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A look inside the nerve – Morphology of nerve fascicles in healthy controls and patients with polyneuropathy

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HIGHLIGHTS

- Normal values of nerve fascicles might be helpful in analysis and treatment of nerve disorders.
- Fascicle enlargement occurs in inherited and inflammatory neuropathies with distinct distribution.
- Fascicle pattern analysis and - ratios might be suitable to differentiate several polyneuropathies.

ABSTRACT

Objective: Polyneuropathies are increasingly analyzed by ultrasound. Summarizing, diffuse enlargement is typical in Charcot-Marie Tooth type 1 (CMT1a), regional enlargement occurs in inflammatory neuropathies. However, a distinction of subtypes is still challenging. Therefore, this study focused on fascicle size and pattern in controls and distinct neuropathies.
Methods: Cross-sectional area (CSA) of the median, ulnar and peroneal nerve (MN, UN, PN) was measured at predefined landmarks in 50 healthy controls, 15 CMT1a and 13 MMN patients. Additionally, largest fascicle size and number of visible fascicles was obtained at the mid-upper arm cross-section of the MN and UN and in the popliteal fossa cross-section of the PN.
Results: Cut-off normal values for fascicle size in the MN, UN and PN were defined (<4.8 mm^2, <2.8 mm^2 and <3.5 mm^2). In CMT1a CSA and fascicle values are significantly enlarged in all nerves, while in MMN CSA and fascicles are regionally enlarged with predominance in the upper arm nerves. The ratio of enlarged fascicles and all fascicles was significantly increased in CMT1a (>50%) in all nerves ($p < 0.0001$), representing diffuse fascicle enlargement, and moderately increased in MMN (>20%), representing differential fascicle enlargement (enlarged and normal fascicles at the same location) sparing the peroneal nerve (regional fascicle enlargement). Based on these findings distinct fascicle patterns were defined.
Conclusion: Normal values for fascicle size could be evaluated; while CMT1a features diffuse fascicle enlargement, MMN shows regional and differential predominance with enlarged fascicles as single pathology.
Significance: Pattern analysis of fascicles might facilitate distinction of several otherwise similar neuropathies.

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; CMT1a, Charcot Marie Tooth Disease Typ 1a; CSA, cross-sectional area; EFNS, European Federation of Neurological Societies; HRUS, high resolution ultrasound; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MMN, multifocal motor neuropathy; MN, median nerve; NCS, nerve conduction study; PN, peroneal nerve; RN, radial nerve; TN, tibial nerve; UN, ulnar nerve; UPSS, ultrasound pattern sum score; VN, vagus nerve.

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1. Introduction

The use of high resolution ultrasound (HRUS) of peripheral nerves in the diagnosis of polyneuropathies has been proven several times (Zaidman et al. 2009, 2013; Goedee et al. 2017; Padua et al., 2012; Grimm et al. 2014; Scheidl et al. 2014). Demyelinating neuropathies show nerve enlargements, while axonal do regularly not (Grimm et al., 2014 and Zaidman et al., 2013). Diffuse nerve enlargement occurs predominantly in inherited neuropathies, e.g. Charcot Marie Tooth Disease Type 1a (CMT1a) and CMT1b, affecting all nerve segments with a uniform distribution (Noto et al., 2015; Grimm et al. 2016). In contrast, in immune-mediated neuropathies nerve enlargement is mostly slight to moderate with a regional pattern, particularly in multifocal motor neuropathy (MMN) and multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) often affecting proximal arm nerves (Beekman et al., 2005 Grimm et al., 2015a; Scheidl et al., 2012; Rattay et al., 2017). Even enlargement of single fascicles is reported (Rattay et al., 2017). In addition, chronic inflammatory demyelinating polyneuropathy (CIDP) may show regional enlarged nerves as well as uniformly enlarged nerves depending on the duration of the disease (Zaidman et al., 2009; Grimm et al., 2016).

A nerve fascicle or fasciculus is a small bundle of axons enclosed by the sheet, the perineurium. A small nerve may consist only of a single fascicle, but larger nerves generally contain several (up to 35 or more) fascicles (Sunderland, 1945). Pioneer work in this context has been made by Sunderland with his histological works in the early 40s of the last century. However, fascicle size measurements of healthy controls and polyneuropathies by imaging tools are sparse in literature so far (Rattay et al., 2017; di Pasquale et al., 2015; Riegler et al., 2016). HRUS can visualize fascicles in peripheral nerves. Preliminary data of 70 MHz ultrasonography probes delivered promising data for the median nerve at wrist (Cartwright et al., 2017). However, these probes are not standard in daily routine.

