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Sudden hearing loss as an early detector of multiple sclerosis: a systematic review

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Abstract. – OBJECTIVE: To evaluate whether Sudden Sensorineural Hearing Loss (S-SNHL) may be an early symptom of Multiple Sclerosis (MS).

MATERIALS AND METHODS: A systematic review was conducted using the following keywords: "Multiple sclerosis, hearing loss, sudden hearing loss, vertigo, tinnitus, magnetic resonance imaging, otoacoustic emission, auditory brainstem responses, white matter lesions, sensorineural hearing loss, symptoms of MS and otolaryngology, nerve disease and MS". Only the articles that included results of at least one auditory test and MRI were considered. We evaluated the prevalence of SNHL in patients with MS, the presence of different forms of SNHL (S-SNHL and Progressive SNHL (P-SNHL)) and their correlation with the stage of MS, the results of electrophysiological tests, and the location (if any) of MS lesions as detected by white matter hyperintensities in the MRI.

RESULTS: We reviewed a total of 47 articles, which included 29 case reports, 6 prospective studies, 6 cohort studies, 4 case-control studies, and 2 retrospective studies. 25% of patients suffered from SNHL. S-SNHL typically occurred in the early stage of the disease (92% of patients) and was the only presenting symptom in 43% of female subjects. Instead, P-SNHL occurred in the late stage of MS (88% of patients). Auditory Brainstem Responses (ABR) were abnormal in all MS patients with S-SNHL. When S-SNHL appeared during the early stage of the disease, MS lesions were found in the brain in 60% of patients and in the Internal Auditory Canal in 40% of patients. ABR remained abnormal after recovery.

CONCLUSIONS: S-SNHL can be an early manifestation of MS and should always be considered in the differential diagnosis of this condition, especially in women. The pathophysiology can be explained by the involvement of microglia attacking the central and/or peripheral auditory pathways as indicated by WMHs.

Key Words
Multiple sclerosis, Hearing loss, Sudden hearing loss, Auditory findings, Disease onset.

Introduction

Multiple sclerosis (MS) is one of the most common neurodegenerative diseases in the United States and Europe[1-3]. Sudden Sensorineural Hearing Loss (S-SNHL) is one of the symptoms of MS[4-34]. In MS patients SNHL can present in different forms; it can appear as S-SNHL early in the disease process or as P-SNHL in late stages of the disease as a result of a progressive involvement of the hearing pathways[5,6,8,11]. The origin of SNHL can be peripheral or central[12-14]; SNHL can be due to damage involving brain, nerve, or inner ear cells[20]. Although more common in early stages of the disease, S-SNHL can also occur in later stages, albeit rarely[4-18]. The often-reported temporary nature of hearing loss can be related to relapsing/remitting events that occur during the course of MS or to the use of corticosteroids[21] which are able to fight the systemic inflammation generated by MS[22].

While the importance of hearing symptoms such as SNHL and tinnitus as early symptoms of MS has been highlighted by many studies, the significance of S-SNHL[20] as a presenting symptom of MS is largely underestimated. Arguably, this is due to its temporary nature and to the relatively high frequency of S-SNHL. There are more than 66,000 new cases of S-SNHL in the United States every year[23] and in 90% of cases S-SNHL is diagnosed as idiopathic and treated with corticosteroids. We speculate that a percentage of patients diagnosed with idiopathic S-SNHL may be affected by MS and a prompt treatment with steroids can contribute

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to under-estimation and delayed diagnosis. The aim of this review is to evaluate whether S-SNHL in MS patients may be an early symptom of the disease. The awareness of MS-associated SNHL as a single presenting symptom of MS could decrease the risk of misdiagnosis and enable early intervention. To this end, we calculated the prevalence of SNHL in our sample of MS patients, we identified the patients with S-SNHL and P-SNHL, and we analyzed whether there is a difference in the hearing frequencies (from 250 to 8000 Hz) involved in each form of SNHL. Finally, we looked for the presence of WMHs in patients' MRIs of hearing pathways and assessed the correlation between WMHs presence and SNHL.

Materials and Methods

Two researchers independently searched PubMed, Scopus, and Google Scholar using the following keywords: "Multiple sclerosis (MS), hearing loss, sudden hearing loss, tinnitus, Magnetic Resonance Imaging (MRI), Pure Tone Audiometry (PTA), Otoacoustic Emission (OAE), Auditory Brainstem Responses (ABR), white matter lesions, White Matter Hyperintensities (WMH), sensorineural hearing loss (SNHL), symptoms of MS and otolaryngology, nerve disease and MS". Both researchers independently selected and reviewed the abstracts that included the term "multiple sclerosis" and at least one of the keywords listed above. The selected articles were then thoroughly read. All publication types from 1960 to December 2017, in English, French, or Italian were considered for analysis, including case reports, case series, epidemiological studies, case-control studies, as well as prospective and retrospective studies. Articles were evaluated by a native speaker. In order to be included the articles had to contain results of at least one auditory test (Pure Tone Audiometry, OAE, and/or ABR).

