

Evaluation of the pathophysiology of classical trigeminal neuralgia by blink reflex study and current perception threshold testing

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Abstract We recruited 49 patients with classical trigeminal neuralgia (TN) according to the latest guidelines of the International Classification of Headache Disorders, and divided them into an acute (≤ 30 days onset; 13 patients) and a chronic (> 30 days onset; 36 patients) group. We used blink reflex study and current perception threshold (CPT) testing to evaluate the painful facial areas and contralateral non-painful areas of patients with classical TN. CPT 5 Hz examinations, which correlate with unmyelinated fiber function, showed significantly decreased CPTs in the acute stage (11.62 ± 6.99 vs. 18.69 ± 9.66 , $P = 0.025$), but significantly increased CPTs in the chronic stage (26.67 ± 18.65 vs. 19.69 ± 13.70 , $P = 0.010$) on the painful side when compared with the contralateral non-painful side. However, CPTs at 250 Hz ($A\delta$) and 2000 Hz

($A\beta$) examinations did not show significant differences between the painful and non-painful sides. In contrast, only three (3/49) patients showed an abnormal trigeminal nerve stimulation on the ipsilateral painful side by blink reflex study. The findings suggest that classical TN is not a simple large-myelinated nerve fiber dysfunction but a more complex process with a main dysfunction of unmyelinated nerve fibers.

Keywords Current perception threshold · Classical trigeminal neuralgia · Unmyelinated fiber · Neuropathic pain

Introduction

Classical trigeminal neuralgia (TN) has an annual incidence rate of 4.5 per 100000 [1]. It is characterized by recurrent episodes of intense, lancinating pain evoked by light touch localized to a small area of the face. Persistent background dull pain is also noted in some chronic cases [2–4]. Most classical TN is caused by the compression of the trigeminal nerve root by tortuous or aberrant vessels within a few millimeters of entry into the pons [5].

Current opinions indicate that pain in classical TN is caused by primary demyelination damage to large rather than small afferent fibers [5–7]. Different neurophysiologic methods have been used in TN investigations but with inconclusive results. Few studies of quantitative sensory testing showed that the cutaneous perception of temperature and light touch is impaired within the affected trigeminal divisions [8, 9], suggesting both small and large diameter sensory fiber involvement. A previous electrophysiological study showed that the trigeminal-evoked potential is abnormal in TN patients, indicating a large

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myelination fiber dysfunction [10]. However, only few patients with idiopathic TN have an abnormal blink reflex [11, 12], which is in conflict with large myelination fiber impairment. There were also reports about using laser-evoked potentials, which resulted in a small myelinated fiber dysfunction in TN [13–15]. A recent study using nociceptive blinking reflex (nBR) and pain-related-evoked potential (PREP) showed a dysfunction of the trigeminal nociceptive pathway caused by small-myelinated A-delta fiber dysfunction [16]. The above studies had inconsistent results, and which types of nerve fibers are most affected is not well clarified yet.

Although the ordinary-evoked potential, blink reflex and laser-evoked potential all can be used to detect electrophysiological abnormalities in TN [10–15], they only offer information on large myelinated fibers and small myelinated fibers, respectively. Small unmyelinated fibers cannot be evaluated. Constant current perception threshold (CPT) testing is another method, which can evaluate both large- and small-fiber functions at the same time [17–19]. CPT relates to the direct stimulation of myelinated and unmyelinated nerve fibers in the skin. The 2000 Hz stimulus-evoked responses from large myelinated fibers ($A\beta$), 250 Hz stimulated small myelinated fibers ($A\delta$), and 5 Hz induced responses from unmyelinated fibers [17–19]. CPT has been widely used in the assessment of diabetic neuropathy [20], uremic neuropathy [21], post-therapeutic neuralgia [22] and Fabry's disease [23].

The purpose of this study aims to clarify which nerve fibers are mainly affected in classical TN by blink reflex and CPT studies. We will also differentiate acute and chronic pain according to different consensus [2, 24–26] and also try to study if there is any electrophysiological change between the acute and chronic stage.

Patients and methods

Clinical evaluation

Patients with paroxysmal attacks of pain, affecting one or more divisions of the trigeminal nerve were recruited. Patients with no clinically evident neurological deficit by image studies including CT or MRI were defined as classical TN according to the latest guidelines of the International Classification of Headache Disorders [2]. We recruited 49 patients in this study. All patients were evaluated by detailed history taking, neurological examinations, and CPT testing and all patients were evaluated by brain computed tomography (CT) or magnetic resonance imaging (MRI) studies (39 and 10 patients, respectively) to rule out symptomatic TN. All patients also had blink reflex study. The durations between the symptoms onset and the

time of receiving examinations are recorded. We tried to set the cut off points at 1, 3, and 6 months to differentiate acute from chronic pain according to the definition of chronic pain by different consensus [2, 24–26]. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital and University.

