SHORT COMMUNICATION
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Salivary alpha-amylase and tooth pulp evoked potentials in paroxysmal trigeminal neuralgia patients

Salivarna alfa amilaza i evocirani potencijali zubne pulpe kod bolesnika sa paroksizmalnom trigeminalnom neuralgijom

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Abstract

Background/Aim. The sudden and excruciating pain that characterizes paroxysmal trigeminal neuralgia (PTN) has a negative effect on the wellbeing of the affected individuals, causing psychological distress. Salivary alpha-amylase (sAA) level represents an objective assessment of physical, physiological, and psychological stress. Evoked potentials (EPs) reflect nerve function and evaluate a functional aspect of the trigeminal nerve conduction. The aim of this study was to analyze possible modifications in painful impulses conduction related to sAA level by registering tooth pulp EPs in PTN patients. **Methods.** The study included ten PTN patients and twelve healthy subjects. The activity of sAA was measured using the Nipro Salivary Amylase Monitor. In order to record EPs response, the dental pulp of vital teeth was electrically stimulated through intact enamel. For stimulation and impulse registration, we used Xltek Protektor 32 system, software EPWorks, version 5.0. **Results.** The results obtained in PTN patients showed a higher number of waves and significantly shorter latencies and lower amplitudes N2-P2 and N3-P3 at the neuralgic side compared to the healthy side of the same patient, as well as to the controls ($p < 0.05$). Moreover, latencies were significantly shorter in patients with higher sAA levels than in those with normal sAA levels ($p < 0.05$). Late latencies (N2 and P2) at the healthy side in patients with higher sAA levels were significantly shorter compared to patients whose sAA levels were normal ($p < 0.05$). **Conclusion.** This study showed that psychical stress associated with PTN probably further increased hyperexcitability and conduction velocity of the affected nerves. Moreover, it seems that anticipation of stressful pain even increases the conduction velocity of unaffected nerves at the thalamocortical level in PTN patients. However, in healthy individuals, stress itself had no influence on painful impulses conduction.

Key words:
alpha-amylases; evoked potentials; neuralgia; pain; stress, psychological; trigeminal neuralgia.

Apstrakt

Uvod/Cilj. Paroksizmalna trigeminalna neuralgija (PTN) se karakteriše iznenadnim i intenzivnim bolom koji nepovoljno utiče na stanje obolelog i može prouzrokovati psihičku uznemirenost. Nivo salivarne alfa amilaze (sAA) predstavlja objektivnu procenu fizičkog, fiziološkog i psihološkog stresa. Evocirani potencijali (EP) odražavaju sprovodnu funkciju neurona, zbog čega se mogu primeniti za procenu neurotransmisije duž puta trigeminalnog nerva. Cilj rada bio je da se kod bolesnika sa PTN registrovanjem EP zubne pulpe ispitaju promene u prenošenju bolnih impulsa u odnosu na nivo sAA. **Metode**. Studijom je obuhvaćeno 10 bolesnika sa PTN i 12 zdravih ispitanika. Aktivnost sAA određivana je upotrebom aparata „Nipro Salivary Amylase Monitor". U cilju dobijanja odgovora EP, zubna pulpa je stimulisana električnom strujom preko intaktne gleđi. Za stimulaciju i registraciju korišćen je apparat „Xltek Protektor 32 sistem", softver „EPWorks", verzija 5.0. **Rezultati**. Rezultati dobijeni od bolesnika sa PTN pokazuju veći broj talasa i značajno kraće latence na neuralgičnoj strani u poređenju sa zdravom stranom i sa kontrolnom grupom ispitanika ($p < 0,05$). Na neuralgičnoj strani su sve latence bile značajno kraće, a amplitude N2-P2 i N3-P3 značajno niže kod bolesnika sa povišenim nivoom sAA u odnosu na one koji su imali normalan nivo sAA ($p < 0,05$). Kasne latence (N2 i P2) na zdravoj strani kod bolesnika sa povišenim nivoom sAA bile su značajno kraće u poređenju sa bolesnicima čiji je nivo sAA bio normalan ($p < 0,05$). **Zaključak.** Naše istraživanje je pokazalo da psihički stres udružen sa

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PTN dodatno povećava hiperekscitabilnost i brzinu sprovođenja neurona. Osim toga, anticipirani stres povećava brzinu sprovođenja na talamokortikalnom nivou čak i na nepogođenoj strani kod pacijenata sa PTN. Međutim, kod zdravih ispitanika, stres sam po sebi nema uticaja na brzinu prenosa bolnih impulsa.