For the patients with SNHL we recorded gender, age, stage of MS, frequency range lost due to the hearing loss (Table I), results of ABR (latency and amplitude shape, presence/absence of response) and OAE (presence/absence) tests, presence and location (brain or IAC/cochlea) of WMHs in T2-MRI sequences, and symptoms resolution. SNHL was classified as S-SNHL or P-SNHL. The MS stage was recorded as reported in each study, namely "early" when patients were first diagnosed with the disease, and "late" when patients had been diagnosed with MS several years (> 2 years) prior to enrollment into the study.

Statistical Analysis

The analysis aimed at investigating whether there was a time difference between S-SNHL and P-SNHL presentation in the disease process. Chi-Square (χ^2) was used to evaluate the time difference in the presentation of S-SNHL and P-SNHL in the early or late stage of the disease. One-way ANOVA and Holm-Bonferroni were used to evaluate the difference in the hearing frequencies for S-SNHL and PSNHL. Spearman test was used to identify the correlation between the location of the lesions in the MRI and the type of SNHL. χ^2-test was used to evaluate whether a gender difference existed in association with onset and type of SNHL. For all tests, p-values <0.05 were considered statistically significant.

Results

Review of Literature

We reviewed 177 publications. Among them, 47 articles matched our criteria for inclusion in the review[4-6,8-18,24,24-57] and included 29 case reports, 6 prospective studies, 6 cohort studies, 4 case-control studies, and 2 retrospective studies (Table I). Data from a total of 1533 patients were collected and analyzed (Figure 1); data from 39 patients were published in the form of case reports (0.02% of patients). 72% of patients were women, 28% were men, and average patient age was 35.7 years old (SD: 9.5; C.I. 95%: 13-82). 83% of patients were affected by relapsing-remitting MS and the remaining 17% by the progressive form. 69% of patients were affected by S-SNHL and the 31% from P-SNHL. 92% of S-SNHL episodes appeared in the early stage of MS, while P-SNHL occurred in late stages in 88% of cases.

S-SNHL vs. P-SNHL, Distribution in the Different Stages of MS, and Involved Frequencies

Of the 1533 patients included in this analysis, 25% were affected by a form of SNHL (Table I) as demonstrated by the results of their audiometric test; the remainder presented normal hearing functions. S-SNHL was present in 69% of cases (78% of cases were bilateral and 22% were unilateral) with variable severity, from complete deafness to middle-to-severe hearing impairment. P-SNHL (91% bilateral, 9% unilateral) was observed in 31% of cases with a severity range from mild hearing impairment to complete hearing loss.

Table I. Summary of the articles included in the review with the main findings used in our analysis.

Author	Year	Type of article	Number of subject	Age	Women (1) Man (0)	SSNHL symptoms vs MS stage	Type HL	Frequencies Hz	Hearing recovery	ABR and BAEP
Rataj et al[24]	1964	case report	1		0	later	Sudden	all from 250 to 8000	yes complete	n/a
Metzeger et al[25]	1965	case report	1		1	later	Sudden	all from 250 to 8000	yes complete	n/a
Ravenna et al[26]	1965	prospective	38	<45	not defined	later	Sequential	(35) 2000 to 8000; (3) 500 to 4000	n/a	n/a
Conraux et al[33]	1969	cohort	25		not defined	later	Sudden	(18) 1500 to 8000	n/a	n/a
Dayal et al[27]	1970	cohort	21	42-82 (average 65)	not defined	not defined	Sequential	(16) 2000 to 8000, (4) all frequecies, (1) 250-1000	n/a	n/a
Romanet et al[28]	1978	multi case report	2	24;51	1	early for both	Sudden	all from 250 to 8000	Completely	n/a
Tabira et al[29]	1981	case report	1	29	1	early	Sudden	all from 250 to 8000	Completely	ABR increased latencies in II and V, Cortical auditory potentials markedly reduced
Jabbari et al[30]	1982	multi case report	2	43;26	1, 0	early	Sudden	not defined	Completely	Presence of wave I only
Daugherty et al[31]	1983	prospective	9		not defined	early and later	Sudden	(7) all from	Completely 250 to 8000	6/7 BAEPs showed poor definition of the waves in the ear affected from HL
Cau et al[32]	1983	case report	1		1	early	Sudden	all from 250 to 8000	Completely	Wave I normal on the right only
Quevedo et al[34]	1984	prospective	29	21-52 (average 35)	not defined	not defined	Sequential	not defined		Complete waves absence (38.7%); 25.8% waves with increased amplitude and latency
Fischer et al[35]	1984	prospective	10	25-51 (average 37)	6 (1), 3 (0)	early	Sudden	all from 250 to 8000	Completely	Increased waves amplitudes

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Table I. Summary of the articles included in the review with the main findings used in our analysis.

