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Disturbed sensory perception of changes in thermoalgesic stimuli in patients with small fiber neuropathies

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ABSTRACT

The assessment of functional deficits in small fibre neuropathies (SFN) requires using ancillary tests other than conventional neurophysiological techniques. One of the tests with most widespread use is thermal threshold determination, as part of quantitative sensory testing. Thermal thresholds typically reflect one point in the whole subjective experience elicited by a thermal stimulus. We reasoned that more information could be obtained by analyzing the subjective description of the ongoing sensation elicited by slow temperature changes (dynamic thermal testing, DTT). Twenty SFN patients and 20 healthy subjects were requested to describe, by using an electronic visual analog scale system, the sensation perceived when the temperature of a thermode was made to slowly change according to a predetermined pattern. The thermode was attached to the left ventral forearm or the distal third of the left leg and the stimulus was either a monophasic heat or cold stimuli that reached 120% of pain threshold and reversed to get back to baseline at a rate of 0.5°C/s. Abnormalities seen in patients in comparison to healthy subjects were: (1) delayed perception of temperature changes, both at onset and at reversal, (2) longer duration of pain perception at peak temperature, and (3) absence of an overshoot sensation after reversal, ie, a transient perception of the opposite sensation before the temperature reached again baseline. The use of DTT increases the yield of thermal testing for clinical and physiological studies. It adds information that can be discriminant between healthy subjects and SFN patients and shows physiological details about the process of activation and inactivation of temperature receptors that may be abnormal in SFN.

1. Introduction

Small fiber neuropathies (SFN) are characterized by sensory disturbances attributable to the involvement of thinly myelinated Aδ-fibers and unmyelinated C-fibers of somatic and autonomic nerves [24,28]. Conventional electrodiagnostic techniques such as nerve conduction studies and electromyography are of little use for assessment of SFN, and therefore, additional techniques should be taken into account [24,29,46]. Probably, the most widely used method to reveal the hypothesized dysfunction of small fibers in patients with suspected SFN is quantitative sensory testing (QST) and, more specifically, quantitative thermal testing (QTT) for determination of thermal thresholds [43,46].

Thermal thresholds are typically examined by applying controlled thermal stimuli. Subjects are expected to detect the stimulus and produce a relatively simple answer [43]. The need for subjects' collaboration and the risk of having equivocal results are still the main drawbacks of the technique. Furthermore, the information obtained with thresholds determination regards typically one point along the whole stimulus-induced experience (the point at which subjects perceive warmth, cold or pain), disregarding the sensations that subjects might experience during the presentation and withdrawal of the stimulus. We considered that analyzing such transient change in sensation could allow for more data points of interesting information and therefore add to the clinical applicability of the test. This requires that the change in temperature is slow enough to allow for the subjects to express the ongoing changes in their sensory perception. A slowly modifying thermal stimulus has been used only scarcely with clinical purposes [23,44,48]. However, we considered that it would reflect the

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processes of activation and inactivation of receptors for heat and cold in the skin under the thermode, albeit filtered through subjective perception and conduction time in the thermoalgesic fibers [5].

In the study presented here, we used relatively long lasting slowly varying wide temperature changes to request our subjects to express their sensation online, using an electronic visual analog scale system. This form of dynamic thermal testing (DTT) has been used so far for the evaluation of refractoriness in the thermoalgesic pathway in healthy subjects [39,40] as well as an additional test for the assessment of patients with syringomyelia [44]. We aimed at expanding our knowledge on psychophysical perception during thermoalgesic stimuli and establishing relevant outcome measures from DTT as well as their normative reference values after exploring a group of healthy volunteers. We also explored the clinical utility of DTT in the assessment of SFN patients through comparison with conventional thermal thresholds determination.

