Clinical Neurophysiology 114 (2003) 702–709

www.elsevier.com/locate/clinph

Laser-evoked potentials in post-herpetic neuralgia

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Accepted 3 January 2003

Abstract

Objective: We evaluated the reliability of laser-evoked potentials (LEPs) as a diagnostic tool in patients with post-herpetic neuralgia (PHN), i.e. a chronic painful condition that causes small-diameter fibre dysfunction. Furthermore, we sought information on pathophysiology of PHN pain.

Methods: We recorded 'late' LEPs after stimulation of the supraorbital, upper cervical, lower cervical, upper thoracic, mid thoracic, and lower thoracic territories in 12 control subjects and 40 patients with PHN. We also determined the correlation of LEP data with age, duration of disease, and severity and quality of pain.

Results: At all stimulation sites, laser pulses invariably evoked high-amplitude brain potentials related to small-myelinated (A-delta) fibre activation. The laser perceptive threshold and LEP latency correlated with the distance of the dermatome from the brain ($P < 0.001$). In patients, the perceptive threshold was higher and the LEP amplitude was lower in the affected dermatome than on the contralateral side ($P < 0.001$). We found no significant LEP-clinical correlation except for a correlation between LEP abnormality and age.

Conclusions: Being sensitive and reliable in assessing sensory function also in proximal dermatomes, LEPs are a promising diagnostic tool in radiculopathies. Although PHN severely impairs small myelinated fibres, the lack of a significant correlation between LEP abnormalities and pain suggests that pain in PHN does not chiefly arise from a dysfunction of small-myelinated afferents.

Keywords: Laser evoked potential; Postherpetic neuralgia; Small fiber function; Neuropathic pain; Radiculopathy

1. Introduction

Herpes Zoster (HZ) is a localized infection caused by the varicella-zoster virus. After remaining dormant in the sensory ganglia since the primary infection (i.e. varicella), the virus reactivates and spreads along the nerve fibres to the skin causing a dermatomally distributed painful rash. In the ganglion, the virus causes neuronal death followed by degeneration of spinal and peripheral axons (Head and Campbell, 1900). The main complication of HZ is post-herpetic neuralgia (PHN), defined as a chronic painful condition lasting for at least 3 months after the HZ skin eruption (Dworkin and Portenoy, 1996). The sensory disturbances in PHN include hypoesthesia and allodynia to various modalities in one or more dermatomes. PHN-induced pains comprise constant (burning or aching) pain, paroxysmal (shooting) pain, and allodynia (most commonly dynamic mechanical allodynia) (Rowbotham and Fields, 1989).

The pathophysiological mechanisms leading to persistent pain in PHN remain unclear. Skin biopsy studies (Oaklander, 2001) have shown a severe loss of epidermal nerve endings in the affected dermatomes. Post-mortem histopathological studies have shown demyelination and axonal degeneration of dorsal root cells, together with dorsal horn atrophy, in patients with PHN but not in patients who had HZ without persistent pain (Watson et al., 1988, 1991). Psychophysiologic measures of mechanical, thermal, and pain thresholds in PHN, showed a multi-modality sensory impairment involving all groups of myelinated as well as unmyelinated fibres (Nurmikko and Bowsher, 1990; Bjerring et al., 1990).

Neurophysiological studies, using peripheral nerve conduction and dermatomal somatosensory evoked potentials, have confirmed damage to large-diameter myelinated

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1388-2457/03/$30.00
doi:10.1016/S1388-2457(03)00009-9

fibres in patients with PHN and HZ (Leardi et al., 1994; Mondelli et al., 1996). The neurophysiological assessment of small-fibre function relies on the laser-evoked potentials (LEPs) after stimulation of the face, hand, and foot (Bromm and Treede, 1984; Bromm and Chen, 1995; Kakigi et al., 1992; Agostino et al., 2000b; Cruccu et al., 2001). Probably because HZ most frequently affects proximal dermatomes, LEPs have been studied in very few patients with PHN (Darsow et al., 1996; Innocenti et al., 1999).

