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Small-fiber dysfunction in trigeminal neuralgia

Carbamazepine effect on laser-evoked potentials

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Article abstract—*Background:* In patients with trigeminal neuralgia, results of clinical examination of sensory function are normal. Reflex and evoked potential studies have already provided information on large-afferent (non-nociceptive) function. Using laser-evoked potentials (LEP), the authors sought information on small-afferent (nociceptive) function. *Methods:* The brain potentials evoked by CO₂-laser pulses directed to the perioral and supraorbital regions were studied in 67 patients with idiopathic or symptomatic trigeminal neuralgia and 30 normal subjects. Of the 67 patients, 49 were receiving carbamazepine. *Results:* All patients with symptomatic and 51% of those with idiopathic trigeminal neuralgia had frankly abnormal LEP on the painful side. The mean latency was significantly higher and mean amplitude lower on the painful than the nonpainful side. However, even on the nonpainful side, the mean latency was significantly longer than that of the age-matched controls. The nonpainful-side latency correlated significantly with the carbamazepine dose. *Conclusions:* LEP detect severe impairment of the nociceptive afferent system on the painful side of patients with idiopathic as well as symptomatic trigeminal neuralgia. A dysfunction of small-myelinated afferents may play an important role in the pathophysiology of neuralgic pain. Carbamazepine markedly dampens these brain potentials. The authors propose that this effect may result from inhibition of nociceptive transmission in the cingulate gyrus.

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Although trigeminal neuralgia (TN) undoubtedly arises from a dysfunction of the trigeminal sensory system, in patients with TN, results of clinical examination of sensory function are normal. Only a few studies using quantitative sensory testing found abnormalities in touch and temperature discrimination, though normal pinprick sensation.^{1,2} Trigeminal reflexes are usually normal in idiopathic TN and abnormal in TN secondary to tumors or MS.³ Studies of evoked potentials have reported controversial results, probably because of the technical differences. Most investigators, however, agree that trigeminal evoked potentials are often abnormal both in idiopathic and symptomatic neuralgia.⁴⁻⁷ On the basis of quantitative sensory testing and neurophysiologic findings, some believe that pain in TN is caused by primary damage to large rather than small afferents, followed by a secondary dysfunction in the central nuclei.⁷⁻¹¹ But trigeminal reflexes and evoked potentials after electrical or mechanical stimulations provide information on large-afferent (non-nociceptive) function only.

Laser-generated radiant heat pulses selectively excite free nerve endings in the superficial skin layers and can activate A δ or C nociceptors or warmth

receptors. Brief low-intensity pulses directed to the hairy skin of the face evoke pinprick sensations and “late” brain potentials, both induced by the activation of Type II AMH mechano-thermal nociceptors; the afferent volley is conducted along small-myelinated (A δ) primary sensory neurons, and relayed to the spinal trigeminal nucleus and brain.¹²⁻¹⁵

To assess the diagnostic usefulness of trigeminal laser-evoked potentials (LEP) and obtain pathophysiologic information on TN, using LEP we investigated small-myelinated afferent function in patients with idiopathic and symptomatic TN; most patients were on carbamazepine, a drug that may interfere with nociceptive transmission and affect brain potentials.

Methods. Three groups of subjects participated in the study: thirty normal controls aged 46 to 83 years (mean age 62); 47 patients with idiopathic TN, aged 45 to 87 years (mean, 66); and 20 patients with symptomatic TN, aged 36 to 73 years (mean, 58 years). Patients assigned to the idiopathic TN group had typical *tic douloureux*, normal results of neurophysiologic study of the trigeminal reflexes from the three trigeminal divisions (R1 and R2 blink reflex after electrical stimulation of the supraorbital nerve, SP1 and SP2 masseter inhibitory reflex after electrical stimulation of the infraorbital and mental nerves, and jaw jerk

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after chin-taps)^{3,16} and normal MRI scans; those assigned to the symptomatic TN group had paroxysmal trigeminal pain, although occasionally the pain was not typically neuralgic, trigeminal-reflex abnormalities, and abnormal MRI (a few patients who had trigeminal-reflex abnormalities with normal MRI were excluded from the study). Of the patients with symptomatic TN, nine had MS, eight had vascular anomalies in the posterior fossa, and three had cerebellopontine-angle tumors. All subjects gave their informed consent, and the local Ethics Committee approved the research.