Introduction

Paroxysmal trigeminal neuralgia – (PTN) is a neuropathic pain condition characterized by paroxysmal, lancinating pain attacks along the somatosensory distribution of one or more divisions of the trigeminal nerve [1–3]. Its pathogenesis is not fully understood. It is believed to be related to microvascular compression of the trigeminal nerve root by aberrant blood vessels [1–4]. However, it seems that additional neurophysiological mechanisms are also involved [2]. Ultrastructural and biochemical changes in axon and myelin are not only seen in the trigeminal root but also in Gasserian ganglion [1, 5]. Chronic nerve compression results in demyelination, with progressive axonal degeneration in small unmyelinated and thin myelinated fibers. Demyelination may give an increase to electrical hyperexcitability, spontaneous and triggered ectopic impulses, and cross excitation among neighboring afferents [1, 3, 5]. Atrophy of the trigeminal nerve [6, 7] and reduced volume of gray matter [1, 8] are also seen.

The sudden and excruciating nature of the pain in PTN has a negative effect on the wellbeing of the affected individuals, leading to psychological distress [9]. Depression and anxiety are the most frequent psychiatric comorbidities associated with trigeminal neuralgia (TN) [7, 9]. Stress is implicated in the etiology of depressive and anxiety disorders [10, 11]. Chronic exposure to stress leads to morphological damage [11, 12], as well as functional disorders like neuronal hypersensitivity [13, 14].

Salivary alpha-amylase (sAA) level is shown to be an objective assessment of physical, physiological, and psychological stress [15, 16]. Evoked potentials (EP) can reflect the function of the trigeminal nerve conduction; therefore, a functional level of the trigeminal nerve conduction pathway may be evaluated by the EP [17]. To our knowledge, studies about the effects of sAA level on the tooth EP in PTN patients have not been previously reported. Thus, the aim of this study was to analyze modifications in painful impulse conduction (registered by the tooth pulp EP) related to sAA level in PTN patients. Although this is a preliminary report, we have studied the tooth pulp EP in stress and pain states and their modulation by analgesics and anxiolytics.

Methods

Ten PTN patients (eight females and two males, mean age 51.40 ± 20.07) were recruited from the Clinic for Oral and Maxillofacial Surgery at the Institute of the Faculty of Stomatology in Pančevo. Additionally, twelve healthy subjects participated in the study. The study was approved by the local Ethics Committee and was in accordance with the Declaration of Helsinki [18]. All subjects gave their written informed consent after a full explanation of the study, focusing on the purpose of the study and precise procedures. Exclusion criteria were as follows: avital central incisors of the upper jaw, prosthetics and fillings on the same teeth, oral mucosal changes, fractures, trauma or surgery in the maxillofacial region, as well as the use of any drug that could contribute to the action of the sympathetic nervous system, such as alpha-blockers, beta-blockers [15, 19], alpha-methyldopa, etilefrine hydrochloride, amezinium metilsulfate, midodrine hydrochloride, L-threo-3,4-dihidroxyphenylserine, and antidepressants [20]. The participants were asked not to smoke, eat or drink anything 30 min prior to testing. All participants were examined under the same conditions, from 8 am to 12 pm.

The activity of sAA was measured using a hand-held sAA monitor manufactured by Nipro (Osaka, Japan). This analyzer enables automatic measurement of sAA activity within one minute from collection to completion of the measurement, using a dry-chemical system [16].

To record cortical somatosensory-evoked response, we stimulated the dental pulp electrically through the intact enamel by a pair of specialized Ag-AgCl electrodes on the vestibular and palatal surface of the intact maxillary incisor under condensation silicone dental impression Zetaplus (Zhermack Clinical, Italy). Single square pulses of 1 ms and 1 mA intensity were delivered at a rate of 1 Hz (machine-delivered stimulation). Brain potentials were collected with surface cup electrodes placed on the Vertex and kept in place by collodion (Aquasonic 100 Ultrasound Transmission Gel, Parker Laboratories Inc., Fairfield, New Jersey, USA), the reference being 2 cm above the Inion. The analysis time was 300 ms. Signals were amplified (10 µV), filtered (0.5–70 Hz), and averaged (2 sweeps). For stimulation and registration, we used Xltek Protektor 32 system, software EPWorks, version 5.0 (Natus Medical Inc., Canada) that contained a complete data acquisition system with built-in amplifiers, A/D converters, digital signal processors, central processing units, and storage devices.