Author	Year	Type of article	Number of subject	Age	Women (1) Man (0)	SSNHL symptoms vs MS stage	Type HL	Frequencies Hz	Hearing recovery	ABR and BAEP
Paludetti et al[36]	1985	case control	13	21-55 (average 40)	10 (1); 3 (0)	later	normal hearing	normal hearing	Absence of ABR recovery	65% of patients (11) increased waves amplitudes
Protti-Patterson et al[37]	1985	multi case report	2	20; 33	2 (1)	not defined	Sequential	(1) normal hearing; (1) 4000 to 8000	n/a	Incresed waves amplitude and latency; Normal ABR
Shea[38]	1986	case report	1		1	early	Sudden	all from 250 to 8000	Completely	Absence of waves before recovery, persistance of altered latency after recovery
Barratt et al[39]	1988	case report	1		0	later	Sudden	1000 to 4000	Completely	n/a
Schweitzer et al[17]	1988	case report	1		0	early	Sequential	all from 250 to 8000	Improved ABR	Prolonged amplitude and latency of waves III-IV
Franklin et al[18]	1989	multi case report	2	22; 38	2 (1)	early; later	Sudden	all from 250 to 8000	n/a	Prolonged aplitude and latencies of waves I, III and V; presence of prolonged latency of wave V only
Furman et al[16]	1989	case report	1		1	early	Sudden	2000 to 8000	Completely; WR recovery delayed, auditory immediate	Presence of wave I only
Cure' et al[40]	1990	retrospective	14	30-59 (average 44)	12 (1); 2 (0)	later	Sequential	not defined	n/a	Increased latency and amplitude of waves I to V
Sasaki et al[14]	1993	case report	1		0	early	Sequential	2000 to 8000	Complete in audio-metry but ABR showed wave I only	Presence of wave I only
Drulovic et al[12]	1993	multi case report	2	43; 37	2 (1)	early	Sudden	all from 250 to 8000	Completely; completely	Only wave I normal on the right; normal waves: I, II and III
Stach et al (15)	1993	case report	1		1	later	Sudden	1000 to 8000	Completely	Delayed latency waves III-V
Silman et al (41)	1995	case report	1		0	early	Sudden	2000 to 8000	Complete with recovered ABR	No waves in left

Continued

Table I. Summary of the articles included in the review with the main findings used in our analysis.

Author	Year	Type of article	Number of subject	Age	Women (1) Man (0)	SSNHL symptoms vs MS stage	Type HL	Frequencies Hz	Hearing recovery	ABR and BAEP
Cevette et al[42]	1995	multi case report	2	41; 33	1 (1); 1 (0)	early for both	Sudden	all from 250 to 8000 both	Partially; not reported	Increased amplitude and latency; presence of wave I only
Nishida et al[43]	1995	case report	1		1	later	Sudden	all from 250 to 8000	yes	Presence ofl wave I with reduced amplitude
Yamasoba et al[44]	1996	case report	1		0	early	Sudden	250 to 2000		Absence of waves on the left side
Marangos et al[45]	1996	multi case report	2	39; 55	2 (0)	later; early	Sudden	not defined	yes	Absence of BAEP on the right, absence of wave I in ABR; Absence of BAEP
Bergamaschi et al[46]	1997	case report	1	28	1	later	Sudden	2000 to 8000	Completely, ABR presented an increased latency of wave I only	Absence of wave I and increased latencies of waves III and V
Ozunlu et al[11]	1998	case report	1		1	early	Sudden	all from 250 to 8000	Completely	Presence of wave I only
Gallico et al[10]	1999	case report	1		1	later	Sudden	2000 to 8000	Complete with recovered ABR	Complete absence of waves
de Seze et al[50]	2001	cohort	14/400	15-48 (average 35.2)	not defined	early	Sudden	all from 250 to 8000	Complete recovery in 13/14	Absence of waves in the side with HL
Rodriguez-Casero et al[51]	2004	case report	1		1	early	Sudden	3000 to 8000 of tinnitus	Persistance	n/a
Tu et al[8]	2004	case report	1		1	early	Sudden	8000	No	Increased latency wave I-V bilaterally
Cadoni et al[52]	2006	case report	1		1	early	Sudden	all from 250 to 8000	Rh complete recovery	Increased latency wave V l on the right side
Zeigelboim et al[53]	2007	prospective	19		1	later	Sequential	8000	n/a	n/a
Coelho et al (13)	2007	prospective	30 (10 with brain lesion)	18-50 (average 35)	not defined	not defined	Sequential	not defined	Not applicable	ABR with abnormal aspect in 90% of patients with brain lesion (9/10): TEOAE abnormal in 80% of subject with alterated ABR

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Table I. Summary of the articles included in the review with the main findings used in our analysis.

