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Research Article

Sensorineural Hearing Loss in Seropositive Neuromyelitis Optica Spectrum Disorder and Myelin Oligodendrocyte Glycoprotein Antibody-Associated Disorder

Soonwook Kwon,[1] **Soyoun Choi**,[2] **Yeon Hak Chung**,[3,4] **and Ju-Hong Min**[3,4,5]

[1]*Department of Neurology, Inha University Hospital, Inha University School of Medicine, Incheon, Republic of Korea*
[2]*Department of Neurology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea*
[3]*Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[4]*Neuroscience Center, Samsung Medical Center, Seoul, Republic of Korea*
[5]*Department of Health Sciences and Technology, Samsung Advanced Institute for Health Sciences & Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea*

Correspondence should be addressed to Ju-Hong Min; juhongm@skku.edu

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Background. Acute sensorineural hearing loss (SNHL) is a rare development in the central nervous system (CNS) demyelinating diseases such as aquaporin-4-IgG-positive neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD). *Methods*. We retrospectively reviewed consecutive patients with seropositive NMOSD or MOGAD in the CNS Inflammatory and Demyelinating Disease Registry at Samsung Medical Center from January 2015 to December 2020. After the medical chart review, the demographic data and the results of brain magnetic resonance imaging (MRI) and audiometry of patients with hearing loss were collected. *Results*. Five patients (NMOSD, $n = 3$; MOGAD, $n = 2$) were diagnosed with SNHL, two developed SNHL before the first core clinical symptom, and another two patients who underwent brain MRI at the timing of hearing loss showed lesions. Only three patients received high-dose steroids; however, hearing loss did not improve in any patients. *Conclusion*. SNHL was observed in a small number of patients with seropositive NMOSD and MOGAD; however, it could be underrecognized. Further large cohort prospective studies are helpful to elucidate the clinical implication of SNHL in NMOSD and MOGAD.

1. Introduction

Sudden sensorineural hearing loss (SNHL) occurs due to a variety of etiologies, identified in 7–45% of cases as infection and vascular or neoplastic trauma. More than half of patients with SNHL show idiopathic or unknown causes [1, 2]. Although autoimmune diseases account for less than 1% of SNHL causes, the prevalence of SNHL was reported as 31–75% in patients with systemic autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis [3]. Brainstem lesions such as the cochlear nucleus, superior olivary complex, lateral lemniscus, trapezoid body, inferior colliculus, and pontomedullary lesions are associated with SNHL [4]. Moreover, SNHL could result from involvement of the vestibulocochlear nerve or inner ear [5, 6].

Multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease (MOGAD) are distinct inflammatory-demyelinating diseases of the central nervous system (CNS) [7]. SNHL in MS and NMOSD has been reported, but its significance as a presenting symptom has been underestimated. SNHL was reported in 3.5–17% of MS and 1.0–2.5% of NMOSD cases [8–10] and has

occurred laterally, bilaterally, or sequentially with diverse severity ranging from mild hearing loss to deafness, although auditory manifestations in MOGAD are rarely reported [11]. However, the characteristics of hearing loss and prognosis in NMOSD and MOGAD are still unknown.

In the present study, we aimed to evaluate the prevalence and clinical characteristics including the audiometry and prognosis of hearing loss in patients with seropositive NMOSD and MOGAD. In addition, we performed a detailed literature review about the available cases of SNHL in NMOSD and MOGAD patients through March 2023 (Table 1).

2. Materials and Methods

We retrospectively reviewed consecutive patients with seropositive NMOSD or MOGAD in the CNS Inflammatory and Demyelinating Disease Registry at Samsung Medical Center from January 2015 to December 2020. NMOSD with anti-AQP4 antibody was diagnosed based on the 2015 international consensus diagnostic criteria [12]. The diagnosis of MOGAD was made by retrospectively applying the recently published proposed MOGAD diagnostic criteria with a cell-based assay for anti-MOG antibody [13]. Among the 92 patients with seropositive NMOSD and 48 patients with MOGAD, only three patients with NMOSD and two patients with MOGAD were found to have hearing loss after reviewing the medical charts. Demographic data such as age and sex and clinical features including location of onset, presence of optic neuritis or myelitis, and disease duration were collected. The characteristics of hearing loss including site and type, time from onset of hearing loss, treatments, and treatment response were also collected.

