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Association of multiple sclerosis and sudden sensorineural hearing loss

S Atula, ST Sinkkonen, R Saat, T Sairanen and T Atula

Abstract
Background: Multiple sclerosis (MS) may affect other cranial nerves besides the optic nerve. Sudden sensorineural hearing loss (SSHL), possibly caused by a deficit in the auditory tract, including the vestibulocochlear nerve, is sometimes associated with MS.

Objectives: We aimed to assess the incidence of SSHL among MS patients, its frequency as an initial symptom of MS, and magnetic resonance imaging (MRI) findings associated with SSHL in MS.

Methods: We collected retrospectively all patients diagnosed with MS and SSHL at the Helsinki University Hospital between 2004 and 2014. Patients with both diagnoses were re-evaluated using hospital medical records, audiograms and head MRI scans.

Results: A total of 2736 patients were diagnosed with MS, 1581 patients with SSHL, and 18 patients (0.7% of all MS patients) with both; two patients presented with SSHL as an initial symptom of MS. The annual incidence of SSHL was 59.8/100 000 (95% confidence interval (CI) 37.7–94.9) in MS patients, and 12.4/100 000 (95% CI 11.8–13.0) in the normal population.

Conclusion: SSHL is a rare symptom of MS and is even less frequent as an initial symptom. Its incidence in MS patients, however, markedly exceeds that in the normal population.

Keywords: Multiple sclerosis, demyelinating disease, sudden deafness, sudden sensorineural hearing loss, vestibulocochlear nerve, cranial nerve

Introduction
In multiple sclerosis (MS), the location of demyelinating lesions is usually associated with the symptoms of the disease. Demyelination in the brain stem can cause cranial nerve symptoms. As the most common cranial nerve manifestation of MS, optic neuritis is an initial symptom for 20% of patients with MS, although the involvement of the optic nerve is normally distal. However, the involvement of other cranial nerves also occurs. Trigeminal neuralgia is a complaint in 6.3% of MS patients.

The involvement of the auditory tract, including the vestibulocochlear nerve, also occurs in relation to MS and can manifest as sudden sensorineural hearing loss (SSHL). SSHL is most commonly defined as sensorineural hearing loss of at least 30 decibels (dB) in three consecutive frequencies in standard pure tone audiometry over a period of 72 h or less. SSHL is usually unilateral and may be the only condition or symptom of a more complex disease process. The exact cause of SSHL often remains uncertain, but several aetiologies have been identified and proposed, including infections (e.g. mumps, varicella zoster), vascular causes, endolymphatic hydrops (Menière’s disease), systemic immune diseases such as Susac’s syndrome, genetic predisposition, vestibular schwannoma, head injuries and ototoxic drugs. SSHL has an estimated annual incidence of 5–30/100,000, with a wide age distribution and no sex preference.

The first case reports suggesting an association between MS and SSHL were published in the 1950s and 1960s. Later, Jabbari and colleagues published the first findings showing abnormal brain stem auditory evoked potential test results in two patients with MS, which implicated the involvement of the vestibulocochlear nerve close to the pontomedullary junction in acute hearing loss. In light of...
the inflammatory mechanisms of MS, SSHL may involve demyelination of the vestibulocochlear nerve.

SSHL occurs at most in 3% of patients with MS,\textsuperscript{13} though several case reports\textsuperscript{14-16} have described SSHL as an initial symptom of MS. Also, repeated bilateral SSHL has been attributed to MS.\textsuperscript{17} The first acute hearing loss in an MS patient verified with magnetic resonance imaging (MRI) showed a lesion in the 8th nerve root-entry zone and cochlear nucleus.\textsuperscript{4} In addition, studies have shown demyelination of the distal tract of the 8th cranial nerve to cause acute hearing loss in MS.\textsuperscript{5,6} MS may cause SSHL via the demyelination process anywhere along the length of the vestibulocochlear nerve arising from the brain stem. Generally, however, SSHL has shown pathological findings both peripherally and in the central nervous system.\textsuperscript{18}

No larger series are available on SSHL among European MS patients, even though the prevalence of MS in Northern Europe is among the highest in the world. In this study, we examined the association between MS and SSHL. To the best of our knowledge, this is the largest series of MS patients evaluated for SSHL.

Material and methods
This is a one-centre retrospective study based on medical charts and MRI imaging. The Helsinki University Hospital approved the study protocol. We collected data on all patients at the Helsinki University Hospital diagnosed with either SSHL (ICD-10 code H91.2) or MS, demyelinating disease of the central nervous system or clinically isolated syndrome (ICD-10 codes G35 or G37.9) during an 11-year period between 1 January 2004 and 31 December 2014. We then combined the patient data to identify patients with both diagnoses. Later, we re-evaluated all the patient records, including clinical examinations and laboratory tests, audiograms and MRI findings to verify the diagnoses of both MS, according to the 2005 McDonald criteria,\textsuperscript{19} and SSHL.\textsuperscript{7}

An experienced radiologist retrospectively re-evaluated the first MRI scans after the onset of SSHL and recorded the number and location of MS lesions as well as any other visible pathology of the cochlear nerve or inner ear.

