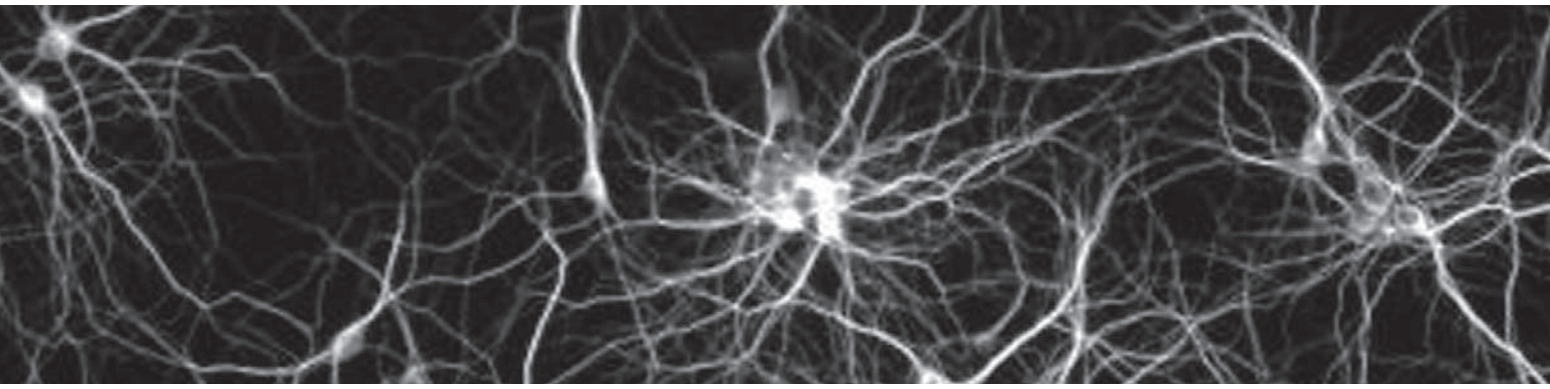

Tongue somatosensory evoked potentials in multiple sclerosis

M. Krbot Skorić[1], I. Adamec[1], T. Gabelić[1], M. Habek[1,2]

ABSTRACT – **Objective:** The aim of this study was to determine the efficacy of tongue somatosensory evoked potentials (tSSEP) in the evaluation of brainstem involvement in patients with multiple sclerosis (MS). **Methods:** tSSEP was performed in ten healthy volunteers and 29 patients with first clinical episode of a demyelinating event suggestive of MS. The data obtained were compared between the two groups and tSSEP findings of MS patients were correlated with their clinical and magnetic resonance imaging (MRI) data. **Results:** Multiple sclerosis patients had statistically significant prolongation of N1, P1 and N2 latencies on the left side compared with healthy controls (17.8±3.5 *vs.* 15.2±1.3, p=0.004; 23.9±3.3 *vs.* 20.8±1.0, p<0.001; 29.9±4.2 *vs.* 26.7±2, p=0.01, respectively) and of P1 and N2 on the right side (23.8±3.5 *vs.* 20.8±1.3, p=0.04; 30.3±3.8 *vs.* 27.3±1.9, p=0.01, respectively). Out of the 29 MS patients, eight (28%) had clinically evident involvement of the brainstem and 19 (66%) had brainstem lesions demonstrated on brain MRI. There were 19 MS patients with prolonged latencies of tSSEP on either side with no clinical signs of brainstem dysfunction and this difference was statistically significant (p<0.0001). Although tSSEP detected brainstem lesions in a higher percentage than MRI, it was not statistically significant (p=0.18). **Conclusion:** This study conducted on a larger number of MS patients confirmed the usefulness of tSSEP in the evaluation of afferent trigeminal pathways in MS.

Key words: tongue somatosensory evoked potentials, trigeminal afferent pathway, magnetic resonance imaging, multiple sclerosis

INTRODUCTION

The role of evoked potentials in the diagnosis of multiple sclerosis (MS) has changed over time, largely due to advances in imaging techniques. It has largely changed clinical practice with magnetic

[1] Clinical Department of Neurology, Referral Center for Demyelinating Diseases of the Central Nervous System, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia

[2] School of Medicine, University of Zagreb, Šalata 3, HR-10000 Zagreb, Zagreb, Croatia

resonance imaging (MRI) becoming the first, and very often the only investigation performed in MS patients. This has been acknowledged in a recently published revision of McDonald's criteria, which along with clinical symptoms use only MRI in providing evidence for dissemination in time and space (1). This is not always justifiable since the information provided by evoked potentials is more related to the function, unlike the information provided by MRI, which is more related to the anatomy (2).

