperintensity on the T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence, hypothesizing a hyperintense signal reflecting the accumulation of fluid in the inner ear. Using this sequence, the authors found a sensitivity of 50% and specificity of 94%.[5] Still, these studies have focused on infants and children with bacterial meningitis, whereas studies on adult populations and other neuroinfections such as viral meningitis and LNB are sparse.

In viral meningitis, SNHL appears to be a rare sequela in infants and children, and the use of MRI in detecting labyrinthitis has only been reported casuistically.[7,8]

In LNB, the incidence of SNHL is unclear. In one study, 1.5% of patients with Lyme disease reported hearing loss, while it has been described in 15%-44% of patients with chronic manifestation of Lyme disease.[9-11] Only a case report documented cochlear enhancement on MRI, suggestive of labyrinthitis.[12]

The aim of this study was to determine the use of routine brain MRI in detecting labyrinthitis in an adult population with neuroinflammation due to bacterial meningitis, viral meningitis, viral encephalitis or LNB. Cochlear enhancement (T1W sequences) and hyperintensity (FLAIR) were analyzed and correlated to the level of SNHL at follow-up.

MATERIALS AND METHODS

Study Design and Setting

Patients with a documented CNS infection were recruited retrospectively from 3 university hospitals between 2017 and 2019: North Zealand University Hospital, Aalborg University Hospital, and Hvidovre University Hospital.

Participants and Inclusion Criteria

Patients aged 18 years and older who suffered from either bacterial meningitis, viral meningitis, viral encephalitis, or LNB were included if the following criteria were met:

1. Brain MRI in the acute phase of infection.
2. Pure-tone audiometry, either before discharge or at follow-up.

MAIN POINTS

- Sensorineural hearing loss (SNHL) is a frequent sequela of bacterial meningitis, but also follows viral meningitis, viral encephalitis, and Lyme neuroborreliosis infections.
- Early identification of patients at risk of developing SNHL following labyrinthitis due to CNS infections is of utmost importance. We found low sensitivity and specificity for both T1W enhancement and Fluid-attenuated inversion recovery (FLAIR) signal hyperintensity in the cochlea with a standard MRI protocol for the prediction of SNHL in patients with a CNS infection.
- Identification of cochlear enhancement on MRI probably requires T1W sequences less sensitive to susceptibility and fat saturation, and FLAIR, axial sequences with fat saturation and a slice thickness of less than 5 mm.

Patients were excluded based on the following criteria: Nosocomial meningitis, concurrent endocarditis, primary brain abscess, history of hearing impairment, history of psychiatric or neurological disease, recent head trauma, recent ear surgery, previous administration of ototoxic medications, prior CNS pathology, current acute otitis media, or severe cognitive impairment.

Diagnostic Criteria

Diagnosis of bacterial meningitis was determined by clinical presentation and symptoms suggesting bacterial meningitis (confusion, fever, headache, impaired level of consciousness, neck stiffness, or petechiae) and one or more of the following:

1. A positive cerebrospinal fluid (CSF) culture
2. Positive blood culture combined with at least one of the following:
   a. Elevated CSF white blood cell (WBC) count ($> 10 \times 10^6$ WBC/L)
   b. Cerebrospinal fluid/serum glucose ratio <0.3
   c. Cerebrospinal fluid glucose <1.9 mmol/L
   d. Cerebrospinal fluid protein >2.2 g/L
3. Presence of bacteria in Gram stain of CSF
4. Identification of bacteria in CSF by either gene amplification or antigen test.
5. Concentration $>100 \times 10^6$ WBC/L with predominance of polymorphonuclear cells in CSF[13]

Diagnosis of viral meningitis was determined by clinical presentation and symptoms suggesting viral meningitis (fever, headache, photo- or phonophobia, or neck stiffness) and one or more of the following: 1) microbiologically verified viral meningitis in CSF. 2) Elevated CSF WBC count ($>10 \times 10^6$ WBC/L) and predominance of mononuclear cells.[13]

Diagnosis of viral encephalitis was determined by clinical presentation suggesting encephalitis (altered mental status >24 hours, fever, generalized or partial seizures, or neurological deficits and a positive microbiological analysis, either PCR or intrathecal antibody ratio, excluding proven or suspected autoimmune encephalitis.[13]