To evaluate the reliability of LEPs as a diagnostic tool in radiculopathy, we recorded LEPs after stimulation of the supraorbital, upper cervical, lower cervical, upper thoracic, mid thoracic, and lower thoracic territories in control subjects and patients with PHN. To gain information on the pathophysiology of pain in PHN we also determined the correlation of LEP data with clinical variables (age, duration of disease, and the severity and quality of pain).

2. Methods

2.1. Subjects

Twelve healthy volunteers, aged 45–82 years (mean 67 years), and 40 patients with PHN aged 54–87 years (mean 70 years) participated in the study. All subjects gave their informed consent to undergo the procedure, and the local Ethics Committee approved the research. All patients had unilateral PHN, involving the supraorbital territory (V1) in 9 patients, upper cervical dermatomes (C2–C5) in 4, upper thoracic dermatomes (T1–T4) in 12, mid thoracic dermatomes (T5–T8) in 11, and lower thoracic dermatomes (T9–T12) in 4. All patients were tested at least 3 months after the onset of shingles.

2.2. Laser stimulation and scalp recordings

Using a CO_2-laser stimulator (Neurolas, Electronic Engineering, Florence, Italy) we delivered brief radiant heat pulses (wavelength 10.6 μm, intensity 1.5–15 W, duration 15 ms, beam diameter 2.5 mm) to the supraorbital skin (V1), the lateral aspect of the neck and shoulder (C2–C5), the back of the hand (C6–C8), and along the median clavicular line to evaluate the thoracic dermatomes at the different levels (T1–T12).

To determine the laser perceptive threshold (PTh) we delivered a series of stimuli at increasing and decreasing intensity, and defined the perceptive threshold as the lowest intensity at which the subjects perceived at least 50% of the stimuli (Cruccu et al., 1999; Agostino et al., 2000a; Pertovaara et al., 1988).

In standard LEP recordings we used a stimulus intensity of about twice the perceptive threshold; in patients with severe sensory loss and absent LEPs we increased the stimulus intensity up to 50 mJ/mm^2. The interstimulus interval was varied pseudorandomly (10–20 s) and the points irradiated were slightly shifted after each stimulus, to avoid damage to the skin, fatigue or sensitization of nociceptors, and central habituation. LEPs were recorded through silver disc electrodes from the vertex (Cz as defined by the International 10–20 System) referenced to linked earlobes (A1–A2). Electro-oculographic recordings monitored possible eye movements or blinks. Electrode impedance was kept below 4 kΩ. For each site of stimulation 8–16 artefact-free trials were selected and averaged off-line. We measured the latency of the main negative and positive components and their peak-to-peak amplitude.

2.3. Clinical-neurophysiological correlations

Before testing, all patients were interviewed and asked to indicate the severity of their current pain on a 0–10 cm visual analogue scale (VAS) and to describe their predominant pain trying to fit it into the following categories: ‘constant’ burning or aching pain (no patient had constant pricking pain), ‘paroxysmal’ shooting or electric-shock-like pain, or ‘pins and needles.’ Patients were also examined for possible hyperalgesia to pinprick and mechanical or thermal allodynia.

A possible correlation was assessed of the amplitude difference between LEPs evoked by stimulation of the normal and affected side with age, duration of disease, pain intensity (VAS), and the quality of pain. We also studied possible correlations between other LEP data (side-difference in PTh and absolute amplitude) and pain intensity.

2.4. Statistical analysis

We stimulated the skin at various body sites ranked according to their distance from the brain as assessed on a skeleton and on topometric atlases (see Table 1; Agostino et al., 2000a). One-way analysis of variance (ANOVA) for repeated measures and post tests for linear trend were used to analyse threshold, latency, and amplitude differences between the various body sites. LEP differences between control subjects and patients and between normal and affected sides of patients were analysed with the Mann-Whitney test. Correlations between LEP data and pain characteristics were evaluated by the Spearman’s correlation coefficient.

