Clinical Neurophysiology 126 (2015) 2216–2225

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

The Ultrasound pattern sum score – UPSS. A new method to differentiate acute and subacute neuropathies using ultrasound of the peripheral nerves

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ARTICLE INFO

Article history:
Accepted 27 January 2015
Available online 3 February 2015

Keywords:
Nerve ultrasound
Polyneuropathy
Ultrasound pattern
Ultrasound score
Inflammatory neuropathy
Nerve enlargement

HIGHLIGHTS

- The recently described ultrasound findings in several neuropathies of heterogeneous origin make classification with pattern analysis necessary.
- The ultrasound pattern sum score (UPSS) and its sub-scores UPS-A, -B and -C enable a differentiation of several acute and subacute axonal and demyelinating neuropathies.
- Enlarged cervical nerve roots and/or the vagus without or with only slight enlargement of the peripheral nerves enable a differentiation from GBS and subacute onset CIDP.

ABSTRACT

Objective: Ultrasound differentiation of neuropathies is a great challenge. We, therefore, suggest a standardized score to operationalize differentiation between several acute and subacute onset neuropathies.
Method: We retrospectively analyzed the ultrasound data of 61 patients with acute or subacute neuropathies, e.g. chronic immune-mediated neuropathies, Guillain–Barré syndrome (GBS), and axonal/vasculitic neuropathies. We compared these data to 28 healthy controls. Based on these results an ultrasound pattern sum score (UPSS) with three sub-scores (UPS-A for the sensorimotor nerves, UPS-B for the cervical roots and the vagal nerve and UPS-C for the sural nerve) was developed. Afterwards, the applicability of the score was prospectively validated in 10 patients with chronic neuropathies and in 14 patients with unknown acute and subacute PNP before performing additional tests.
Results: UPS-A and UPSS were significantly higher in CIDP than in other neuropathies and controls ($p < 0.001$). UPS-B was significantly more often pathologic in GBS than in CIDP and other neuropathies ($p < 0.001$). Using receiver operation characteristics curve analysis boundary values for each score were defined. Positive predictive value (PPV) of these scores for CIDP and GBS was >85%. Vasculitic neuropathies showed an intermediate type of UPSS compared to other axonal neuropathies ($p < 0.001$). In the prospective application the pattern score could be used with good accuracy in several types of neuropathy.
Conclusion: UPS-A and UPSS operationalize to diagnose acute and subacute-onset CIDP and its variants with high sensitivity, specificity, and PPV. An increased UPS-B with normal UPSS and other sub scores may point to the diagnosis of GBS with high PPV and enables the differentiation from CIDP.
Significance: Using the UPSS and its sub-scores gives a new diagnostic power to the method of the peripheral nerve ultrasound.
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Abbreviations: AIDP, acute inflammatory demyelinating polyneuropathy; AMAN, acute motor axonal neuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CIP, critical illness polyneuropathy; CMAP, compound muscle action potential; CSA, cross sectional area; CSF, cerebrospinal fluid; CV, conduction velocity; GBS, Guillain–Barré syndrome; GvHD, graft versus host disease; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MMN, multifocal motor neuropathy; ms, millisecond; m/s, meter per second; mV, milli volt; μV, micro volt; PNP, polyneuropathy; SNAP, sensory nerve action potential; UPSS, ultrasound pattern sum score.

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http://dx.doi.org/10.1016/j.clinph.2015.01.011
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1. Introduction

The diagnostic approach in polyneuropathies (PNP) is challenging for each neurophysiologist due to heterogeneity of symptoms and etiologies. The gold standard of syndrome diagnosis is the combination of clinical and electrophysiological examination (Latov, 2014). Etiologic diagnosis requires laboratory testing including blood, cerebrospinal fluid (CSF), and in selected cases nerve biopsy or genetic testing. While more than 30% of PNP remain unclear in spite of extensive testing, accurate and non-invasive identification of treatable PNP such as immune-mediated neuropathies is essential.

Ultrasonography of the peripheral nervous system is a relatively new method in the diagnosis of PNP, but it revealed encouraging results in different neuropathies (Beekman et al., 2005; Cartwright et al., 2008; Zaidman et al., 2009, 2013; Padua et al., 2012, 2014; Kerasnoudis et al., 2013, 2014a; Grimm et al., 2014a,b,c; Scheidl et al., 2014; Schreiber et al., 2013; Noto et al., 2014). Ultrasound differentiation of axonal and demyelinating PNP has been reported as well as the possibility to distinguish between acute and chronic inflammatory neuropathies using ultrasound (Grimm et al., 2014a; Kerasnoudis et al., 2014b,c). Since currently and to the best of our knowledge no clearly defined patterns of ultrasound findings in different PNP syndromes are available, we aimed to create a standardized score of ultrasound findings to support and complement conventional classification of PNP.