Evidence suggests that brainstem involvement in MS is one of the major predictive factors for future disability. A recent work demonstrates that brainstem pathology is more frequent than can be depicted either clinically or with the use of MRI, and evoked potentials have been shown to reliably predict disability in MS patients (3). Brainstem involvement in MS can be manifested with different symptoms, and from these, diplopia is by far most common, followed by facial sensory symptoms, unstable gait, vertigo, oscillopsia, facial weakness/hemispasm, nausea and/or vomiting, trigeminal neuralgia, dysarthria (constant/paroxysmal), hypacusia, myokymia, dysgeusia, somnolence and dysphagia (4). Trigeminal nerve is the most commonly involved isolated cranial nerve in MS (5). Trigeminal involvement detected by MRI in MS is usually associated with trigeminal neuralgia or painless paresthesia in the distribution of the fifth nerve (6).

We have recently shown in a small cohort of early MS patients that the tongue somatosensory evoked potentials (tSSEP) are an efficient method for evaluating the afferent trigeminal pathway in patients with early MS (7). The aim of the present study was to determine the efficacy of (tSSEPs) in the evaluation of afferent trigeminal pathway in a larger cohort of MS patients.

SUBJECTS AND METHODS

The study included ten healthy volunteers, 5 female and 5 male, age range 27-66, mean age 33.2 years, and 29 patients with the first symptom of MS, 15 female and 14 male, age range 18-51, mean age 31.4 years. All patients underwent brain MRI and cerebrospinal fluid (CSF) analysis. Exclusion criteria for the study were molar surgery and any preexisting lesion of trigeminal nerve that could influence outcome of the study.

All participants were informed about the details of the experiment and they all signed informed consent forms. The study was approved by the Ethics Committee of the Zagreb University Hospital Center. The methods of data recording and analysis were designed according to the previously described details (8).

During the experiment, study subjects were sitting in a comfortable chair. After explaining them the experiment in detail, they were instructed to relax in order to avoid muscle tension. Electroencephalography (EEG) electrodes mounted on the plastic clip were used for stimulation and they were located on the lateral side of the first two-thirds of the tongue. The subjects opened the mouth slightly and the tongue with stimulation electrodes was held relaxed inside the mouth. Each side of the tongue (left and right) was stimulated twice with 300 trials in order to confirm the repeatability of the cortical response obtained. Stimulation was produced with a constant current stimulator (Twister, Germany). The frequency of the stimulation was 3 Hz and the duration of each stimulus was 0.2 ms. The polarity of the stimulation was alternating in order to avoid large baseline shifts.

At the beginning of each set of trials, the perceptive threshold was assessed in each subject. The intensity of stimulation during each set of trials was set at three times the perceptive threshold. It varied

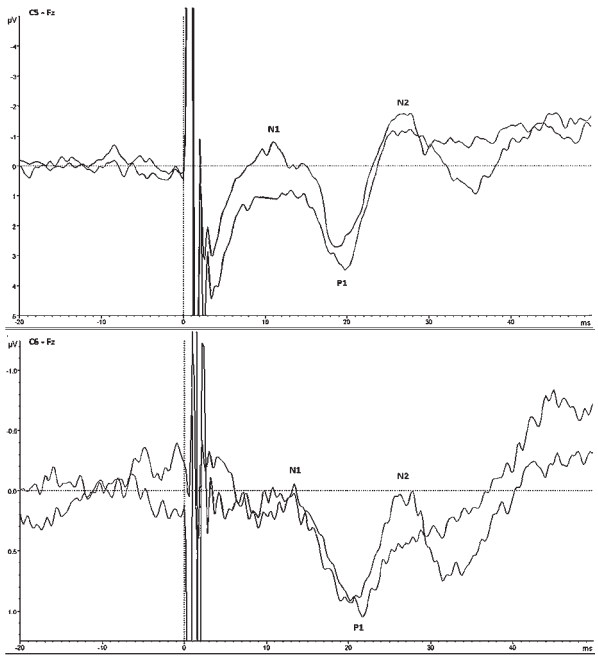

Fig. 1. *Superimposed tracings from two repeats of the tongue somatosensory evoked potentials (tSSEP) in the healthy control. Upper panel: tSSEP from the stimulation of the right side of the tongue; lower panel: tSSEP from the stimulation of the left side of the tongue.*