3. Results

3.1. Normative values for threshold, latency and amplitude

In all normal subjects laser stimulation readily evoked brain potentials consisting of a negative component (N) at about 200 ms latency, followed by a positive component (P) at about 300 ms latency, corresponding to the so-called N2-

Table 1
Laser-evoked potentials in 12 normal subjects (mean ± SD, range)

Territory	Perceptive threshold (mJ/mm^2)	N Latency (ms)	P Latency (ms)	Amplitude (μV)
Upper cervical '(C2–C5)	8.0 ± 3.5 (3.2–13.5)	169 ± 23 (132–200)	255 ± 33 (194–300)	15 ± 6 (8–25)
Supraorbital (V1)	8.2 ± 2.9 (3.2–13.5)	170 ± 12 (150–198)	246 ± 23 (216–313)	18 ± 7 (6–36)
Upper thoracic (T1–T4)	11.7 ± 3.8 (4.5–18)	202 ± 25 (164–270)	280 ± 37 (222–370)	13 ± 4 (9–19)
Mid thoracic (T5–T8)	13.5 ± 7.1 (4.5–22.5)	220 ± 26 (180–260)	295 ± 14 (276–310)	18 ± 5 (8–23)
Lower thoracic (T9–T12)	13.8 ± 6.2 (4.5–22.5)	234 ± 11 (220–244)	317 ± 11 (300–328)	11 ± 4 (6–16)
Lower cervical (C6–C8)	13.6 ± 4.9 (4.5–18)	238 ± 20 (206–276)	322 ± 27 (288–394)	16 ± 10 (6–30)
Correlation with distance[a]	$P < 0.001$	$P < 0.001$	$P < 0.001$	$P > 0.20$

[a] The territories were ranked according to their distance from the brain (Agostino et al., 2000a). Significance was evaluated with Spearman (R) correlation coefficient.

P2 components of the late LEPs commonly seen after hand stimulation and attributed to activation of A-delta nociceptors (Fig. 1).

The perceptive threshold and LEP latency differed at the various body sites ($P < 0.001$, ANOVA). Post hoc analysis found a significant linear trend according to distance from the brain ($P < 0.001$) (Table 1). In contrast, stimulation of the different areas yielded similar amplitude LEPs (Table 1). The LEP latency and amplitude did not correlate with age ($P > 0.2$).

The intraindividual latency difference between sides was relatively small (mean 9.6 ± 7.1, range 0–26).

3.2. Patients

The perceptive threshold, N-latency, and amplitude of LEPs after stimulation of the normal side matched those of healthy subjects ($P > 0.5$) (Fig. 2). The perceptive threshold was higher after stimulation of the affected side than after stimulation of the normal side ($P < 0.002$) and

