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Ultrasound of the peripheral nerves in systemic vasculitic neuropathies

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ABSTRACT

Introduction: Ultrasound of the peripheral nerves (PNUS) can be used to visualize nerve pathologies in polyneuropathies (PNP). The aim of this study was to investigate, whether PNUS provides additional information in patients with proven systemic vasculitic neuropathies (VN).
Material and methods: Systematic ultrasound measurements of several peripheral nerves, the vagal nerve and the 6th cervical nerve root were performed in 14 patients and 22 healthy controls. Nerve conduction studies of the corresponding nerves were undertaken. Finally, the measured results were compared to a study population of demyelinating immune-mediated and axonal neuropathies.
Results: Patients with VN displayed significant smaller amplitudes of compound muscle action potentials (CMAP) ($p < 0.05$) and sensory nerve action potentials (SNAP) compared to healthy controls, while conduction velocity did not differ between groups. The mean nerve cross-sectional areas (CSA) were increased in several peripheral nerves compared to the controls, most prominent in tibial and fibular nerve ($p < 0.01$). PNUS revealed nerve enlargement in most of the clinically and electrophysiologically affected nerves (22 out of 31) in VN. Nerve enlargement was more often seen in vasculitic neuropathies than in other axonal neuropathies, but significantly rarer than in demyelinating neuropathies.
Conclusion: Focal CSA enlargement in one or more nerves in electrophysiologically axonal neuropathies can be a hint for VN and thus facilitate diagnostic and therapeutic procedures.

1. Introduction

The vasculitides comprise a heterogeneous spectrum of disorders involving different organs including skin and nerve system due to inflammatory destruction of vessel walls and focal ischemia [1,2]. Vasculitides may be classified according to involvement of small, medium, or large vessels and granulomatous or non-granulomatous inflammation. Primary or secondary systemic or non-systemic vasculitis can be differentiated [3,4]. Primary vasculitides can be divided in anti-neutrophil cell antibodies (ANCA) associated vasculitides (AAV) and non ANCA associated vasculitides. The non-systemic vasculitides show no signs of systemic involvement including organ involvement, certain laboratory findings (e.g. ANCAs), cryoglobulins, or reasons for secondary systemic vasculitis (e.g. connective tissue diseases, drugs, and underlying infections).

A major neurological focus is the affection of the peripheral nervous system – so-called vasculitic neuropathy (VN). Patients often present with sensory and/or motor deficits as well as pain in different nerve regions – called mononeuritis multiplex. Involvement is mostly asymmetric, lower limb- and distal-predominant. However, it should be appreciated that the majority of patients have a confluence of multiple mononeuropathies, producing a generalized but multifocal and asymmetric polyneuropathy [5]. Also distal-symmetric polyneuropathies are described in rare cases. Some patients are rapidly progressive; others show mild symptoms only for many years prior to diagnosis [2].

The diagnostic gold standard for vasculitic neuropathy consists of clinical examination, nerve conduction studies (NCS), and laboratory tests such as ANCA, erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA) and rheumatoid factor (RF). Definite diagnosis can only be done by a peripheral nerve biopsy, e.g. the sural nerve [2]. However the sensitivity of nerve biopsy is no more than 50–60% [3]. In non-systemic cases skin biopsy may have additional diagnostic value [6].

The value of the peripheral nerve ultrasound (PNUS) for the diagnosis of peripheral nerve damage and for evaluating polyneuropathy (PNP) has been proved recently in inherited and acquired neuropathies [7–17]. In inherited neuropathies, above all in Charcot-Marie-Tooth (CMT) 1A, but also in rarer forms of mostly demyelinating pathology, diffuse, generalized nerve enlargement occurs [14–17], whereas in immune-mediated neuropathies different patterns of nerve alteration exist – ranging from normal to focal and diffuse [18]. The pathophysiology of nerve enlargement remains quite unclear so far. In very chronic neuropathies it has been assumed that nerve enlargement due to de-

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and remyelination may cause increased cross-sectional areas (CSA) of the peripheral nerves in ultrasonography, which may be in correlation with onion bulbs seen in histology [19]. In acute and subacute neuropathies focal edema, increased blood flow and focal inflammation could cause focal nerve enlargement. In all, nerve enlargement and increased echogenicity occur mostly in chronic and acute demyelinating neuropathies, whereas in non-immune-mediated axonal neuropathies such alterations have regularly not been found. Therefore, PNUS can be used to differentiate between axonal and demyelinating neuropathies [20,21].

In contrast, vasculitic neuropathy may be an exception of these findings as Ito et al. [22] and Boehm et al. [23] described several cases with enlarged distal tibial or ulnar nerves in PNUS. Therefore, the aim of this study was to determine, whether nerve enlargement is a characteristic in clinically and/or electrophysiologically involved nerves in patients suffering from vasculitic neuropathy. The second study objective was the comparison of the ultrasonic findings in VN to the partly already published results of demyelinating immune-mediated and axonal non-immune-mediated neuropathies of our study group [20].

2. Methods

2.1. Subjects

Between June 2013 and July 2014, we prospectively performed standardized nerve ultrasound examinations in patients who suffered from polyneuropathy (PNP) with primary or secondary systemic vasculitis, defined by the American College of Rheumatology [24] and according to the revised Chapel-Hill Consensus Conference [25]. Diagnosis of vasculitic neuropathy was ascertained by clinical examination, organ and/or nerve biopsy, laboratory findings, and electrophysiological examinations. The study was registered in the German Clinical Trials Register (DRKS0005253) and was approved by the local ethics committee (3663-01/13). Informed consent was obtained from all patients and controls.