3. Results

Table 2 shows the characteristics of 5 patients with hearing loss. All patients were female, and 3 patients had optic neuritis as initial presentation, but all patients had a history of optic neuritis. Three patients with seropositive NMOSD had a history of myelitis, but 2 patients with MOGAD did not. The site of hearing loss was right in 3 patients and bilateral in 2 patients. All patients had SNHL, but two patients had concomitant conduction hearing loss (CHL). On audiometry, 3 patients showed hearing loss primarily at high frequencies, but 2 patients showed hearing loss across the entire range. Two patients had confirmed hearing loss symptoms after diagnosis, two before, and one at diagnosis. Four patients had oral or intravenous high-dose corticosteroids for the treatment of hearing, but the treatment response was poor. A brief history of each patient was described below.

3.1. Case 1. Patient with NMOSD—Bilateral Steroid Nonresponsive SNHL as the Initial Manifestation. A 49-year-old woman developed dizziness and bilateral hearing loss. Despite oral prednisolone therapy, hearing loss was not recovered. Nine months later, she presented with left-side arm and leg paresthesia and weakness with constipation. Brain magnetic resonance imaging (MRI) showed lesions in the pons, the right periependyma of the fourth ventricle, and the left lateral medulla. However, no lesions were observed in the vestibulocochlear nerve and cochlea. Spine MRI showed long extensive transverse myelitis, located centrally and extended from the medulla to the eighth level of the cervical spinal cord. AQP4-IgG was positive. Audiometry showed bilateral SNHL (Figure 1). She is currently being treated with rituximab and has an expanded disability status scale (EDSS) score of 5.5; however, her hearing difficulty has not improved.

3.2. Case 2. Patient with NMOSD—Unilateral Steroid Nonresponsive Mixed-Type HL as a Suspicious Relapse. A 70-year-old woman with seropositive NMOSD had 2 occurrences of optic neuritis and 3 occurrences of myelitis and had been treated with rituximab, followed by azathioprine. Four months after rituximab, she had newly developed vertigo, ear fullness, tinnitus, and hearing loss in the right ear. Neurological examination showed left beating spontaneous nystagmus and corrective saccade in the right direction. Audiometry showed a mixed-type hearing loss, presenting traits of both SNHL and CHL at all frequencies (Figure 2). Brain MRI revealed a nonenhancing T2 high-signal lesion in the right corpus callosum splenium, but no lesion which is related to hearing was found. After IV high-dose methylprednisolone, dizziness, nystagmus, and right tilt during walking were improved, but the hearing loss in the right ear was not improved.

3.3. Case 3. Patient with NMOSD—Steroid Nonresponsive Bilateral SNHL. A 34-year-old woman was diagnosed with NMOSD with anti-AQP4-IgG due to repeated myelitis and optic neuritis since the age of 15 years. She became bedridden and showed an EDSS score of 9.0. At the age of 26, hearing loss was detected due to decreased verbal responses. Audiometry revealed bilateral SNHL at high frequency (2000–8000 Hz), although the left side was more severe. Brain MRI was performed 2 years after the onset of hearing loss and showed no newly developed lesions compared to the previous scan performed 4 years prior. Although she had been treated with azathioprine 100 mg per day and oral prednisolone 10 mg every other day before and after SNHL, bilateral SNHL did not improve.

3.4. Case 4. Patient with MOGAD—Unilateral, Steroid Nonresponsive SNHL. A 22-year-old woman had symptoms of headache, eye pain, and blurred vision when she was 16 years old. Brain MRI showed multiple scattered T2 high-signal intensity lesions in the bilateral cerebral hemispheres, deep gray matter, and brain stem with subtle enhancement. She was treated with IV high-dose steroids but returned one month later with right-sided hearing loss with headache, eye pain, and double vision. Audiometry showed right SNHL in the high-frequency region, and a new lesion was identified in the left midbrain on brain MRI. After treatment with IV high-dose steroids, the eye pain and diplopia improved, but the hearing loss persisted. Since then, optic neuritis has recurred and was treated with interferon-beta; recently, a cell-based assay for anti-MOG antibody was

Table 1: Literature review of previous reports in NMOSD or MOGAD with hearing loss.