Five recordings were performed for each participant. Normal EP values were collected from all volunteers (six females and six males, mean age 21.59 ± 1.08). In PTN patients, the recording was performed on both upper central incisors. The peak latencies and the peak-to-peak amplitude of all components were measured.

Data were statistically analyzed with the SAS System for Windows, release 9.3 [21]. We used the Kruskal-Wallis test to determine statistical significance. Values of $p < 0.05$ were considered significant. Results are expressed as mean ± the standard error of the mean.

Results

The tooth pulp EP obtained from PTN patients demonstrated a higher number of waves with significantly shorter latencies at the neuralgic side compared to the healthy side and the controls ($p < 0.05$). The amplitudes decreased at the neuralgic side vs. the healthy side and controls but without statistical significance (Figure 1, Tables 1 and 2). There were no significant differences in the tooth pulp EP components (latencies and amplitudes) between the healthy side and the controls (data not shown).

Higher sAA levels were found in 2 (20%) patients and 5 (41.67%) controls.
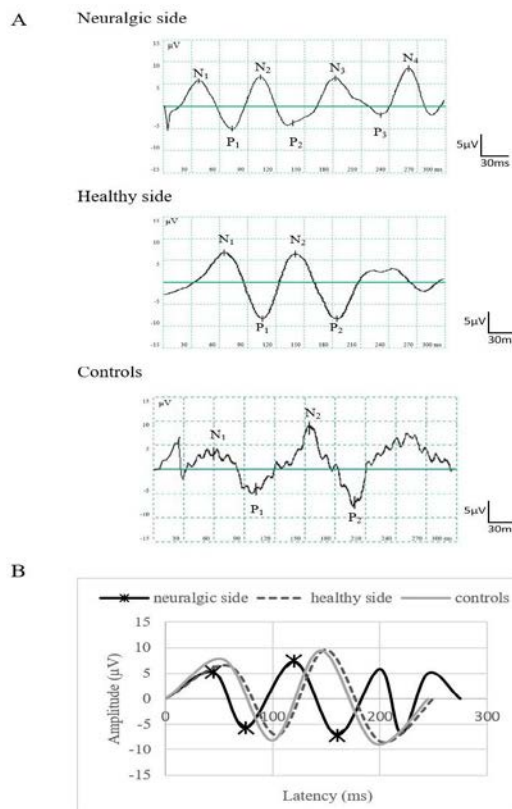

Fig. 1 – A) Original waveform recordings from Vertex after stimulation of the tooth at the neuralgic side, healthy side, and controls: An upward deflection of the evoked potential (EP) waveform was defined as N (negative) and downward deflection as P (positive); B) The pattern of the mean values of EP from the neuralgic side, healthy side, and controls: There were higher numbers of waves and the latencies significantly shorter at the neuralgic side compared to the other two groups [* - statistically significant difference ($p < 0.05$)].

Table 1
Comparison of evoked potential (EP) parameters in paroxysmal trigeminal neuralgia patients between neuralgic and healthy side

EP parameters	Side		p
	neuralgic	healthy	
Latency (ms)			
N1	44.91 ± 2.48	58.63 ± 1.93	0.0008^*
P1	77.21 ± 1.57	102.80 ± 3.80	0.0001^*
N2	118.50 ± 4.13	151.98 ± 6.67	0.0018^*
P2	157.70 ± 7.31	202.20 ± 5.76	0.0014^*
N3	199.40 ± 11.22		
P3	217.62 ± 11.09		
N4	243.00 ± 12.30		
Amplitude (µV)			
N1-P1	10.96 ± 1.33	13.62 ± 2.04	0.1720
N2-P2	14.54 ± 1.64	18.04 ± 2.16	0.0585
N3-P3	12.95 ± 2.35		

All values are expressed as mean ± standard error; $^*p < 0.05$ (Kruskal-Wallis test).

