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Research Article

Central and Peripheral Auditory Pathway Integrity in Multiple Sclerosis: A Case-Control Study Utilizing ABR and OAE

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Abstract

Background: Multiple Sclerosis (MS) is a demyelinating neurodegenerative autoimmune disease. Auditory brainstem response (ABR) testing can detect subtle disturbances in auditory signal transmission, localize retrocochlear pathway lesions, and evaluate treatment effectiveness in MS patients. ***Objective***: Evaluate the function of central and peripheral auditory pathways in MS patients using ABR and OAE. ***Methods***: A case-control study was conducted involving 42 MS patients and 42 matched healthy controls. All participants underwent full clinical and audiological evaluation, including pure tone audiometry (PTA), tympanometry, ABR, and OAE. ***Results***: Symmetrically Prolonged Absolute latencies of Wave III, Wave V, and interpeak latencies (IPLs) were observed in MS patients compared to controls, with no significant effects of sex or disease duration. ABR abnormalities were more frequent in MS than in controls, while no significant differences were found between study groups regarding transient evoked and distortion product Otoacoustic Emissions (DPOAE). ***Conclusions***: The central auditory pathway appears to be mainly affected in MS, evidenced by the prolonged absolute latencies and ILPs on ABR testing. Peripheral auditory pathway involvement is generally less common, though significant dysfunction at 8 kHz can indicate early cochlear involvement. These findings reflect the importance of comprehensive audiological evaluation in the diagnosis and monitoring of MS patients.

Keywords: ABR, Auditory pathway, Autoimmune diseases, Demyelinating diseases, Multiple sclerosis, Otoacoustic emissions.

سلامة المسار السمعي المركزي والمحيطي في التصلب المتعدد: دراسة حالة وشواهد باستخدام ABR و OAE

الخلاصة

الخلفية: التصلب المتعدد (MS) هو مرض مناعي ذاتي تنكسي عصبي مزيل للمايلين. يمكن لاختبار استجابة جذع الدماغ السمعية (ABR) اكتشاف الاضطرابات الدقيقة في نقل الإشارات السمعية، وتحديد موقع آفات المسار خلف القوقعة، وتقييم فعالية العلاج لدى مرضى التصلب المتعدد. **الهدف**: تقييم وظيفة المسارات السمعية المركزية والمحيطية لدى مرضى التصلب العصبي المتعدد باستخدام ABR و OAE. **الطرائق**: أجريت دراسة حالة وشواهد شملت 42 مريضا بمرض التصلب العصبي المتعدد و 42 من الضوابط الأصحاء المتطابقين. خضع جميع المشاركين لتقييم سريري وسمعي كامل، بما في ذلك قياس السمع النقي (PTA)، وقياس طبلة الأذن، و ABR، و OAE. **النتائج**: لوحظ زمن انتقال مطلق ممتماثل للموجة الثالثة والموجة الخامسة وزمن انتقال الذروة (IPLs) في مرضى التصلب العصبي المتعدد مقارنة بالضوابط، مع عدم وجود آثار كبيرة على الجنس أو مدة المرض. كانت تشوهات ABR أكثر تواترا في مرض التصلب العصبي المتعدد مقارنة بالضوابط، بينما لم يتم العثور على فروق ذات دلالة إحصائية بين مجموعات الدراسة فيما يتعلق بالانبعاثات الصوتية العابرة والمنتج المشوه (DPOAE). **الاستنتاجات**: يبدو أن المسار السمعي المركزي يتأثر بشكل أساسي بمرض التصلب العصبي المتعدد، كما يتضح من زمن الوصول المطلق المطول و ILPs في اختبار ABR. عادة ما تكون مشاركة المسار السمعي المحيطي أقل شيوعا، على الرغم من أن الخلل الوظيفي الكبير عند 8 كيلو هرتز يمكن أن يشير إلى تورط القوقعة المبكرة. تعكس هذه النتائج أهمية التقييم السمعي الشامل في تشخيص ومراقبة مرضى التصلب المتعدد.

