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Subclinical Trigeminal Dysfunction in Multiple Sclerosis Detected by Pulp Sensibility Testing

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ABSTRACT

Introduction: Trigeminal involvement in multiple sclerosis (MS) may remain clinically silent despite measurable functional disturbance. Subclinical dysfunction of afferent pathways can precede overt neurological findings. We aimed to investigate whether pulp sensibility testing can detect subclinical trigeminal afferent dysfunction in patients with MS who have no clinical evidence of trigeminal neuropathy.

Methods: Thirty-nine patients with MS (19 relapsing–remitting and 20 progressive) and 27 healthy controls were included. Electric pulp testing (EPT) and cold stimulation were applied to the right maxillary central incisor in all participants. For EPT, sensory threshold values were recorded. For the cold test, response latency was measured in seconds. Correlation analyses were performed to assess associations with age and disease duration.

Results: Compared with controls, patients with MS demonstrated higher EPT thresholds and prolonged cold response times. Within the MS cohort, both measures were greater in progressive disease. The difference reached statistical significance for cold testing (7.15±3.60 vs 4.89±2.58 s, p=0.038), whereas EPT values showed a similar but non-significant trend (9.80±4.15 vs 7.84±4.59, p=0.084). Age correlated weakly with cold response latency (r_s=0.321, p=0.046) and EPT values (r_s=0.326, p=0.043). Disease duration showed a weak correlation with EPT (r_s=0.334, p=0.037), but not with cold responses.

Conclusion: Despite the limitations of our study, our results indicate that pulp sensibility testing may provide meaningful information regarding the functional status of trigeminal afferent pathways. The more pronounced alterations observed in the progressive disease subgroup are consistent with cumulative conduction disturbance along the trigeminal system. Further studies directly comparing this approach with trigeminal SEP and high-resolution brainstem MRI are needed to better define its diagnostic value and clinical relevance.

Keywords: Cranial neuropathies, electric pulp test, multiple sclerosis, pulp sensitivity tests, trigeminal nerve

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INTRODUCTION

The dental pulp is one of the most densely innervated tissues in the human body and contains sensory, sympathetic and parasympathetic nerve fibers. These neural structures originate from the trigeminal ganglion and the cervical sympathetic ganglion (1). Pulpal nerves play a critical role in maintaining the vitality and sensitivity of the tooth. Pulp sensibility tests are routinely used diagnostic tools in dental practice to evaluate the vitality status of the pulp in outpatient clinical settings. Thermal tests (cold and heat) and the electric pulp test (EPT) assess the response of pulpal nerve fibers to stimulation and provide information on whether the pulp is vital or necrotic while also offering indirect insights into the functional status of pulpal innervation (2).

Highlights

- **Pulp vitality tests may reflect functional impairment of the trigeminal nerve.**
- **Pulp vitality tests may detect silent trigeminal involvement in MS.**
- **Can pulp vitality tests replace trigeminal SEP in clinical practice?**

Multiple sclerosis (MS) is a clinically heterogeneous disease characterized by demyelinating lesions disseminated in time and space. Clinical examination findings often do not fully reflect the true lesion burden within the central nervous system (3,4). Lesions located in the brain, brainstem, and particularly within the cranial nerves—most notably the optic nerve—may remain clinically silent and can only be detected through imaging or neurophysiological methods. Prolongation of visual evoked potential (VEP) latency has been detected in 50–70% of MS patients who have no visual complaints and no history of optic neuritis, indicating the presence of subclinical optic nerve involvement (5,6).

