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Large and Small Fiber Dysfunction in Peripheral Nerve Injuries With or Without Spontaneous Pain

Inge Petter Kleggetveit and Ellen Jørum

Section of Clinical Neurophysiology, Department of Neurology, Oslo University Hospital - Rikshospitalet and University of Oslo, Oslo, Norway.

Abstract: Few data have been available on the functional role of small fiber damage in patients with peripheral nerve injuries with and without spontaneous pain. The aim of the present study was to investigate the function of large myelinated nerve fibers as well as small nerve fibers in a material of 60 patients with peripheral nerve injuries in upper or lower extremities, 30 patients with spontaneous pain, and 30 patients without pain. Patients were questioned about the characteristics of pain and investigated clinically with EMG/neurography and assessment of thermal thresholds in the innervation territory of the lesioned nerve as well as in the contralateral area. Sensation of touch and warmth and cold detection was significantly reduced in the injured side in both groups. There was a tendency, not significant, for heat pain thresholds to be more elevated in the affected side compared with the healthy side in the pain group only (47.8°C versus 45.1°C). There were no significant differences in thermal thresholds between the 2 groups of patients. The main finding was a high percentage of hyperphenomena (allodynia to light touch and reduced mechanical pain thresholds) in the pain group only.

***Perspective:** Small fiber function did not significantly differ between patients with and without pain, indicating that elevated thermal thresholds alone will not reflect mechanisms responsible for the generation of pain. Hyperphenomena were present in the affected side of the pain group only.*

***Key words:** Peripheral nerve injuries, pain, quantitative sensory tests, small nerve fibers, allodynia.*

Peripheral nerve injuries are from a clinical perspective a common cause of neuropathic pain. However, the incidence of neuropathic pain after nerve lesions caused by various forms of injury such as trauma/entrapment is largely unknown. Neuropathic pain after peripheral nerve injury has been reported to occur in a range from 2.5% to 5%[9,28] up to 22.9% of the patients.[20] It has been claimed that more accurate clinical data are needed.[15] Large fiber lesions may account for pain mechanisms, for instance, due to disinhibition mechanisms,[30,32,34] but overall a dysfunction of small nerve fibers is considered crucial for the generation of pain.[22] Although there are reports of small nerve fiber dysfunction in patients with nerve injuries and pain,[3,4] there is a general lack in the literature of studies examining small nerve fiber abnormalities in patients with nerve lesions with and without pain. Alterations in thermal sensitivity have been described for traumatic lesions of the trigeminal nerve, both in patients with pain and in patients with no pain.[4,7] In a previous study on patients with trigeminal neuropathy with and without pain, thermal hyposensitivity on the lesioned side did not differentiate the neuropathic conditions with pain from those without pain.[7] To be able to state the role of the small nerve fibers, it is mandatory also to include nerve injuries without pain. Results from previous studies on neuropathic pain in polyneuropathies have been conflicting. Regarding diabetic neuropathy, a common cause of neuropathic pain, some clinical studies on painful and nonpainful neuropathy have not been able to prove any clear distinction of small-fiber function by quantitative sensory testing (QST) or neuropathological studies between patients who experience pain and those that do not.[11,14,26,29] Other reports confirm a relationship between pain and the affection of small

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Address reprint requests to Dr Ellen Jørum, Section of Clinical Neurophysiology, Department of Neurology, Oslo University Hospital - Rikshospitalet Sognsvannsveien 20, 0027 Oslo, Norway. E-mail: ellen.jorum@rikshospitalet.no
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fibers.[6,35] Also for sensory neuropathies due to HIV infection, results have been diverging.[1,16] No large study on peripheral nerve injuries in the extremities, including investigations of small fiber function in patients with and without pain, has to our knowledge previously been published.

The aim of the present study was to investigate the function of both large myelinated nerve fibers as well as small nerve fibers by means of EMG/neurography, clinical testing, and QST in a material of 60 patients with peripheral nerve injury in the extremities of various causes. We included 30 patients with and 30 patients without spontaneous pain.