None of the patients was asked to interrupt their treatment before examination. Most of them ($n = 44$) were taking carbamazepine alone, three carbamazepine + gabapentin, two carbamazepine + antidepressants, three gabapentin alone, and 10 were taking no neurotropic drugs. Five patients were unable to give us clear information about their treatment, or they had recently changed it. Patients were dosed to analgesic effect and taught to interrupt treatment when their neuralgia became less active and they felt able to bear the pain.

We studied LEP after stimulation of the supraorbital region (V_1), upper lip (V_2), and lower lip (V_3). Details of trigeminal laser stimulation and evoked potential recording are reported elsewhere.¹⁵ In brief, laser stimuli (1.5 to 15 W; duration, 10 to 15 msec; beam diameter 2.5 mm; irradiated area 5 mm²) at approximately twice the perceptible threshold were delivered at 10–20-second interstimulus intervals with a CO₂-laser stimulator (Neurolas, Electronic Engineering, Florence, Italy). Signals (bandpass 0.5 to 50 Hz) were recorded with disc electrodes from the vertex referenced to linked earlobes. Simultaneous electroculography monitored ocular movements or eyeblinks. Two series of 10 artifact-free trials were collected and averaged off-line. We measured the peak latencies of the main negative (N wave) and positive (P wave) components and the peak-to-peak amplitude (figure 1).

Because no significant differences were found between the three trigeminal divisions in the control group, we defined abnormal laser responses as those exceeding the maximum range in the pooled data from the 90 divisions examined in the control group: the maximum right–left difference was 21 msec for the N latency, 45 msec for the P latency, and 16 μ V for the peak-to-peak amplitude.

Patients who were taking no medication at the time of examination had only mild pain or no pain (“inactive” neuralgia). We examined whether this group differed from patients who had to take medication for more severe pain (“active” neuralgia). For this comparison, we excluded the five patients who were unable to give us clear information about their treatment.

We analyzed the differences in frequency of normal and abnormal responses in the three trigeminal divisions with Fisher’s Exact Test, intraindividual differences with Wilcoxon matched-pairs test, and correlations between different variables with Spearman r correlation coefficient. Because the variance of latency values differed significantly between groups, we assessed these data with Welch’s corrected test. Because the amplitude values had a nongaussian distribution, we assessed the mean amplitude differences between groups with the Mann-Whitney U test. For statistics and graphs we used Prism 3.0 (GraphPad, Sorrento Valley, CA). Throughout text and tables, data are given as means \pm 1 SD.

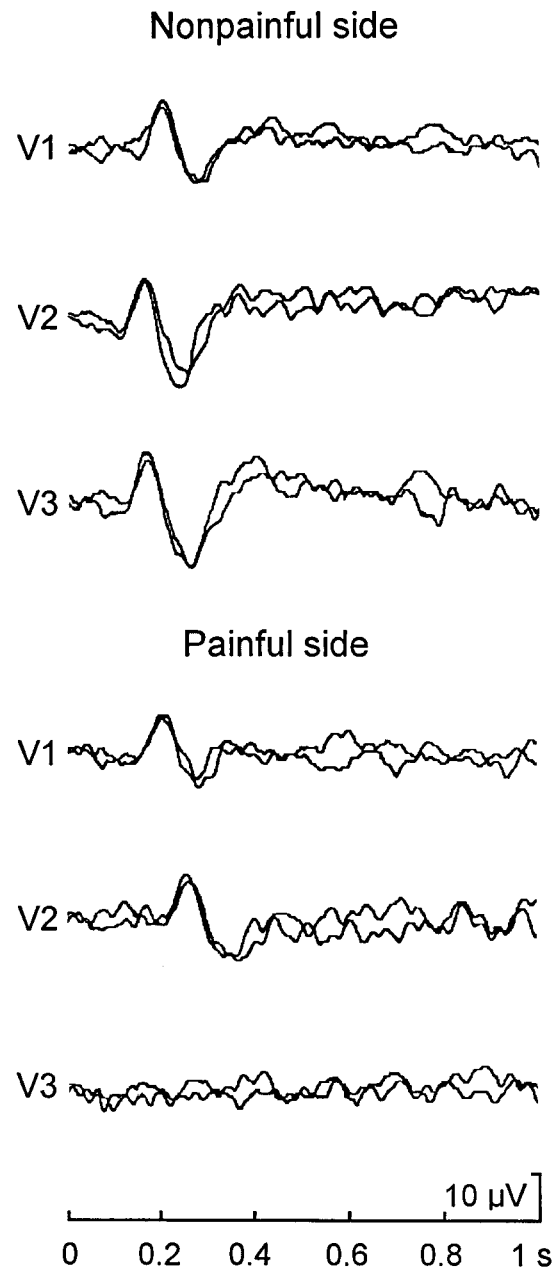


Figure 1. Laser-evoked potentials (LEP) in a representative patient who had idiopathic trigeminal neuralgia in the perioral region and was taking no drugs. Two series of 10 artifact-free trials were collected and averaged after stimulation of the supraorbital (V_1), upper lip (V_2), and lower lip skin (V_3) on the right and left sides. Recordings from the vertex referenced to linked earlobes. Note the high reproducibility of the signals after a relatively low number of trials and delay (V_2) or absence (V_3) of the LEP after stimulation of the painful territory.