Blink reflex studies

Surface electrodes were used to stimulate the nerve and record the evoked muscle action potentials [27]. The recording and reference electrodes were placed on the lower aspect of the orbicularis oculi muscle with a ground electrode over the forehead. A constant-current unit was used to stimulate the supraorbital nerve. The reflex responses from the orbicularis oculi muscle were then simultaneously recorded on both sides.

CPT testing

All patients were required to cease medications including anticonvulsants, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, opioid analgesics, topical lidocaine patches or gels and non-steroidal anti-inflammatory drugs (NSAIDs) for 3 days before receiving CPT testing. The methodology was similar to the one described previously [17]. The Neurometer (Neurotron Inc., Baltimore, MD) was used. The Neurometer is a constant-current stimulator capable of delivering stimuli at three different frequencies. Each patient was tested at three sinusoidal stimulation frequencies (2000, 250, 5 Hz) within the painful facial area and the contralateral mirror image area. The current was applied to the face skin via a pair of 1 cm diameter standard gold-plated electrodes. CTPs defined 0.01 mA as “1” and 10 mA as “1000”. At each frequency (2000, 250, 5 Hz), the current was slowly increased from 0.01 to 9.99 mA until the patients reported sensation. The stimulus then was turned off and lowered by 0.1 mA, and then turned on again. This procedure was repeated until a ranged of 0.1 mA was established. Double blind methodology then was used to present the patient with 6–20 cycles of randomly selected real and false stimulus until the exact CPT value could be determined within $a \pm 20 \mu\text{A}$ range [22, 23].

Statistical analysis

Continuous variables were expressed as mean \pm SD and compared by performing the paired or unpaired *t* test. Paired *t* tests were used to compare the CPT values between painful and contralateral non-painful sites of the same patient with classical TN. In addition, unpaired *t* tests were used to compare the CPT values on the painful side

between acute and chronic stages of different patients with classical TN. The level of significance was 0.05. All *P* values were two sided. Statistical analyses were performed with a statistical software package (SPSS for Window 15.0; SPSS Inc.).

Results

After statistical analyses, we found that there was a trend that the values of 5 Hz CPT on the painful site were lower (hypersensitive) than the non-painful site within the first month, but they became higher (hyposensitive) than those on the non-painful site after 1 month (Fig. 1) If we set the cutoff point at 1 month to differentiate acute from chronic pain, there will be a statistically significant result. We identified 13 patients with acute classical TN with symptoms onset ≤ 30 days and 36 patients with chronic classical TN with symptoms onset >30 days. All patients evaluated by brain CT or MRI showed a normal finding. The mean durations were 10.85 ± 10.03 days in the acute classical TN and 21.74 ± 27.76 months in the chronic classical TN. The mean ages were 54.38 ± 13.66 and 57.23 ± 12.79 years for the acute and chronic groups, respectively. Overall, there were 85 and 66% females with acute and chronic classical TN, respectively. The age and gender ratios were not significantly different in patients with acute and chronic classical TN (Table 1).

At the 5 Hz examinations, the values of CPTs on the painful side were significantly lower in the acute stage

(11.62 ± 6.99 vs. 18.69 ± 9.66 , $P = 0.025$), but they became significantly higher (26.67 ± 18.65 vs. 19.69 ± 13.70 , $P = 0.010$) than those on the contralateral side in the chronic stage. At the 250 Hz examinations, the values of CPTs were not significantly different between the painful and non-painful sides in patients with acute (30.23 ± 12.29 vs. 38.00 ± 14.62 , $P = 0.168$) and chronic classical TN (41.00 ± 22.17 vs. 36.42 ± 16.34 , $P = 0.179$). Also at the 2000 Hz examinations, the values of CPTs were not significantly different between the painful and non-painful sides in patients with acute (101.23 ± 40.11 vs. 122.77 ± 31.89 , $P = 0.066$) and chronic classical TN (125.67 ± 43.23 vs. 124.58 ± 45.83 , $P = 0.851$) (Table 2).

At the 5 Hz examinations, the values of CPTs were significantly higher in the chronic stage than in the acute stage on the painful side of classical TN (26.67 ± 18.65 vs. 11.62 ± 6.99 , $P = 0.000$). However, there were no significant differences on the painful side between the acute and chronic stage at the 250 and 2000 Hz examinations, respectively (30.23 ± 12.29 vs. 41.00 ± 22.17 , $P = 0.105$, 101.23 ± 40.11 vs. 125.67 ± 43.23 , $P = 0.082$) (Table 3).