Diagnosis of LNB was determined by clinical presentation and symptoms suggesting neuroborreliosis (a history of tick bite, erythema migrans, fever, headache, neck stiffness, photosensitivity) and elevated CSF WBC count ($>10 \times 10^6$ WBC/L) and one or both of the following: i) positive intrathecal *Borrelia burgdorferi* antibody production. ii) Positive blood *B. burgdorferi* antibody production.[13]

Data Collection

Data collected from electronic medical records included medical history, symptoms and their onset, CSF and blood culture results, discharge diagnosis, pure-tone audiometry results, and brain MRI.

Audiometric Data

The audiometric evaluation was performed by pure-tone audiometry including frequencies from 125 to 8000 Hz for both ears. Air conduction pure-tone average (PTA_4) was calculated based on the hearing thresholds of 500, 1000, 2000, and 4000 Hz. In the case of

conductive hearing loss, marked by an air–bone gap of at least 10 dB, the ear was excluded. Hearing was classified for each ear as follows: No hearing loss (20 dB or below); mild or moderate (M-M) hearing loss (21-55 dB); and severe or profound (S-P) hearing loss (56 dB or higher). The PTA_4 average for both ears (PTA_{avg}) for each patient was compared to age- and gender-matched normative data set provided by ISO-7029.[14]

Radiological Imaging

All patients underwent brain MRI during the acute phase of the disease. A secondary assessment was performed by a neuroradiological expert (B.D.) who was blinded to the diagnosis, the first description of the MRI, and the audiological outcome. All MRI protocols had an axial T2-weighted 5 mm slice thickness sequence with gaps of 1.0 mm, except one, where a slice thickness of 3 mm was used.

The cochlea on each side was evaluated according to the degree of contrast enhancement on T1W and signal hyperintensity on post-contrast FLAIR. The degree of abnormality was scored on a 4-point scale: 0, no enhancement/hyperintensity; 1, mild enhancement/hyp erintensity; 2, moderate enhancement/hyperintensity; and 3, marked enhancement/hyperintensity (Figures 1 and 2).

Statistical Analysis

All analyses were performed using R (R Development Core Team, Vienna, Austria) and RStudio (Posit PBC, Boston, MA, USA). Continuous variables were summarized using median, range, and interquartile range (IQR) values. The Wilcoxon rank-sum test and Fisher's exact test were used when comparing patients with and without SNHL. The Wilcoxon rank-sum test was used when comparing PTA_{avg} with normative data. Categorical variables were summarized using frequencies and percentages. Sensitivity, specificity, positive predictive value, and negative predictive value were calculated using any enhancement on T1W and hyperintensity on FLAIR, respectively, compared with the audiometric data as a reference standard.

Ethical Approval

The study was approved by the Danish Data Protection Agency (Approval No: 2012-58-0004, I-Suite 03637). The Regional Committee on Health Research Ethics has been notified, but did not require registration as the study did not interfere with the patient treatment (Ethical Committee ID: h-1-2012-086). The study follows the Declaration of Helsinki. Informed, written consent was obtained from all subjects before enrollment. The study was registered at www.ClinicalTrials.gov (Identifier: NCT03715569). The manuscript was