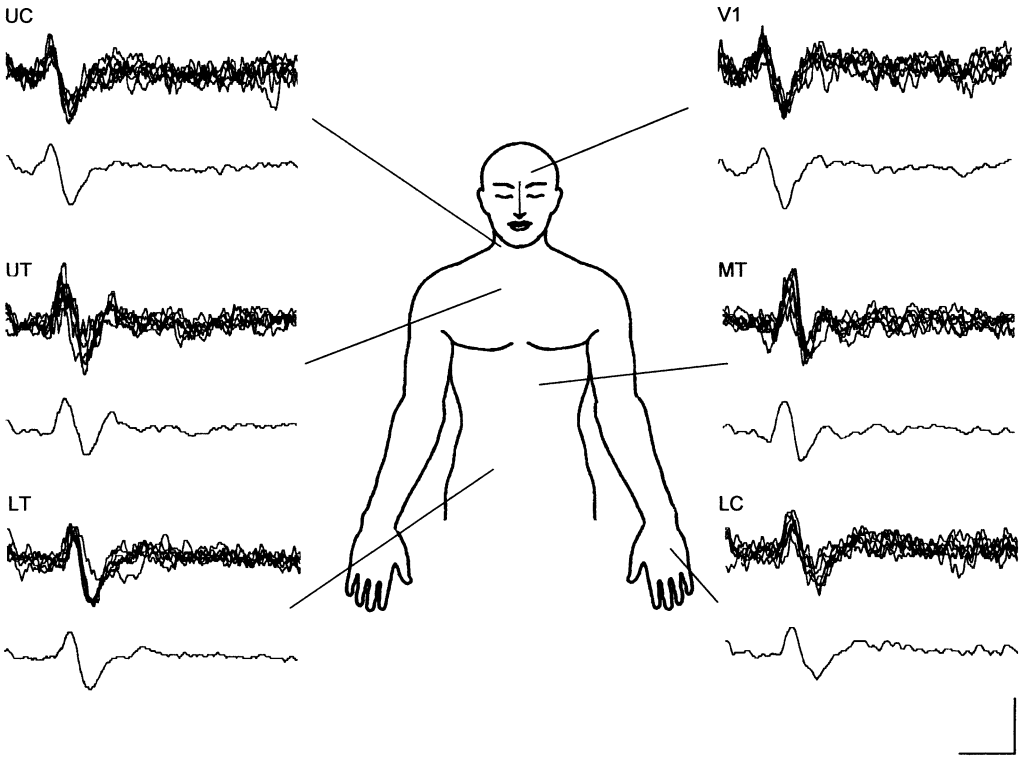


Fig. 1. Laser-evoked potentials in a representative subject. Scalp potentials after stimulation of the supraorbital area (V1), upper cervical (UC), upper thoracic (UT), mid thoracic (MT), lower thoracic (LT) and lower cervical (LC) dermatomes. Superimposition and average of 8 artefact-free trials. Calibration 200 ms/20 μV.

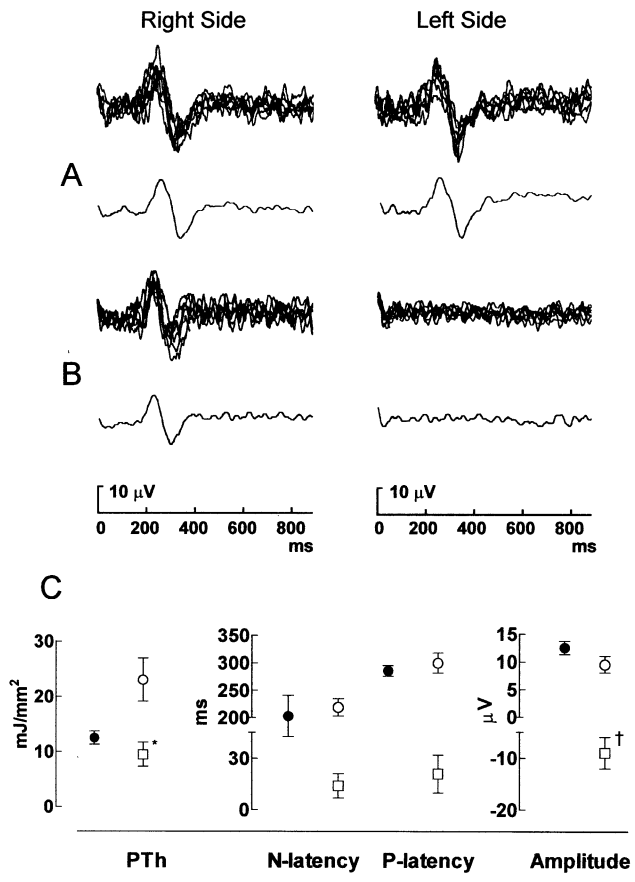


Fig. 2. LEP findings in patients. (A,B) LEPs after stimulation of the T3–T4 dermatomes in a control subject (A) and in a patients (B) with PHN involving the left T3–T4 dermatomes. Superimposition and average of 10 artefact-free trials. (C) First *Y*-axis: perceptive threshold (mJ/mm^2); second *Y*-axis: latency (ms) of the N and P components; third *Y*-axis: amplitude (μV). Each symbol indicates mean ± standard error. Black dots, absolute values from the normal side; white circles, absolute values from the affected side; white squares, intraindividual differences between sides. The perceptive threshold was higher and the LEP amplitude lower after stimulation of the affected side than after stimulation of the normal side: $^{*}P < 0.002$, $^{\dagger}P < 0.01$. There were no significant differences in latency.