Table 1. *Characteristics of study patients*

Gender (M/F)	Age (yrs)	EDSS	BS FS	MRI	tSSEP	Conduction block	tSSEP_R	tSSEP_L
M	30	1.0	0	1	1	0	1	0
F	31	2.0	2	1	1	1	0	1
F	42	1.0	0	0	1	1	1	0
F	33	3.5	0	1	1	0	0	1
M	42	2.0	0	1	0	0	0	0
M	29	0	0	0	1	0	1	1
F	23	3.0	0	1	1	0	1	0
F	22	3.0	0	1	1	1	1	1
M	23	2.0	2	1	1	0	1	1
M	38	0	0	1	1	1	1	0
M	29	3.5	0	1	1	0	1	1
M	26	2.0	0	0	1	0	1	1
F	28	0	0	0	1	0	0	1
M	36	2.5	0	0	1	0	1	1
F	18	0	0	0	1	0	1	0
M	51	0	0	1	1	0	1	0
M	28	0	0	1	1	0	0	1
M	20	1	0	1	1	0	1	1
F	27	2	2	1	0	0	0	0
F	31	1	0	1	0	0	0	0
F	26	3	3	0	1	0	1	1
F	30	0	0	0	1	0	0	1
M	29	2	0	1	1	1	1	1
F	35	0	0	0	1	1	1	1
F	33	1	0	1	1	0	1	1
F	34	1	1	1	0	0	0	0
F	41	2	2	1	1	1	1	1
M	34	1	1	0	1	0	0	1
M	42	3.5	2	1	1	1	1	1

EDSS = Expanded Disability Status Scale; BSFS = brainstem functional system (part of the EDSS); F = female; M = male; tSSEP = tongue somatosensory evoked potentials; R = right; L = left; 0 = negative; 1 = positive.

from 4.5 mA to 10 mA for patients and from 3.5 mA to 9 mA for healthy controls.

Cortical response was recorded from four surface disk electrodes situated at the surface of the scalp. Active electrodes were situated on the contralateral side of the scalp, according to the international 10/20 system, at the middle position between C3 and T3 for stimulation of the right side of the tongue (C5 electrode) and at the middle position between C4 and T4 for stimulation of the left side of the tongue (C6 electrode). Both electrodes were referred to the frontal electrode Fz. The electrode situated at the vertex (Cz) was used as a ground electrode.

Responses obtained with electrical stimulation of the tongue were recorded with a Brain Products Vision Recorder (Germany) and analysis of the recorded data was performed using a Brain Products Vision Analyzer (Germany). Signals were filtered with a bandpass filter from 0.1 Hz to 1000 Hz. Sampling rate was 5000 Hz. For the purpose of averaging, signals were divided in segments of 70-ms duration according to the time position of the stimulus (20 ms before the appearance of the stimulus and 50 ms after the appearance) and averaged for each set of 300 trials. The grand average was computed from two averaged sets and used for analysis.

The responses obtained consisted of three main components (N1, P1 and N2), as shown in Figure 1. Latencies and peak to peak amplitude values (N1-P1 and P1-N2) were analyzed in order to detect the difference between healthy controls and MS patients.

Statistical analysis was performed using the SPSS 17.0 software. Differences in qualitative variables were analyzed by the χ^2-test, while differences in quantitative variables, in respect of distribution, were analyzed by the parametric t-test or non-parametric Mann-Whitney test. The p values less than 0.05 were considered statistically significant.

RESULTS

Multiple sclerosis patients had a statistically significant prolongation of N1, P1 and N2 latencies on the left side compared with healthy controls (17.8±3.5 *vs*. 15.2±1.3, p=0.004; 23.9±3.3 *vs*. 20.8±1.0, p<0.001; and 29.9±4.2 *vs*. 26.7±2, p=0.01, respectively), and P1 and N2 on the right side (23.8±3.5 *vs*. 20.8±1.3, p=0.04; and 30.3±3.8 *vs*. 27.3±1.9, p=0.01, respectively).

