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Trigeminal small-fibre dysfunction in patients with diabetes mellitus: a study with laser evoked potentials and corneal reflex

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Abstract

Objective: To investigate trigeminal small-fibre function in patients with diabetes mellitus.

Methods: In 52 diabetic patients we studied the trigeminal laser evoked potentials after stimulation of the skin bordering the lower lip. In the 21 patients with the severest peripheral nerve damage we also studied the electrically evoked corneal reflex. Both responses are mediated by small myelinated afferents.

Results: Laser evoked potentials had a longer mean latency and lower amplitude in diabetic patients than in normal subjects ($P < 0.005$). The abnormality frequency of the laser evoked potentials correlated with the severity of polyneuropathy ($P < 0.005$). In contrast, the corneal reflex was normal.

Conclusion: Dysfunction of small afferents of the mandibular nerve is frequent in patients with diabetic polyneuropathy. We speculate that the primary cause could be segmental demyelination.

Keywords: Diabetic neuropathy; Trigeminal nerve; Small-fibre function; Laser evoked potentials; Corneal reflex

1. Introduction

Neurophysiological studies using recordings of the blink and masseter inhibitory reflexes, and the jaw jerk-techniques that assess the function of large myelinated afferents alone (Cruccu et al., 1987; Ongerboer de Visser and Cruccu, 1993; Cruccu and Deuschl, 2000) have shown frequent subclinical involvement of the mandibular nerve in patients with diabetes mellitus (Cruccu et al., 1998; Cruccu and Deuschl, 2000).

Sural nerve biopsy and neurophysiological data (Dyck et al., 1986; Agostino et al., 2000) indicate that diabetic polyneuropathy affects both large and small myelinated fibres to a similar extent. The laser evoked potentials (LEPs) and the corneal reflex are mediated by small myelinated (Aδ) afferents (Bromm and Treede, 1991; Ongerboer de Visser and Cruccu, 1993; Arendt-Nielsen, 1994; Cruccu et al., 1999).

In this study, to investigate trigeminal small-fibre function in a group of patients with diabetes mellitus and peripheral nerve damage of various degrees, we recorded LEPs after stimulation of the skin bordering the lower lip. In patients with severe polyneuropathy, we also recorded the electrically evoked corneal reflex. Trigeminal small-fibre function has never been assessed in diabetic patients.

2. Methods

Control values were obtained in 34 healthy subjects aged 32–78 years (mean 60). We studied 52 patients, aged 33–76 years (mean 65), all of whom had a definitive diagnosis of diabetes mellitus. On clinical grounds, 3 patients with an acute onset in their third decade of life were classified as having Type I diabetes mellitus, while the remainder had Type II diabetes mellitus. When studied, all patients had

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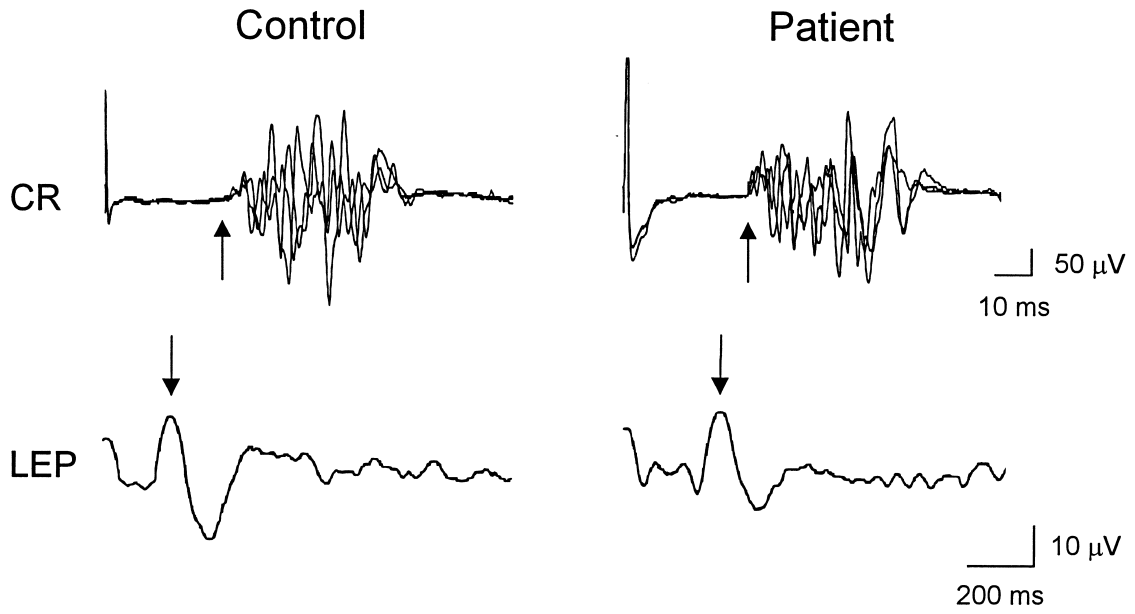

