

Trigeminal Neuralgia: Update on Reflex and Evoked Potential Studies

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Brainstem Reflexes and Trigeminal Evoked Potentials after Electrical Stimulation

In patients reporting pain in the trigeminal territory, neurophysiological testing of trigeminal function offers the clinician useful information. An objective demonstration of dysfunction is provided in all patients with pain secondary to a documented disease such as symptomatic trigeminal neuralgia (TN), postherpetic neuralgia, vascular malformations, benign tumors of the cerebellopontine angle and multiple sclerosis, even in those patients who have no clinical signs or complaints other than pain.^{1–3} Brainstem reflexes are more extensively and markedly affected in patients with constant pain than in those with paroxysmal pain. This finding agrees with the common notion that a dysfunction of few fibers provokes paroxysmal pain, whereas severe damage does not. In symptomatic trigeminal pains, the trigeminal reflexes yield a very high sensitivity, probably because they allow examination of all three divisions. The most sensitive reflexes are the R1 blink reflex and the SP1 masseter inhibitory period.^{1–3}

Although, like others, we have occasionally seen patients with mild reflex abnormalities, in the majority of patients with idiopathic TN (tic douloureux), all reflexes are normal.^{1–3} A diagnostic protocol for patients with trigeminal pain should rely primarily on brainstem reflexes; the technique is easier and less invasive than that for evoked potentials, and the finding of any abnormality suggests an underlying structural lesion. In patients with paroxysmal pain, the presynaptic waves of the scalp-evoked potential after infraorbital stimulation are more sensitive, possibly because a slight slowing of conduc-

tion or loss of few axons may leave reflex responses, which are influenced by the temporal–spatial summation at each synapse, practically unaltered.^{2–4} The finding of any abnormality should nonetheless promote further investigation to search for a cause that may require surgical attention; this holds particularly true in young patients. The most commonly reported causes of symptomatic neuralgia are benign tumors of the cerebellopontine angle and vascular anomalies in the posterior fossa (including the so-called “neurovascular conflict”), all impinging on the proximal portion of the trigeminal root, and multiple sclerosis with a plaque in the root entry zone.^{2,5} As in neuralgia secondary to well-documented lesions, the most likely site of conduction impairment in idiopathic TN is the region of the root entry into the pons.^{2,5}

On the basis of quantitative sensory testing and neurophysiological 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.^{5–8} But trigeminal reflexes and evoked potentials after electrical or mechanical stimulations provide information on large-afferent (non-nociceptive) function only.

Laser Evoked Potentials

Laser-generated radiant heat pulses selectively excite free nerve endings in the superficial skin layers and can activate A δ or C nociceptors or warm 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.^{9–11}

To assess the diagnostic usefulness of trigeminal laser-

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evoked potentials (LEPs) and obtain pathophysiological information on TN using LEPs, we recently investigated small-myelinated afferent function in a group of 67 patients with idiopathic or symptomatic TN. Most patients were on carbamazepine.¹² Patients assigned to the idiopathic TN group had typical tic douloureux normal neurophysiological study of the trigeminal reflexes from the three trigeminal divisions^{1,3} (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 after chin-taps), and normal magnetic resonance imaging (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. None of the patients were asked to interrupt their treatment before examination. Most of them ($n = 44$) were taking carbamazepine.

We studied LEPs after stimulation of the supraorbital region (V_1), upper lip (V_2), and lower lip (V_3). In brief, laser stimuli (1.5–15 W; duration, 10–15 msec; irradiated area, 5 mm²) at approximately twice the perceptive threshold were delivered at 10- to 20-second interstimulus intervals with a CO₂-laser stimulator (Neurolas, EI.EN., Florence, Italy). Signals were recorded (0.5–50 Hz) with disc electrodes from the vertex referenced to linked earlobes. Simultaneous electrooculography 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 (Fig. 1). We defined abnormal laser responses as those exceeding the maximum range in the pooled data from 90 divisions examined in normal subjects in our laboratory; the maximum right-left difference was 21 msec for the N latency, 45 msec for the P latency, and 16 μV for the peak-to-peak amplitude.

In most of the patients, we examined three trigeminal divisions, for a total of 157 divisions. Of the patients with idiopathic TN, 23 had normal LEP values and 24 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. LEPs were less frequently delayed in V_1 than in V_2 - V_3 (Fig. 2). Although the proportion of normal and abnormal LEPs was similar in the painful divisions, LEPs were far more frequently abnormal in the painful than in the nonpainful divisions of the affected side ($P < 0.001$; Fisher's exact test) (Fig. 2). In