Table 2

Comparison of evoked potential (EP) parameters parameters in paroxysmal trigeminal neuralgia patients between neuralgic side and controls

EP parameters	Neuralgic side	Controls	p
Latency (ms)			
N1	44.91 ± 2.48	62.21 ± 2.54	0.0001*
P1	77.21 ± 1.57	102.46 ± 2.35	< 0.0001*
N2	118.50 ± 4.13	153.42 ± 3.99	0.0002*
P2	157.70 ± 7.31	201.71 ± 4.59	0.0012*
N3	199.40 ± 11.22		
P3	217.62 ± 11.09		
N4	243.00 ± 12.30		
Amplitude (μV)			
N1-P1	10.96 ± 1.33	12.55 ± 0.69	0.1129
N2-P2	14.54 ± 1.64	15.33 ± 0.75	0.0985
N3-P3	12.95 ± 2.35		

All values are expressed as mean ± standard error; *$p < 0.05$ (Kruskal-Wallis test).

At the neuralgic side, all latencies were significantly shorter, and amplitudes N2-P2 and N3-P3 were significantly lower in patients with higher sAA levels ($p < 0.05$) than in those with normal sAA levels (Figure 2, Table 3).
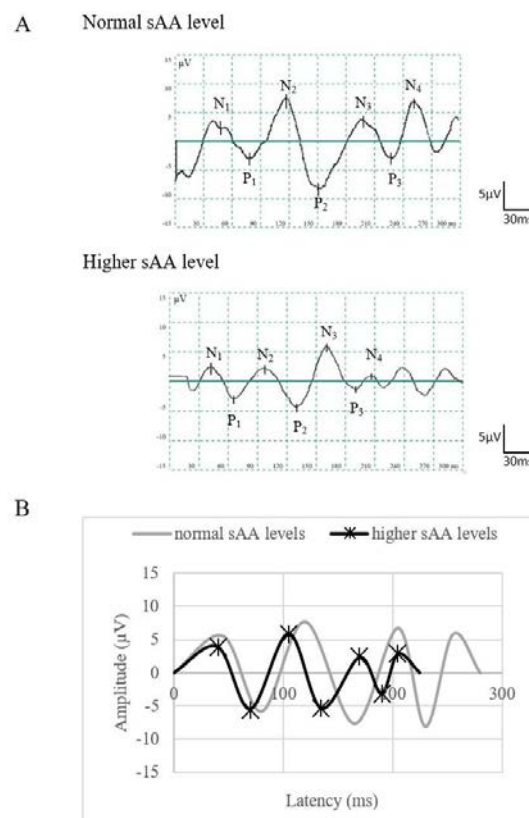

Fig. 2 – A) Original waveform recordings from patients with normal and higher salivary alpha-amylase (sAA) levels after stimulation of the tooth at the neuralgic side; B) The pattern of the mean values of evoked potential (EP) from the neuralgic side related to normal and higher sAA levels: All latencies were significantly shorter, and amplitudes N2-P2 and N3-P3 were significantly lower in patients with higher sAA levels than in those with normal sAA levels [* - statistically significant difference ($p < 0.05$)].

Table 3

Comparison of evoked potential (EP) parameters in paroxysmal trigeminal neuralgia patient at the neuralgic side related to salivary alpha-amylase (sAA) levels

EP parameters	Normal sAA levels	Higher sAA levels	p
Latency (ms)			
N1	46.00 ± 3.00	39.85 ± 0.45	0.0293*
P1	79.13 ± 1.15	69.53 ± 1.07	0.0345*
N2	122.13 ± 4.17	104.58 ± 1.53	0.0345*
P2	163.25 ± 7.93	135.27 ± 2.10	0.0345*
N3	207.00 ± 12.64	168.09 ± 4.04	0.0345*
P3	227.33 ± 12.31	188.15 ± 8.36	0.0417*
N4	255.00 ± 12.81	206.45 ± 6.95	0.0417*
Amplitude (μV)			
N1-P1	11.35 ± 1.57	9.42 ± 0.11	1.0000
N2-P2	15.35 ± 1.15	11.53 ± 0.09	0.0339*
N3-P3	15.44 ± 1.22	5.75 ± 0.25	0.0417*

All values are expressed as mean ± standard error; *$p < 0.05$ (Kruskal-Wallis test).