Author	Year	Type of article	Number of subject	Age	Women (1) Man (0)	SSNHL symptoms vs MS stage	Type HL	Frequencies Hz	Hearing recovery	ABR and BAEP
Mi-Oh et al[6]	2008	case report	1		1	early	Sudden	all from 250 to 8000	Complete in audiometry but ABR showed wave I only	Complete absence of waves
Peyvandi et al[55]	2010	cohort	30	17-45 (average 30.8)	not defined	not defined	Sequential	(27) from 4000 to 8000	not applicable	In 80% abnormal amplitude and/ or latency
Hellmann et al[5]	2011	retrospective	11/253	17-52 (average 34.5)	not defined	early	Sudden	not defined	Complete for all	no
Saberi et al[56]	2012	case-control	60	20-50 (average 29.86)	42 (1); 18 (0)	not defined	Sequential	(7) 250 to 2000; (5) 4000 and 8000Hz; (40) 2000 to 8000	not applicable	TEOAE 20/60 frequency band between 3.5 -4.5; DPOAE abnormal
Doty et al[57]	2012	case control study	73 vs 73 CG	36-60 (average 49.20)	not defined	not defined	not defined	all from 250 to 8000	n/a	n/a
Cabbarzade et al[58]	2013	case report	1		1	later	Sequential	1000 to 8000	Complete recovery in the righ ear	Reduced latencies waves IV and V
Barbosa et al[59]	2014	cohort	7	22-51 (average 32.5)	not defined	early	Sudden	all from 250 to 8000	Complete for all	no
Fernandez-Menendez et al[56]	2014	multi case-report	3	29; 29; 25	3 (1)	later; early; early	Sudden	all from 250 to 8000	1 recover; 1 not complete; complete	Complete absence of waves; as previous
Takanashi et al[57]	2014	case control	1		1	early	Sequential	2000	Complete with recovered ABR	Reduced aplitude and latency in the Rh; DPOAE normal
Tanaka et al[4]	2016	cohort	6/17	38 to 65 (average 30)	not defined	later	Sequential	not defined	not applicable	not reported

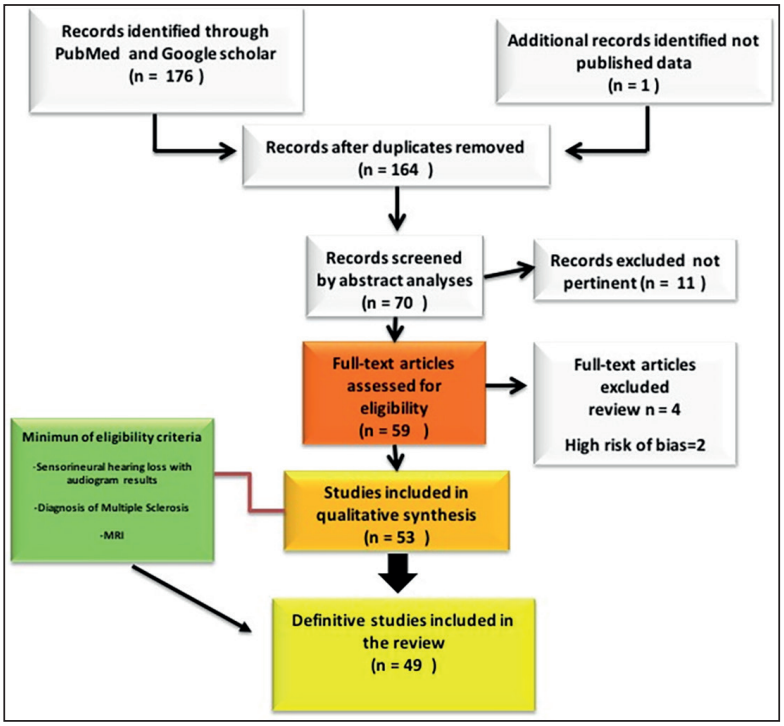

Figure 1. The plot shows the method used to identify the articles that were included in this review.

S-SNHL and P-SNHL were differently distributed in the different stages of MS (Figure 2). S-SNHL was more frequent in the early stage of MS (92%) (χ^2: p<0.0001) (Odds Ratio: 316; CI 95%: 81.1-1232), while P-SNHL prevalently occurred in the late stage of the disease (88%) (χ^2: p<0.0001) (Odds Ratio: 316 CI 95%: 82-1132).