two patients did not perceive maximum-intensity laser stimuli (50 mJ/mm^2). No patient had a lower perceptive threshold on the affected dermatome. The mean stimulus intensity used in LEP recordings (about twice the perceptive threshold) was 21.8 ± 0.9 mJ/mm^2 on the normal side and 39 ± 3.9 mJ/mm^2 on the affected side (excluding the two patients insensitive to laser stimulation). The LEP amplitude was lower after stimulation of the affected side than after stimulation of the normal side ($P < 0.01$). Although the mean latency was slightly longer after stimulation of the affected side, the asymmetry did not reach statistical significance ($P > 0.1$) (Fig. 2C).

In 26 patients, laser stimulation of the affected dermatome failed to evoke reproducible brain potentials. In 6 of these patients, LEPs were not reproducible or markedly dampened even after stimulation of the contralateral side.

3.3. Clinical-neurophysiological correlations

The pain score ranged from 2 to 10 cm on the VAS (mean 5.3 cm). Patients reported suffering from constant, paroxysmal, and allodynic pain. The worst kind of pain was constant in 20 patients and paroxysmal in 15 (4 of these patients also had dynamic mechanical allodynia). Five patients were unable to provide an adequate description of their pain. No patient had hyperalgesia. Only 9 patients had a clinically manifest sensory impairment in the affected areas involving every sensory modality. All these patients also had abnormal LEPs; of the other 31 patients without a clinically manifest sensory impairment 17 had abnormal and 14 normal LEPs; the association between clinical and neurophysiological abnormalities was statistically significant (Fisher's exact test, $P < 0.02$). The side difference in LEP amplitude correlated with age ($r = 0.54$, $P < 0.01$) (Fig. 3A). In contrast LEP abnormalities did not correlate with the duration of disease ($r = 0.04$, $P > 0.5$).