Methods

Patients

The patients included in this study were patients investigated at the Section of Clinical Neurophysiology with verified peripheral nerve lesion by EMG/neurography, with or without spontaneous pain. The study was started January 1, 2006, and ended in February of 2009. Patients diagnosed with complex regional pain syndrome (CRPS) were excluded from the study.

A clinical investigation, with an emphasis on pain and the occurrence of allodynia to light touch as well as QST, found place immediately after EMG/neurography. In both groups of patients, sensory testing was conducted within the innervation territory of the lesioned nerve and for the patients with pain, at the site of maximal spontaneous pain. The homologous contralateral site was also tested. All these investigations are performed routinely at the Section of Clinical Neurophysiology and the study was approved by the institutional review board. All patients consented to take part in the study.

Pain Assessment

The patient was asked about the occurrence of spontaneous ongoing and paroxysmal pain. If the patient suffered from ongoing pain, he or she was asked to rate the intensity of the pain on a numerical scale from 0 to 10, where 0 indicated no pain and 10 the worst imaginable pain.

EMG/Neurography

A Dantec counterpoint EMG machine was used, measuring motor amplitude, distal latency and conduction velocity as well as sensory amplitude and conduction velocity of the nerve in question. EMG of appropriate muscles was performed, both assessing the properties of the motor unit potential as well as searching for possible signs of denervation.

Quantitative Sensory Testing

1. Thermal Sensibility

Threshold temperatures for the sensation of warmth, cold, heat pain and cold pain were determined using a computerized Thermotest (Somedic AB, Hörby, Sweden) as described elsewhere.[31] Warmth detection threshold (WD), cold detection threshold (CD), heat pain detection threshold (HPD), and cold pain detection threshold (CPD) were determined from a baseline temperature of 32°C with a 1°C/s rate of change and with cutoff temperatures of 10°C and 50°C. WD, CD, HPD, and CPD were determined in the innervation territory of the lesioned nerve as well as in the contralateral nonlesioned area. The actual values (for WD, CD, HPD, and CPD or cutoff temperatures when the patient lacked the sensation) (for comparisons within subjects and between groups of patients) as well as the difference between injured/noninjured site (for comparisons between groups of patients) constituted the basis for further statistical analyses.

2. Mechanical Detection and Pain Thresholds

Assessment of mechanical detection as well as mechanical pain thresholds was performed within the innervation territory of the injured nerve and in the contralateral area with 17 von Frey nylon filaments (Somedic AB, Hörby, Sweden) with a bending force ranging from .26 to 1078 mN. Series of ascending and descending magnitude was applied until a threshold was found. The final threshold was calculated as the geometric mean of 5 series.[21]

Assessment of Allodynia

The presence or not of allodynia to light touch was investigated by stroking a light brush (SENSElab; Somedic AB, Hörby, Sweden) to the painful/nonpainful area and within the innervation territory of the nerve in question.

Skin Temperature

Skin temperature was measured at the sites of sensory testing and preceded each test session. An IR thermometer, (SENSELab Tempett; Somedic AB, Hörby, Sweden) was used.

Statistical Analyses

Nonparametric statistical methods were used (SPSS 16.0 for Windows; SPSS, Inc, Chicago, IL), the median as a measure of location and the interquartile range as a measure of distribution. The Wilcoxon signed rank test was used to calculate differences between values from injured and noninjured areas in both groups of patients. Differences between thermal thresholds in injured and noninjured side in the 2 patient groups was evaluated using the Mann-Whitney *U* test, both directly as well as based on side-to-side differences in thermal thresholds within each group of patients. We further investigated a possible significant association (Crosstabs, Pearson χ^2 test) between:

1. lack or reduced sensory response by neurography and the existence of spontaneous pain
2. spontaneous pain and cold allodynia
3. allodynia to light touch and cold allodynia
4. severe or minor degree of small fiber hyposensibility and the presence of allodynia to light touch

Values of $P < .05$ were considered statistically significant.