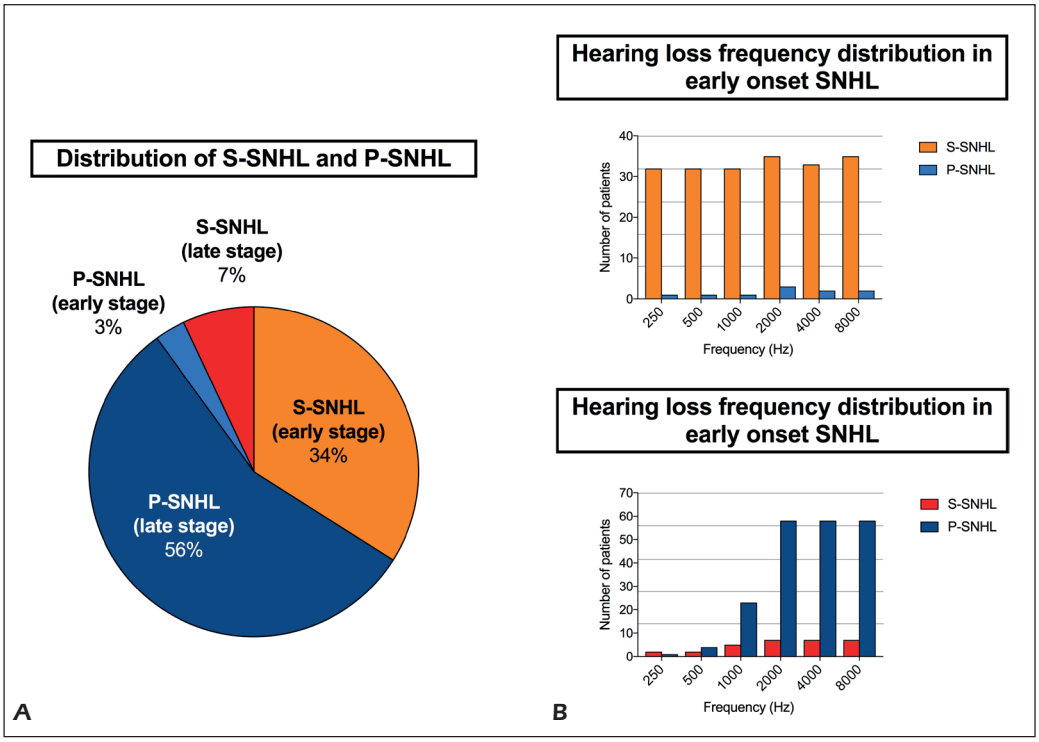

Figure 2. A, Distribution of S-SNHL and P-SNHL in the early and later stages of MS. **B**, Hearing loss frequencies distribution in the early stage (up) and later stage (down) of the disease.

S-SNHL and P-SNHL affected different frequencies as shown in Figure 2. S-SNHL equally affected frequencies from 250 to 8000 Hz without statistically significant differences (One-way ANOVA p=0.3). P-SNHL mainly affected high frequencies (2000 to 8000 Hz) (p<0.0001 for 2000, 4000 and 8000 Hz). 43% of women developed S-SNHL in the early stage of MS. In women, S-SNHL was more common than in men (73% and 27%, respectively; p<0.0001) and presented more frequently than P-SNHL both in early and late stages of MS (81% and 19% respectively). In men, there was no significant difference between the prevalence of S-SNHL and P-SNHL (49% *vs.* 51%), and both forms of hearing loss equally occurred in early and late stages of the disease (χ^2: p=0.12). OAEs were altered in 34% of MS patients (52). ABR waves were altered in terms of latency and/or amplitude in all MS patients, even in presence of a hearing threshold near the instrument detection limit (20 dB), as shown in Figure 3. The most common ABR abnormality was a non-specific abnormal wave shape (45%) with abnormal latency and/or amplitude. Residual abnormal ABR waves following S-SNHL recovery were observed in 18% of patients.

WMH Distribution in Brain and Ear

Seventy percent (70%) of patients with S-SNHL in the early stage of MS displayed WMHs in their MRIs in brain and medulla (upper auditory pathways). 75% of patients with P-SNHL in the late stage of MS displayed WMHs in the Roof Entry Zone (REZ), cochlear nerve and cochlea (Figure 4). In patients who manifested S-SNHL as early symptom, the presence of WMHs in the upper hearing pathways was statistically significant (Spearman: p=0.006). Additionally, there was a statistically significant correlation between the lower hearing pathways involvement and the presence of P-SNHL (Spearman: p=0.004).

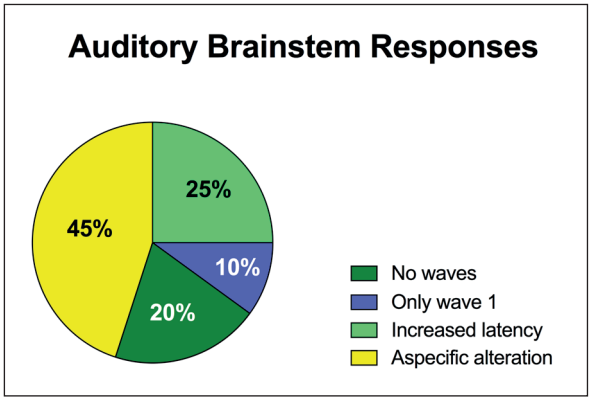

Figure 3. The figure shows the different findings related to ABR observed in our sample.

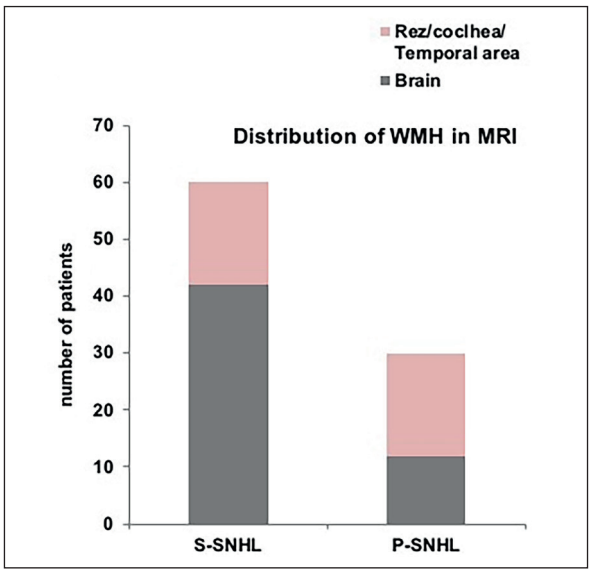

Figure 4. The plot shows the distribution of the WMHs in the presence of S-SNHL and P-SNHL.