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Although the trigeminal nerve (TN) is one of the cranial nerves that can be affected in MS, such involvement does not always produce clinical symptoms and may not be evident on neurological examination. In the study by Eisen et al., trigeminal somatosensory evoked potential (TSEP) abnormalities were identified in 41.4% of MS patients without clinical signs of trigeminal nerve involvement (7,8). Similarly, Gabelić, Skorić, and colleagues have demonstrated electrophysiological evidence of trigeminal afferent pathway dysfunction in patients without clinical trigeminal symptoms (9). These findings indicate that trigeminal afferent pathways are frequently affected at a subclinical level in MS and that such involvement can be detected in the early stages through neurophysiological testing. However, electrophysiological methods such as TSEP require specialized laboratory conditions and have limitations regarding widespread use in routine outpatient clinical practice. This highlights the need for non-invasive, easily applicable, reproducible methods that can be performed in an outpatient clinic, serve as an extension of the clinical examination, and provide indirect yet reliable information about trigeminal afferent function.

The dental pulp is densely innervated by the terminal branches of the trigeminal nerve. Electric and thermal pulp sensibility tests primarily evaluate the functional response of myelinated A-delta fibers (1,10). Therefore, pulp sensibility tests may offer indirect insights into central demyelinating processes through the peripheral extension of trigeminal afferent transmission. The aim of this study was to evaluate the results of electric pulp testing and cold testing in MS patients without clinical signs of trigeminal neuropathy and to investigate whether pulp sensibility tests could serve as a feasible and supportive tool for detecting asymptomatic trigeminal involvement.

METHODS

This prospective case–control study was conducted through a collaboration between the Neurology Clinic of Etlik City Hospital and the Department of Endodontics, Gülhane Faculty of Dentistry. Ethical approval was obtained from the institutional review board (Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee, Approval No. AEŞH-BADEK-2024-767), and written informed consent was secured from all participants prior to enrollment.

Patients aged 20–50 years who had been diagnosed with MS according to the 2017 McDonald criteria and whose diagnosis had been established for at least one year were eligible for inclusion. Patients were classified as having relapsing–remitting MS (RRMS) or progressive MS (PMS), including both primary and secondary progressive subtypes. The control group consisted of healthy individuals without any known neurological or systemic disease and not receiving any regular medication. Sample size was determined using the G*Power 3.1.9.7 program, with an effect size of 1.20, an alpha (α) error margin of 0.05, a study power (ß) of 0.90, and a design effect of 0.1, thus determining the number of participants in each group.

Inclusion Criteria

MS Group

Participants were required to meet the following criteria: absence of current or prior trigeminal neuralgia; no clinical evidence of sensory or motor trigeminal nerve involvement at the time of evaluation; no nutritional or metabolic disorders; ability to cooperate with the examination procedures; non-pregnant status; no history of trauma to the tested tooth; absence of severe periodontal disease; no orthodontic brackets or recent orthodontic treatment; absence of extensive caries or large restorations in the tested tooth; no evidence of apical periodontitis; no prior root canal treatment, and absence of full-coverage crowns on the examined teeth.

Control Group

Inclusion criteria for the control group were: no history of neurological or systemic disease; no nutritional or metabolic disorders; no regular medication use; ability to cooperate with the examination procedures; non-pregnant status; no history of trauma to the tested tooth; absence of severe periodontal disease; no orthodontic brackets or recent orthodontic treatment; absence of extensive caries or large restorations; no apical periodontitis; no prior root canal treatment; and no full-coverage crowns on the examined teeth.

Electric Pulp Testing (EPT)

Pulp sensibility testing was performed on the right maxillary central incisor (tooth #11) in all participants. Following isolation with cotton rolls and gentle air-drying, a toothpaste (Crest, New York, USA) was applied to the buccal surface of the tooth to serve as a conducting medium. The probe of the electric pulp tester (Parkell, Edgewood, NY, USA) was positioned on the intact coronal third of the labial surface of tooth #11 (Figure 1A and 1B). The stimulus intensity was gradually increased until the participant reported the first sensation, typically described as a tingling feeling. The corresponding numerical value displayed on the device at the moment of perception was recorded as the electrical threshold.

Cold Test

After isolation with cotton rolls and drying of the tooth surface, ethyl chloride refrigerant spray (Chloraethyl, Elektro Teknik Medikal, Türkiye) was applied to a cotton pellet and placed on the buccal surface of tooth #11 for up to 15 seconds or until the participant reported a sensation (Figures 2A and 2B). The latency between application of the cold stimulus and the participant's response was recorded in seconds.