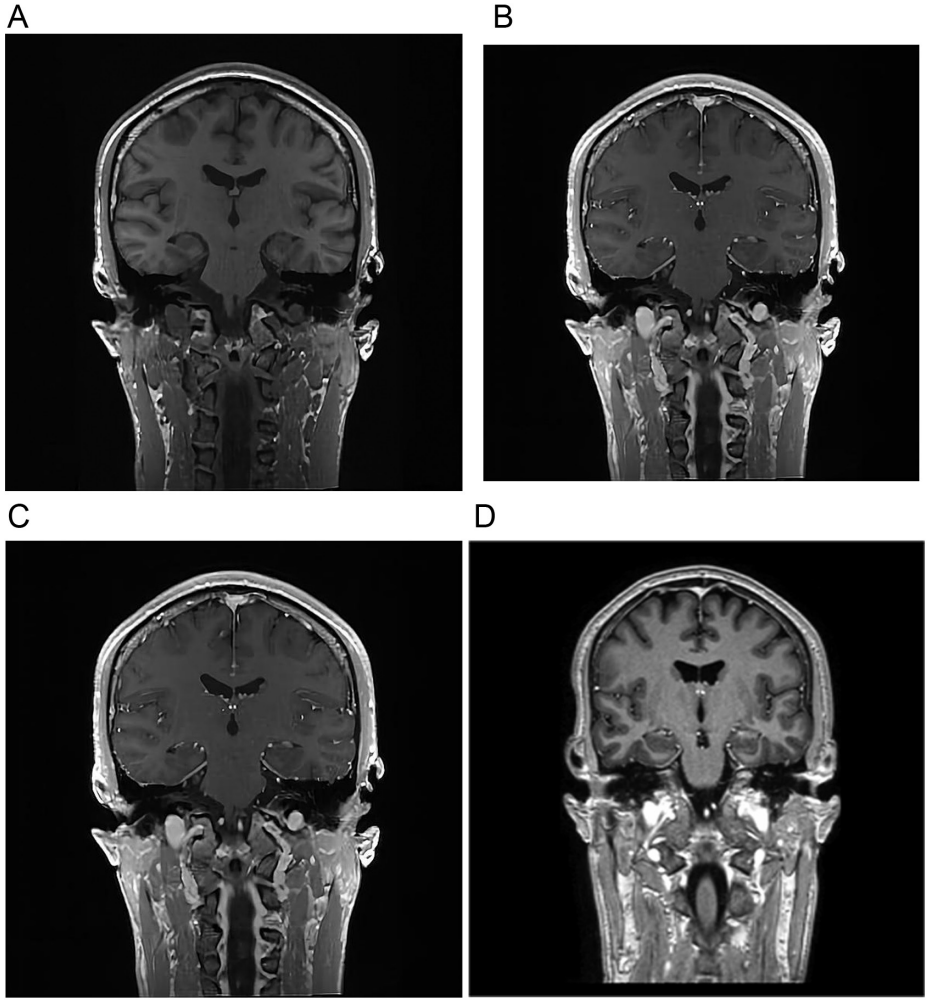

Figure 1. Coronal precontrast (A) and postcontrast (B) T1-weighted magnetic resonance (MR) images of the same patient (no. 11), rated as 0, no enhancement, bilateral. The patient did not develop hearing loss. Coronal precontrast (C) and postcontrast (D) T1-weighted MR images of the same patient (no. 15), rated as 0, no enhancement, bilateral. The patient developed left-sided mild-to-moderate hearing loss hearing loss.

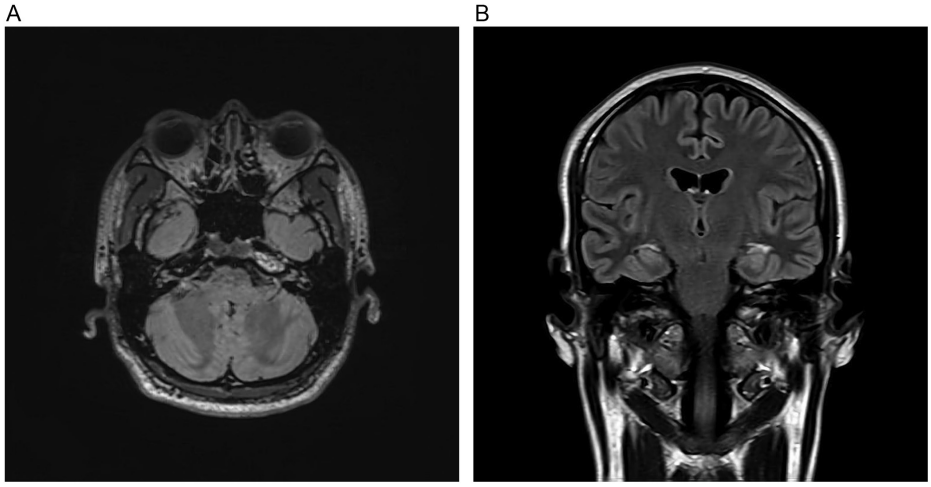

Figure 2. Axial (A) FLAIR sequence of patient no. 11. Each inner ear was rated 3, marked enhancement. The patient did not develop hearing loss. Coronal (B) FLAIR sequence of patient no. 15. The right inner ear was rated 0, no enhancement, and left inner ear was rated 1, mild enhancement. The patient developed left-sided mild-to-moderate hearing loss. FLAIR, fluid-attenuated inversion recovery.