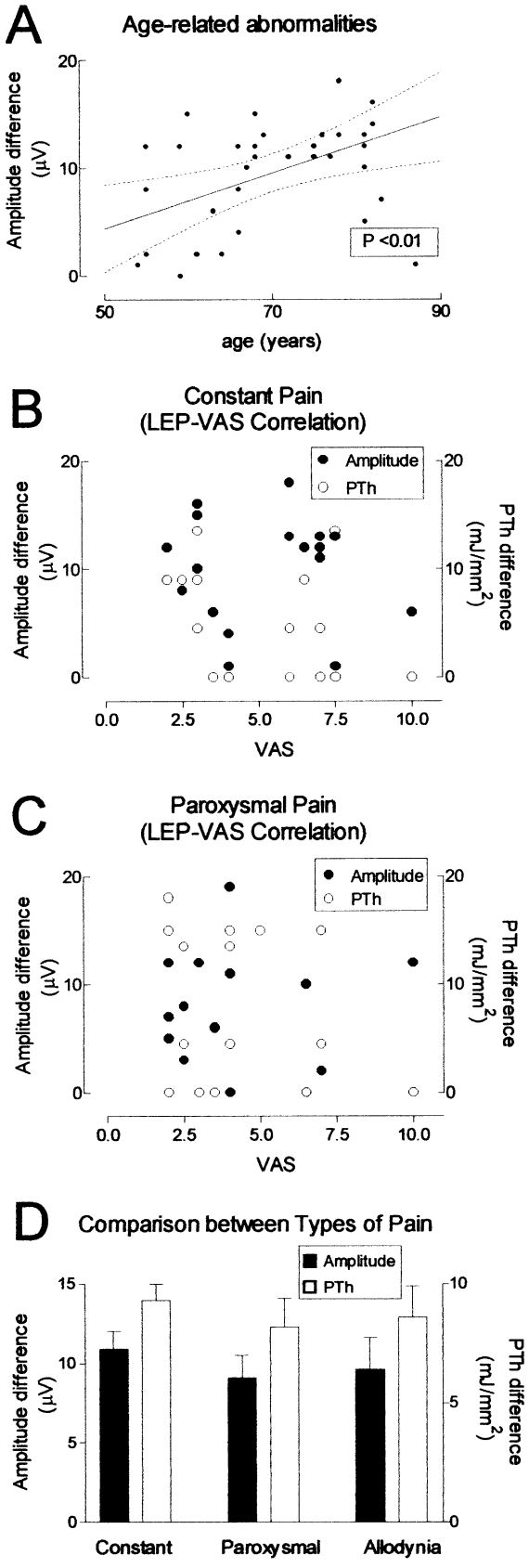
The side to side difference in LEP data (perceptive threshold, latency, or amplitude) did not correlate with pain intensity as assessed by VAS ($P > 0.5$) (Fig. 3B,C). Similarly, there was no correlation between the LEP absolute amplitude and VAS score either after normal or affected side stimulation ($P > 0.2$). Nor did LEP data differ in patients with constant pain and those with paroxysmal pain (Fig. 3D). We did not study differences or correlations related to allodynia, because only 4 patients indicated allodynia as their worst pain, two of them had absent responses on the affected side, and one had absent responses bilaterally.

4. Discussion

Our findings show that in healthy subjects, laser stimulation of proximal dermatomes readily evokes large brain potentials. The latency slightly increases with the distance from the brain, as does the perception threshold, probably because of the longer conduction distance and lower receptor density (Agostino et al., 2000a). In patients with PHN, stimulation of the affected dermatomes yielded markedly altered LEPs, thus demonstrating a severe impairment of A-delta nociceptive neurons. None of these LEP abnormalities correlated with the severity or quality of pain.

4.1. LEPs as a diagnostic tool for radiculopathy

Because of their anatomical characteristics, the proximal cervical and thoracic territories cannot be investigated by a standard nerve conduction study. The most common technique for studying sensory function in these territories is to test scalp potentials evoked by electrical stimulation (dermatomal SEPs), mediated by large afferents (Slimp et al., 1992). As a diagnostic tool, dermatomal SEPs have



certain limitations: they require a large number of trials and in cervical radiculopathies have a low sensitivity even in patients with sensory deficits (Schmid et al., 1988).

In this study, we showed that laser stimulation of proximal dermatomes, after only a few trials, yields clear and large-amplitude scalp potentials related to A-delta afferent activation, also in elderly subjects. Furthermore the latency barely differed between sides.

In normal subjects, neither the latency nor the amplitude of our dermatomal LEPs changed with age. The absence of age-related changes in amplitude is in contrast with an earlier study on LEPs after perioral stimulation (Cruccu et al., 1999). Studying LEPs after hand stimulation, however, Gibson et al. (1991) did not find age-related changes except for a very elderly group (80–100 years). We do not know whether the presence or absence of an age-amplitude correlation depends on the different anatomical territory or the different age ranges.

These responses proved sensitive enough to confirm abnormalities in 9 out of 9 patients who had a clinical sensory loss and to disclose subclinical abnormalities in 17 out of 31 patients. In LEP recordings we used a stimulus intensity twice PTh; because the perceptive threshold was higher on the affected than the normal side, the stimulus intensity differed between sides. This might compensate for dysfunction and thus hinder LEP abnormalities. Nevertheless, 26 out of 40 patients had absent LEPs on the affected side and we found a strong mean difference in LEP amplitude between normal and affected side. Probably LEPs have a high sensitivity because they are mediated by a small number of afferents; the dysfunction of even few afferents may prevent adequate spatial-temporal summation of impulses at central synapses (Agostino et al., 2000b).