Discussion

Our review included 1533 patients with MS, 25% of whom reported either S-SNHL (17%)[4,5,11-18,22,24] or P-SNHL (8%)[6,8-10]. S-SNHL was more common than P-SNHL (70% of patients).

S-SNHL and P-SNHL presented in different stages of MS with different manifestations, with the former being more common in the early stage of MS (92%) and involving all frequencies (similarly to the common form of Sudden Idiopathic SNHL), and the latter being more prevalent in the late stage of MS (88%) and involving mainly high frequencies.

S-SNHL was the only initial symptom in the early stage of MS in 43% of women, consistently with the results observed from other authors[18,47]. In women, S-SNHL was more common than P-SNHL. In men, S-SNHL and P-SNHL presented with equal frequency.

The presence of S-SNHL in the early stage of MS in women was statistically significant compared to men (p<0.05). In men, S-SNHL and P-SNHL equally manifested (no statistically significant difference) in all stages of the disease. S-SNHL in women was also more common (81%)

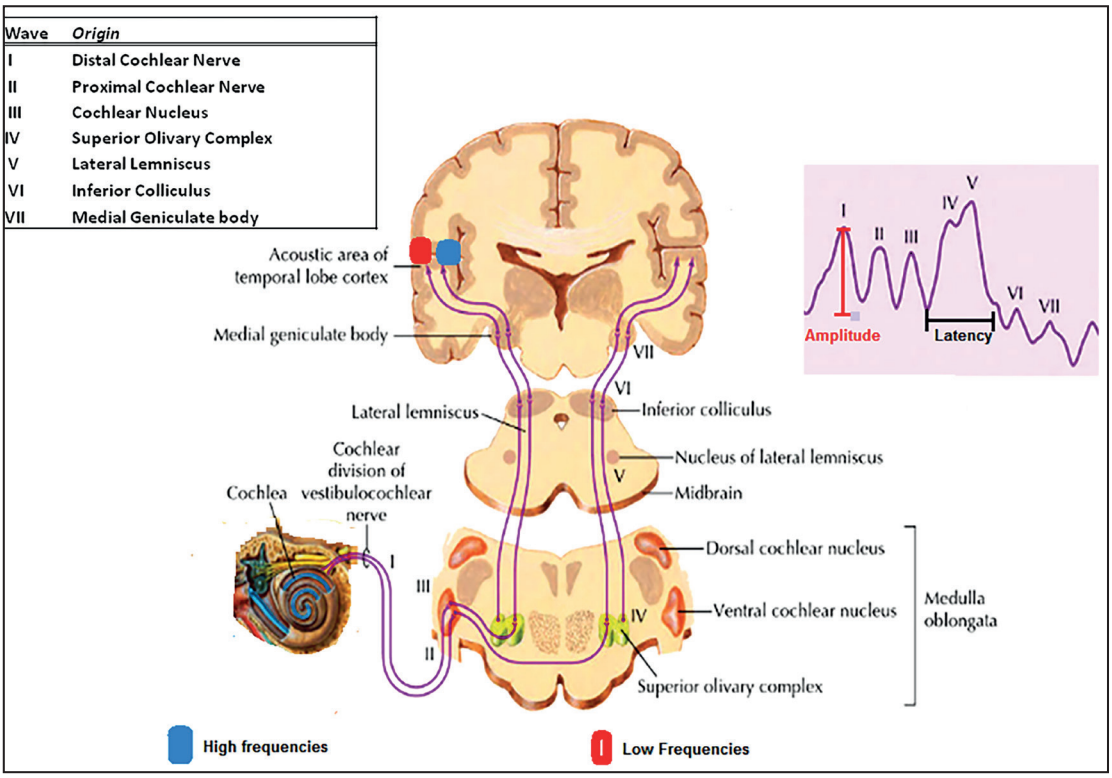

Figure 5. Upper side corner: the table summarizes the hearing pathways where each wave originates. Center: hearing pathways from periphery (cochlea) to the acoustic brain area are shown. Top right: the images show the amplitude and latency of a normal ABR.

than P-SNHL, which strongly supports the idea that S-SNHL should be considered as an early symptom of MS in young women, especially if they don't have a history of hearing disorders.

P-SNHL occurred more often in later stages of MS (88%) in both genders. The altered audiometric threshold, which involves frequencies between 2000 and 8000 Hz, can mimic presbycusis and it could be misdiagnosed as early presbycusis rather than a symptom of MS when it appears in young subjects. The average age of the patients we analyzed was less than 40 years old, which supports the idea that MS-related P-SNHL may be easily missed.

ABR allows the investigation of different areas of the hearing pathways (Figure 5); its sensitivity and high specificity in the detection of demyelination[43-45,59-59] is extremely valuable in studying auditory disorders in MS patients, as widely supported by many studies[35,43,45,56-58]. ABR amplitude and latency were altered in all MS patients with SNHL. The abnormal latency and amplitude reflect the location of the damage in the auditory pathways, as detailed in the table in the left panel of Figure 5. Wave I was detectable only in 10% of cases, indicating a very high chance of cochlear nerve injury during MS attacks. The latency of all waves was increased in 20% of cases indicating a reduction in the velocity of impulse transmission in auditory pathways. Waves were completely absent in 25% of the cases; although damage can occur in one or more areas of the auditory pathways, an early cochlear nerve involvement is plausible. Finally, we identified a 45% of "unspecific alterations" of ABR, namely generic wave alterations for which authors did not provide details.