prepared in accordance with STARD guidelines for studies on diagnostic accuracy.[15]

RESULTS

Study Population

A total of 143 consecutive patients diagnosed and treated for a CNS infection during the recruitment period. Twenty-eight patients had an MRI during admission and audiometry at discharge or first follow-up and were therefore eligible for inclusion. The study population comprised 18 males and 10 females with a median age at admission of 53 years (range 22-80 years).

Nine patients had bacterial meningitis, 7 viral meningitis, 3 viral encephalitis, and 9 LNB (Figure 3). A specific causative pathogen was identified in 23 (76,7%) patients (Table 1).

Sensorineural Hearing Loss

Fourteen patients (50%) were diagnosed with SNHL, affecting 26 ears (46%)—3 ears were diagnosed with severe to profound SNHL and 23 ears with mild-to-moderate SNHL (Table 2). Bacterial meningitis: 5 patients were diagnosed with bilateral SNHL, thus affecting 10 ears. Viral meningitis and viral encephalitis: 3 patients were diagnosed with bilateral SNHL and 1 patient with unilateral SNHL, thus affecting 7 ears. LNB: 4 patients were diagnosed with bilateral SNHL and 1 patient with unilateral SNHL, thus affecting 9 ears (Table 1).

The median age at diagnosis of patients with SNHL was 67 years (IQR 52-74 years) compared to 48 years (IQR 30-63 years) for patients without SNHL ($P = .02$). Sensorineural hearing loss was equally prevalent for both genders (5 of 10 female patients, and 9 of 18 male patients) ($P = 1.0$). The median time from admission to MRI was 7.5 days (IQR

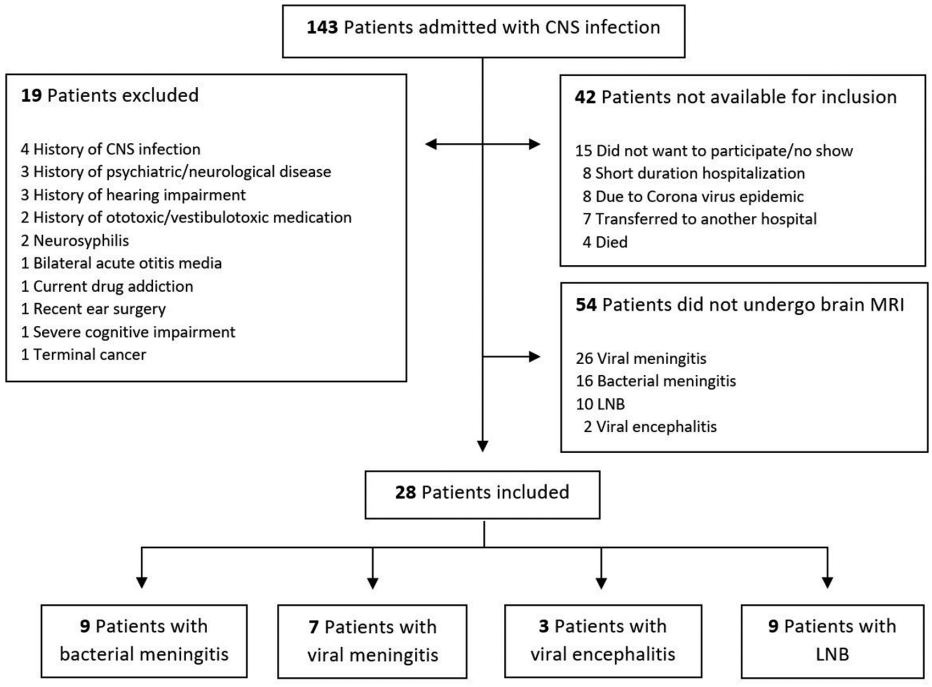

Figure 3. Study profile: screening, exclusion, and inclusion. CNS, central nervous system; LNB, Lyme neuroborreliosis; MRI, magnetic resonance imaging.