Statistical Analysis

All statistical analyses were performed using IBM Statistical Package for Social Sciences (SPSS) program version 25.0 (IBM Corp., Armonk, NY, USA). The distribution of age and other continuous variables was evaluated with the Shapiro–Wilk test. As the numerical variables did not demonstrate normal distribution, they were summarized as median (interquartile range, 25th–75th percentile). For age, mean and standard deviation were also reported to provide additional descriptive information. Categorical variables were expressed as frequency and percentage.

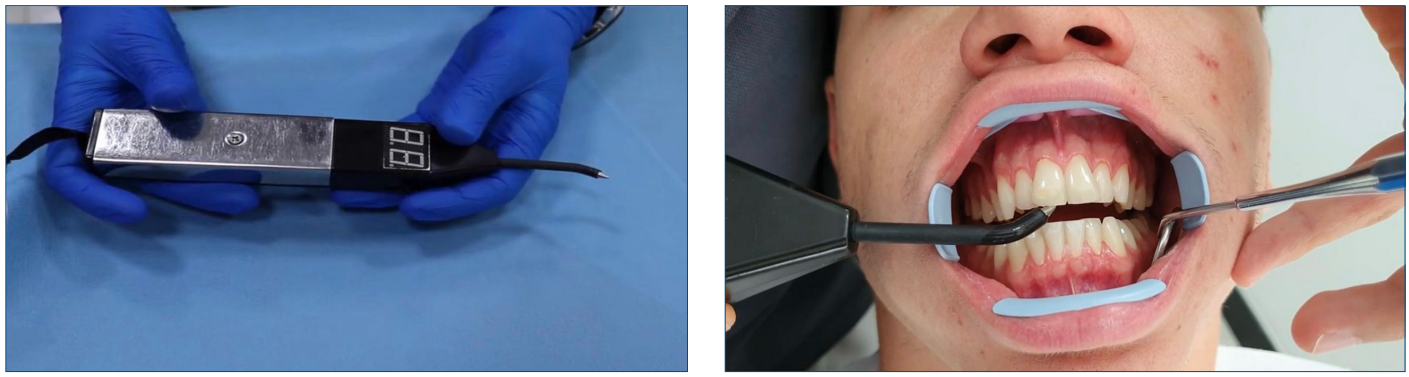
Comparisons of continuous variables between the MS and control groups, as well as between the RRMS and PMS subgroups, were conducted using the Mann–Whitney U test. The distribution of sex between the patient and control groups was examined using the Pearson chi-square test. The relationship between disease duration and continuous variables was assessed using Spearman's rank correlation coefficient. A two-sided p value of less than 0.05 was considered statistically significant.

RESULTS

A total of 39 patients diagnosed with MS (20 with PMS and 19 with RRMS) and 27 healthy controls were included in the study.