Results. Idiopathic TN. In most of the 47 patients, we examined three trigeminal divisions, for a total of 112 divisions. In 23 patients, LEP values were within normal limits. The remaining 24 patients had absent or delayed responses (N wave latency compared with the contralateral division) in at least one division. No patient had a selective abnormality of the P-wave latency or the N-P amplitude accompanied by a normal N-wave latency.

Table 1 Laser-evoked potentials in 47 patients with idiopathic trigeminal neuralgia

N wave latency, msec			Amplitude, μ V		
Painful side	Nonpainful side	Controls	Painful side	Nonpainful side	Controls
197 \pm 40, n = 94*	189 \pm 34, n = 112	171 \pm 20, n = 90	14.8 \pm 11.9, n = 112	16.8 \pm 10.9, n = 112	26 \pm 8.5, n = 90
*Absent responses in 18 divisions, 16%	Difference with painful side, $p^1 < 0.001$	Differences with painful or nonpainful sides, $p^2 < 0.001$		Difference with painful side, $p^1 < 0.01$	Differences with painful or nonpainful sides, $p^3 < 0.001$

n = number of trigeminal divisions; p^1 = matched-pairs, Wilcoxon signed-rank test; p^2 = Welch's test for populations with different variances; p^3 = Mann-Whitney *U* test.

LEP were often normal in the three divisions, and less frequently delayed in V1 than in V2-V3. Although laser stimulation yielded a similar proportion of normal and abnormal LEP in the painful divisions (34 and 36 of 70), LEP were more frequently abnormal in the painful than in the nonpainful divisions of the affected side (36 of 70 versus 7 of 42; $p < 0.001$; Fisher's exact test).

In none of the patients, including eight in whom cleaning the area around the lips before the examination triggered the typical neuralgic pain, did the laser stimulations evoke electric-shock-like sensations.

Symptomatic TN. In the 20 patients with symptomatic TN (all of whom had evident abnormalities of the trigeminal reflexes), the LEP were always abnormal in one or more trigeminal divisions. We studied 45 divisions. The LEP were absent after stimulation of 16 of 45 divisions, that is a percentage more than double that found in patients with idiopathic TN.

Group analysis. The LEP had a longer latency and a lower amplitude after stimulation of the painful side than the nonpainful side, in both the patients with idiopathic TN (table 1) and those with symptomatic TN (table 2). LEP after stimulation of the painful side also had a longer mean latency ($p < 0.001$) and lower amplitude ($p < 0.001$) than LEP in the age-matched controls.

Contralateral abnormalities. Even on the nonpainful side, LEP were dampened (longer latency and smaller amplitude in TN patients than in controls, (see tables 1 and 2). When we analyzed the data for the patients with idiopathic TN separately (because patients with MS or tumors might have bilateral dysfunction), the latency on the "normal" side was almost 20 msec longer than the control values ($p < 0.001$). Conversely, the patients receiving no medication had a contralateral latency (172 \pm 19 msec) almost identical to that of controls.

The latency of LEP from the nonpainful side correlated

strongly with the daily carbamazepine dose ($p < 0.0001$; Spearman's *r*) (figure 2), but did not correlate with age ($p > 0.10$).

Active versus inactive neuralgia. LEP had a significantly lower latency in patients with "inactive" than in those with "active" neuralgia (181 \pm 27 msec versus 203 \pm 31 msec; $p < 0.01$; Welch). To determine whether the difference arose from a drug-induced effect in patients currently taking carbamazepine for active neuralgia, we examined the intraindividual differences between sides. Despite a significant mean latency difference (painful side minus nonpainful side) in both groups (patients with inactive neuralgia, 8.9 \pm 16 msec, n = 25 divisions, $p < 0.01$; those with active neuralgia, 9.3 \pm 23 msec, n = 58 divisions, $p < 0.005$; Wilcoxon) the two groups did not differ ($p > 0.50$; Welch).