All patients also received a blink reflex study and only three patients showed an abnormal finding by this study. All of the three patients showed prolonged ipsilateral R1 and bilateral R2 potentials after stimulation of the ipsilateral trigeminal nerve on the painful sides. One patient was in an acute stage and the other two were in a chronic stage. Although blink reflex study relates to large-myelinated nerve fiber dysfunction [27], these three patients did not show abnormal findings at the CPT 2000 Hz examinations.

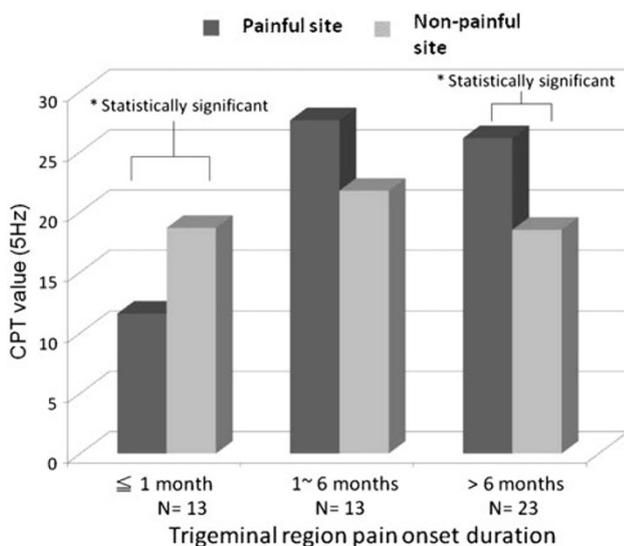


Fig. 1 Comparisons of the values of 5 Hz CPT between painful and non-painful sides at different times. There is a trend that the values of 5 Hz CPT on the painful side are lower than the non-painful side within the first month, but they evolved to be higher than the non-painful side after one month. ($*P < 0.05$)

Discussion

Our results show that classical TN is commonly found in female patients, which is similar to previous studies [1]. Our study also showed that unmyelinated nerve fiber sensation thresholds of classical TN decrease in the acute stage but increase in the chronic stage when the cut off duration is set to 1 month. We propose that the probable underlying mechanisms of classical TN is mainly a dysfunction of the unmyelinated nerve fibers, which are in a dynamic phase over times. It might increase neuronal excitability and ectopic firing in the acute stage, and then evolves to permanent nerve injuries with overwhelming injury discharges to the central nervous system and induces subsequent central sensitization in the chronic stage. This hypothesis is compatible with the clinical signs and symptoms of patients with classical TN. Patients with classical TN usually initially present with frequent brief electric shock-like pains, abrupt in onset and cessation, and sometimes gradually convert to a

Table 1 Demographic data of classical trigeminal neuralgia

	Acute (<i>n</i> = 13)	Chronic (<i>n</i> = 36)	<i>P</i>
Duration (days/months)	10.85 ± 10.03 (days)	21.74 ± 27.76 (months)	<0.001
Age (years)	54.38 ± 13.66	57.23 ± 12.79	0.603
Female:male	11:2	2:1	

Table 2 Comparisons of the values of CPT testing at three different frequencies on the painful and non-painful sides

	Painful	Non-painful	<i>P</i>
5 Hz			
Acute (<i>n</i> = 13)	11.62 ± 6.99	18.69 ± 9.66	0.025*
Chronic (<i>n</i> = 36)	26.67 ± 18.65	19.69 ± 13.70	0.010*
250 Hz			
Acute (<i>n</i> = 13)	30.23 ± 12.29	38.00 ± 14.62	0.168
Chronic (<i>n</i> = 36)	41.00 ± 22.17	36.42 ± 16.34	0.179
2000 Hz			
Acute (<i>n</i> = 13)	101.23 ± 40.11	122.77 ± 31.89	0.066
Chronic (<i>n</i> = 36)	125.67 ± 43.23	124.58 ± 45.83	0.851

Values are mean ± standard deviations in 0.01 mA

* Statistically significant

Table 3 Comparisons of the values of CPTs at three different frequencies on the painful sides between acute and chronic stage of classical trigeminal neuralgia

	Acute (<i>n</i> = 13)	Chronic (<i>n</i> = 36)	<i>P</i>
5 Hz	11.62 ± 6.99	26.67 ± 18.65	0.000*
250 Hz	30.23 ± 12.29	41.00 ± 22.17	0.105
2000 Hz	101.23 ± 40.11	125.67 ± 43.23	0.082

Values are mean ± standard deviations in 0.01 mA

* Statistically significant

dull background pain or numbness with less electric shock-like pains in a chronic stage [2, 3, 28].