Late latencies (N2 and P2) at the healthy side in patients with higher sAA levels were significantly shorter compared to patients whose sAA levels were normal, whereas amplitudes showed no significant changes (Figure 3, Table 4). In the control group (healthy patients), tooth pulp EP components showed no significant difference in relation to sAA levels (data not shown).
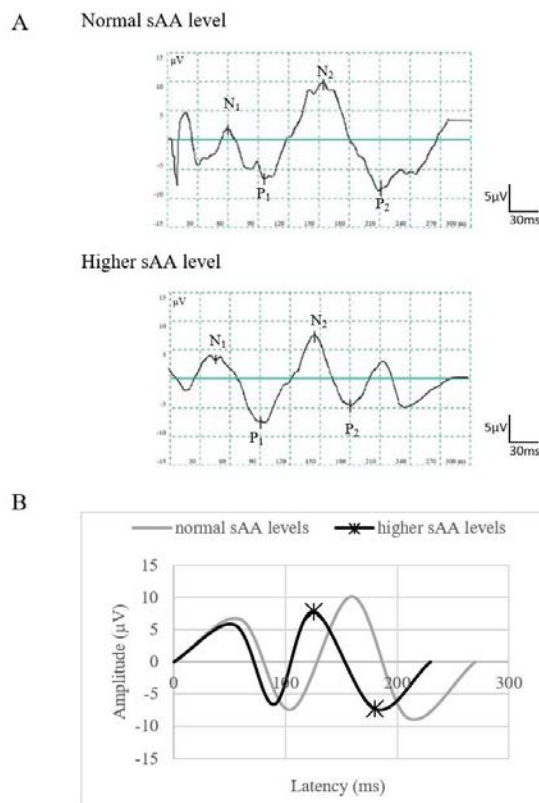

Fig. 3 – A) Original waveform recordings from patients after tooth stimulation at the healthy side related to normal and higher salivary alpha-amylase (sAA) levels; B) The pattern of the mean values of EP from the healthy side related to normal and higher sAA levels: Late latencies (N2 and P2) at the healthy side in patients with higher sAA levels were significantly shorter compared to patients whose sAA levels were normal [* - statistically significant difference ($p < 0.05$)].

Table 4

Comparison of evoked potential (EP) parameters in paroxysmal trigeminal neuralgia patients at the healthy side related to salivary alpha-amylase (sAA) levels

EP parameters	Normal sAA levels	Higher sAA levels	p
Latency (ms)			
N1	59.78 ± 2.24	54.38 ± 0.27	0.2888
P1	105.75 ± 4.02	89.60 ± 0.15	0.2765
N2	158.10 ± 6.58	127.12 ± 1.49	0.0339*
P2	207.88 ± 5.39	179.78 ± 1.53	0.0339*
Amplitude (μV)			
N1-P1	13.95 ± 2.37	12.78 ± 2.51	1.0000
N2-P2	12.30 ± 0.05	15.11 ± 0.10	1.0000

All values are expressed as mean ± standard error; *$p < 0.05$ (Kruskal-Wallis test).

Discussion

To our knowledge, this is the first study investigating sAA activity in relation to painful impulses registered by tooth pulp EP in PTN patients.

The present findings support previous results that PTN patients show a higher number of waves at the neuralgic side [4, 22–24]. However, the results of EP latencies are inconsistent. Some publications describe prolonged EP latencies [4, 22, 24], while others found no changes in the EP latencies length [25, 26]. We could presume that prolonged EP latencies are due to the compression of Gasser ganglion, which is mentioned as a cause of neuralgia in previous studies. It is well established that compression of the peripheral nerve produces both conduction block and decreased conduction velocity [4, 24]. Our results showed shortened mean latencies of all EP components at the neuralgic side compared to both the healthy side and healthy controls. This is in agreement with the findings of Lekić and Cenić [23] and suggests an increased conduction velocity at the second-order neurons and a greater number of synaptic discharges in the ventral posteromedial nucleus of the thalamus, which is reflected in twice the number of waves in the thalamocortical pathway after a latency period of 150 ms. According to the ignition hypothesis, due to microvascular compression near the root, focal demyelination of the trigeminal sensory root generates spontaneous ectopic impulses responsible for the short-lasting attacks.

Psychological stress can produce several effects in a variety of physiological systems, similar to those produced by physical challenges due to activation of two stress response systems: the sympathoadrenal medullary (SAM) system and the hypothalamic-pituitary-adrenal axis [27]. Stress requires heightened excitability or arousal, which can be operationally measured using electroencephalography, behavioral (motor) activity, or neurochemical (adrenaline, glucocorticoid) levels [14]. There have been many attempts to quantify stress by various methods, including psychological tests and measurements of hormonal, cardiovascular responses, and other physiological parameters. However, sAA is increasingly used as an indicator of stress because sAA activity is a reliable stress marker of the sympathoadrenal system, not being influenced by the salivary flow [28]. In contrast to other parameters, sAA seems to have the advantages of being a noninvasive, painless, and fast method, allowing easy and stress-free quantification and multiple sampling [16]. The role of biological stress markers as mediators between stress and pain is confirmed [27–29].

