Neuroscience Letters 612 (2016) 62–65

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research paper

Trigeminal somatosensorial evoked potentials suggest increased excitability during interictal period in patients with long disease duration in migraine

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HIGHLIGHTS

- TSEP parameters between patients with migraine and healthy subjects showed no difference.
- Stimulation thresholds decreased as the attack frequency increased.
- Ipsilateral N1/P1 amplitude increased as prolonged disease duration.
- Migraine with long duration affects the excitability of the cortical and brainstem trigeminal pathways even during interictal periods.

ARTICLE INFO

Article history:
Received 24 October 2015
Received in revised form
25 November 2015
Accepted 26 November 2015
Available online 28 November 2015

Keywords:
Trigeminal nerve sensory evoked potentials
Trigeminal pathway
Migraine

ABSTRACT

Introduction: Migraine pathogenesis is suggested to involve many structures in cerebral cortex, brainstem and trigeminovascular system. Electrophysiological studies revealed loss of habituation, decreased cortical preactivation, segmental hypersensitivity and reduction in control of inhibitory descending pathways. Given these information, we aimed to evaluate the excitability changes of the trigeminal pathway in the cortex and brainstem in migraine using trigeminal nerve somatosensory evoked potentials (TSEP).
Patients and method: Fifty-one women with migraine without aura and 32 age-matched healthy women were included. TSEPs were recorded in migraine patients during interictal period and in healthy subjects. Sensory thresholds, stimulation intensities, latencies of N1, P1, N2 and P2 waves as well as N1/P1 and N2/P1 amplitudes were measured.
Results: Comparisons of ipsilateral latencies with N1–P1 and N2–P1 amplitudes between migraine and control groups showed no difference. Sensory thresholds were also similar. Stimulation thresholds decreased as the attack frequency increased and ipsilateral N1/P1 amplitude increased with prolonged disease duration ($p = 0.043$).
Conclusion: Our study did not show significant difference between migraine patients and healthy subjects during interictal period. However, migraine with long duration affects the excitability of the cortical and brainstem trigeminal pathways even during interictal periods.

1. Introduction

Migraine is an episodic primary headache disorder which presents with attacks of various combinations of symptoms attributed to neurological, gastrointestinal and autonomic nervous system.

The possible pathophysiological mechanism has been explained by the integrated neurovascular theory which involves the interaction between vascular structures and central and peripheral components of trigeminal system [1,2]. Large cerebral vessels, pial vessels and large dural venous sinuses get dilated secondary to a cascade of neurological changes like spreading depression. These structures are innervated by trigeminal nerve, largely ophtalmic branch and are also sensitive to pain. Pain is conducted by unmyelinated small C fibers and the generator is the caudal trigeminal nucleus. Central pathway includes trigeminal lemniscus, ventroposteromedial nucleus of thalamus and primary somatosensorial

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http://dx.doi.org/10.1016/j.neulet.2015.11.045
0304-3940/

cortex. Trigeminal pain sensitive fibers cross before the formation of trigeminal lemniscus [3,4].

Functional neuroimaging studies showed the important role of ipsilateral dorsolateral pons [5,6]. Increased activation is shown in ipsilateral locus ceruleus and dorsal raphe nucleus, periaqueductal gray matter during attacks. Contralateral brainstem also demonstrates some changes probably secondary to thalamic pain control mechanisms.

Trigeminal nerve somatosensory evoked potential (TSEP) reflects functional and structural status of the peripheral (early components) and central (late components) pathways of trigeminal sensory branches [7–10].

Here, we aimed to analyze structural and functional status of central and peripheral pathways of trigeminal system using the early and late components of TSEP in migraine.

2. Patients and method

2.1. Patients

This is a case-control study conducted between January 2011 and January 2012. A total of consecutive 51 female patients with the diagnosis of migraine without aura and age-matched 32 healthy women who did not experience any kind of headache were enrolled in this study. Mean ages of migraine patients and healthy controls were 38.0 ± 10.4 years (age range: 18–65 years) and 36.5 ± 12.8 years (age range: 18–65 years), respectively. Secondary causes of headaches were excluded in all patients by history, laboratory investigations and cranial magnetic resonance imaging.