Fig. 1. Corneal reflex (CR) and laser evoked potentials (LEP) in one control subject and one representative patient with severe diabetic neuropathy. Arrows indicate latency. The corneal reflex latency was 38 ms in the control subject and 40 ms in the patient. The LEP latency was 190 ms in the control subject and 285 ms in the patient. In the patient, the LEP latency was markedly delayed and the amplitude normal.

stable glycemic control and were referred to undergo a standard diagnostic nerve conduction test for suspected polyneuropathy. None of the patients had evidence of central nervous system damage or diseases other than diabetes causing polyneuropathy. Nerve conduction studies in the 52 patients identified 21 patients who had severe polyneuropathy (Group A: absent or suppressed sensory action potentials of sural and ulnar nerves), 13 patients who had mild polyneuropathy (Group B: suppressed sensory action potentials of the sural nerve alone), and 18 patients who had normal sensory action potentials (Group C). No patients showed a marked slowing of conduction velocity in either sensory or motor nerve fibres and 18 patients also had a carpal tunnel syndrome. Five subjects lacked detailed clinical data. Thirty six patients had abnormal findings on clinical examination: typically, a sensory loss in the limbs alone or in combination with abnormal tendon reflexes. Sensory loss had a distal glove-and-stocking distribution and when present in the 4 limbs was more pronounced in the legs than in the arms. Eleven patients had normal clinical examination. Of the 47 patients with detailed clinical information, 5 complained of facial paraesthesia or pain while none had a clinically evident sensory loss or masticatory and facial muscle weakness. All patients and normal subjects gave their informed consent and the local Ethics Committee approved the research.

Details of trigeminal laser stimulation and of electrical stimulation of the corneal mucosa are reported elsewhere (Ongerboer de Visser and Cruccu, 1993; Cruccu et al., 1999). In brief, laser stimuli (1.5–15 W; duration 10–15 ms; beam diameter 5 mm^2) at about twice the perceptive threshold were delivered at 10–20 s interstimulus intervals to the skin bordering the lower lip by means of a CO_2-laser stimulator (Neurolas, Electronic Engineering, Florence, Italy). Signals (bandpass 0.5–50 Hz) were recorded with silver disc electrodes from the vertex referenced to linked earlobes. Poststimulus 2 s periods were examined and stored. Two series of 10 artefact-free trials were collected and averaged off-line.

The corneal reflex was harmlessly evoked by delivering electrical stimuli (0.2–3 mA, 1 ms) to the corneal mucosa at 20–30 s interstimulus intervals, by means of a thin cotton thread emerging from a pipette filled with saline-soaked gauze and connected to the cathode of the stimulator (Accornero et al., 1980). The stimulus intensity was set to evoke a nearly maximal and stable response. Electromyographic signals were recorded with surface electrodes (bandwidth 20–2000 Hz) from the lower part of the orbicularis oculi muscle ipsilateral to the stimulated side (direct response). All the patients underwent the LEP study; only the 21 patients with severe polyneuropathy did the corneal reflex study.

To detect abnormal responses we considered the latency of the negative component and the peak-to-peak amplitude of LEPs and the latency of the corneal reflex (Fig. 1). As the normal limits we took the maximum value of LEP latencies (204 ms) and corneal latencies (51 ms) and the minimum value of LEP amplitude (8 μV) found in the control group. Intergroup differences were analysed by Welch's corrected test for populations with different variances; the frequency of abnormal responses in the 3 groups of diabetic patients classified according to the severity of peripheral nerve damage were analysed by Chi-squared (χ^2) test. Data are means ± 1 SD.

3. Results

The 52 diabetic patients had a significantly longer LEP latency than normal subjects (186 ± 33 vs. 167 ± 18 ms; $P < 0.005$) and lower amplitude (21.2 ± 12.3 vs. 29.1 ± 10.4 μV; $P < 0.005$). Of the 21 patients with severe polyneuropathy (group A), 3 had absent, 7 had delayed and 11 had normal LEPs. Of the 13 patients with mild polyneuropathy (group B) 4 had delayed and 9 had normal LEPs. All the 18 patients without peripheral polyneuropathy (group C) had normal LEPs. The frequency of abnormal responses differed significantly in the 3 groups ($P < 0.005$).

All the patients with severe polyneuropathy (Group A) underwent the corneal reflex study. Diabetic patients and normal subjects had similar latencies (42 ± 5 and 41 ± 4 ms). Only one patient showed a slight latency delay (52 ms).