The pain was identified as psychological stress [30] and, *vice versa*, stress is a factor that causes and maintains the pain intensity [29]. Several studies have shown morphological as well as functional changes in both neuralgic [1, 3, 5–8] and stress states [11–14]. We noticed that latencies at the neuralgic side were shorter as a result of the hyperexcitability of dysfunctional nerves. Findings in which the latency period was additionally reduced when the activity of sAA was increased suggest that psychical stress associated with PTN further increases hyper-excitability and conduction velocity. In patients with higher sAA levels, at the neuralgic side, late amplitudes were significantly lower than in those with normal sAA levels. The progressive reduction in late amplitude could be induced by cortical plastic modification in the pain matrix structures or in the brainstem monoaminergic nuclei. These structures are central effectors of the endogenous pain control system and play a crucial role in the central processing of sensory stimuli [31]. A recent study [32] also showed that reduced EP amplitude significantly predicted higher questionnaire scores of anxiety/depression, reports of increased life dysfunction, greater comorbidity, and clinician ratings of heightened severity and poorer prognosis. Moreover, EP amplitudes decreased in post-traumatic stress disorders [33], attention-deficit/hyperactivity disorders, and schizophrenia [34].

Late latencies at the healthy side in PTN patients with higher sAA levels were significantly shorter compared to the patients whose sAA levels were normal. Although these results relate to the nerves unaffected with TN, they reflect stress possibly due to anticipating a painful procedure. This is because TN patients live in fear of receiving the next pain attack. According to Capranica et al. [35], increases in sAA indicate psychological arousal due to anticipating the upcoming event. Pain modulatory networks in the brain play an active role in controlling nociceptive responses so that pain perception is influenced by our state of arousal, attention, and expectation [36]. Endogenous factors, such as the state of the subject, vigilance, psychological meaning, and demands of the stimulus, determine the EP [37, 38]. Stimuli associated with emotions, such as surprise, shock, uncertainty, obtrusiveness, or pain, also influence late EP components. Late EP components are not specific to the modality of the eliciting stimulus; they reflect the emotional-motivational aspects of pain, relating to factors such as degree of discomfort or unpleasantness associated with pain [37]. In contrast, early EP components are determined by the characteristics of the afferent input and, hence, the eliciting stimulus. In reality, the two phenomena cannot always be clearly separated [38].

This study confirms the involvement of stress in the PTN-affected nerve hyperexcitability. Furthermore, the results might support a functional rather than a structural

alteration in the trigeminal sensory pathway. As for the results, the following limitations should be considered: this is a preliminary study, limited by its sample size; however, the design, findings, and inclusion of physiological measures present a contributory role in the essential line of research. Those results, nevertheless, require further observation in a larger number of participants.

PTN is a relatively rare condition and can be sometimes confused with other painful conditions affecting the orofacial region [1]. These patients usually seek many health care providers before receiving a proper diagnosis and management. Dentists and physicians tend to consider, first of all, more common conditions that are likely to occur in the facial region (like a toothache) rather than PTN [39]. The initial misdiagnosis may lead to unnecessary interventions in many patients, especially unneeded dental restorative and surgical procedures [40]. In addition, the mean age of the TN patients is in the sixth decade [1, 9]. At that age, many persons have already lost their teeth for various reasons and have prosthetic replacements. Moreover, many PTN patients are in fear of an upcoming pain attack. It is not surprising to note that any sensation can be perceived as pain and may cause retreatment. It is also difficult to establish age-matched controls since persons after their fifties usually take medications for some other health condition. However, these criteria are not necessary because EP waveforms tend to be remarkably stable within and across the subject age in both amplitude and latency [41].

Conclusion

We found that psychical stress associated with PTN further increased hyperexcitability and conduction velocity. Besides, stress anticipation increased conduction velocity at the thalamocortical level even of unaffected nerves in PTN patients. However, in healthy individuals, stress itself had no influence on painful impulses conduction.

Acknowledgement

R E F E R E N C E S

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