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Research article

Bilaterally prolonged latencies of pain-related evoked potentials in peripheral nerve injuries

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ABSTRACT

Objective: Cross-sectional study to test the applicability of pain-related evoked potentials (PREP) for the diagnosis of peripheral nerve injuries (PNI).
Introduction: Patients with generalized polyneuropathies show prolonged latencies and decreased amplitudes of PREP indicating an impairment of A-delta fibers. Although these fibers are frequently affected in PNI, it is unclear, if PREP-testing detects PNI comparable to Nerve Conduction Studies (NCS).
Methods: 23 patients with PNI of one upper limb underwent bilateral PREP-testing (using concentric surface electrodes) and NCS. 41 healthy controls underwent PREP-testing only. We determined pain thresholds, N1-latencies and N1P1-amplitudes of PREP and analyzed them for group and side-to-side differences. Small-fiber function was evaluated using thermal detection thresholds of Quantitative Sensory Testing (QST). N1-latencies above a cut-off calculated by ROC-analysis were defined as abnormal in order to compare detection rates of PREP and NCS.
Results: Patients with PNI showed bilaterally prolonged N1-latencies (ipsilateral: 167.0 ± 40.7 ms vs. 141.2 ± 20.5 ms / contralateral: 160.0 ± 41.0 ms vs. 140.2 ± 23.9 ms) without a significant side-to-side difference. Pain thresholds were increased on the affected side only (4.6 ± 5.2 mA vs. 2.4 ± 1.4 mA (controls)). N1P1-amplitudes did not differ between patients and controls. 7 (32%) patients showed prolonged N1-latencies (> 176 ms) of PREP. NCS were abnormal in 16 (73%) cases. 13 (59%) patients showed thermal hypoesthesia in QST.
Conclusion: Contrary to our expectations, we found bilaterally prolonged N1-latencies and normal N1P1-amplitudes in patients with PNI. Our findings support the hypothesis of a bilateral generation of PREP and indicate that PREP are not suitable for the diagnosis of PNI.

1. Introduction

The examination of peripheral nerve injuries (PNI) mainly relies on electrophysiological examination methods like nerve conduction studies (NCS) and electromyography. These methods give proof of a dysfunction of A-alpha and A-beta nerve fibers [1]. However, about 55% of all patients with PNI suffer from thermal hypoesthesia indicating a loss of function of small A-delta and C-fibers [2]. These fibers can only be examined using more complex examination methods which are subject to several limitations. For example, the application of skin biopsies for the measurement of epidermal nerve fiber density [3] is limited due to its invasiveness, Quantitative Sensory Testing (QST) [4] is time consuming and dependent on the participant's active participation and laser-evoked potentials (LEP) [5] require a large technical expenditure. Pain-related evoked potentials (PREP) might be an alternative because they are a non-invasive, reliable [6] electrophysiological procedure which can assess the signal transmission of A-delta fibers without large expenditure [7,8]. PREP detect small fiber dysfunctions in systemic disorders which are associated with generalized polyneuropathies, e.g. HIV-neuropathy [9,10], diabetic small-fiber polyneuropathy [11], fibromyalgia [12], mixed fiber neuropathy (MFN) [13], hepatitis C-associated polyneuropathy [14] and Fabry disease [15]. However, to our knowledge, it is still unclear, if focal affections, e. g. unilateral PNI, lead to focal or systemic abnormalities of PREP. Therefore, we performed PREP-testing in unilateral PNI of one upper limb and compared our findings with NCS.

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2. Material and methods

2.1. Subjects and study design

The study was approved by the local ethics committee of the Faculty of Medicine, Ruhr-University Bochum, Germany (Reg. Nr. 15-5300; 06-16-2015) and performed in accordance with the latest version of the Declaration of Helsinki. Patients with known peripheral nerve injury (PNI) of one upper limb were recruited between April 2015 and March 2016 from outpatients and in-patients of the University Hospital Bergmannsheil in Bochum, Germany. Inclusion criteria were 1) definite PNI verified by use of nerve conduction studies or during surgery or 2) appropriate clinical symptoms restricted to the cutaneous supply area of a single nerve with proof of sensory loss in clinical examination and a relevant trauma in history (probable PNI). Exclusion criteria were age < 18 years, cervical radiculopathy, upper limb neuropathy, nerve injuries on the other side, polyneuropathy, painful disease other than PNI in the last 4 weeks with a pain rating > 3 (numerical rating scale 0–10), communication problems, cognitive limitations, severe psychiatric disorders, topical therapy with lidocaine or capsaicin and severe allodynia. Based on a clinical examination and previous findings an experienced neurologist checked the diagnosis. 41 healthy, age-matched volunteers were recruited as a control group among employees and visitors of the hospital. Subjects were screened for small-fiber polyneuropathy using a modified version of Michigan Neuropathy Screening Instrument (MNSI) [16] and for major depression with the Patient Health Questionnaire-4 (PHQ-4) [17]. Patients were additionally screened with small fiber neuropathy screening list (SNFSL) [18]. Participants with conspicuous findings (> 48 points in SFNSL, > 6 points in MNSI, ≥9 in PHQ-4) were excluded from the study. The patients' pain perception was evaluated by PainDetect [19]. Handedness was inquired using Edinburgh Handedness Inventory [20]. All subjects underwent PREP-testing and an examination of thermal detection thresholds. NCS were performed with patients only. All examinations of each participant were accomplished within no more than 3 months.