In contrast, there were no significant differences of sensation thresholds in both small- and large-myelinated fibers during the acute and chronic stages. These findings may suggest a less important role of small- and large-myelinated fibers in trigeminal neurologia. Blink reflex study is routinely used to diagnose TN, which is a main study for detecting large-myelinated ($A\beta$) nerve fiber function [29], however, it did not show an adequate sensitivity in detecting trigeminal nerve dysfunction in classical TN. In our study, only 3/49 (6.1%) patients showed an abnormal finding by blink reflex study, which is consistent with the previous studies [11, 12]. Moreover, on neurological examination, patients with TN commonly had normal light touch and vibration sensory modalities, which also suggest a normal large fiber function on their trigeminal nerve distributions. Several reports using

laser-evoked potentials also showed small-myelinated fiber dysfunction in TN [13–15]. A more recent study using nBR and PREP showed dysfunction of the trigeminal nociceptive pathway, which suggested that thinly myelinated A-delta fibers are more susceptible and prone to compression than A-beta fibers in the trigeminal root entry zone [16]. According to the above findings, we suggest that in addition to the traditional hypothesis of large-myelinated fiber dysfunction in TN, it seems that small-myelinated and unmyelinated nerve fiber dysfunctions also play an important role in classical TN.

In the past, vessels compression producing large fiber demyelination and ephaptic contact between adjacent denuded axons has been widely accepted as the etiology of classical TN [5, 6]. This hypothesis is supported by clinical observations including trigeminal nerve root compression by aberrant vessels and the improvement of clinical signs/symptoms after a decompression surgery. However, there are only few pathological studies to support the hypothesis [6, 30–32].

Our hypothesis seems to conflict with previous nerve pathological studies in classical TN [30, 31]; however, previous reports mainly focus on the pathology of large-myelinated nerve fibers under a light microscope, which is unable to detect the pathology of unmyelinated fibers. In Devor's (12 patients) and Rappaport's reports (12 patients), disruption of axon structure, reduced axon population, de- and dys-myelination of large myelinated nerve fibers were found by electronic microscopy; however, they did not pay much attention to the pathological changes of unmyelinated nerve fibers [31, 33]. In contrast, there was a pathology report mainly showing unmyelinated fiber loss in a rat model of neuropathic pain under the electron microscope [34]. On the other hand, skin biopsy stained with antibody against protein gene product 9.5 (PGP 9.5) which is a pan-axonal markers may show the intra-epidermal nerve fiber density including small-myelinated nerve ($A\delta$ -fiber) and unmyelinated nerve (C-fiber) [35, 36], which can potentially be used to evaluate TN theoretically. Further studies of skin biopsies and detailed trigeminal nerve electron microscopic studies to evaluate small-myelinated and unmyelinated nerve fiber pathology in classical TN patients may be warranted.

The finding that unmyelinated fibers are mainly affected in classical TN can be explained well by a loose ligation animal model. One study has shown that unmyelinated fibers are more vulnerable than large myelinated fibers

when the compressed area is restricted to a short segment (0.5–1 mm) [37]. In a rat animal study, increased skin blood flow and myeloperoxidase activity were found in the hind-paw distal to the ligations of the sciatic nerve; and these findings indicated that the ligation of the sciatic nerve induced an neurogenic inflammation and nociceptive C-fibers activation [38]. In primate study, Ali et al. [39] also found a reduced number of unmyelinated nerve terminals in the epidermis of the skin of the limb distal to the L6 spinal nerve ligation as compared to the contralateral limb, which showed a major C-fiber degeneration after nerve ligation. Spontaneous activity in C-fibers is thought to be responsible for persisted burning pain and central sensitization in the dorsal horn neurons [40]. There are also studies that showed that decreased intra-epidermal C-fiber density is related to increased pain severity in HIV-associated neuropathy and diabetes patients [41, 42]. Repeated noxious stimulation to peripheral C-fiber nociceptors may generate prolonged post-stimulus sensory disturbances and a decreased threshold of the nociceptive system called central sensitization [43]. Central facilitation of trigeminal nociceptive processing with over-activation of central sensory transmission was also observed in patients with TN with chronic pain in Obermann's study [16]. These studies probably imply that the damaged C-fiber after a compression injury in the trigeminal nerve may show spontaneous activities related to frequent brief electric shock-like pain sensations in the acute stage; and long-term repeated damage may cause a permanent injury related to increase in pain thresholds of the peripheral nociceptors and central sensitization in the chronic stage.

From this study and previous reports, it seems that classical TN is not a simple large-myelinated fiber dysfunction, but a more complex involvement of large-, small-myelinated and unmyelinated nerve fibers with a main dysfunction of the unmyelinated nerve fibers over times. However, this study has some limitations. First, this study only analyzes a small sample size. Secondly, this study lacks of a longitudinal series of CPT tests in these patients. Thirdly, no skin or trigeminal nerve biopsy was available in our patients to confirm small-myelinated or unmyelinated nerve fiber injuries. Understanding the underlying pathophysiology of classical TN may improve the therapy in the future. Thus, a well designed and longitudinal series of CPTs and pathological study is warranted.

Conflict of interest None.

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