OAEs investigate the function of outer hair cells in the cochlea, and detect cochlear damage that is not otherwise detectable using ABR. Thirty-four percent (34%) of MS patients displayed abnormal OAE, which suggests cochlear involvement in the context of MS. The relevance of the investigation of outer hair cell function in MS has been recently discussed by Di Stadio and Ralli[59,60]. We speculate that the altered OAE we observed in our sample may reflect a damage of outer hair cells[61]. In MS hair cells can be directly attacked by macrophages and suffer irreversible damage as a result of oxidative stress[59]; involvement of hair cells can lead to abnormal OAE.

McKenna et al[62] found microglia and macrophages in cochlear structures that have been damaged by autoimmune diseases, including spiral ligament, scala tympani, vestibuli surrounding spiral ganglions, modiolus, and the 8th cranial nerves. Microglia has been also found in WMHs of MS patients[63,64]. In our study, we found that WMHs were mostly present in the brain/medulla areas (70%) in the early stages of MS, which supports the idea that MS lesions in the upper auditory pathways can cause S-SNHL[6,38]. WMHs in IAC were more common in later stages of MS, which supports the idea that the nerves of IAC can be affected by the same demyelization process that affects other structures in MS[42]. In this study, we found WMHs in different parts of the auditory pathways (cortical area, medulla, cochlear nerve, and cochlea). WMHs are associated with activated, pathogenic microglia; the presence of WMSs in different anatomical areas can be explained by the microglia's ability to move, which is typical of macrophages[60]. Both S-SNHL and P-SNHL may be associated with the pathogenic form of activated microglia. We could define two origins for these forms: a peripheral SNHL when cochlear nerve or cochlea is affected (as in P-SNHL) and a central SNHL when the upper auditory pathways are involved (as in S-SNHL).

The temporary nature of S-SNHL can be explained by the microglia ability to change their phenotype from an aggressive (M1) to a neuroprotective (M2) form[65-67]. Microglia can be present in a "*non-active*" or "*active*" form, although the active form is usually differentiated in M1 or M2 phenotypes (respectively pathogenic and neuroprotective). The M1 form is particularly aggressive and can induce damage by destroying upper auditory pathways[64-70] or by directly attacking the peripheral auditory structures such as the cochlear nerve and the cochlea[60] (Figure 6). Microglia can also induce a progressive degeneration of the nerve sheath that mimics presbycusis as in P-SNHL; the slow progression of the degeneration may become symptomatic as reduced adaptation to noise [70,71], or as recruitment phenomenon[71]; all these symptoms have been described in MS patients[69-71]. It is also possible that a massive microglia attack induces an enormous inflammation in the auditory pathways (central and/or peripheral) thereby causing a S-SNHL event[71].

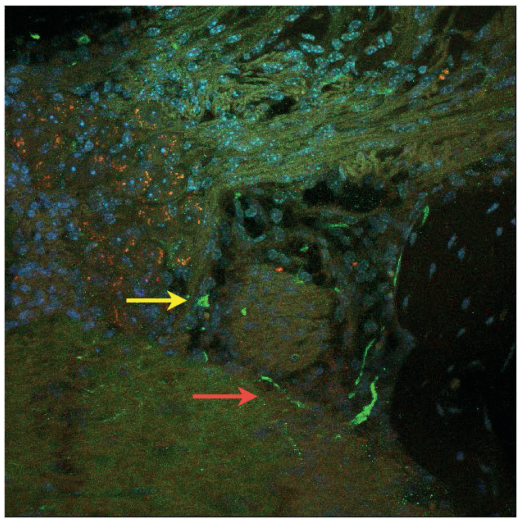

Figure 6. The ear modioulus of a mouse where it is possible to observe microglia. The red and yellow arrow indicates the staying and active form of microglia, respectively.

As discussed above, microglia can change their form (active *vs.* non-active) and phenotype (M1 *vs.* M2), and this ability to change state has been associated with the relapsing and remitting phases of MS[72]; the same mechanism may explain the spontaneous regression of S-SNHL in patients with MS when benign M2 form is prominent[14,39]. The change of microglia state can also be induced by drugs such as corticosteroids[73]. Corticosteroids that are the gold standard in the treatment of S-SNHL, may also contribute to under-diagnosis of MS-related S-SNHL, in fact their anti-inflammatory and immunosuppressive action is systemic by acting also on the inflammatory phenomena that arise from MS.

In the advanced phases of MS, the ability of microglia to change phenotype and state is reduced due to the increase of the oxidative stress[72-73]. M1 is the prevalent form of microglia and induce progressive neuro-degeneration, which can involve the cochlear nerve and lead to P-SNHL.