Table 1. Audiometric and Fluid-Attenuated Inversion Recovery Data

Patient No./Age at Diagnosis, Years	Organism	MRI Timing, Days After Admission	Audiometry Timing, Days After Admission	Hearing Outcome		FLAIR Score*	
				Right	Left	Right	Left
Bacterial Meningitis							
1/66	*NA*	2	10	Normal	Normal	2	2
2/69	*NA*	3	3	Normal	Normal	2	3
3/69	*NA*	9	10	Normal	Normal	NA	NA
4/76	*S. dysgalactiae*	14	37	Normal	Normal	2	1
5/67	*S. pneumoniae*	10	19	M-M	M-M	2	1
6/71	*S. aureus*	3	10	M-M	M-M	0	0
7/76	*Hib*	12	22	M-M	M-M	1	0
8/72	*S. pneumoniae*	12	14	S-P	M-M	0	1
9/53	*S. pneumoniae*	14	17	S-P	S-P	NA	NA
Viral Meningitis							
10/24	*VZV*	2	1	Normal	Normal	NA	NA
11/28	*NA*	2	35	Normal	Normal	3	3
12/34	*HSV 2*	11	40	Normal	Normal	0	0
13/35	*NA*	5	30	Normal	Normal	0	0
14/42	*HSV 2*	5	5	Normal	Normal	0	0
15/42	*VZV*	4	2	Normal	M-M	0	1
16/74	*VZV*	5	9	M-M	M-M	0	0
Viral Encephalitis							
17/53	*VZV*	3	30	Normal	Normal	1	1
18/67	*HSV 2*	2	3	M-M	M-M	1	1
19/80	*VZV*	21	170	M-M	M-M	0	0
Lyme Neuroborreliosis							
20/22	*Borrelia*	4	3	Normal	Normal	1	1
21/26	*Borrelia*	40	5	Normal	Normal	1	1
22/51	*Borrelia*	1	15	Normal	Normal	0	0
23/53	*Borrelia*	4	4	Normal	Normal	0	0
24/52	*Borrelia*	17	3	Normal	M-M	0	0
25/49	*Borrelia*	0	13	M-M	M-M	0	0
26/48	*Borrelia*	1	13	M-M	M-M	1	1
27/58	*Borrelia*	2	7	M-M	M-M	1	0
28/74	*Borrelia*	35	14	M-M	M-M	2	1

Patients are listed in order of hearing outcome stratified after central nervous system infection.
FLAIR, fluid-attenuated inversion recovery; Hib, Haemophilus influenzae type b; HSV 2, Herpes simplex virus type 2; M-M, mild-to-moderate hearing loss; MRI, magnetic resonance imaging; NA, not available; *S. aureus*, *Staphylococcus aureus*; *S. dysgalactiae*, *Streptococcus dysgalactiae*; S-P, severe-to-profound hearing loss; *S. pneumoniae*, *Streptococcus pneumoniae*; *VZV*, varicella-zoster virus.
*FLAIR hyperintensity score: 0, no hyperintensity; 1, mild hyperintensity; 2, moderate hyperintensity; and 3, marked hyperintensity.

2.3-14 days) for patients with SNHL and 4 days (IQR 2.3-8 days) for patients without SNHL ($P = .50$). The median time from admission to audiometry was 13 days (IQR 7.5-16 days) for patients with SNHL and 10 days (IQR 4.3-30 days) for patients with normal hearing ($P = .98$). The median time from MRI to audiometry was 4.5 days (IQR 1.3-9.8 days) for patients with SNHL and 4.5 days (IQR 0-25 days) for patients with normal hearing ($P = .75$) (Table 1).

The average PTA_{avg} was 22 dB in patients compared with 11 dB for age- and gender-matched controls ($P = .007$).