Authors	Age	Sex	Race	Antibody	HL before (negative) or after (positive) onset (years)	Previous neurological symptoms	Immunosuppressive treatment prior to HL	HL type	Simultaneous neurological symptoms with HL	Brain MRI at HL	Treatment	Prognosis
Jarius et al. [16]	51	M	NA	AQP4+	2	ON and LETM	MMF	Unilateral (left)	None	No lesions	Oral prednisone	Fully recovered after 4 weeks
Kremer et al. [9]	NA*	NA*	One Caucasian Two non-Caucasians	One, AQP4+ Two, AQP4-	NA	NA	NA	NA	NA	NA	NA	One, not recovered Two, completely recovered
Gratton et al. [17]	54	F	NA	AQP4+	NA	NA	NA	Bilateral, central SNHL		T2 lesions near the cochlear nuclei, more prominent on the right	IV mPD, PE	Resolved
Takanashi et al. [20]	40	F	Japanese	AQP4+	0	None		Unilateral (right) retrocochlear-type SNHL	Diplopia, upper hemianopsia, numbness in the hands and feet, and dysuria	T2 lesions in the optic chiasma, optic tract, hypothalamus, and left cerebral fornix	IV mPD	Improved
Tanaka and Tanaka [8]	26	F	Japanese	AQP4+	6	NA	NA	NA	NA	NA	NA	Improved
Jarius et al. [14]	19	M	Caucasian	MOG+	0.17	ON and myelitis[$]	NA	NA	Recurrent ON, myelitis, disorientation, headache, and fever	T2 lesions in the pons, basal ganglia, corpus callosum, periventricular, pulvinar thalami, rostral putamen, optic chiasm, optic tract, and leptomeningeal contrast enhancement	IV mPD	Fully recovered
Bonnan and Cabre [18]	53	F	Caribbean	AQP4+	0.75	ON	No	Unilateral (right) SNHL	Area postrema syndrome, tinnitus, and vertigo	Right eighth cranial nerve and the adjacent meninges are enlarged and enhanced	IV high-dose steroid, followed by mitoxantrone infusion	Highly improved

Table 1: Continued.

Authors	Age	Sex	Race	Antibody	HL before (negative) or after (positive) onset (years)	Previous neurological symptoms	Immunosuppressive treatment prior to HL	HL type	Simultaneous neurological symptoms with HL	Brain MRI at HL	Treatment	Prognosis
Shaw et al. [23]	54	F	Caucasian	AQP4+	9	NA	NA	Right-sided low-to-mid-frequency moderate SNHL and mild low-frequency left-sided SNHL with 1-year interval	Left-sided vestibular hypofunction	No lesions	High-dose oral mPD	Left SNHL normalized and right SNHL showed unchanged
Tugizova et al. [15]	54	F	Japanese-American	AQP4+	NA	Area postrema syndrome and LETM	None	Bilateral, mild to moderate SNHL at 3000-8000 Hz in the right ear and at 6000-8000 Hz in the left ear	Vertigo and tinnitus	NA	IV mPD, several months after SNHL	Fully recovered
	26	F	Caucasian	AQP4+	-1	ON	None	Unilateral (left) mild CHL at low frequency	Bilateral tinnitus	NA	Worsening after RTX	Persisted
	45	F	Hispanic	MOG+	NA	ON	RTX, IVIG, PE, MMF, AZA, and steroids	Unilateral (right) mild SNHL at 1500-6000 Hz	Tinnitus	Symmetric enhancement of the bilateral distal internal auditory canals and cochlea	Oral prednisone	Resolved

*Three patients with NMOSD had hearing loss but unknown age and sex. $The first symptoms developed within 2 weeks after vaccination for diphtheria, tetanus, pertussis, polio, and influenza. AQP4: antiaquaporin-4 antibody; AZA: azathioprine; CHL: conduction hearing loss; F: female; HL: hearing loss; IV mPD: intravenous methylprednisolone; IVIg: intravenous immunoglobulin; LETM: longitudinal extensive transverse myelitis; M: male; MMF: mycophenolate mofetil; MOG: myelin oligodendrocyte glycoprotein; NA: not available; NMOSD: neuromyelitis optica spectrum disorder; ON: optic neuritis; PE: plasma exchange; RTX: rituximab; SNHL: sensorineural hearing loss.