Figure 7 summarizes the differential diagnosis of SNHL in MS patients. Microglia can play a predominant role in damaging any area of the auditory pathways, as shown by the presence of WMHs in these locations[62] and supported by the alteration observed in ABR (100% of subjects).

The nature and timing of S-SNHL and P-SNHL manifestation depends on the MS stage. S-SNHL seems to be more common at MS onset, especially in women. In this case, hearing loss is likely correlated to lesions in the auditory pathways, including brain (temporal area and auditory cortex) and medulla; IAC seems to be involved less frequently.

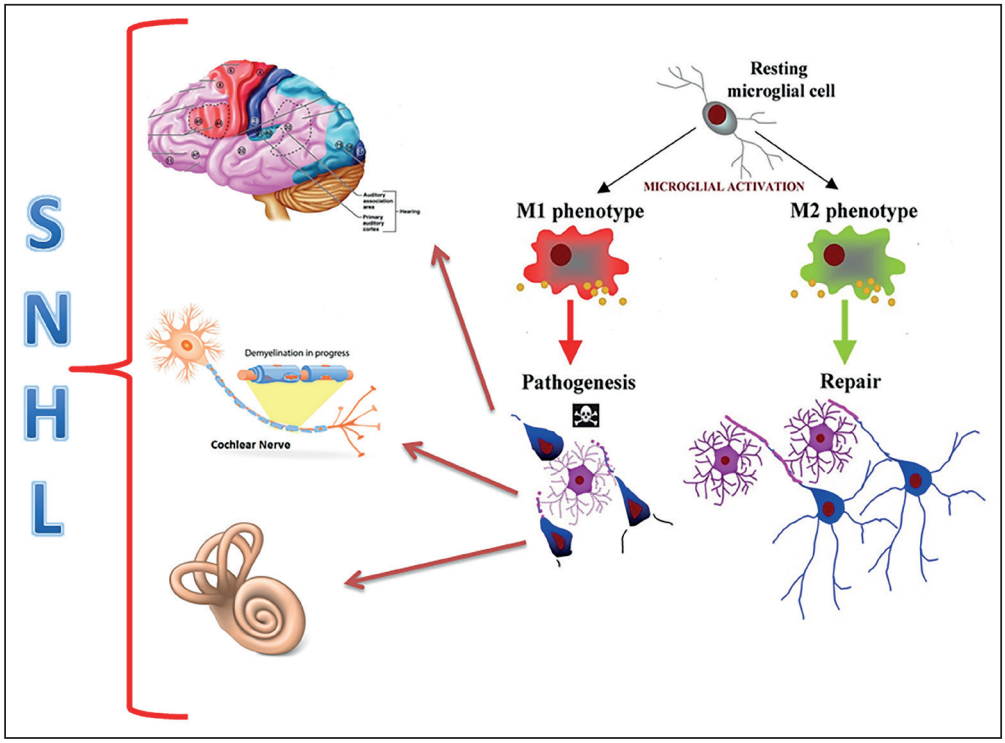

Figure 7. The figure summarizes how M1 microglia aggression may involve the different structures of the hearing pathways (brain, cochlear nerve and cochlea). Microglia have two forms, resting and active: the active form has two phenotypes, the M1 form that induces pathogenesis and the M2 form that is responsible for neurodegeneration.

Generally, 90% of patients who suffer from S-SNHL have been previously treated in a hospital setting and dismissed as "idiopathic" S-SNHL[23]. We identified a 17% of S-SNHL in patients with MS. We believe that this percentage is included in the 90% of idiopathic S-SNHL cases and that this data could increase the detection of misdiagnosed MS-related S-SNHL. In the relapsing-remitting MS, corticosteroids are commonly used as first-line treatment; these drugs reduce inflammation and promote SNHL recovery, but at the same time, can mask the actual origin of the symptom[74].

Our work presents some limitations. There are several case reports included in the study; this may have biased the percentage of MS patients with SNHL. Another limitation is the insufficient number of case-control studies and cohort studies available in the literature, which precluded us from conducting a meta-analysis to correctly estimate the incidence and prevalence of SNHL in MS patients. Only a few studies analyzed hearing parameters in patients with SNHL, and some of these studies had to be excluded from our systematic review due to lack of data or important limitation in the study design[72].

Conclusions

S-SNHL and P-SNHL present with different timing and frequency features, depending on the MS stage. S-SNHL seems to be more common in the early stage of MS especially in women, but this is probably related to the greater prevalence of the disease in this gender. Hearing loss is likely to be correlated with lesions in the auditory pathways, including brain and medulla; the involvement of the IAC structure during the inflammatory attack is less common. ABR was abnormal in 100% of MS patients; this test detects damage in the auditory pathways even when patients do not perceive it due to the involvement of high frequencies only. In conclusion, SNHL should be always considered in the differential diagnosis of MS, especially given its increased occurrence of S-SNHL in youth[75]. Otolaryngologists should always consider S-SNHL as either an only and/or first symptom of MS, particularly in young women without a history of hearing impairment. Moreover, diagnostic protocols should include ABR and MRI, in addition to a detailed history and neurological examination.

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Conflict of Interest:

Authors' declaration of personal interests: The authors declare no competing financial interests.

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