2. Methods

Overall 85 patients with PNP were enrolled in this study, and the ultrasound pattern score was evaluated – partly retrospectively, partly prospectively – in all patients. Inclusion criteria were acute or subacute onset polyneuropathies (referred symptom onset not longer than 9 months) of axonal and demyelinating NCS results. Exclusion criteria were rare neuropathies, such as multifocal motor neuropathy (MMN), anti-Myelin-associated glycoprotein neuropathy, or paraneoplastic neuropathies. Diagnosis of all patients was ascertained by the diagnostic gold standards as suggested (EFNS guidelines). The results were compared to 28 healthy controls.

2.1. First exploratory survey

Between August 2013 and October 2014, standardized nerve ultrasonic examinations were performed in 61 patients who presented in our neuromuscular center or in the emergency unit of both departments (Basel University Hospital and Jena University Hospital) with sensory, motor, or autonomic symptoms of acute or subacute neuropathy. Diagnosis of polyneuropathy was ascertained by clinical course, laboratory findings, and electrophysiological examinations. All patients received additional unilateral ultrasound and nerve conduction studies (NCS) of the right side in symmetric neuropathies and the most involved side in asymmetric cases as applied in former studies (Grimm et al., 2014b,c). In addition, 28 healthy controls were examined using the same ultrasonic and electrophysiological protocol. The study was registered with the German clinical trial register (DRKS-ID00006140) and approved by the local ethics committee (No. 3663-01/13 and EKZN 2014-230). Informed consent was obtained from all patients and from all controls.

2.2. Development and evaluation of UPSS

Based on the results of the first explorative survey an ultrasound score was created, which enabled a classification and pattern analysis. The score consists of three ultrasound sub-scores and an overall sum-score (UPSS). The sub-score UPS-A is a summary of the unilateral findings of the peripheral sensorimotor nerves (median nerve upper arm, elbow and mid-forearm; ulnar nerve upper arm and mid-forearm; tibial nerve popliteal and in the ankle, and peroneal nerve popliteal). In this score each nerve enlargement <50% of the defined maximal values (with regard to Grimm et al., 2014a,b) is scored with 1 point and each enlargement >50% is scored with 2 points. Thus, the sum of all these eight measurement points maximally can reach 16 points.

The second sub-score UPS-B consists of the diameter of the 5th and 6th cervical nerve roots and the cross-sectional area (CSA) of the vagal nerve as proximal primarily somatic autonomic nerve (Grimm et al., 2014c). Each enlargement is scored with 1 point, so that UPS-B maximally reaches 3 points.

The third sub-score UPS-C consists of the sural nerve as purely sensory nerve. This was based on the hypothesis, that ultrasonic findings of the sural nerve may be different in patients with GBS and CIDP or between pure motor neuropathies and sensorimotor neuropathies (Derksen et al., 2014).

The final sum score is the sum of each sub-score result (ultrasound pattern sum score UPSS). Therefore, UPSS can reach 0 to maximally 20 points. The boundary value of UPSS and its subscores to differentiate between different etiologies of PNP was evaluated using receiver operating curves (ROC) analysis. In consequence, each PNP entity was evaluated according to its specific ultrasound pattern with optimized sensitivity, specificity, and positive predictive value.

2.3. Validation of the UPSS

10 patients suffering from the same entities of neuropathy as in the exploratory group but with longer disease duration (12–60 months) received the same ultrasound protocol with the examiner blinded to the diagnosis in order to perform a verification of the value of UPSS in patients, which were not used to develop the score.

In addition, clinical applicability of the UPSS in daily routine was evaluated in 14 patients, who presented in our department with suggested acute or subacute neuropathy (median disease duration not longer than 4 months). The ultrasound examiners were blinded to the clinical stage and the suggested neuropathy.

2.4. Statistics

For statistical analysis, we used IBM SPSS Statistics, version 22 (Chicago, IL) and PrismGraph (LaJolla, CA). *T*-test and One-way ANOVA was used for evaluating differences concerning epidemiological data (age, gender, disease duration, height, and weight). Unpaired t-test was used for the comparison between the different groups. Post-hoc analysis was done using Bonferroni correction due to multiple *t*-tests. ANOVA was used to detect differences of nerve CSAs between all groups. ROC curve analysis was used to define boundary values for each ultrasound score. Chi-Square-Test was used to calculate differences between the frequencies of pathologic sub-scores and the sum-scores between all groups. Finally, sensitivity, specificity, and positive predictive value of each subscore, the sum-score or the different combinations of all scores were calculated.

3. Results

3.1. Exploratory survey

Diagnoses of the different neuropathies were made according to the results of clinical examination, laboratory testing, nerve

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