Cochlear Enhancement and Fluid-Attenuated Inversion Recovery Hyperintensity on Brain Magnetic Resonance Imaging

A contrast-enhanced T1W sequence was performed in 27 patients, and a FLAIR sequence in 26 patients. One imaging session could not be assessed due to motion artifacts (patient no. 9) on both post-contrast T1W and FLAIR, see Table 1. Contrast enhancement of the cochlea on T1W images was observed unilaterally in 1 (4%) of 27 patients (a patient with bacterial meningitis). Fluid-attenuated inversion recovery signal hyperintensity of the cochlea was observed in 15 (58%) of 26 patients (6 with bacterial meningitis, 2 with viral

Table 2. Hearing Outcome for 56 ears, Correlated to Central Nervous System Infection

CNS Infection	Hearing Outcome n (%)			
	Normal	Mild–Moderate SNHL	Severe–Profound SNHL	Total
Bacterial Meningitis	8 (44)	7 (39)	3 (17)	18 (100)
Viral Meningitis	11 (79)	3 (21)	0 (0)	14 (100)
Viral Encephalitis	2 (33)	4 (67)	0 (0)	6 (100)
LNB	9 (50)	9 (50)	0 (0)	18 (100)
Total	30 (54)	23 (41)	3 (5)	56 (100)

Data given as number of ears. Normal hearing (PTA4 ≤ 20 dB), mild or moderate hearing loss (PTA4 = 21-55 dB), severe or profound hearing loss (PTA4 ≥ 56 dB).
LNB, Lyme neuroborreliosis; SNHL, sensorineural hearing loss.

meningitis, 2 with viral encephalitis, and 5 with LNB). The FLAIR signal hyperintensity was bilateral in 11 patients and unilateral in 4 patients.

Correlation of hearing outcome with T1W cochlear enhancement and FLAIR labyrinthine signal hyperintensity is shown in Table 3. T1W cochlear enhancement was only seen in 1 ear with normal hearing. Fluid-attenuated inversion recovery signal hyperintensity identified patients with SNHL with a sensitivity of 50% (12/24 patients) and a specificity of 46% (12/26), the PPV was 46% (12/26), and the NPV was 50% (12/24).

DISCUSSION

In the present study, we found low sensitivity and specificity for both T1W enhancement and FLAIR signal hyperintensity in the cochlea with the standard MR brain imaging protocol to predict SNHL in patients with a CNS infection. Among patients with bacterial meningitis, irrespective of disease pathogen, SNHL was both more prevalent and more severe compared to the other etiologies included. Also, we found no differences between the patients with SNHL and the patients without SNHL regarding gender, time from admission to MRI, and time from admission to pure-tone audiometry. Patients diagnosed with SNHL were not surprisingly significantly older (median age 67 vs. 48 years). Our findings show that our standard MRI protocols for brain imaging are insufficient for the evaluation of cochlear involvement in neuroinfections, of which especially bacterial meningitis carries a high risk of SNHL. This is in contrast to previous studies where MRI sequences selected for this evaluation have been shown to diagnose the presence of neuroinflammation reliably and with high sensitivity.[16]

Table 3. Hearing Outcome for 52 ears, Correlated with the Degree of Cochlear Enhancement on T1W and Cochlear Fluid-Attenuated Inversion Recovery Signal Hyperintensity

Hearing Outcome	Degree of MRI Abnormality				
	0 (None)	1 (Mild)	2 (Moderate)	3 (Marked)	Total
	T1W Cochlear Enhancement				
Normal	29	1	0	0	30
Mild–Moderate SNHL	21	0	0	0	21
Severe–Profound SNHL	1	0	0	0	1
Total	51	1	0	0	52*
	FLAIR Cochlear Signal Hyperintensity				
Normal	12	7	4	3	26
Mild–Moderate SNHL	11	10	2	0	23
Severe–Profound SNHL	1	0	0	0	1
Total	24	17	6	3	50**

FLAIR, Fluid-attenuated inversion recovery; T1W, T1-weighted gadolinium-enhanced magnetic resonance imaging; SNHL, sensorineural hearing loss.
Data given as number of ears.
*GdMRI enhancement not available for 2 ears with mild-to-moderate SNHL and 2 ears with severe to profound SNHL.
**FLAIR signal Intensity not available for 4 ears with normal hearing and 2 ears with severe to profound SNHL.