There was no statistically significant difference in latency and amplitude values between the left and right sides. From the values of the left and right sides, the averaged values of latencies and amplitudes were calculated. There was a statistically sig-

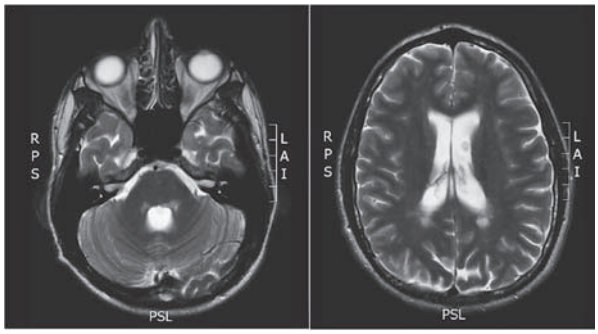

Fig. 2. *Brain magnetic resonance imaging: T2 sequences of the patient with multiple sclerosis who presented with double vision. Left figure shows demyelinating lesion present in the brainstem, Right figure shows multiple periventricular lesions.*

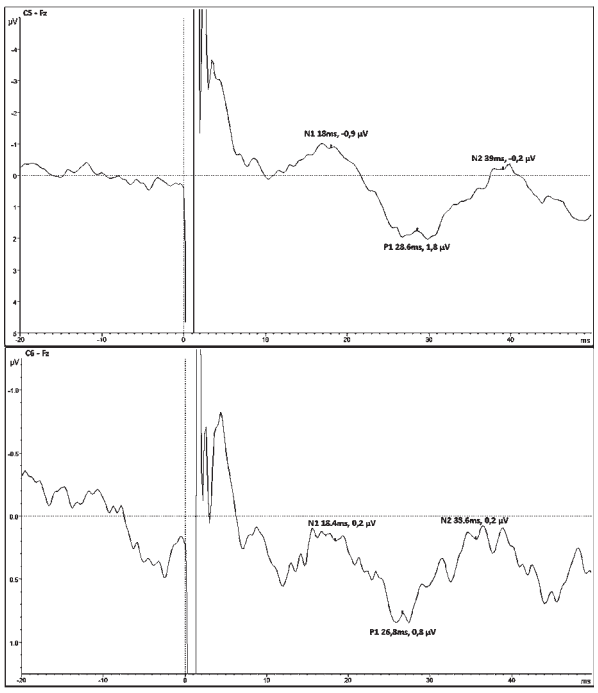

Fig. 3. *Results of the tongue somatosensory evoked potentials (tSSEP) in the multiple sclerosis patient from Figure 2. Upper panel: tSSEP from the stimulation of the right side of the tongue showing prolonged latencies. Lower panel: tSSEP from the stimulation of the left side of the tongue showing prolonged latencies.*

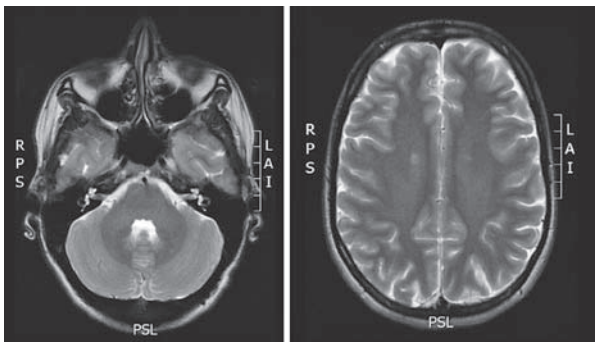

Fig. 4. *Brain magnetic resonance imaging (MRI), T2 sequences of the patient with multiple sclerosis who presented with paraparesis. Left figure shows normal MRI at the level of the brainstem. Right figure shows multiple periventricular lesions.*