Inclusion criterion was the diagnosis of vasculitic neuropathy. All patients received a clinical neurological examination and nerve ultrasound, and nerve conduction studies as recommended [26]. All healthy controls received the same protocol. Furthermore, laboratory analysis, analysis of cerebrospinal fluid (CSF) and biopsy of sural nerve, or kidney and other organs were performed in patients for clinical reasons.

2.2. Nerve conduction studies

Nerve conduction studies were performed using a standard electroneurophysiologic device (Synergy 15.0, VIASYS Healthcare UK Ltd.). Measurements were carried out on the right median nerve including F-waves, left ulnar nerve including F-waves, right tibial nerve including F-waves, left fibular nerve, and both sural nerves. This is the standard examination scheme for electrophysiological assessment at our institution for detecting acute and chronic neuropathies. In addition, clinically involved nerves were analyzed.

2.3. Ultrasound

Ultrasonography was performed using a high frequency 14 MHz probe real-time linear array scanner (ZONARE Ultrasound systems). Ultrasonography was performed bilaterally in different nerves of the upper and lower limbs and the neck. The nerves were scanned in axial planes, and the cross-sectional area (CSA) of each nerve was measured at standardized anatomical points as described before [15]. In short: median nerve in axilla (proximal), before pronator teres muscle (middle), and at the mid-forearm (distal); ulnar nerve at mid-humerus (proximal) and at the mid-forearm (distal); tibial nerve in popliteal space (proximal) and at medial malleolus before the nerve division into plantar nerves (distal); fibular nerve 2 cm above fibular head; and sural nerve between lateral and medial gastrocnemic head. In addition, the CSA of the vagal nerve in carotid sheath beneath the carotid bifurcation and the longitudinal diameter of the 6th cervical nerve root after leaving the processus transversus were measured. CSA was traced inside the hyperechoic rim of the nerve. Analysis of ultrasound data was performed both online and offline. Approximately 40 min is needed for a complete ultrasound examination of each patient. A second examiner evaluated all ultrasound measurements offline for a second time. Both examiners were blinded to the electrophysiological measurements of the patients.

2.4. Statistics

IBM SPSS Statistics, version 19 (Chicago, IL) was used for statistical analysis. Student's *t*-test was used for evaluating differences concerning epidemiological data (age, gender, disease duration, height and weight). One-way ANOVA was used to detect differences of nerve CSAs and electrodiagnostic studies between patients and healthy controls and to calculate differences concerning mean CSAs of vasculitic neuropathies in comparison to axonal neuropathies of other origin and immune-mediated demyelinating neuropathies. Pearson correlation coefficients were calculated to quantify correlations between electrodiagnostic studies, ultrasonic findings and clinical course as well as laboratory findings. Chi-square-test was used for comparing the frequency of pathological nerve or root enlargement in vasculitic patients compared to healthy controls and other neuropathies.

Intraclass correlation coefficients (ICC) were calculated to evaluate interrater and intrarater reliability for the evaluation of nerve CSA as well as 6th cervical nerve root diameter.

3. Results

Fourteen patients with vasculitic PNP and 22 healthy controls were enrolled in the study. Baseline characteristics of both groups are shown in Table 1. The groups were of similar age, height, weight, and gender. All patients fulfilled the peripheral nerve society guidelines for vasculitic PNP [3,26]. Twelve out of 14 patients had an initial asymmetric beginning pointing to mononeuritis multiplex. None of the patients showed cranial nerve involvement. In 8 patients diagnosis was ensured by sural nerve biopsy, and in 4 patients by other organ biopsy. In two patients diagnosis was made by clinical course, laboratory findings, and therapy response. Eleven patients had primary and 3 patients had secondary systemic VN (rheumatoid arthritis, systemic lupus erythematosus, and Sjögren's syndrome). No patient has been diagnosed with NSVN during screening period.

Table 2 shows conduction velocities and amplitudes of median and tibial nerves in the different study groups. Results of the other nerve measurements are not shown in this table but were used for diagnosis of the different types of neuropathy according to the literature [3,26]. ANOVA revealed a significant reduction of CMAP amplitudes in all motor nerves compared to healthy controls ($p < 0.05$), endorsing the diagnosis of axonal neuropathy as required [3]. Furthermore, in tibial nerve distal motor latency, F-wave-latency, and conduction velocity were significantly affected compared to healthy controls ($p < 0.05$).

According to EFNS criteria [27], 9 out of 14 patients (64.3%) showed slight signs of demyelinating neuropathy in at least one nerve (such as prolongation of motor distal latency, reduction of conduction velocity, abnormal temporal dispersion, F-wave latency prolongation, and conduction blocks), mainly conduction blocks as a sign of focal ischemia.

Intrarater intraclass correlation coefficient (ICC) of the offline nerve ultrasound measurements was 0.995, and interrater ICC was 0.990. Table 3 shows CSA measurements of median, ulnar, fibular, tibial, vagal, and sural nerves as well as the 6th cervical nerve root diameter in each group. ANOVA revealed significant enlarged mean CSA values