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INTRODUCTION

Multiple Sclerosis (MS) is a demyelinating neurodegenerative autoimmune disease, marked by inflammation, demyelination, gliosis, and axonal injury [1–3]. It occurs in individuals between the ages of 20 and 40 years [4]. Females are more likely to have the disease than males by a ratio of 2:1 [5]. Although hearing loss is reported among the least frequent symptoms in MS [6,7], it can occur due to either plaques affecting the brainstem, the site of cochlear nerve entry into the brainstem, or the auditory cortex [8] or due to autoimmune inner ear disease [9]. Diagnosis typically relies on clinical evidence and MRI verification, supported by laboratory tests, according to the revised McDonald's criteria [10,11]. Further diagnosis can be supported by ABR [12,13], which can detect subtle disturbances in auditory signal transmission, localize retrocochlear pathway lesions, and serve as an indicator for treatment effectiveness [9,14]. Otoacoustic emissions (OAE) provide a simple, objective method for screening peripheral

auditory pathway function [15–17]. OAEs are usually present in MS patients, as hearing losses in MS are mainly central. However, macrophages can invade and infiltrate the cochlea and hair cells, leading to peripheral auditory pathway involvement and alterations in OAE responses [18]. Since OAEs are highly influenced by the condition of the outer and middle ear, a comprehensive evaluation that includes tympanometry is essential [19]. Though most research on ABR in MS revealed anomalies, the nature of these anomalies remains unknown, and factors such as disease duration or sex differences were rarely addressed in previous studies. Also, limited studies utilized distortion product otoacoustic emissions (DPOAE) to investigate peripheral auditory function in MS patients [20]. The current study can address these gaps and assist in identifying subclinical auditory pathway involvement by systematically assessing auditory function utilizing ABR and OAE. The objective of this study is to evaluate the function of central and peripheral auditory pathways in MS patients using ABR and OAE.

METHODS

Study design and setting

A case-control was considered to design the study. The study was carried out at the Multiple Sclerosis Center, Department of Neurology, and the National Center for Hearing and Speech, Medical City, Baghdad, Iraq, over a five-month period from October 15, 2024, to March 15, 2025. The case group comprised a consecutive sample of 42 participants aged 20-45 years, with a definitive diagnosis of relapsing-remitting multiple sclerosis (RRMS) and no history of relapse or expanded disability status scale (EDSS) change in the past 3 months, who attended a specialized Multiple Sclerosis Center for follow-up visits. The control group comprised a convenient sample of 42 healthy individuals recruited from volunteer hospital staff, with no psychiatric or neurological diagnosis and a normal neurological examination. Controls were selected to ensure that the overall age and sex distributions were comparable between the study groups (frequency matching). All participants should have an average PTA threshold of 25 dB HL or below and type A tympanograms.

Exclusion criteria

Participants with active ear infections, prolonged use (>14 days) of ototoxic drugs such as aminoglycosides, furosemide, and platinum derivatives [21], current use of CNS-interfering medications such as antiepileptics, benzodiazepines, and anesthetic agents [22], and a history of occupational or recreational noise exposure (sound levels ≥85 dBA for ≥8 hours/day) [23], obtained via self-report and verified when possible by occupational history, were excluded. Additionally, participants with comorbidities such as hypertension, diabetes, other autoimmune diseases, or neurological disorders and medical conditions known to affect hearing—including Alport syndrome, mitochondrial disorders, autoimmune inner ear disease, neurofibromatosis type 2, congenital TORCH infections, and chronic renal disease—were also screened for and excluded from the study. Participants were initially interviewed to collect demographic and clinical data, including disease type, treatment history, and disease duration. These data were verified with medical records to ensure accuracy. MS Patients were then categorized into two groups based on the distribution of disease duration of the sample (<5 and ≥5 years) for subsequent analysis. Additionally, patients were stratified according to treatment status and efficacy of disease-modifying therapies (DMTs) into three categories: no treatment, moderate-efficacy DMT (including interferon β and teriflunomide), and high-efficacy DMT (including natalizumab, rituximab, and fingolimod) [5].