Table 2: Characteristics of NMOSD or MOGAD patients with SNHL.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age	49	70	34	22	57
Sex	F	F	F	F	F
Diagnosis	NMOSD	NMOSD	NMOSD	MOGAD	MOGAD
Location of onset*	Brain	Optic neuritis	Myelitis	Optic neuritis	Optic neuritis
Disease duration, years	9	18	19	7	6
History of optic neuritis	+	+	+	+	+
History of myelitis	+	+	+	-	-
Site of HL	Bilateral	Right	Bilateral (more severe on the left)	Right	Right
Time from onset to hearing loss	0.8 years before onset	16 years after onset	8 years after onset	At onset	8 years before onset
Type	SNHL	SNHL+CHL	SNHL	SNHL	SNHL+CHL
Audiometry (Hz)	2000–8000	All	2000–8000	8000	All
Treatment at the time of HL	Steroid	Steroid	Steroid	Steroid	None
Prognosis of HL	Not improved	Not improved	Not improved	Not improved	Not improved

NMOSD: neuromyelitis optica spectrum disorder; MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease; NA: not available; SNHL: sensorineural hearing loss; CHL: conduction hearing loss. *Disease onset was based on the presentation of the first core clinical characteristic with objective clinical evidence.

positive. There have been no relapses without treatment for 6 years and no neurological disabilities except hearing loss, which was not recovered.

3.5. Case 5. Patient with MOGAD—Unilateral Mixed-Type HL as a Suspicious Initial Manifestation. A 57-year-old woman developed recurrent optic neuritis several times after the onset at age 52 and finally was diagnosed with MOGAD. Her past medical history included right-side hearing loss 10 years prior to the onset of optic neuritis, for which she had not been treated. Audiometry showed right-side SNHL over the entire frequency range. Brain MRI showed no other lesions except for atrophy of both optic nerves at onset.

4. Discussion

Our study suggests that hearing loss in seropositive NMOSD and MOGAD is not uncommon, can be unilateral or bilateral, more severe at higher frequencies with poor prognosis, and may precede the typical attack of NMOSD or MOGAD. In addition, SNHL can be accompanied by CHL, resulting in a variety of clinical presentations.

SNHL was 3.3% (3/92) in NMOSD and 4.2% (2/48) in MOGAD. Only three patients underwent brain MRI for hearing loss, two patients had lesions in the brainstem (case 1 with NMOSD and case 4 with MOGAD), and one patient (case 2 with NMOSD) had a lesion in the splenium of the corpus callosum. None had a vestibulocochlear nerve lesion. Two patients had bilateral and 3 patients had unilateral SNHL. Hearing loss was more severe at 2 kilohertz (KHz) or higher in all but two patients, who had severe hearing loss at all frequencies (cases 2 and 5). SNHL in all patients was poorly recovered despite high-dose steroids.

A previous study suggested that sudden hearing loss can be the initial symptom in Japanese patients with MS and seropositive NMOSD [8]. SNHL was observed in 3.5% ($n = 6/173$) of MS cases, 1% ($n = 1/101$) of seropositive NMOSD cases, and 8.1% ($n = 3/37$) of clinical isolated syndrome (CIS) cases. Particularly, SNHL occurred prior to onset in 4 MS patients and all 3 CIS patients. Those authors suggested that SNHL is rare but may be a risk factor for CNS demyelinating disorders and conversion to MS from CIS. A multicenter study of NMOSD confirmed SNHL in 3 (2.5%) of 258 patients; one of these patients was AQP4-IgG-positive, and one was non-Caucasian (Table 1) [9]. A multicenter study of MOGAD showed one Caucasian with brainstem involvement and hearing loss with pons lesions on brain MRI [14]. A recent study reported hearing loss in two NMOSD patients (Japanese-American and Caucasian) and one MOGAD patient (Hispanic) [15]. Our patients were Korean and seropositive for AQP4-IgG- or MOG-IgG-positive.