2. Methods

2.1. Subjects

The study was carried out in 20 healthy subjects (HS) and in 20 patients with SFN. HS were 12 men and 8 women with a mean age of 42.4 ± 16.9 years (range 22 to 76 years). None of them reported neurological symptoms or had personal or family history of diseases that could potentially lead to polyneuropathy. They referred no exposure to alcohol or other social, pharmacological or environmental toxins and their basic physical neurological exam of motor and sensory domains was normal. The SFN patients were recruited among those followed in the Neuropathic Pain Unit of the Neurology Department of the Hospital Clinic in Barcelona due to painful polyneuropathy. They were selected according to the diagnostic criteria for SFN on clinical and electrodiagnostic exams [14,23,28]. Patients considered were those that complained of neuropathic pain of length-dependent topographical distribution, with history of a disease known to cause SFN or that, in the absence of an etiological diagnosis, had histological evidence of decreased density of intraepidermal nerve fibers in skin biopsy [9]. Candidate patients were all screened before inclusion using clinical assessment, conventional electrodiagnostic tests, nociceptive evoked potentials recording and thermal threshold determination (see below). Exclusion criteria were: (1) unilateral, asymmetrical or multifocal symptoms or signs; (2) suspicion of radiculopathy or myelopathy; (3) clinical signs of relevant dysfunction in large sensory fibres or signs of demyelinating, predominantly motor or predominantly large fibre polyneuropathies after assessment with conventional nerve conduction studies; (4) patients who were unable to understand the instructions. All participants gave their informed consent for the study, which was approved by the ethics committee of the Hospital Clinic.

2.2. Characterization of patients

2.2.1. Clinical assessment

Patients were presented with questions in regard to their sensory symptoms which included the quality of their spontaneous sensation and the distribution of their symptoms. We assessed muscle strength, patellar and ankle tendon jerks; joint position at the first toe, vibration sensation at the first toe and the internal malleolus; tactile sensation (with a cotton swab) and pricking pain (with a disposable needle) in the dorsum of the foot, mid leg, and thigh.

2.2.2. Conventional electrodiagnostic tests

Nerve conductions studies (NCS) of the lower limbs were performed using either a Mystro5Plus electromyograph (Oxford Instruments, Oxford, UK) or a KeyPoint Net (Alpine Medical Instruments). We calculated nerve conduction velocity and measured compound action potential amplitude of common peroneal (motor) and sural (sensory) nerves, according to standard methods [22]. We determined whether or not the results were within normal limits, according to the reference values of our department [35].

2.2.3. Nociceptive evoked potentials

Contact heat stimuli were applied to the left ventral forearm and to the distal third of the left leg, with a thermofoil thermode stimulator, with a surface area of 572.5 mm^2 (Pathway, Medoc Ltd, Israel). Baseline temperature of the thermode was set at 32°C and increased at a rate of 70°C/s, to reach a peak temperature of 53°C. Contact heat-evoked potentials (CHEPs) were recorded from Cz (vertex potentials) referenced to linked earlobes (A1–A2), which is where CHEPs have their maximal amplitude [5]. Impedance was kept below 5 kΩ. Blinking was monitored for artifact control with surface electrodes attached over the orbicularis oculi muscle. For recording, we used a KeyPoint (Alpine Medical Instruments) electromyograph. Filters were set at 0.1 to 30 Hz and signals were sampled at a rate of 500 Hz.

CHEPs were recorded in a warm and dimly lit room. Stimulus sites were randomized (foot and hand) according to established recommendations [18]. Care was taken to maintain the patient's attention while applying 18 to 20 consecutive stimuli at each region. A random interval of 10 to 20 s was left between 2 consecutive stimuli. In each subject, we obtained a minimum of 12 blink and artifact free traces that were conveniently stored for off-line analysis. We performed an electronic averaging to measure mean N2 latency and N2/P2 amplitude. Results were compared to the reference values of our laboratory for CHEPs latency and amplitude [9]. Results above or below 95th percentile were considered abnormal.

2.3. Psychophysical testing

2.3.1. Thermal thresholds determination

All psychophysical studies were performed in a quiet room at a constant temperature of 24°C. Thermoalgesic stimuli were applied with a Peltier thermode with a surface area of 12.5 cm^2 (MSA, Somedic, Sweden). Stimulation sites were the left ventral forearm and the distal third of the left leg. Baseline thermode temperature was always set at 32°C. The same technician (MM) performed all psychophysical tests.

We used the method of limits [46] to determine warm detection threshold (WDT), heat pain threshold (HPT), cold detection threshold (CDT), and cold pain threshold (CPT). Four stimuli were provided at a pace of one every 20 s, with ramps of 1°C/s. Cutoff temperatures were 10°C and 50°C. Subjects were given a switch button to press at the moment at which they perceived the sensation under examination (either warmth, heat pain, cold, or cold pain). After each stimulus, subjects were asked for the quality of sensation perceived in order to detect possible paradoxical sensations [37,38].

2.3.2. DTT examination

The study of DTT was done in a separate session, the same time of the day, in the same body sites, and by the same examiner (MM) as for thermal threshold determination. We devised a simple stimulus paradigm according to preliminary experiences and previous