2.1.1. Inclusion criteria

1. Migraine without aura which was diagnosed according to the criteria of International Headache Society 2004.

2.1.2. Exclusion criteria

1. Neurological disorders other than migraine, psychiatric or systemic disorders, any medication use.
2. Age <18 years.
3. Abnormal neurological or systemic examination findings.
4. Acute attack within 3 days before and after electrophysiological examination.

The study was approved by the Institutional Review Board and all participants gave informed consent.

2.2. Clinical assessments

Age, duration of migraine, attack frequency and localization of pain in most of the episodes were noted. Patients were grouped according to age as young (18–40 years) and elderly (40–65 years), according to localization of pain (right, left, variable and bilateral), according to attack frequency (≥5 attacks/month and <5 attacks/month) and according to duration of migraine (1–7 years, 8–15 years and >16 years).

2.3. Electrophysiological assessments

All electrophysiological recordings were done using Neuropack Sigma MEB-5504K, Nihon Kohden Medical, Tokyo, Japan.

Recording electrodes were placed over representative trigeminal sensory area, specifically 2 cm behind C5′ and C6′ according to 10–20 electrode positioning system. Responses were recorded over scalp after stimulation of contralateral corner of mouth. Reference electrode was located over Fpz′. Stimulus duration was 0.2 ms and the stimulus intensity was 3 times of sensory threshold. The instrument was set with a sweep ranging from 10 to 20 ms per division.

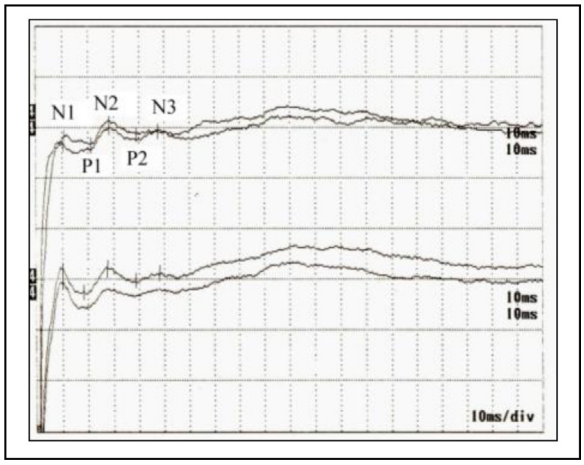

Fig. 1. A representative example of trigeminal somatosensory potential in a healthy individual showing N1, P1, N2, P2 and N3 waves.

The gain was 10 μV per division depending on the response. Filter settings were 0–3000 Hz. Recordings were averaged for 200 times and repeated twice. TSEP values which were on the same side as the pain were named as ipsilateral, the ones contralateral to pain were named as contralateral.

2.4. Statistical analysis

We measured latency N1, P1, N2, and P2 waves and peak-to-peak amplitudes of N1–P1 and N2–P1 waves in both groups using cursors. Fig. 1 shows a representative example of TSEP in a healthy individual. We first made comparisons of right-sided and left-sided parameters in control group. As there were no differences, we combined right-sided and left-sided parameters in control group forming a big group and compared latencies and amplitudes between patient and controls.

Data were pooled to obtain mean values and standard deviations (SD). Data analyses were performed using the SPSS 11.5 software statistical package (SPSS Inc., Chicago, IL, USA). Comparisons were made by *t*-test for quantitative data with normal distribution and by Mann–Whitney-*U* test or Kruskal–Wallis test for quantitative data with not normal distribution, and by chi-square test for qualitative data. As we performed multiple comparisons, we have used Bonferroni correction.

Comparisons of TSEP parameters were also done according to groups which were formed using age (young vs elderly), localization of pain (ipsilateral vs contralateral), attack frequency (≥5 attacks/month vs <5 attacks/month) and duration of migraine (1–7 years, 8–15 years vs >16 years). Ipsilateral and contralateral groups were formed according to side of pain. For this grouping, we excluded patient with bilateral headache episodes or variable headache side.

Correlation between stimulation threshold and attack frequency or disease duration were analyzed using Spearman's correlation test.

3. Results

3.1. Clinical assessments

Age range was between 18 and 65 years in both groups with almost equal distribution of younger and elderly groups. All patients were female due to inclusion criteria. Pain was lateralized in more than 60% of patients.