Intervention and outcome measurements

All participants underwent full clinical evaluation and audiological evaluation, which included PTA, tympanometry, auditory brainstem response (ABR), and otoacoustic emissions (OAE). Additionally, all MS patients underwent new brain MRI scans, including T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences, and post-contrast T1 and diffusion-weighted imaging. All scans were reviewed by a single experienced neuroradiologist, blinded to the audiological results, followed by evaluation by a neurologist. The MRI data were categorized based on the presence or absence of brainstem lesions, defined as T2-hyperintense foci within the midbrain (cerebral peduncles, periaqueductal grey), medulla oblongata (paramedian region), or pons (near cisterns, floor of the fourth ventricle, pontine surface, pontine trigeminal root entry zone), and exhibiting a typical MS pattern such as ovoid shape and peripheral location, to distinguish them from other conditions [24]. PTA was conducted using a calibrated Madsen A450 Audiometer (Otometrics Natus Medical, Denmark) at octave frequencies from 0.25 to 8 kHz in a soundproof test booth following the Modified Hughson Westlake method. The average of frequencies 0.5, 1, 2, and 4 kHz was calculated for each participant. Tympanometry was conducted using Interacoustics Titan/IMP440 (Interacoustics A/S, Middelfart, Denmark) for exclusion purposes. ABR was conducted using a two-channel Eclipse EP15 system (Interacoustics A/S, Middelfart, Denmark). During testing, subjects were lying comfortably supine in a sound-treated room. The skin was cleaned thoroughly, and electrodes were placed on the upper forehead (active), bilateral mastoids (reference), and the lower forehead (ground), with conductive paste; impedances were kept under 3kOhms at all trials. The stimulus used was a short-duration click of alternating polarity at an intensity of 80 dB nHL delivered via insert earphones at a rate of 19.9 per second. The filters used were 100 Hz high-pass and a 3000 Hz low-

pass filter, and a recording window of 15 msec was set. A minimum of 2000 sweeps per trial, with at least 2 trials for each ear, were applied. Recordings were repeated until at least two replicable waveforms were obtained, and the average of these replicable waveforms was used for analysis. The absolute latencies of waves I, III, and V were measured, along with I-III, III-V, and I-V interpeak latencies (IPLs). Abnormality was defined as a delay exceeding 2.5 standard deviations from normal values. Abnormalities were further categorized as Low brainstem (LB) abnormality (prolonged I-III IPL with a normal III-V IPL), High brainstem (HB) abnormality (prolonged III-V IPL with a normal I-III IPL), and combined High and LB abnormalities (prolonged I-III, III-V, and I-V IPLs). ABR recordings were performed by a trained audiologist and initially interpreted by the same audiologist. All interpretations were cross-checked by a second blinded audiologist, and any disagreements were reviewed by a third audiologist to reach consensus. OAEs were tested using Interacoustics Titan TEOAE 440 and DPOAE 440 modules (Interacoustics A/S, Middelfart, Denmark). Testing was performed in a sound-treated room, with adequate probe fitting ensured before data acquisition. Testing was performed by a trained audiologist, and responses were reviewed by the same audiologist; any suboptimal recordings were re-measured to ensure reliability. TEOAEs were evoked by employing a non-linear click stimulus at frequencies of 1 to 4 kHz, with a sound level of 83 peak equivalent dB SPL and a stimulus rate of 50 stimuli/second. The accepted noise level was set at 47 dB SPL. Transient Evoked Otoacoustic Emissions (TEOAEs) were considered present if the reproducibility rate exceeded 50% and the Signal-to-Noise Ratio (SNR) was greater than 6 dB in at least 3 out of 5 tested frequencies. Distortion Product Otoacoustic Emissions (DPOAEs) were measured at frequencies from 0.5 to 8 kHz; the primary tones were presented at 65 dB SPL for f1 and 55 dB SPL for f2, with the f2/f1 ratio set at 1.22 and a minimum DP amplitude criterion set to -10 dB SPL. Emissions were considered present if the SNR was ≥ 6 dB in at least four frequencies. Responses were also analyzed per frequency to determine the presence or absence of emissions at each tested frequency.

Ethical Consideration

The study protocol was approved by the Local Scientific Committee of the Surgery Department, College of Medicine, Mustansiriyah University (Reference number: 8040 on 8/10/2024). It was carried out in accordance with the Declaration of Helsinki, and informed consent was obtained from all participants before enrollment.

Statistical analysis

The analysis was done using SPSS version 26. Data were presented as mean, standard deviation, median, frequencies, and percentages. An independent t-test was used to compare the continuous variables. The Chi square test was used to assess the association between categorical variables, while Fisher's exact test was used when the expected frequency was less than 5. p-value < 0.05 was considered significant.