Because LEP testing requires a very low stimulus intensity, it does not injure the skin. When we used high-intensity pulses in patients with no responses, the laser stimulation induced small dyschromic spots that disappeared within 1 or 2 weeks. None of the patients considered this an unduly bothersome problem. We believe that LEPs will prove a sensitive and reliable tool for assessing sensory function mediated by A-delta fibres in proximal dermatomes, particularly in radiculopathy. Because the thin fibres of the nociceptive system do not overlap between adjacent spinal segments to the same extent as the thick fibres of the

Fig. 3. Clinical-neurophysiological correlations. (A) correlation with age. *Y*-axis: amplitude difference between normal and affected side. *X*-axis: age. The side difference in LEP amplitude correlated with age ($r = 0.54$, $P < 0.01$). (B,C) correlation with pain intensity in patients with predominantly constant pain (B) and paroxysmal pain (C). Left *Y*-axis: amplitude difference; right *Y*-axis: perceptive threshold (PTh) difference; *X*-axis: pain intensity (visual analogue scale, VAS 0–10 cm). Each subject is represented by a black dot (amplitude) and a white circle (PTh). LEP data did not correlate with pain intensity in either pain group. (D) Mean ± standard error of the side differences in amplitude (black bars) and perceptive threshold (white bars) of 3 groups of patients, divided according to their predominant type of pain. The 3 groups did not differ significantly.

mechanoreceptive system, the border between skin areas with normal or absent LEPs is very sharp (Lorenz et al., 1996). Hence LEPs are expectedly more sensitive than SEPs in disclosing lesions restricted to one spinal root.

4.2. LEPs in post-herpetic neuralgia

Psychophysical studies have demonstrated dysfunction of all sensory modalities in PHN (Nurmikko and Bowsher, 1990; Bjerring et al., 1990). Although skin biopsy studies have shown a severe loss of epidermal free nerve endings in the affected dermatomes (Oaklander, 2001), they could not differentiate the nerve endings of myelinated (A-delta) from those of unmyelinated (C) neurons. Because only a small percentage of the superficial free nerve endings are A-delta receptors, skin biopsy studies have demonstrated a severe loss of C receptors. Our study provides the objective evidence of A-delta neuron impairment in a large cohort of patients with PHN. Because LEPs were reduced in amplitude rather than being delayed, the dysfunction probably originates not from demyelination but from the degeneration of the dorsal root ganglion cells invaded by the varicella-zoster virus. Using scalp recordings, we could not ascertain whether some of our patients also had dorsal horn lesions, as found in some patients with HZ or PHN (Watson et al., 1988, 1991; Haanpää et al., 1998; Innocenti et al., 1999).

Studying CO_2-laser-evoked potentials in a patient with circumscribed pruritus attributed to a previous HZ infection, Darsow et al. (1996) found a lower laser perceptive threshold and higher LEP amplitudes in the affected dermatomes. In a study of perceptive thresholds to argon-laser stimulation in PHN, Bjerring et al. (1990) reported that their stimuli sometimes induced allodynic pain. None of our patients had clinical hyperalgesia to pinprick stimuli; accordingly, none had a lowered laser perceptive threshold. Because threshold stimuli evoke pinprick sensations (i.e. pain), LEPs are unsuitable for testing allodynia (by definition, pain caused by a normally innocuous stimulus). The contrasting findings in the foregoing studies probably reflect the various pain mechanisms that operate in PHN and the different types of laser stimulators used.

We found a strong correlation between age and LEP abnormality, measured as the amplitude difference between sides. Small-diameter myelinated fibres are therefore more severely affected in elderly patients. This age-related difference may reflect the general vulnerability of the nerve fibres and impaired fibre regeneration in the elderly or the more severe fibre damage caused by a weakened immune response to HZ. The predisposition of the elderly to more severe neural damage may contribute to their elevated risk and to the greater severity of PHN.