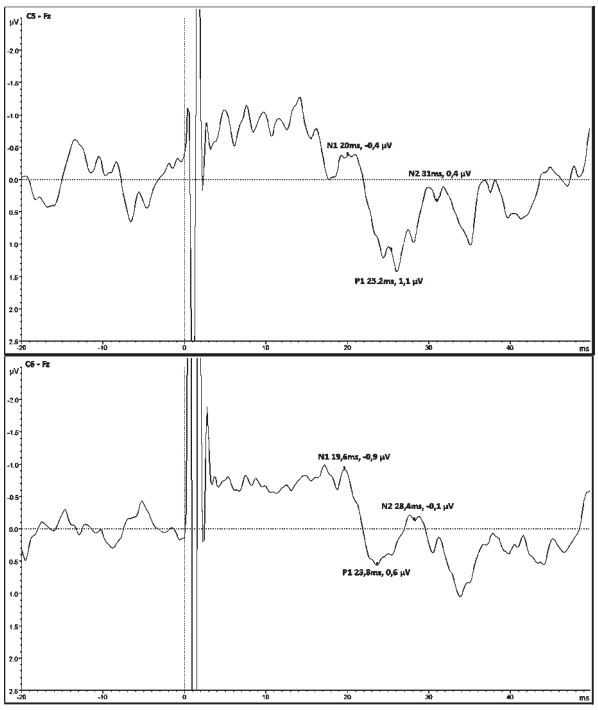

Fig. 5. *Results of the tongue somatosensory evoked potentials (tSSEP) in the multiple sclerosis patient from Figure 4. Upper panel: tSSEP from the stimulation of the right side of the tongue showing prolonged latencies of the P1 wave; lower panel: tSSEP from the stimulation of the left side of the tongue showing prolonged latencies of the P1 wave.*

nificant difference between healthy controls and MS patients in the averaged N1 latency (15.5±1.4 *vs*. 17.7±2.6, p=0.003), averaged P1 latency (20.8± 0.8 *vs*. 23.7±2.6, p<0.001) and averaged N2 latency (26.9±1.6 *vs*. 30.3±4.1, p<0.001), while there was no statistically significant difference in the amplitudes.

Out of the 29 MS patients, eight (28%) had clinically evident involvement of the brainstem and 19 (66%) had brainstem lesions demonstrated on brain MRI (Table 1). There were 19 MS patients with prolonged latencies and/or complete block of tSSEP on either side with no clinical signs of brainstem dysfunction and this difference was statistically significant (p<0.0001). Although tSSEP detected brainstem lesions in a higher percentage than MRI, it was not statistically significant (p=0.18). Figures 2 and 3 present a patient with demyelinating lesions in the brainstem and prolonged latencies in tSSEP. Figures 4 and 5 present a patient with normal brainstem MRI and prolonged latencies in tSSEP.

DISCUSSION

This study confirmed our previous findings on the usefulness of tSSEP in the evaluation of afferent trigeminal pathway in MS (7). Patients with MS showed prolonged latencies compared to healthy controls and this method is more precise in detecting brainstem involvement than clinical examination. Although tSSEP were pathologic in a higher percentage than MRI, the difference was not statistically significant.

The recording of evoked potentials is a noninvasive routine clinical testing procedure in neurology. For trigeminal nerve stimulation, however, evoked potentials have not received widespread clinical attention. The main reason for this is a variety of protocols and procedures that have been used; differences encountered include the stimulation mode, site and frequency, the recording electrode position and data acquisition parameters (9). This has resulted in a diversity of recorded trigeminal somatosensory evoked potentials signals, making comparisons almost impossible.

Nevertheless, there are only few studies employing this methodology in MS.

Bergamaschi *et al*. used trigeminal somatosensory evoked potentials by surface electric pulse stimulation in 70 MS patients, 13 of whom presenting clinical trigeminal impairment. The authors observed significant prolongation of all evoked potential parameters in MS group with trigeminal somatosensory evoked potentials being abnormal in 64.3% of patients. Clinical and neurophysiological data were consistent in 36 (51%) patients on 84 (60%) sides with trigeminal somatosensory evoked potentials being able to detect clinically silent lesions 54 times (10). Similarly, another group found changes in trigeminal evoked potentials (showing distorted waveforms and/or prolonged latencies) in 69.4% of patients (11). The presence of demyelinating plaques in the brainstem often causes involvement of the trigeminal nerve, demonstrable by blink and jaw reflexes (12). Trigeminal somatosensory evoked potentials have proved to be quite informative in the evaluation of the sensory 5th nerve function but have remained underused in the workup for MS.

Compared to trigeminal somatosensory evoked potentials, tSSEP have an excellent sensitivity for pathological processes involving the somatosensory afferents of the tongue, however, they do not seem to provide further information on the nature of the lesion (8).

In conclusion, this study confirmed, in a larger number of MS patients, the usefulness of tSSEP in the evaluation of afferent trigeminal pathways in MS.

REFERENCES

1. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69: 292-302.
2. Comi G, Martinelli V, Locatelli T, Leocani L, Medaglini S. Neurophysiological and cognitive markers of disease evolution in multiple sclerosis. Mult Scler 1998; 4: 260-5.
3. Habek M. Evaluation of brainstem involvement in multiple sclerosis. Expert Rev Neurother 2013; 13: 299-311.
4. Sastre-Garriga J, Tintore M, Nos C *et al*. Clinical features of CIS of the brainstem/cerebellum of the kind seen in MS. J Neurol 2010; 257: 742-6.
5. Zadro I, Barun B, Habek M, Brinar VV. Isolated cranial nerve palsies in multiple sclerosis. Clin Neurol Neurosurg 2008; 110: 886-8.
6. Gass A, Kitchen N, Macmanus DG, Moseley IF, Hennerici MG, Miller DH. Trigeminal neuralgia in patients with multiple sclerosis: lesion locali-

zation with magnetic resonance imaging. Neurology 1997; 49: 1142-4.