2.2. PREP

PREP-testing was conducted under the same stimulation and recording conditions using the same equipment as previously described [6]. 3 parallel-connected surface electrodes [8] were placed inside the sensory supply area of the affected nerve (patient group), respectively inside the supply area of the superficial radial nerve (control group). First, we determined pain thresholds (PT) for both sides. Afterwards we applied 30 stimuli each on both sides in a pseudo-randomized order with an intensity of the twofold of the PT. In patients, the twofold of the PT of the unaffected hand was used for both hands. In some cases, we had to modify the stimulus intensity according to the algorithm shown in Fig. 1. Pain ratings were assessed every 10 stimuli for both sides using a numerical rating scale (0 = no pain, 100 = strongest pain imaginable). Pain ratings after the first and last 10 stimuli were compared to exclude habituation. PREP were recorded above Cz referred to linked earlobes (A1–A2) according to the international 10–20 system. An examiner blinded to the study analyzed evoked potentials in between 200 ms before and 800 ms after stimulus onset. Potential curves were averaged separately for both sides. We assessed N1-latencies and N1P1-amplitudes (Fig. 2A) of both sides.

2.3. QST and NCS

Cold (CDT) and warm (WDT) detection thresholds were assessed according to the standardized protocol of the German Research Network on Neuropathic Pain (DFNS) [4], at the department's certified QST lab by a trained investigator, according to the published standards for quality assessment [21]. QST was categorized as abnormal in the sense of small-fiber dysfunction when a z-value of CDT or WDT was lower than −1.96.

Nerve conduction studies were performed according to the in-house protocol of the department of Neurology, Bergmannsheil Bochum, Germany. We assessed sensory and motor conduction velocities and amplitudes as well as distal motor latencies. The used reference values are shown in Table 1.

2.4. Statistical analysis

The statistical analysis was conducted with SPSS, Version 23 (IBM, Chicago, IL, USA). Normal distribution was verified by visual validation of Q-Q plots and Kolmogorov-Smirnov tests. Normally distributed PREP-parameters were analyzed using one-way ANOVA for repeated testing (between subject factor: "group", patients vs. controls; within subject factor: "side", affected/dominant vs. unaffected/non-dominant side). In case of non-normal distribution, PREP-parameters were analyzed with Mann-Whitney-U test (patients vs. controls) and Wilcoxon test (affected vs. unaffected side). Unpaired *t*-tests were used to test for group differences in QST-values, age, height and weight. The gender distribution of both groups was compared with a chi-square test. A cut-off for N1-latencies was determined by use of a graphical interpretation of a receiver-operating characteristics (ROC) curve. Values above the cut-off were classified as abnormal.

3. Results

3.1. Demographic data and questionnaires

26 patients were enrolled after a first interview (Fig. 3). One patient was excluded because of a conspicuous SFNSL rating. Two patients were excluded from analysis because PREP was not feasible. One of them did not tolerate painful stimuli. In the other case, we could not stimulate both sides with the same stimulus intensity. Clinical and demographic data of the remaining patients are shown in Table 2. 20 patients had definite nerve injuries (inclusion criterion 1) and 3 patients fulfilled inclusion criterion 2. Mean interval since trauma was 4.8 years (range: 0.2–19 years). 21 patients reported spontaneous pain within the sensory supply area of the affected nerve. The patients' pain symptoms and their analgesic medication is shown in Table 3. One patient could not participate in NCS due to a finger amputation. He was excluded from the calculation of absolute and relative frequencies. Patients and controls were similar regarding age (53.3 ± 11.5 vs. 47.4 ± 14.5 years, $p > 0.05$), sex (65.2% vs. 53.7% female, $p > 0.05$), height (169.4 ± 8.3 vs. 174.2 ± 11.6 cm, $p > 0.05$), weight (78.5 ± 15.0 vs. 78.4 ± 16.4 kg, $p > 0.05$) and handedness (all right-handed).

3.2. PREP

20 (87%) patients were stimulated with the twofold of the PT of the unaffected side. In 3 (13%) cases, the current intensity was raised in accordance with our algorithm (Fig. 1), but the elicited potential curves showed no abnormalities. Fig. 2 shows one example each for PREP of both sides of a patient and a healthy volunteer. N1P1-amplitudes, but not N1-latencies, were distributed normally. PT were normally distributed in log-space. Hence, they were logarithmized for further analysis. Patients' ipsilateral and contralateral N1-latencies were significantly prolonged compared to controls (Table 4). No significant side-to-side difference was measurable (Fig. 4). Patients showed higher PT on the affected side in comparison to controls and the unaffected side. N1P1-amplitudes neither differed between groups nor between sides. Using ROC-analysis, we set the cut-off for the N1-latency to 176 ms. This value coincides with Obermann et al. [9]. The area under the curve amounted to 0.69. 7 (32%) patients, including 2 (9%) patients with normal NCS findings, and 1 (2%) healthy control showed N1-latencies above the cut-off (Fig. 5).