RESULTS

The current study included 42 MS participants and 42 healthy controls. No significant differences (p> 0.05) were found in the age and sex distribution between study groups, as displayed in Table 1.

Table 1: Demographic Data of the study groups

Characteristics		MS group	Control group	p-value
Mean age (year)		36.21±8.3	35.98±8.0	0.894
Sex	Males	12(28.6)	11(26.2)	
	Females	30(71.4)	31(73.8)	0.807

Values were expressed as frequency, percentage, and mean±SD. p< 0.05 is considered statistically significant. Age and sex matching between groups was achieved at the group level (frequency matching).

Clinical Profile of the MS Group is displayed in Table 2.

Table 2: Clinical Profile of the MS group

Variable	Statistics/Subcategory	Value
Duration of MS (year)	Mean±SD	6.23±4.46
	Median	4.5
	Range	0.08-14
Duration of MS (categorical)	<5 years	21(50)
	≥5 years	21(50)
Treatment status (categorical)	No DMT	4(9.52)
	Moderate efficacy DMT	9(21.43)
	High efficacy DMT	29(69.05)
EDSS score	Mean±SD	1.94±2.0
	Median (IQR)	1 (0.5-2.5)
	Range	0-8

Categorical values are expressed as frequency and percentage. DMT: disease-modifying therapy; IQR: Interquartile range.

Among the 9 MS participants receiving DMTs, 2 participants (5.3%) were on interferon β-1a, 5 (13.2%) on interferon β-1b, and 2 (5.3%) on teriflunomide, and among the 29 participants on high-efficacy DMTs, 3 (7.9%) were on fingolimod, 15 (39.5%) on natalizumab, and 11 (28.9%) on rituximab. No significant differences (p> 0.05) were found in the absolute and IPLs between the right and left ears in either group. Therefore, the results of both ears were combined for subsequent analysis. Wave III, Wave V, and IPLs were significantly prolonged (p< 0.05) in MS ears compared to control ears; no significant differences (p> 0.05) were found in wave I Latency between study groups (Table 3).

Table 3: Comparison of ABR absolute latencies and IPLs between MS and control ears

ABR component	Case	Control	p-value
Wave I	1.55±0.2	1.55±0.1	0.931
Wave III	3.77±0.4	3.6±0.1	0.001
Wave V	5.67±0.6	5.43±0.3	0.001
I-III Interpeak latency	2.23±0.5	2.04±0.1	0.001
III-V Interpeak latency	2.02±0.5	1.85±0.2	0.007
I-V Interpeak latency	4.13±0.4	3.89±0.2	0.001

Values were expressed as mean±SD.

In the MS group, no significant differences were observed in the absolute latencies and IPLs between male and female ears (p> 0.05), refer to Table 4.

Table 4: Comparison of ABR mean absolute latencies and IPLs between male and female ears in the MS group

ABR component	MS Ears		*p*-value
	Male	Female	
Wave I	1.53 0.2	1.56±0.2	0.401
Wave II	3.72±0.3	3.79±0.4	0.377
Wave III	5.77±0.5	5.62±0.6	0.274
I-III Interpeak latency	2.21±0.2	2.24±0.6	0.772
III – V Interpeak latency	2.04±0.4	2.01±0.6	0.799
I–V Interpeak latency	4.26±0.3	4.08±0.5	0.087

Values were expressed as mean±SD.

Similarly, no significant differences were found when comparing ears with disease duration < 5 years to those ≥ 5 years (p> 0.05), as seen in Table 5.

Table 5: Comparison of ABR mean absolute latencies and IPLs in MS ears according to disease duration

ABR component	Disease Duration		*p*-value
	<5 years	≥5 years	
Wave I	1.55±0.2	1.56±0.2	0.900
Wave II	3.74±0.3	3.80±0.4	0.413
Wave III	5.73±0.4	5.62±0.7	0.375
I-III Interpeak latency	2.20±0.2	2.27±0.6	0.501
III – V Interpeak latency	2.05±0.6	2.00±0.5	0.680
I–V Interpeak latency	4.18±0.3	4.09±0.5	0.335

Values were expressed as mean±SD.