7. Gabelic T, Skoric MK, Adamec I, Mayer D, Habek M. Tongue somatosensory-evoked potentials: evaluation of the afferent trigeminal pathway in patients with early multiple sclerosis. Clin EEG Neurosci 2013; 44: 286-90.
8. Altenmüller E, Cornelius CP, Buettner UW. Somatosensory evoked potentials following tongue stimulation in normal subjects and patients with lesions of the afferent trigeminal system. Electroencephalogr Clin Neurophysiol 1990; 77: 403-15.
9. Van Loven K, Jacobs R, Van Hees J, Van Huffel S, van Steenberghe D. Trigeminal somatosensory evoked potentials in humans. Electromyogr Clin Neurophysiol 2001; 41: 357-75.
10. Bergamaschi R, Romani A, Versino M, Callieco R, Gaspari D, Citterio A, Cosi V. Usefulness of trigeminal somatosensory evoked potentials to detect subclinical trigeminal impairment in multiple sclerosis patients. Acta Neurol Scand 1994; 89: 412-4.
11. Soustiel JF, Hafner H, Chistyakov AV, Yarnitzky D, Sharf B, Guilburd JN, Feinsod M. Brain-stem trigeminal and auditory evoked potentials in multiple sclerosis: physiological insights. Electroencephalogr Clin Neurophysiol 1996; 100: 152-7.
12. de Pablos C, Agirre Z. Trigeminal somatosensory evoked potentials in multiple sclerosis: a case report. Clin EEG Neurosci 2006; 37: 243-6.

Address for correspondence: Magdalena Krbot Skorić, MSc EE, Clinical Department of Neurology, Zagreb University Hospital Center, Kišpatićeva 12, HR-10000 Zagreb, Croatia; e-mail: mkrbot@gmail.com

Somatosenzorni evocirani potencijali jezika u bolesnika s multiplom sklerozom

SAŽETAK – **Cilj:** Cilj ovoga istraživanja bio je ispitati učinkovitost somatosenzornih evociranih potencijala jezika (tSSEP) u procjeni zahvaćenosti moždanog debla u bolesnika s multiplom sklerozom (MS). **Metode:** Metoda tSSEP je provedena na deset zdravih ispitanika i 29 bolesnika s prvim kliničkim znakovima koji upućuju na MS. Dobiveni podatci uspoređeni su između dvije skupine i tSSEP rezultati dobiveni kod bolesnika s MS-om korelirani su s njihovim kliničkim podatcima i magnetskom rezonancom (MR). **Rezultati:** Bolesnici s MS-om su imali statistički značajno produžene latencije komponenata N1, P1 i N2 na lijevoj strani u usporedbi sa zdravim kontrolama (17,8±3,5 *vs*. 15,2±1,3, p=0,004; 23,9±3,3 *vs*. 20,8±1,0, p<0,001; 29,9±4,2 *vs*. 26,7±2, p=0,01) te latencija komponenata P1 i N2 na desnoj strani (23,8±3,5 *vs*. 20,8±1,3, p=0,04; 30,3±3,8 *vs*. 27,3±1,9, p=0,01). Od 29 bolesnika s MS-om osam (28 %) ih je imalo kliničke znakove oštećenja moždanog debla i 19 (66 %) ih je imalo lezije moždanog debla vidljive na MR-u. Devetnaest bolesnika s produženim latencijama nije imalo kliničkih znakova zahvaćenosti moždanog debla (statistički značajno, p<0,0001). Metoda tSSEP je otkrila lezije moždanog debla u većem postotku nego MR, ali to nije bilo statistički značajno (p=0,18). **Zaključak:** Ovo istraživanje provedeno na većem broju bolesnika s MS-om potvrdilo je učinkovitost metode tSSEP u procjeni aferentnog trigeminalnog puta kod bolesnika s MS-om.

Ključne riječi: somatosenzorni evocirani potencijali jezika, aferentni trigeminalni putovi, magnetska rezonanca, multipla skleroza