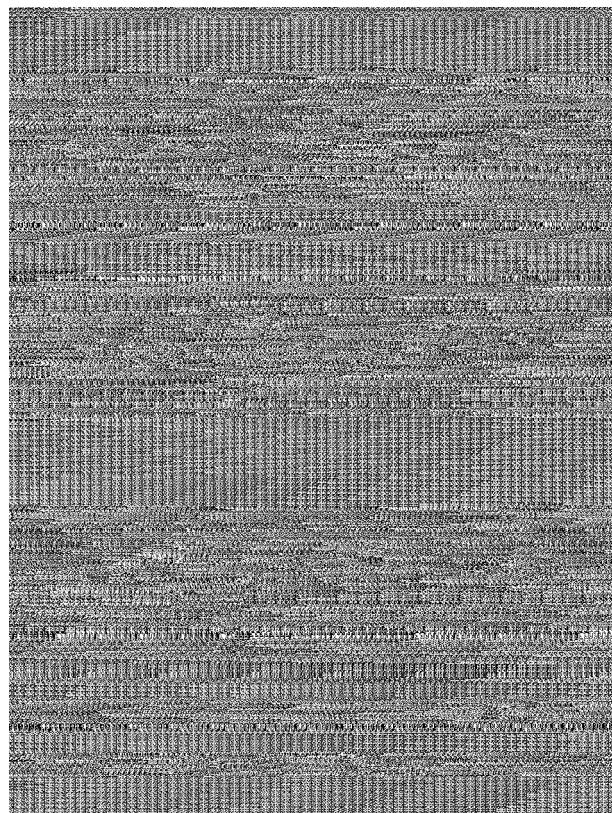


FIG. 1. Trigeminal laser evoked potentials (LEPs). Two series of 10 artifact-free trials were collected and averaged after laser stimulation of the supraorbital (V_1), upper lip (V_2), and lower lip skin (V_3). Recordings from the vertex referenced to linked earlobes. N, negative; P, positive.

the 20 patients with symptomatic TN (all of whom had evident abnormalities of the trigeminal reflexes), the LEPs were always abnormal in one or more trigeminal divisions. The LEPs were absent after stimulation of 16 of 45 divisions, a percentage more than double that found in patients with idiopathic TN. Group analysis showed that both in idiopathic and symptomatic TN, the LEPs had a longer latency and a lower amplitude ($P < 0.001$) after stimulation of the painful side than the nonpainful side, and a longer latency and lower amplitude ($P < 0.001$) than LEPs in age-matched controls.

Even on the nonpainful side, LEPs were dampened (longer latency and smaller amplitude in TN patients than in controls). The latency of LEPs from the nonpainful side correlated strongly with the daily carbamazepine dose ($P < 0.0001$; Spearman's R) but did not correlate with age ($P > 0.10$).

Trigeminal LEPs as a Diagnostic Tool

Patients with symptomatic TN invariably had abnormal LEPs, in at least one trigeminal division. As ex-

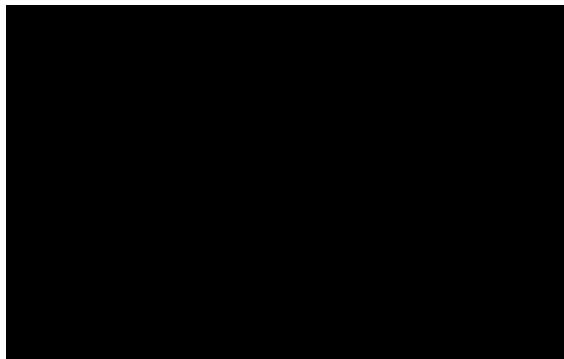


FIG. 2. Abnormality frequency of laser evoked potentials per trigeminal division (**A**) and correlation with pain (**B**) in 112 affected-side divisions of patients with idiopathic trigeminal neuralgia. Y-axis: number of examined divisions. In **A**, the responses are less frequently abnormal after V_1 than after V_2/V_3 stimulations (Fisher's exact test; $P < 0.05$); in **B**, the responses are less frequently abnormal in the non-painful divisions (Fisher's exact test; $P < 0.001$).

spected in symptomatic TN, they also had clear abnormalities of the short-latency trigeminal reflexes (the R1 blink reflex, SP1 masseter inhibitory reflex, or jaw jerk).^{1,3} Although the patients with idiopathic TN (all of whom had normal trigeminal reflexes) often had abnormal LEPs in one or more divisions, slightly less than 50% of them had normal LEPs, i.e., a proportion similar to that found with conventional electrically elicited trigeminal evoked potentials.^{2,4,5}

Hence, LEPs, 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 LEPs in patients with facial pain demonstrates trigeminal-system dysfunction and provides indication for neuroimaging. But the finding of normal LEPs by no means excludes the diagnosis of idiopathic TN. This diagnosis relies on the clinical description of the paroxysmal pain.

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 pathophysiological mechanisms of pain differ in the two conditions: peripheral in symptomatic and central in idiopathic TN. Intraoperative recordings have demonstrated focal damage to the trigeminal root also in patients with idiopathic TN.⁴ Most probably the mechanisms are the same; sim-

ply, in patients with idiopathic TN, the lesion remains undetected.

The common finding of a normal sensitivity to pinprick together with that of delayed neurophysiological responses mediated by large, nonnociceptive fibers^{2–7} has promoted the notion that TN pain could arise from a primary dysfunction of nonnociceptive fibers only, either through ephaptic transmission of bursts of impulses from nonnociceptive to nociceptive afferents, or through functional derangement of wide-dynamic-range neurons (receiving both nociceptive and nonnociceptive terminals) in the spinal trigeminal nucleus.^{5,6,8,13}

Our findings, nonetheless, indicate dysfunction of the small-myelinated nociceptive fibers. 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.^{14,15} Furthermore, insofar as experimental studies indicate that ephaptic transmission usually moves from a normal to a demyelinated fiber, a nociceptive fiber dysfunction would also explain better 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.

CONCLUSIONS

Brainstem reflexes are usually normal in idiopathic TN. In symptomatic TN the early cutaneous responses (R1 and SP1) are most commonly affected. The electrically or mechanically elicited scalp potentials are often abnormal, even in idiopathic TN. All these responses are mediated by large (nonnociceptive) afferents.

The first neurophysiological assessment of function of mechanothermal nociceptive afferents in TN has been carried out by means of the laser evoked potentials. All the patients with symptomatic TN and many of those with idiopathic TN had abnormal LEPs. Although abnormal LEPs 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.

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