SNHL has been an initial presenting symptom of MS or NMOSD, but the significance was underestimated [8]. SNHL was observed between before 17 years and after 6 years of the onset of neurological symptoms in CIS and MS patients [8]. Rare patients have experienced SNHL almost simultaneously with other neurological symptoms at relapse or at the onset of MS, suggesting that SNHL is related to disease activity [4, 8]. In the present study, 2 patients ($n = 1$, NMOSD; $n = 1$, MOGAD) developed SNHL before onset and another 2 ($n = 1$, NMOSD, $n = 1$, MOGAD) showed SNHL at relapse or onset. Since the most common causes of SNHL are idiopathic, it should be determined whether SNHL is associated with disease activity at relapse and whether SNHL can be a preceding symptom before the onset or initial manifestation of NMOSD or MOGAD. In addition, previous studies have shown that

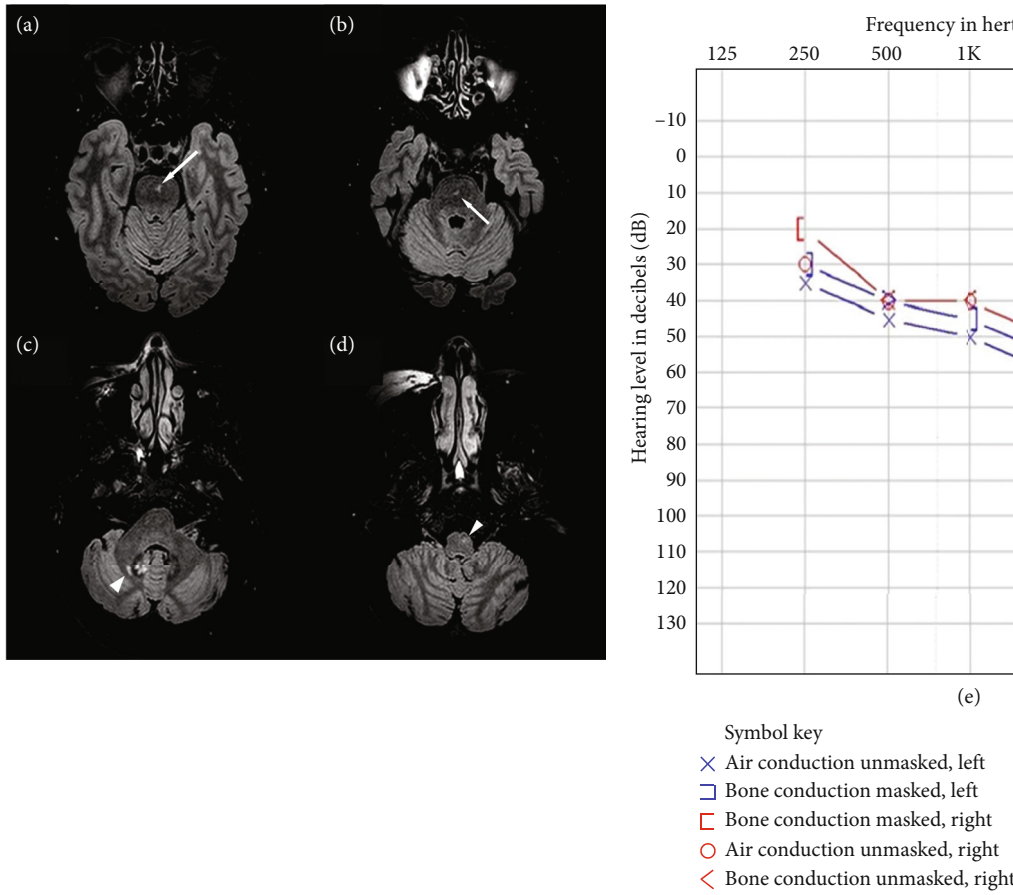

Figure 1: Brain MRI and audiometry of case 1. Fluid attenuated inversion recovery (FLAIR) images of brain MRI showed high signal intensity in the (a, b) pons (white arrows), (c) right cerebellum (black arrowhead), and (d) medulla (white arrowhead) upon presentation of dysarthria, dizziness, and bilateral hearing loss. (e) Audiometry at 1 year after hearing loss showed bilateral sensorineural hearing loss.

SNHL in NMOSD and MOGAD occurred unilaterally or bilaterally and at high frequency [15–18]. This is consistent with our results of two patients showing bilateral SNHL and more severe hearing loss at higher frequency in all patients. Three patients (cases 1, 2, and 4) in our study received high-dose steroids at the onset of SNHL. However, the treatment response was poor, although other accompanying neurological symptoms improved. This was not consistent with previous studies showing an overall good response to immunotherapy including high-dose steroid and cyclophosphamide [15, 18–20]. Further studies are needed on the prognosis of treatment response in SNHL of NMOSD or MOGAD.