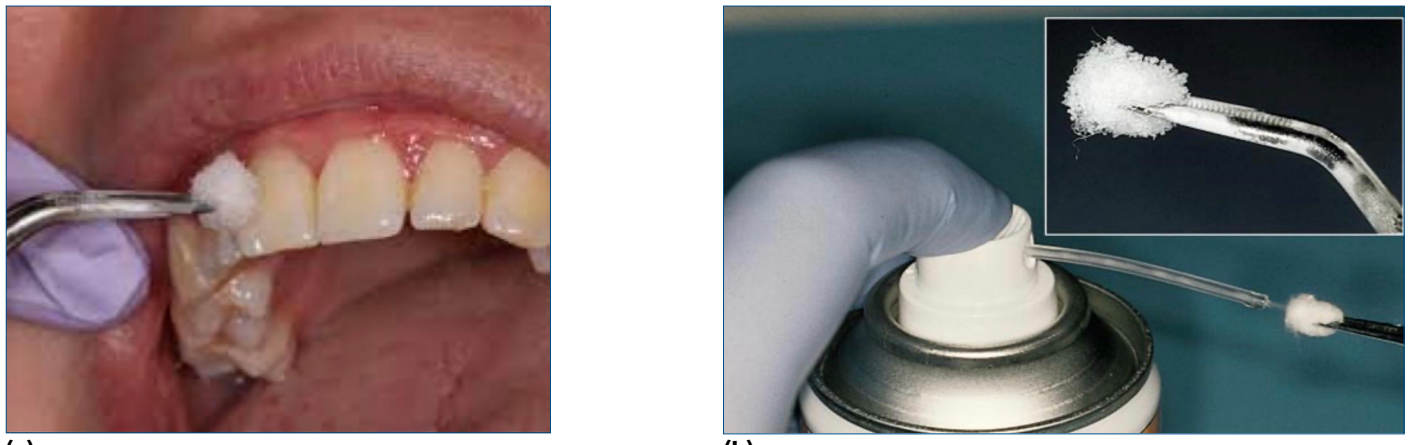
The mean age of the MS group was 39.31±11.09 years (median: 40; interquartile range [IQR]. 31–45), whereas the mean age of the control group was 34.22±11.62 years (median: 30; IQR: 26–43). There was no statistically significant difference in age between the groups (Z=1.834, p=0.067).

In the patient group, 76.9% (n=30) were female and 23.1% (n=9) were male. In the control group, 55.6% (n=15) were female and 44.4% (n=12) were male. No statistically significant difference was observed between the groups with respect to sex distribution (p=0.067).



(a) **(b)**

Figure 1. Images related to electric pulp testing. Electric pulp tester device **(a)**. Application of the device on the maxillary right central incisor **(b)**.



(a) **(b)**

Figure 2. Images related to cold testing. Cooling spray **(a)**. Application of the cold test on the maxillary right central incisor **(b)**.

All vitality measurements (cold test and EPT) were significantly higher in the MS group compared with the control group (Table 1). These findings indicate reduced pulpal sensitivity in patients with MS relative to healthy controls.

Although all pulp vitality measurements were higher in the progressive multiple sclerosis group compared with the RRMS group, this difference reached statistical significance only for the cold test (Table 2).

A weak positive correlation was identified between increasing age and both cold test and EPT measurements. In addition, a weak positive correlation was observed between disease duration and only the EPT measurement (Table 3).

Table 1. Pulp vitality measurements in MS patients and healthy controls

Vitality measurement	MS patients (n=39)	Healthy controls (n=27)	Z	p
Cold test	6.05±3.31 (5(3–9))	3.48±2.01 (3(2–5))	3.443	0.001
EPT	8.85±4.42 (7(5–12))	5.63±3.56 (4(3–7))	3.688	<0.001

Data are presented as mean ± standard deviation and median (IQR); EPT: electric pulp test; IQR: interquartile range.

Table 2. Pulp vitality measurements in PMS and RRMS subgroups

Vitality measurement	PMS (n=20)	RRMS (n=19)	Z	p
Cold test	7.15±3.60 (7(4–9))	4.89±2.58 (4(3–7))	2.086	0.038
EPT	9.80±4.15 (9.5 (7–13.75))	7.84±4.59 (7(5–8))	1.741	0.084

Data are presented as mean ± standard deviation and median (IQR); PMS: progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; EPT: electric pulp test; IQR: Interquartile range.

Table 3. Correlation between vitality measurements, age, and disease duration

Vitality measurement	Age (rS)	Age (p)	Disease duration (rS)	Disease duration (p)
Cold test	0.321	0.046	0.293	0.070
EPT	0.326	0.043	0.334	0.037

Spearman correlation analysis was used; EPT: electric pulp test.