Abnormal ABR results were observed in 24 out of 84 MS ears (28.6%); no ears in the control group had abnormal ABR results. This difference was statistically significant (p< 0.0001). Among the abnormal 24 ears detected, 11 ears (45.8%) had LB abnormality, 9 ears (37.5%) had HB abnormality, and combined abnormalities were seen in 4 ears (16.7%). Among untreated MS participants, 6 out of 8 ears (75.0%) showed ABR abnormalities, compared to 4 out of 18 ears (22.2%) in the moderate-efficacy DMT group and 14 out of 58 ears (24.1%) in the high-efficacy DMT group. There was a significant association between DMT use and ABR abnormalities (p= 0.009). No significant association was found between the presence or absence of brainstem lesions on MRI and ABR abnormalities (p= 0.451). Table 6 shows no significant differences in TEOAE and DPOAE between study groups (p> 0.05). DPOAE frequency-specific analysis revealed no significant differences at any tested frequency except 8 kHz, where abnormal results were observed in 9 out of 84 MS ears (10.7%) compared to 2 out of 84 control ears (2.4%) (p= 0.029).

Table 6: Comparison of OAE findings between the study groups

OAE Type	Result	Case (%) n=84	Control (%) n=84	*p*-value
TEOAE	Present	79(94)	80(95.2)	1.000
	Absent	5(6)	4(4.8)	
DPOAE	Present	76(90.5)	81(96.4)	0.119
	Absent	8(9.5)	3(3.6)	

Values were expressed as frequency and percentage. TEOAE: Transient Evoked Otoacoustic Emissions, DPOAE: Distortion Product Otoacoustic Emissions.

DISCUSSION

Brainstem evaluation in MS patients is crucial since brainstem involvement is a key predictor of future disability [25]. The present study demonstrated no considerable differences in ABR latencies between the right and left ears of MS patients. This aligns with previous ABR studies on both pediatric and adult populations with MS, also reporting no significant interaural differences in MS, which suggests symmetrical involvement of the auditory brainstem pathway [14,25,26]. Wave I appears to be spared in MS patients, as revealed by this study (Table 3) and several other studies [25–29]. The most likely explanation is the origin of this wave from the distal portion of the auditory nerve, as it is less likely to be affected by demyelination [25]. However, Kaytanci *et al*. assessed 40 ears of MS patients and reported significantly prolonged wave I in 12.5% of cases [30]. In contrast, prolonged wave III and wave V mean latencies were found in MS patients (Table 3), likely because these waves have a more central origin (from the brainstem's cochlear nuclei to the inferior colliculus) [25]. Several other studies reported similar results [25,26,30,31]. Prolonged IPLs were also observed in MS patients (Table 3), likely as a result of decreased transmission and synchronization of neural signals, which disrupts subcortical encoding [27]. Previous studies have reported a similar increase in I-III, III-V, and I-V IPLs [25,28,29,31]. Notably, ABR latencies in the MS group exhibited greater variability, particularly for wave III, wave V, and the IPLs (Table 3). This variability can be attributed to several factors. While higher EDSS scores have been associated with greater ABR abnormalities [31], the low EDSS scores and mild disability in the current study suggest that other factors are more likely responsible. Brainstem lesion presence may also contribute, since demyelinating plaques along the auditory pathway can prolong conduction times [32]. Variation in treatment status may further influence latencies, since untreated patients tend to show more pronounced delays [26]. Individual factors, including sex, may play a role, with males typically exhibiting longer latencies than females [22]. Fatigue severity has also been linked to greater latency prolongation, with those experiencing severe fatigue showing longer latencies compared to individuals with mild or moderate fatigue [29]. Differences in disease duration may additionally influence ABR latencies, potentially contributing to some of the observed variability, although evidence remains limited and conflicting [20]. There is generally a lack of studies that have evaluated ABR differences according to sex in MS patients. Still, studies on the general population revealed shorter latencies and shorter IPLs in females than males, except for wave I, which remained similar in both sexes [33]. However, the current study revealed no significant sex-related variations in ABR latencies or IPLs in MS patients (Table 4). This may be attributed to the effect of the disease on the central auditory pathway, which can override the usual neurophysiological difference between males and