4. Discussion

The novel finding in this study is that LEPs disclosed evident trigeminal small-fibre dysfunction in many patients with diabetes. The LEP abnormality frequency correlated with the severity of peripheral nerve damage in the limbs, as assessed by a standard nerve conduction study. Unlike the LEPs, the corneal reflex was unaffected.

Because the trigeminal territory is not amenable to a standard nerve conduction study, trigeminal LEPs and reflexes (Ongerboer de Visser and Cruccu, 1993; Cruccu et al., 1998, 1999) are a useful tool for the neurophysiological assessment of trigeminal function in patients with diabetic polyneuropathy. The data from trigeminal LEPs in this study indicate that diabetic patients frequently have damage to the thermal-pain fibres of the mandibular branch of the trigeminal nerve. Most patients in this study had subclinical damage (only 5 of the 21 patients with severe polyneuropathy complained of facial pain or paresthesias). Quantitative psychophysical testing might of course have detected a thermal-pain dysfunction.

Skin thickness influences the excitability of free nerve endings to laser stimuli (Agostino et al., 2000). In diabetic patients the skin is often thicker than that in normal subjects (Huntley, 1989). To avoid any bias due to skin thickness, we evoked LEPs using the same multiple of the perceptive threshold in both normal and diabetic subjects.

The LEPs elicited by stimulating the lower lip investigate the function of the Aδ afferents (Bromm and Treede, 1991; Cruccu et al., 1999) running along the inferior alveolar and mandibular nerves. These fibres run in a constrained path in the mandibular canal and below the pterygoid muscle and undergo repeated microtrauma during mastication. This microtrauma may add to the damage related to generalized neuropathy. Yet, we consider it unlikely as the primary cause of abnormal LEPs in our patients because compression affects thin fibres less than large fibres, also in the cranial nerves (Cruccu et al., 1987; McLean, 1988).

Eleven patients had delayed LEPs; in 5 patients, despite having a normal amplitude LEPs were strongly delayed (by 27–90 ms). Hence these patients, and possibly others, probably had segmental demyelination. Even the absent responses (3 patients) may result from demyelination. In diabetic patients the most common cranial neuropathy is oculomotor mononeuropathy. Its pathophysiology is commonly related to segmental demyelination due to a focal ischemia in the border zone between the posterior and middle vascular territories of the third nerve (Asbury et al., 1970; Weber et al., 1970). Interestingly, a group of diabetic patients without a history of ocular palsy still had histopathological damage attributed to ischemia (Smith and Dyck, 1992). Although in diabetic patients metabolic mechanisms may contribute to myelin damage (Giannini and Dyck, 1999), the sparing of the ophthalmic division in our patients makes this possibility unlikely. We propose that the subclinical LEP abnormalities found in this study therefore originate from a segmental demyelination, possibly of ischemic origin.

Why patients with diabetes mellitus and severe polyneuropathy had abnormal LEPs yet sparing of the corneal reflex raises some interesting points.

We can exclude the possibility that damage within the brain concurred in determining our results. The reported frequency of central abnormalities in somatosensory evoked potential studies is in general low, and in diabetic patients without peripheral neuropathy is extremely low (Comi, 1997; Di Mario et al., 1995). Our study design explicitly excluded patients with overt signs of CNS damage. Most importantly, a possible damage to the brain would also affect the corneal reflex, which, like the blink reflex, is mediated by reticular interneurons and is susceptible to suprasegmental lesions (Ongerboer de Visser, 1981; Berardelli et al., 1999).

We consider it unlikely that the difference depended on the number of afferents mediating the two responses. Like LEPs, which arise from stimuli delivered over a small skin spot, the corneal reflex is mediated by few afferents (Lele and Weddel, 1959). It is also reportedly highly sensitive in detecting trigeminal nerve lesions (Cruccu et al., 1987; Ongerboer de Visser and Cruccu, 1993; Berardelli et al., 1999). Furthermore, while a cerebral potential can often be elicited even by the smallest afferent volley, reflex responses usually require a relatively large and synchronized afferent volley: this would only make the reflex more sensitive than the cerebral potential.

Differences in the afferent pathways and vascular supply of the two responses might offer a tentative explanation. Unlike LEPs after stimulation of the mental territory, the corneal afferents reach the first trigeminal division along the ciliary nerves in an unconstrained route. The afferents mediating LEPs run in the mandibular canal and receive their supply from the alveolar artery alone. Thus, this could be a region of vascular vulnerability. Conversely, the ciliary nerves mediating the corneal reflex receive their blood supply from branches originating from the

ophthalmic artery, the site of rich anastomoses between the internal and external carotid arteries. These anatomic features might make the corneal afferents less susceptible to compression and ischemic damage than the LEP afferents of the mandibular division.

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