Poisson regression served to compare the annual incidence of SSHL in MS patients and the normal population. The results appear as incidence rate ratios (IRR) with 95% confidence intervals (CIs). Poisson distribution served in calculating 95% CIs for annual incidences. Statistical analyses were performed with IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY).

Results
A total of 2736 patients with MS or demyelinating disease were diagnosed and/or treated during the study period at the Helsinki University Hospital, and 1581 were diagnosed with SSHL. Of the 18 patients (0.7% of all MS patients) with both diagnoses, 17 patients were diagnosed with MS, and one patient with neuromyelitis optica with features of MS. On the other hand, MS was present in 1.1% of all SSHL cases. The annual incidence of SSHL was 59.8/100,000 inhabitants (95% CI 37.7–94.9) in MS patients and 12.4/100,000 inhabitants (95% CI 11.8–13.0) in the normal population of our catchment area. The annual incidence was higher in patients with MS than in the normal population (IRR 4.8, 95% CI 3.0–7.7, \( p < 0.0001 \)).

For two patients, SSHL was the first symptom of MS, which was diagnosed later in investigations. For one of them, however, SSHL was the only symptom; the other one had simultaneous double vision, also a cranial nerve symptom, and still another patient had presented with SSHL 2 years before the first symptoms of MS. No MRI scan was available from that period, so the presence of any demyelinating lesions at that time could not be verified.

Table 1 shows the demographic data, audiometric findings and hearing outcomes of patients with both MS and SSHL. A total of 13 patients were women and five were men. The mean age of MS diagnosis for all 18 patients was 32.8 years. Regarding co-morbidities, one patient each had or had had following diseases: both a peripheral facial nerve paresis 1 year and a stable unilateral acoustic trauma on the contralateral side to SSHL 4 years previously, otosclerosis on the ipsilateral side to SSHL, right-sided hemiparesis due to stroke 6 years before the diagnosis of left-sided SSHL, migraine, depression, juvenile-onset diabetes mellitus and both arterial hypertension and hypothyreosis.

The mean time from MS diagnosis to the diagnosis of SSHL was 9.3 years, ranging from onset of the initial symptoms to 48 years. The mean age of patients at the time of SSHL diagnosis was 40.1 years. One patient had two episodes of SSHL with a 13-year time interval. The initial hearing level at time of SSHL diagnosis (pure tone average (PTA),
mean hearing threshold at 0.5, 1, 2 and 4 kHz) was 67.8 ± 7.0 dB (mean ± SEM). The audiogram at diagnosis usually revealed profound (44%) or flat (28%) hearing loss over a large frequency range. Two patients (11%) had an ascending (low frequency) and three patients (17%), a descending (high frequency) audiogram type.

The mainstay of SSHL treatment is oral corticoids over a period of 1–2 weeks, with no contraindications. The treatments for SSHL in our study population included oral corticoids (methyl prednisolone) for 14 patients, and hyperbaric oxygen treatment for one; three patients received no treatment. When looking at hearing recovery after SSHL, the patients were divided into two groups: those treated with oral corticoids and those without corticoids (Table 1). In the oral corticoid group, 64% of the patients experienced full hearing recovery, 21% experienced partial hearing recovery, and only 14% (two patients) experienced no recovery at all. PTA after follow-up in the corticoid group was 29.9 ± 7.8 dB, corresponding to a recovery of 37.2 ± 8.2 dB. In the group of patients with no corticoid treatment, PTA after follow-up was 56.1 ± 5.2 dB, and recovery only, 12.5 ± 9.7 dB. None of the patients recovered fully; one recovered partially, and three of the patients experienced no recovery at all. Altogether nine patients (50%) complained of persistent hearing symptoms during the study period. For those whose symptoms disappeared, remission took from 1 week to 5 months.

Head MRI was available for 15 patients. MRI was performed within 4 months of SSHL diagnosis for 14 patients and immediately, 4 days before the onset of SSHL symptoms, for one patient. Of these patients, nine underwent MRI within 2 months of SSHL onset. Demyelinating brain stem lesions were present in eight patients; seven of the lesions were ipsilateral and four were within or adjacent to the ipsilateral cochlear nucleus. Gadolinium (Gd)-enhanced scans were available for 12 patients, of which four showed enhancing brain lesions. All these four patients underwent MRI within 1 month of SSHL onset. High-resolution Gd-enhanced images of the vestibulocochlear nerve were available for seven patients. The mean delay from SSHL onset to vestibulocochlear nerve MRI was 2.6 months (range 0–7 months).