Lesions in NMOSD are localized at sites of high AQP4 expression including regions of cochlear and vestibular nuclei in the brainstem [21], and cases of hearing loss associated with those lesions have been reported. In addition, one NMOSD case showed hearing loss with involvement of the extraaxial part of the vestibulocochlear nerve, and another report revealed "cochlear-type" hearing loss with involvement of the extraaxial part of the vestibulocochlear nerve [18]. Therefore, cases without brain lesions may be associated with the involvement of the cochlear nerve or cochlea in NMOSD and MOGAD.

SNHL in NMOSD and MOGAD can occur with damage to the auditory pathway. Hearing loss in NMOSD or MOGAD patients has been mostly due to SNHL; however, conduction hearing loss was also reported [15, 18]. Our 5 patients had SNHL, and cases 2 and 5 also had conductive hearing loss. SNHL can be divided into cochlear and retrocochlear types, and most previous reported cases were retrocochlear type [16, 17, 20], although one case of cochlear SNHL was reported in NMOSD. Those authors suggested that abundant expression of the AQP4 water channel not only in the optic nerve, brain, and spinal cord but also Claudius cells, Hensen's cells, and inner sulcus cells of the organ of corti in the inner ear indicates SNHL caused by an inner ear lesion could be a pathological mechanism in NMOSD [22, 23]. A recent report of a MOGAD patient with SNHL showed subtle symmetric enhancement of the bilateral distal internal auditory canals and cochlea [15].

There are some limitations in the study. First, because of the retrospective design, an appropriate sequence of imaging and electrophysiologic study such as brainstem auditory evoked potential (BAEP) were not performed and there were no controls without CNS demyelinating diseases to compare the prevalence. Second, the study was conducted in a single tertiary center and had a relatively small sample size. Finally,