DISCUSSION

Cranial nerve involvement is frequently observed in MS, most notably affecting the optic nerve. Isolated TN involvement is among the more common cranial neuropathies encountered in MS (11). Clinical manifestations of TN involvement in MS typically present as trigeminal neuralgia or facial sensory disturbances (8). Advances in magnetic resonance imaging (MRI) technology have made MRI an essential preclinical tool for establishing the diagnosis of MS and monitoring disease activity (12). Magnetic resonance imaging is indispensable in the radiological evaluation of cranial nerve involvement and can elucidate the etiology of cranial neuropathies in many cases (13). However, given MRI's primary reliance on anatomical information, it may prove insufficient in situations where functional impairment exists without overt structural abnormalities. In such situations, evoked potentials—which assess neural conduction—may offer clinically relevant insight into functional disturbances within affected neural pathways (5).

Several studies have demonstrated trigeminal nerve involvement via TSEP in MS patients who report no trigeminal symptoms or in cases where clinical findings do not correlate with MRI evidence of TN lesions (9,14). Gabelić and colleagues suggested that the higher detection rate of TN involvement with TSEP compared with MRI may be attributed to the fact that MRI typically visualizes demyelination only once it becomes macroscopically detectable. Small pontine lesions may escape detection on conventional MRI because of the anatomical complexity of the brainstem and inherent technical limitations of imaging. In contrast, TSEP can detect conduction delays along the trigeminal afferent pathway and may therefore be more sensitive to subtle neural involvement (9). Nonetheless, it is important to acknowledge that many of these studies were conducted during earlier phases of MRI integration into clinical practice. Therefore, the apparent superiority of TSEP in detecting trigeminal involvement may, in part, be related to the lower resolution and limited technical capabilities of MRI scanners used at that time.

The detection of infratentorial lesions in MS is of considerable importance. In clinically isolated syndrome, the presence of at least one brainstem lesion has been shown to increase both the risk of conversion to MS and the risk of future disability (15). In another study, the presence of two or more infratentorial lesions was reported to be among the strongest radiological predictors of long-term disability progression in MS (16). In a cohort comparing patients with symptomatic versus asymptomatic brainstem lesions, the probability of conversion to MS was significantly higher in those with symptomatic brainstem involvement (17). Collectively, these findings underscore the clinical relevance of detecting brainstem involvement at an early stage in demyelinating disease, as it bears substantially on long-term outcomes.

At present, MRI is the most sensitive modality for demonstrating brainstem involvement. However, optimal visualization is not always achievable due to the complex anatomy of the posterior fossa, the technical characteristics and spatial resolution of the MRI system used, the choice of sequences included in the protocol, slice thickness, and the possibility that lesions may not yet be morphologically apparent. In addition to MRI protocols capable of depicting brainstem pathology, there remains a need for functional assessment methods that are noninvasive, economical, and amenable to frequent repetition. Although somatosensory evoked responses (VEP and TSEP, somatosensory evoked potentials) meet many of these criteria, their reliance on dedicated laboratory infrastructure and the time required for testing can limit their routine clinical applicability. This highlights the need for simpler tests that can be implemented in outpatient clinical settings. In this context, the aim of the present study was to evaluate whether dental pulp sensibility testing could, similar to TSEP, reflect the functional status of the trigeminal afferent pathway.

In our study, among MS patients without a history of trigeminal neuralgia and without clinical signs suggestive of trigeminal nerve involvement, responses to both cold and electrical stimuli on pulp sensibility testing were significantly prolonged (i.e., higher thresholds/latencies) compared with healthy controls. This finding suggests that functionally relevant yet clinically silent trigeminal involvement may be present in MS. Our results are consistent with prior studies reporting VEP latency prolongation in MS patients without a history of optic neuritis (18) and with reports demonstrating TSEP abnormalities in patients lacking clinical signs attributable to the trigeminal system (9,14). Considered together, the literature indicates that cranial afferent pathways in MS can be affected prior to the emergence of clinical signs and that such involvement can be detected through electrophysiological or other functional methods.

In our study, patients were stratified into RRMS and PMS groups to enable analyses by clinical course, and they were compared both within MS subgroups and against healthy controls. Subgroup analyses showed that EPT and cold test responses were significantly higher (i. e., delayed) in the MS cohort compared with controls, with the delay being more pronounced in the PMS group than in RRMS and reaching statistical significance particularly for the cold test. This pattern suggests that the progressive phenotype may be associated with a more widespread or persistent afferent conduction abnormality and that functional involvement of the trigeminal system may vary by disease phenotype.