We found no correlation between LEP abnormalities and the duration of PHN. Hence we could not provide evidence – in the 4–18 month disease duration in our patients – of a possible A-delta fibre regeneration. Because we studied only healthy volunteers and patients with PHN but not those without PHN after HZ, we cannot be sure that our findings are typical of the painful sequelae after HZ. We would need to study LEPs longitudinally in patients with HZ to find out whether LEP abnormalities are associated with persistent PHN.

In a few patients, stimuli applied to the normal side also elicited abnormal LEPs. These bilateral abnormalities were not correlated with age. For their neuropathic pain, all patients were being treated with drugs acting on the nervous system. As previous studies have underlined these drugs can dampen LEPs (Cruccu et al., 2001). A drug-induced effect also receives support from the readily reproducible LEPs in our healthy elderly subjects none of whom were taking drugs. Alternatively, the bilateral abnormal finding may be due to bilateral dysfunction analogous to the bilateral abnormality in EMG or quantitative somatosensory testing in some patients with unilateral HZ (Haanpää et al., 1997, 1999).

4.3. Pain mechanisms

Although PHN is a very common chronic pain syndrome, the mechanisms leading to pain are poorly understood. Among the many studies on this subject (Nurmikko et al., 1990; Haanpää et al., 2000; Rowbotham and Fields, 1996; Baron and Saguer, 1993), a recent review (Fields et al., 1998) proposes 3 main mechanisms of pain in PHN. In patients with no evidence of sensory loss, pain and allodynia could be due to 'irritable nociceptors.' In these cases, pain is related to intact but hyperactive primary nociceptors (probably unmyelinated) that induce and maintain sensitization in the spinal dorsal horn. Large-myelinated (A-beta) afferents can activate the sensitized spinal nociceptive pathways causing allodynia. In patients with selective thermal-pain sensory loss, pain and allodynia are due to the loss of nociceptive primary afferents that induce a synaptic reorganization in the dorsal horn, with abnormal connections between large non-nociceptive afferents and nociceptive second order neurones that have lost their primary afferents. Finally, in patients who have a severe sensory loss and constant pain (but not allodynia), pain is due to a massive degeneration of both myelinated and unmyelinated primary afferents that induces spontaneous hyperactivity in the deafferented spinal neurones. Although in many patients all these mechanisms presumably coexist, one often predominates.

In accordance with a deafferentation mechanism, most of our patients had abnormal LEPs. Yet we found no significant correlation between LEP abnormality and pain intensity (Fig. 3B,C) in either the 'constant' or 'paroxysmal' pain groups (we did not study intraindividual correlations in the 4 patients with allodynia). A possible explanation of this lack of correlation is that pain in PHN arises from a source other than damage in the A-delta pathway. Although CO_2-laser pulses can excite both myelinated and unmyelinated

nociceptors, with the stimulus characteristics used in this study the evoked sensation (pinprick) and brain potentials (200 ms latency) were both related to A-delta activation. Similarly, dermatomal SEPs after electrical stimulation of large afferents are severely impaired in PHN but their abnormality does not correlate with pain (Leardi et al., 1994). The fact that none of our patients had lowered thresholds for LEPs on the affected side argues against irritable A-delta nociceptors as the prime generators of their pain.

The lack of correlation between A-delta afferent damage and pain found in this study makes a quantitative assessment of C-afferent function in PHN the more interesting. Several investigators have reported methods of studying C-fibre related ('ultralate') LEPs after stimulation of the hand (Bromm et al., 1983; Treede et al., 1988; Bragard et al., 1996), a territory which is affected only in a small proportion of PHN patients. A recently reported method of eliciting both A-delta and C-related LEPs after stimulation of the skin overlying the spine (Cruccu et al., 2000; Qiu et al., 2001; Iannetti et al., 2003), however, may be applied to patients with PHN in thoracic or cervical dermatomes.

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