females. Also, several factors, such as treatment status variability, as effective treatments and symptom alleviation are linked to changes in ABR latencies [26], and unequal sample sizes, may have contributed to these findings. Future studies are recommended to examine the influence of sex differences on ABR components in MS. The current study also revealed that disease duration had no discernible impact on ABR absolute latencies and IPLs in MS (Table 5). This agrees with the limited available studies, which reported either no or only a weak correlation with disease duration, attributing ABR changes encountered to lesion location and individual variability rather than to disease duration [29]. ABR abnormalities were found in nearly one-third of MS ears in this study. The rate of abnormal ABR in MS patients varies and has been reported by earlier research at a rate of 20% [28], 36% [34], 47% [35], 68% [26], 72.5% [30], 74% [36], and 80% [37]. Additionally, Stadio *et al*. reported abnormal ABR in 100% of patients during a systematic review of 1533 MS patients [38]. Reported abnormalities included reduced amplitudes, amplitude ratio alterations, poor morphology, increased wave and inter-wave latencies, and absent waves [20]. A higher occurrence of LB abnormalities, compared to HB and combined abnormalities, was noted in ABR results in the current study. Similar results were reported by Matas *et al*., who observed the occurrence of LB abnormalities in 41% of cases, while high and combined brainstem abnormalities were found in only 29.5% of cases [26]. Such observation may be explained by the predilection of the demyelinating lesions to affect lower brainstem regions, particularly the medulla oblongata and inferior pons, along with the corresponding auditory nuclei and tracts located within these structures. However, the inflammatory process in the brainstem is variable and may involve other regions, which could account for the remaining variability in lesion localization [39]. ABR abnormalities were significantly more frequent among untreated MS participants (75%) compared with those receiving DMTs, where rates were substantially lower (moderate efficacy: 22%; high efficacy: 24%), suggesting that DMT use may help preserve or improve central auditory pathway conduction, likely through reduced CNS inflammation and stabilization of axonal function [40]. Although these therapies do not directly induce remyelination, their anti-inflammatory and axonal-protective effects appear sufficient to enhance evoked potential conduction [41]. These findings support the use of auditory evoked potential as a tool for monitoring treatment effectiveness and long-term prognosis in MS [14,26]. The lack of association between ABR abnormalities and MRI results observed in this study may be primarily due to limited sample size or lesion characteristics (location, size, and activity), since ABR detects only lesions along the auditory brainstem pathway; similarly, MRI may miss small or inactive lesions in the CNS [30]. These results are in agreement with other previous studies [14,35]. Cochlear health (outer hair cell function) did not differ significantly between MS patients and controls when assessed by two modalities of OAE, TEOAE and DPOAE (Table 6), which was also reported in other studies [28,30]. However, higher rates of DPOAE abnormalities were noted at 8 kHz among the MS group, despite normal PTA and ABR results in the same ears, suggesting possible subclinical cochlear involvement in these individuals at high frequencies. On the contrary, Mauro et al. reported lower OAE amplitudes at low to mid frequencies, but not in the high frequencies, in newly diagnosed RRMS patients with normal hearing [42]. Studies that have evaluated cochlear involvement in MS remain limited, and further studies are recommended, considering the recently emerging evidence of cochlear involvement [18]. These subclinical cochlear dysfunctions may result from the selective destruction of hair cells due to the transfer of inflammatory cytokines or cellular components into the inner ear [18]. Other proposed mechanisms are related to inflammation and demyelination affecting the medial olivocochlear bundle, or glutamate buildup and excitotoxicity, which can activate glutamate receptors on hair cells, triggering intracellular events that result in hair cell death [42]. This study suggests that central and peripheral auditory pathways can be involved even without clinically obvious hearing impairment in MS. It also adds to the value of ABR as an adjunct for early detection of brainstem involvement, especially when MRI is unavailable or inconclusive.

Study limitations

The assessment of the central auditory pathway was done using ABR alone; mid-latency and cortical responses were not included due to unavailability. Additionally, as most participants in the current study had mild disability, correlations with EDSS scores could not be assessed. Future studies including patients with a broader range of disability levels are warranted to investigate potential associations between these factors and ABR results.

Conclusion

The central auditory pathway appears to be mainly affected in MS, evidenced by the prolonged absolute latencies and IPLs on ABR testing. Peripheral auditory pathway involvement is generally less common, though significant dysfunction at 8 kHz can indicate early cochlear involvement. These findings reflect the importance of comprehensive audiological evaluation in the diagnosis and monitoring of MS patients.

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Conflict of interests

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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