The use of the tooth pulp as the stimulation site for TSEP in the study by Lekić et al., underscores the relevance of the dental pulp in probing the structural and functional integrity of the trigeminal system (19). In that work, controlled electrical stimulation of an intact dental pulp elicited cortical potentials recorded from the scalp, with a pronounced latency prolongation reported especially in the second negative component. This has been interpreted as an objective electrophysiological indicator of central conduction delay along the trigeminal afferent pathway. By contrast, the EPT and cold tests employed in our study assess distal afferent threshold responses rather than cortical potentials. Although the methodologies differ technically—our approach focusing on peripheral thresholds and the TSEP approach on cortical responses—both are designed to evaluate the functional integrity of the trigeminal afferent system, and both converge on a shared pathophysiological signal consistent with conduction delay.

A case–control study conducted by Owlia et al. in 2021 that examined pulp sensibility in MS reported EPT thresholds to be significantly lower in MS patients than in healthy individuals (20). While this appears at variance with our findings, a subsequent study by the same group in 2024 with a larger sample demonstrated that both EPT thresholds and cold test response times increased significantly with longer disease duration, indicating delayed responses. Our results—particularly the higher thresholds in the progressive phenotype and the association with longer disease duration—align more closely with the 2024 data from Owlia and colleagues (21). The initially lower EPT thresholds in their 2021 report may reflect their inclusion of only RRMS patients and the possibility that early demyelination produces membrane instability and ectopic discharges, thereby increasing excitability in the initial phases. In this context, the inclusion of PMS patients and the relatively longer disease duration in our sample may account for the more prominent conduction delay we observed. Indeed, the higher vitality measurements in the progressive group bolster this interpretation.

In our study, a weak positive correlation was observed between increasing age and both cold test and EPT measurements. This finding suggests that pulp sensibility may show a slight decline with advancing age. A weak

positive correlation was also noted between disease duration and EPT measurements alone, indicating that the influence of MS duration on pulp sensibility may be more pronounced in responses to electrical stimulation. This result is consistent with the findings reported by Owlia et al. (21).

Another important implication of our results is the need for dentists to interpret pulp vitality testing in patients with MS with caution. In MS, a delayed or diminished pulp response may not necessarily indicate dental pathology. Our findings suggest that impaired trigeminal afferent conduction attributable to MS—even in the absence of structural pulp abnormalities—may influence test outcomes. Clinicians should therefore consider this possibility when forming diagnostic and treatment plans for patients with MS.

As a preliminary study, our results demonstrate that trigeminal afferent function can be indirectly evaluated in MS patients without dental pathology using pulp sensibility tests (electric pulp testing and cold testing). Several limitations should be noted: patient selection was based solely on clinical examination without standardized thin-cut brainstem MRI; the study did not include trigeminal SEP measurements and the potential influence of immunomodulatory therapies was not analyzed. Despite these limitations, the observation that these noninvasive, rapid, and easily applicable tests may help detect clinically silent trigeminal neuropathy in MS patients without dental pathology or trigeminal system-related clinical findings is noteworthy.

In future research, we plan to combine pulp sensibility testing with high-resolution brainstem MRI and TSEP evaluations to determine the sensitivity and specificity of this approach. If these associations are confirmed, pulp sensibility testing—given its repeatability, low cost, and noninvasive nature—may serve as a valuable complementary tool for the early detection of trigeminal pathway involvement in MS under routine outpatient clinical conditions.

Ethics Committee Approval: Ethical approval was obtained from the institutional review board (Ankara Etlik City Hospital Scientific Research Evaluation and Ethics Committee, Approval No. AEŞH-BADEK-2024-767).

Informed Consent: Written informed consent was secured from all participants prior to enrolment.

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Conflict of Interest: The authors declared that there is no conflict of interest.

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