Discussion. The distinctive feature of this study is that it provides the first neurophysiologic assessment of function of mechanothermal nociceptive afferents in TN. All of the patients with symptomatic TN we studied and many of those with idiopathic TN had abnormal LEP. Although abnormal LEP indicate trigeminal damage, their sparing does not exclude it. Because these potentials are mediated by nociceptive small-myelinated afferents, dysfunction of these fibers may play an important role in generating paroxysmal pain. Stimulation of the contralateral side elicited delayed LEP, probably because of a carbamazepine-induced effect.

Trigeminal LEP as a potential diagnostic tool. Patients with symptomatic TN invariably had abnormal LEP, in at least one trigeminal division. As expected in symptomatic TN, they also had clear abnormalities of the short-latency trigeminal reflexes (the R1 blink reflex, SP1 masseter inhibitory reflex, or jaw

Table 2 Laser-evoked potentials in 20 patients with symptomatic trigeminal neuralgia

N wave latency, msec			Amplitude, μ V		
Painful side	Nonpainful side	Controls	Painful side	Nonpainful side	Controls
205 \pm 30.5, n = 29*	190 \pm 34, n = 45	171 \pm 20, n = 90	15.6 \pm 11.6, n = 45	21.6 \pm 12, n = 45	26 \pm 8.5, n = 90
*Absent responses in 16 divisions, 36%	Difference with painful side, $p^1 < 0.01$	Differences with painful or nonpainful sides, $p^2 < 0.001$		Difference with painful side, $p^1 < 0.001$	Differences with painful or nonpainful sides, $p^3 < 0.001$

n = number of trigeminal divisions; p^1 = matched-pairs, Wilcoxon signed-rank test; p^2 = Welch's test for populations with different variances; p^3 = Mann-Whitney *U* test.

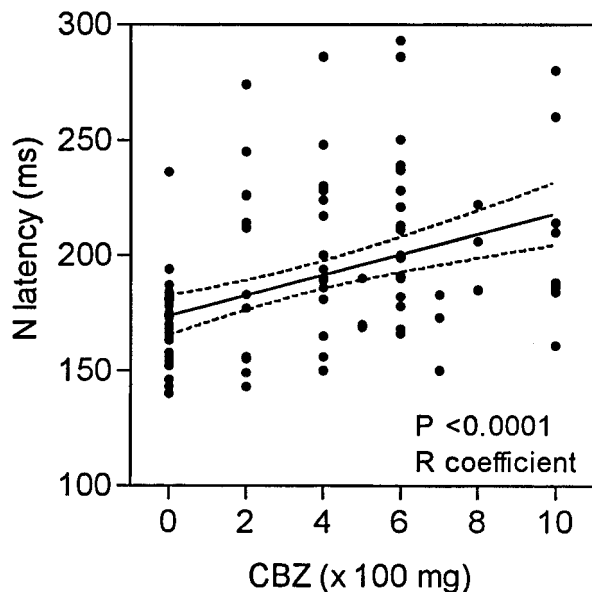


Figure 2. Correlation between the daily carbamazepine dose (CBZ, X-axis) and the latency of the N wave of laser evoked potentials (Y-axis) after stimulation of the contralateral-side divisions in the patients with idiopathic trigeminal neuralgia. Solid line: regression; dashed curves: 95% CI. The latency strongly correlated with carbamazepine (Spearman r correlation coefficient).

jerk).^{3,17} Although the patients with idiopathic TN (all of whom had normal trigeminal reflexes) often had abnormal LEP in one or more divisions, slightly less than 50% of them had normal LEP, that is, a proportion similar to that found with conventional electrically elicited trigeminal evoked potentials.^{6,10,17}

Hence, LEP, possibly because they are mediated by a small number of afferents, are diagnostically more sensitive than trigeminal reflex testing, but no better than electrically elicited evoked potentials. The finding of abnormal LEP in patients with facial pain indicates trigeminal-system dysfunction. However, the finding of normal LEP clearly does not exclude the diagnosis of idiopathic TN. Furthermore, the LEP abnormalities seem unrelated to the current intensity of neuralgic pain.

The diagnosis of TN therefore remains primarily a clinical one. Trigeminal LEP nonetheless add useful information and will help in distinguishing idiopathic from secondary forms, because no patient with secondary trigeminal neuralgia had normal LEP. The diagnostic value of LEP in selecting patients for neuroimaging, however, requires further studies.