Three patients had high-resolution Gd-enhanced MRI of the vestibulocochlear nerve within 2 months of SSHL symptoms. Two of them underwent MRI at the time of SSHL onset and showed enhancing brainstem lesions; the third patient underwent MRI 1 month after the SSHL onset, but MRI showed no active lesions. Four patients, all of whom had undergone MRI within a month of SSHL onset, had enhancing, active lesions; none of those patients,

<table>
<thead>
<tr>
<th>Table 1. Demographics, audiometric findings and hearing outcome in patients with MS and sudden sensorineural hearing loss.</th>
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<tbody>
<tr>
<td>All (n = 18)</td>
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<tr>
<td>Age at MS diagnosis, mean (range)</td>
</tr>
<tr>
<td>Age at SSHL diagnosis, mean (range)</td>
</tr>
<tr>
<td>Sex, male / female (%)</td>
</tr>
<tr>
<td>PTA at diagnosis, mean ± SEM</td>
</tr>
<tr>
<td>Audiogram type, n (%)</td>
</tr>
<tr>
<td>Ascending</td>
</tr>
<tr>
<td>Descending</td>
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<tr>
<td>Flat</td>
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<tr>
<td>Profound</td>
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<tr>
<td>Recovery, n (%)</td>
</tr>
<tr>
<td>Full</td>
</tr>
<tr>
<td>Partial</td>
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<tr>
<td>No recovery</td>
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<tr>
<td>PTA after follow-up, mean ± SEM</td>
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<td>PTA change, mean ± SEM</td>
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PTA: pure tone average (mean hearing threshold at 0.5, 1, 2 and 4 kHz)
however, showed any visible lesions of the vestibulocochlear nerve, and one presented with diffuse enhancement within the fluid-filled cochlea, indicative of labyrinthitis.

Only one of the MS patients with SSHL had concomitant vestibular symptoms. She suffered profound hearing loss (PTA 116 dB) with full recovery after corticoid treatment. The MRI revealed demyelinating lesions in the ipsilateral brain stem adjacent to the cochlear nucleus, but not in the cochlea or on the vestibulocochlear nerve.

**Discussion**

In this study, 0.7% of MS patients were diagnosed with SSHL during an 11-year period. In a Brazilian survey of 405 MS patients with a relapse, seven (1.7%) were diagnosed with SSHL. In another series from Israel, 4.4% of MS patients (11 of 253 patients) were diagnosed with SSHL within a 6-year study period. These smaller samples showed a higher frequency of SSHL. The Brazilian study included only patients with an acute relapse, and both studies took place outside Europe, which may account for the differences. However, the annual incidence of SSHL among MS patients in our series was 59.8/100,000 and 12.4/100,000 in general, calculated from the population of our hospital catchment area. Schreiber et al. estimated that the incidence of SSHL in the normal population is 5–30/100,000. As compared with these figures, the incidence of SSHL among MS patients is 2–12 times higher than the normal population. Therefore SSHL seems to associate with MS, probably through the formation of a demyelinating lesion somewhere along the path of the vestibulocochlear nerve or its central nucleus in the brainstem, yet invisible in MRI.

In our series of 1581 patients with SSHL, only two (0.13%) lacked a previous MS diagnosis. Another study from Fitzgerald and Mark showed MS to be more common among patients with SSHL: in a series of 78 consecutive patients, two (2.6%) were diagnosed with MS. However, another series showed similar figures to our results: 1070 patients with sensorineural hearing loss underwent MRI, and only one patient (0.1%) received a radiological diagnosis of MS. It is worth noting that the diagnostic accuracy of MRI may be suboptimal, as vestibular evoked myogenic potentials have detected demyelinating lesions, invisible to MRI, beneath the acoustic symptoms in MS. In summary, our results are in line with these earlier results, thus confirming the infrequency of MS as a potential aetiopathological factor behind SSHL.

SSHL could be interpreted as a relapse in patients with MS: its onset is sudden, MRI may reveal a new contrast-enhancing lesion in the brain stem, and patients tend to recover from it. Our finding, which shows SSHL to be more common among MS patients than in the general population, supports this view. It is also worth noting that SSHL is usually treated with oral methyl prednisolone, though with much lower doses (initially at about 60 mg daily) than in MS relapses.

Nevertheless, SSHL occurs in MS patients much less frequently than optic neuritis, which is diagnosed in nearly 50% of patients with MS. The reason for this difference is open to discussion, but may stem from histological features of the cranial nerves. The optic nerve is an extension of the central nervous system, and oligodendroglial cells produce its myelin sheath. In other cranial nerves from the third nerve onwards, except for the short segment at the root entry zone, Schwann cells produce the myelin sheath. As a disease of central nervous system, the inflammatory mechanisms of MS might be more prone to attacking directly the oligodendrocytes or myelin derived from oligodendroglial cells rather than from Schwann cells. The same reasons might also explain the rarity of SSHL as an initial symptom of MS.