To our knowledge, only 4 studies, comprising a total of 197 patients, predominantly children with bacterial meningitis, have evaluated the ability of MRI to predict SNHL using audiometric data as the reference standard.[3-6] These studies, performed, as ours, with 1 or 2 radiologists assessing the images in a blinded design, found a sensitivity of 50%-87% and specificity of 81%-100% in predicting SNHL. In our study, all patients underwent pure-tone audiometry, whereas patients in the previous studies were tested differently, with each study including 3-4 different audiometric tests, including pure-tone audiometry, auditory brainstem response, and otoacoustic emission. Brain imaging was performed in the acute phase but ranging from 0 to 79 days after diagnosis, which is very much delayed compared to our study.

A direct comparison between previous findings and our study should be performed with caution since we included a broad spectrum of CNS infections. Though SNHL has been reported as a sequela of viral CNS infections and LNB, the degree and the timely evolution of inflammation as well as degree of blood–labyrinth barrier permeability - the prerequisite for MRI enhancement—may differ from bacterial meningitis. Importantly, patients with bacterial meningitis are admitted within hours from the onset of symptoms, while patients with LNB are admitted weeks to months after onset of symptoms but of course still presenting with neuroinflammation. Also, the present study included adults aged 22 to 80 years, whereas previous studies, besides Van Loon et al,[3] included only infants and children. Studies focusing exclusively on 1 disease entity and doing so in a more homogeneous population with a much lower risk of having an unrecognized SNHL prior to the CNS infection would, as previous studies also show, improve sensitivity. Finally, MRI sequences vary between the present study and previous studies. Though all studies, including ours, investigated GdMRI with the T1W sequence, the specific sequences applied differ.

Our study has limitations related primarily to the retrospective nature of the study where any coherence between time of MRI and time of audiometry was incidental. Ultimately MRI should have been performed during the acute phase of admission and audiometry performed at a fixed time during follow-up. Our rather old population and the possibility of having a pre-existing hearing loss despite careful interview is present, and the SNHL found in our study may represent aggravation of a pre-existing hearing loss. Also, the uncertain bias related to patients undergoing MRI and audiometry could have suggested a population with a higher risk of MRI abnormalities and a pre-existing hearing loss.

The present study shows that not all standard MRI sequences can be used to reliably predict SNHL. Dedicated T1W sequences less sensitive to susceptibility and fat saturation seem to be required to show cochlear enhancement. Regarding FLAIR, axial sequences with fat saturation and a slice thickness of less than 5 mm seem to be required.

Since the breakdown of the blood–labyrinth barrier is involved in the pathogenesis of SNHL in bacterial meningitis, post-contrast FLAIR sequences appear to be the best MRI sequence in the early stages of the disease as investigated in our study.

In conclusion, the standard brain MRI protocols are not ideally suited for assessment of the cochlea.

Future studies should address dedicated imaging protocols of the cochlea in combination with fixed times for the evaluation of hearing.

Ethics Committee Approval: The study was approved by the Danish Data Protection Agency (Approval No: 2012-58-0004, I-Suite 03637). The Regional Committee on Health Research Ethics has been notified, but did not require registration as the study did not interfere with the patient treatment (Ethical Committee ID: h-1-2012-086) 2012 with an update in 2015). The study was registered at www.ClinicalTrials.gov (Identifier: NCT03715569). The manuscript was prepared in accordance with STARD guidelines for studies on diagnostic accuracy.

Informed Consent: Informed consent was obtained from the all participants who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – P.C-T., C.T.B., M.K.; Design – F.J.V., P.C-T., C.T.B., M.K.; Supervision – P.C-T., C.T.B., M.K.; Resources – E.S.J., C.T.B.; Materials – F.J.V., E.S.J., C.T.B.; Data Collection and/or Processing – F.J.V., E.S.J.; Analysis and/or Interpretation – F.J.V., E.S.J., B.D., C.T.B., M.K.; Literature Search – F.J.V.; Writing – F.J.V., B.D., C.T.B., M.K.; Critical Review – F.J.V., E.S.J., B.D., P.C-T., C.T.B., M.K.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study has been funded by grants from the Nordsjællands Hospital Foundation, Oticon Foundation, Jascha Foundation, Tvergaards Foundation, Helene Rudes Foundation, and Kaptain Løjtnant Harald Jensen og Hustrus Foundation.

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