Pathophysiology of trigeminal neuralgia. Although LEP signals are generated by brain structures, evidence that the primary damage involves the afferents, rather than the postsynaptic central pathways, comes from MRI scans in patients with symptomatic TN, all having an extra- or intra-axial lesion near the entry zone of the trigeminal root. The identical paroxysmal attacks of neuralgia in these patients and those with normal MRI scans make it unlikely that the pathophysiologic mechanisms of pain differ

in the two conditions: peripheral in symptomatic and central in idiopathic TN. Intraoperative recordings have shown focal damage to the trigeminal root also in patients with idiopathic TN.¹⁸ Most probably the mechanisms are the same; simply, in patients with "idiopathic" TN the lesion remains undetected.

The common finding of a normal sensitivity to pinprick, together with that of delayed neurophysiologic responses mediated by large, non-nociceptive fibers,^{6,10,17} has promoted the notion that TN pain could arise from a primary dysfunction of non-nociceptive fibers only, either through ephaptic transmission of bursts of impulses from non-nociceptive to nociceptive afferents, or through functional derangement of wide-dynamic-range neurons (receiving both nociceptive and non-nociceptive terminals) in the spinal trigeminal nucleus.^{8,9,11,19,20}

Technical differences influencing the sensitivity of the various methods prevented us from ascertaining whether small-myelinated fibers are more or less impaired than large-myelinated or unmyelinated fibers. Our findings nonetheless indicate dysfunction of the small-myelinated nociceptive fibers. The afferents mediating pricking pain are probably less amenable to a fine clinical assessment than those mediating other sensations.

Nociceptive fibers may play an important role in generating pain in TN. Patients with peripheral or central neurogenic pains, such as painful neuropathies or post-stroke pain, always have a nociceptive-fiber dysfunction.²¹⁻²⁴ Furthermore, insofar as experimental studies indicate that ephaptic transmission usually moves from a normal to a demyelinated fiber,²⁵ a nociceptive fiber dysfunction also would better explain the phenomenon of trigger zones (areas where light touch stimuli evoke the electric-shock-like pain typical of TN). The trigger phenomenon could also arise from central mechanisms. Accordingly, our finding of a primary dysfunction of the nociceptive afferents by no means excludes a secondary derangement of central neurons, possibly important for the development of neuralgia.

Effect of carbamazepine. The LEP abnormalities after stimulation of the contralateral side in patients with idiopathic TN were an unexpected finding. Unlike symptomatic TN, idiopathic TN is strictly unilateral, and in our experience the contralateral electrically elicited responses are normal.^{3,6,7} Neither are we aware of published reports mentioning contralateral abnormalities.

Either in TN the nociceptive system undergoes a bilateral dysfunction, or brain signals of this kind, LEP, are particularly sensitive to a drug-induced dampening effect. Because most patients were taking carbamazepine, we sought and found a strong correlation between the LEP latency and carbamazepine (figure 2). We also considered an effect induced by the drug and age combined. But the LEP latency did not correlate with age. Hence we presume that LEP were dampened by carbamazepine.

The more severe LEP abnormalities on the painful side and markedly abnormal LEP also in patients not

receiving neurotropic drugs specified that the LEP abnormalities did not depend on drug-induced effects alone.

Anticonvulsants may decrease the conduction velocity in the distal portion of long limb nerves.^{26,27} Reports on somatosensory evoked potentials and carbamazepine are controversial; however, the slowing of central conduction, if any, is small.³⁰⁻³²

At trigeminal level, in particular, carbamazepine leaves conduction in the trigeminal nerves unaffected.^{28,29} Unlike the trigeminal reflexes or the electrically elicited evoked potentials, LEP may be particularly sensitive to carbamazepine either because they are transmitted along small-fiber pathways or because they are generated by deep midline structures, probably the anterior cingulate gyrus.¹⁴ Considering its known clinical efficacy in patients with anterior cingulate and other frontal epilepsies, in particular the autosomal dominant nocturnal frontal lobe epilepsy,^{33,34} carbamazepine may be highly effective in reducing neuronal excitability at this level. Carbamazepine, like lidocaine and phenytoin, can prevent or suppress paroxysmal discharges along hyperexcitable trigeminal fibers.^{10,19} However, carbamazepine may concurrently exert its antinociceptive activity also by inhibiting nicotinic acetylcholine receptors in the cingulate,^{33,34} thus dampening perceived pain in the brain.

Although we believe it useful to report this possible carbamazepine-induced effect, the correlation between contralateral LEP latency and carbamazepine does not prove causality. Whether a carbamazepine-induced effect is favored by a dysfunction of the system that generates the signals remains unclear, and we cannot exclude that in TN the nociceptive system undergoes a previously unrecognized bilateral dysfunction.

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