In polyneuropathy (PNP) analysis of fascicles, which may show distinct changes, might help to assign the PNP to defined subtypes. With this study, we aimed to define cut-off-values for fascicle size in upper arm nerves and the easily assessed peroneal nerve in the popliteal fossa with a 14 MHz probe. In a second step, we analyzed fascicular pattern types in predefined already diagnosed PNPs (Zaidman et al., 2013; Grimm et al. 2016, and Rattay et al., 2017).

2. Methods

Healthy controls, recruited from medical staff or their relatives and patients with genetically proven CMT1a (PMP22 duplication) or proven MMN according to EFNS guidelines were included (Joint Task Force, 2010). The study was registered with the German clinical trial register (DRKS-ID 00005253) and approved by the local ethics committees (No. Jena 3663-01/13, EKZN Basel 2014-230 and Tübingen 702/2015BO2). Written informed consent to study participation was obtained from all patients and controls.

B-mode ultrasound studies of peripheral nerves were performed with a high-resolution probe (14 MHz, linear array, Mindray T7, Ultrasound systems, Darmstadt, Germany). The ulnar (UN) and median nerves (MN) were screened from wrist to axilla, the peroneal nerve (PN) from ankle to popliteal fossa. Cross-sectional areas of these nerves were measured at predefined landmarks: mid-upper arm, elbow and forearm in UN and MN, popliteal fossa in PN. CSA of the largest fascicles were measured in the MN and UN at the mid-upper arm (half distance between elbow and acromion) and the PN in the popliteal fossa 5 cm above fibular head inside the hyperechoic rim of the fascicles (corresponding to the measurement of the CSA), Fig. 1 A and B. The total number of fascicles was counted and the cross-sectional area of all fascicles was calculated; the CSA of the largest fascicle was used for statistical analysis. We chose not to analyze the minimal cross-sectional area of a single fascicle as the used ultrasound device could not calculate fascicle area values below 1 mm^2. Enlargement of any fascicle was defined by singular fascicle area larger than mean values of our normal controls plus 2 SD. The number of overall enlarged fascicles was counted. The nerve ultrasound protocol took in total between 30 and 40 min for each patient when performed by an experienced user.

2.1. Statistical analysis

For statistical analysis IBM SPSS Statistics, version 24 (Chicago, IL, USA) was used. For all tests, a two-sided P-value < 0.05 was considered as statistically significant. When evaluating differences concerning epidemiological data (age, gender, height, and weight) Mann-Whitney-test with Bonferroni correction was used. To test differences of nerve CSA, fascicle area between patients and controls the same test was used. Reference values for fascicle area and CSA were defined (mean + 2 standard deviations). Additionally, we calculated the ratio of enlarged fascicles/all measured fascicles (enlarged fascicles in MN + UN + PN/all fascicles MN + UN + PN) with minimum ratio 0 and maximum ratio 1 as parameter for the overall proportion of enlarged fascicles (sum of enlarged-fascicle-ratio = SEF-ratio). Further, the fascicle-ratio of each nerve was calculated, named local (L) EF-ratio of MN, UN and PN to further determine regional predominance of fascicle enlargement. Intra- and interrater intraclass correlation coefficient (ICC) was measured for two examiners blinded to the diagnoses.

3. Results

Between May 2015 and December 2016 50 healthy controls were analyzed by ultrasound and clinical examination. In addition, 15 patients with CMT1a and 13 patients with MMN were measured. Most of these patients were already part of other studies of our group (Grimm et al., 2015a and Rattay et al. 2017). All but four MMN patients were under treatment with immunoglobulins. Baseline data of the three groups concerning age, height and weight did not differ significantly (t-Test with Bonferroni correction $p = 0.8–1.0$). Table 1 summarizes those baseline data.

3.1. Cross-sectional area

In the control group the mean CSA values of the nerves are consistent with previously published values (Grimm et al., 2014; Scheidl et al., 2014; Zaidman et al., 2009). No significant correlation could be demonstrated between age, height, weight and nerve CSA. The mean CSA values of our cohort showed significant differences between CMT1a and the other groups (t-Test with Bonferroni correction $p < 0.0001$), but also for MMN and controls ($p < 0.001$), particularly in the upper arm nerves. Nerve enlargement was diffuse in CMT1a, affecting all nerve landmarks with even distribution, while it was regional and inhomogeneous in MMN with proximal predominance. Table 2 summarizes the CSA values.

3.2. Fascicle number and size

The mean fascicle number visible by ultrasound in our controls ranged from 3 to 5 in all nerves with highest number of fascicles in MN (Table 3). In patients with CMT1a the mean number of fascicles in the MN and UN was significantly higher in comparison to controls and MMN (t-test with Bonferroni $p < 0.001$). In MMN no significant increase of fascicle numbers was found. In the control

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