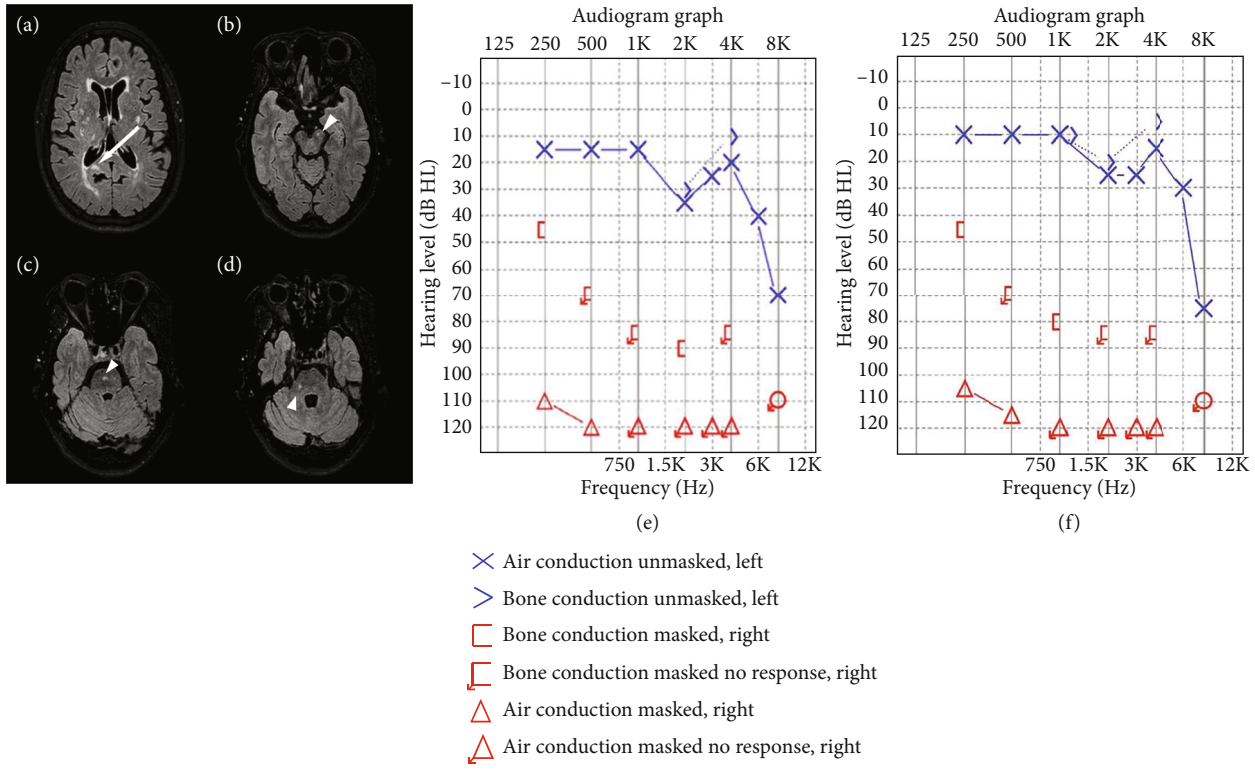

Figure 2: Brain MRI and audiometry of case 2. Brain MRI showed a new focal high-signal lesion in the (a) right corpus callosum splenium (white arrow) and (b–d) previous brainstem lesion (white arrowheads). (e) Audiometry showed right-side SNHL and CHL in all frequency ranges. (f) Posttreatment audiometry showed persistent right hearing loss.

the subclinical abnormalities in the auditory pathway detectable by audiometry or BAEP were unknown due to a lack of data in patients without hearing loss.

5. Conclusions

In conclusion, this study showed that hearing loss is not uncommon in seropositive NMOSD and MOGAD and may be a prodromal or clinical symptom by either central or peripheral lesions, especially affecting the high-frequency range. Because severe hearing disability may persist without appropriate management, hearing loss in NMOSD and MOGAD should be considered as a warning sign of relapse and requires appropriate evaluation and treatment. Further prospective studies with a large number of patients are needed to have an in-depth understanding of the epidemiology, clinical features, and risk factors and to establish the proper management of hearing loss in NMOSD and MOGAD.

Abbreviations

CIS: Clinical isolated syndrome
CNS: Central nervous system
EDSS: Expanded disability status scale
MOGAD: Myelin oligodendrocyte glycoprotein antibody-associated disease
MRI: Magnetic resonance imaging
MS: Multiple sclerosis
NMOSD: Neuromyelitis optica spectrum disorder
SNHL: Sensorineural hearing loss.

Data Availability

Data is available on request.

Conflicts of Interest

JHM is funded by and has received research support from the National Research Foundation of Korea (MIST and KHIDI) and SMC Research and Development Grant. She has lectured, consulted and received honoraria from Bayer Healthcare, Merk, Biogen Idec, Sanofi, UCB, Samsung Bioepis, Mitsubishi Tanabe, Celltrion, Roche, Janssen, and AstraZeneca.

Authors' Contributions

Soonwook Kwon and Soyoun Choi contributed equally as first authors.

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