Audiograms in MS patients with SSHL in most cases showed profound (44%) or flat (28%) hearing loss, which is also common in patients without MS. However, two of the patients (14%) showed ascending low-frequency hearing loss, which is quite rare in patients without MS. Hearing recovery in the oral corticoid group was 37.2 dB, which is comparable to the recovery seen in SSHL patients without MS.

In our series, MRI scans failed to reveal signs of demyelination of the vestibulocochlear nerve, possibly because in most sequences the changes in the vestibulocochlear nerve would fall below the resolution level of MRI. To detect active enhancing lesions, MRI should ideally take place within 1–2 months of the symptom onset; however, SSHL as an isolated symptom does not necessitate an instant MRI. In our series, only three patients met the criteria for having high-resolution Gd-enhanced MRI of the vestibulocochlear nerve within 2 months of SSHL symptoms. Two of them underwent MRI at the time of SSHL onset and showed enhancing brainstem lesions; the third patient underwent MRI...
1 month after the SSHL onset, but MRI showed no active lesions. Of the 12 patients scanned with Gd contrast agent, four showed enhancing brain lesions, and all underwent MRI within 1 month of SSHL onset.

The causes of SSHL in our patients remained unclear, as MRI verification in the form of a definite new demyelinating lesion along the vestibulocochlear nerve tract was unobtainable. Likewise, in most SSHL patients without MS, the imaging findings are usually negative. Still, the higher incidence of SSHL among the MS patients suggests a connection between these diseases. Regarding co-morbidities, with a possible exception of diabetes mellitus, associations between them and SSHL seem unlikely. The patient with otosclerosis on the ipsilateral side of SSHL had full recovery of the SSHL. The possible sensorineural hearing loss component of otosclerosis is not reversible, indicating that SSHL of this patient was not related to otosclerosis but fulfilled the criteria of SSHL. We did not have any patients with Susac’s syndrome, which is one of the aetiological factors for SSHL.

A point worth mentioning is that in our series, only one (6%) of the MS patients presented with vestibular symptoms concomitant with SSHL, even though vestibular symptoms generally occur in about 28–57% of SSHL patients. This finding suggests that the aetiology of MS-related SSHL may differ from that of SSHL unrelated to MS. One possible explanation, taking into account the difficulty locating the lesions in vivo along the auditory pathway, is that MS causes SSHL by affecting more central parts of the auditory tract. The finding of labyrinthitis in one patient confirms that the mechanism of SSHL in a patient with MS needs not always involve demyelination.

In our series, SSHL in MS patients without signs of brain stem lesions might be explained by the lack of high-resolution Gd-enhanced MRI within 2 months of SSHL symptoms in some cases. Inability of the MRI to detect demyelinating lesions in the vestibulocochlear nerve reflects that the demyelinating process falls below the detection limit of the current MRI protocols, or sometimes other mechanisms than demyelination cause SSHL also in MS patients. Typically, in patients without MS no obvious cause for SSHL can be found and the MRI scans remain normal. Therefore a thorough clinical examination with relevant additional investigations, such as MRI, is justified to rule out other possible underlying pathologies, such as vestibular schwannoma.

Our results must be interpreted with the understanding that the study was a single-centre, retrospective evaluation. Both the departments of Neurology and of Otorhinolaryngology — Head and Neck Surgery at the Helsinki University Hospital serve patients from a population of 1.16 million. Virtually all patients with MS as well as those with SSHL within the serving area are treated at the Helsinki University Hospital, which makes population-based estimates feasible. Because of the retrospective nature of the study, we re-evaluated and confirmed the diagnoses of all patients initially diagnosed with both MS and SSHL using patient files, audiograms and MRI scans. However, we were unable to re-evaluate all 4299 patients with either an MS or SSHL diagnosis, leaving open the question of whether other cases might also have met the diagnostic criteria. Nevertheless, the patients with SSHL normally undergo MRI scan to rule out vestibular schwannoma and therefore possible underlying, asymptomatic demyelinating lesions would have been visible. Ideally, patients should undergo MRI within 1–2 months in order to detect active enhancing lesions. Three patients did not undergo MRI after SSHL onset, and only nine patients underwent MRI within 2 months. This may have affected our scarce findings as regards MRI scans.

In conclusion, this study shows that MS associates with SSHL, but that SSHL is rarely an initial symptom of MS. Even though MS seldom causes SSHL, its incidence among patients with MS is markedly higher than in the normal population.

Declaration of conflicting interests
None declared.

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