High resolution sonography of peripheral nerves: normal values in healthy individuals and the role of sonography in rare disorders of peripheral nerves

PhD Thesis

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Budapest

2014

1. Introduction

Nerve imaging became an important method in patient management by providing information on lesion morphology, anatomic location, relationship of lesions to surrounding soft tissue, and evaluation of areas difficult to access with electrodiagnostic methods. Types of peripheral nerve abnormalities suited for visualization by ultrasound (US) include changes in nerve caliber, continuity, echogenicity, echotexture, and vascularisation. Imaging can identify peripheral nerve tumours, traumatic lesions, entrapments with nerve damage, inflammation, demyelinating features, infections, and it can be used for imaging-guided interventions. US modified in a former study diagnostic and therapeutic management beyond the electrodiagnostic findings in as many as 43% of patients and had a confirmatory role in 40% of the patients. US complements neurophysiological assessment even in routine practice, and this confirms the increasing interest in US in a multidimensional evaluation of peripheral nervous system diseases. In normal-weight people, all major nerves of the extremities and the cervical roots C5-C7 can be visualized by US. Nerve size change is one of the most important ultrasonographic features of nerve pathology. Therefore it is crucial to have normal (reference) values of all nerves routinely assessed. Nerve width (medial to lateral diameter), thickness (anterior to posterior diameter) and cross-sectional area (CSA) measured on transverse scans, and antero-posterior diameter (LAPD) measured on longitudinal scans are the most frequently used quantitative parameters for the US investigation of peripheral nerves. CSA reference values for peripheral nerves and brachial plexus have been reported in some previous studies, mostly of the median and ulnar nerve, but data were less abundant concerning normal values for cervical roots, radial nerve, lower limb nerves and pure sensory nerves.

2. Objectives

The first objective of our study was to establish a set of normal CSA values for C5, C6, and C7 cervical roots, and several upper and lower limb nerves, including some pure sensory nerves, at pre-defined anatomical sites, and to assess whether CSAs correlated with age, gender, height, and body weight. Our second objective was to systematically assess the reliability of these measurements on several nerves in the upper and lower limbs, with respect to intra-rater, inter-rater and inter-equipment variation. CSA values of two independent cohorts from the two study sites were also compared in order to determine the external validity of collected normal values.

A large body of ultrasonographic literature is available on common neuropathies such as carpal tunnel syndrome and ulnar neuropathy at the elbow, but literature data on uncommon conditions are lacking. As the third objective of our study, we analysed cases of rare neuropathies assessed by ultrasonography in order to establish the role of HRUS in rare disorders of the peripheral nerves.

3. Methods

3.1 Normal values assessments

Between May 2011 and December 2011, 56 healthy subjects were investigated with high-resolution nerve ultrasound at the Dept. of Neurology of Semmelweis University in Budapest (Hungary) and at the Dept. of Neurology of the District Hospital in Freiberg (Germany). Subjects were recruited from the hospital staff and patients. None of the study subjects had symptoms or signs suggesting polyneuropathy or systemic diseases potentially associated with polyneuropathy, nor any history of neuromuscular disease. Demographic data (age, gender, height, and body weight) were recorded. For the inter-rater

reliability assessments in addition to the healthy subjects, patients from a polyneuropathy study in Budapest were also included.

For US examinations, a Philips HD15XE ultrasound device with a small part imaging software and a 15 MHz 3 cm “hockey stick” linear array transducer was used for 25 subjects in Budapest. In Freiberg, the same device was used for 10 subjects, and an additional 21 subjects were examined with a Toshiba Aplio SSA-700A device with small part imaging software and a 12 MHz PLT-1204 4.5 cm linear array transducer. In both devices, compound imaging software (*SonoCT* for the Philips HD15XE and *ApliPure* for Toshiba Aplio SSA-700A) was used to improve image quality.

The following 14 CSA measurements on the upper and lower extremities were carried out, all on the left side: C5, C6 and C7 cervical roots; median, ulnar and radial nerves at the mid-upper arm; ulnar nerve at the elbow at the level of the medial epicondyle, median, ulnar and superficial radial nerves at the distal third of the forearm; median nerve at the proximal entrance of the carpal tunnel; peroneal nerve at the fibular neck; tibial nerve at the ankle; and sural nerve at the proximal calf. The measurements were time-consuming (approximately 45-55 minutes) and therefore they have been performed only on the left side. These sites included common areas of nerve entrapment (ulnar nerve in the ulnar groove, median nerve in the carpal tunnel), sites largely inaccessible for electrophysiologic studies (cervical roots), as well as sites corresponding to those usually evaluated by electrodiagnostic studies. The superficial radial and the sural nerves were chosen as pure sensory nerves. Subjects were examined mostly in supine position, with the exception of the peroneal nerve examined with the subject lying on one side, and the sural nerve examined in prone position. The CSA of the nerves was measured using the trace function of the ultrasound device by manually tracing inside the hyperechoic rim of each nerve. The angle of insonation was adjusted perpendicular to the nerve where the nerve

appeared the brightest with the best discernible outer margins. The CSA of each nerve segment was measured three times. The three measurements were averaged and the mean value was used for analysis.

3.2 Reliability assessments

The *inter-rater reliability* was assessed at the start of the study. Two ultrasonographers measured nerve cross-sectional areas in 7 subjects (on all 14 sites in each subject, as described above). Both examiners were neurologists and clinical neurophysiologists who performed neuromuscular ultrasound in a clinical setting on a daily basis. Both ultrasonographers received training for this study prior to the initiation of data collection. The repeated measurements were done in one session: the examination of all 14 nerve segments by one rater was repeated in the same session by the other rater who was blinded to the results of the first.

To assess *intra-rater reliability*, 6 subjects in Freiberg were re-examined with the same Toshiba device by the same investigator 24 hours after the first sonographic examination.

To assess *inter-equipment reliability*, 6 subjects in Freiberg were examined by the same examiner first with the Philips, and 8-11 weeks later with the Toshiba ultrasound device.

The *validity of normal values* was tested by comparing CSA values of the 14 nerve segments in the two independent cohorts of the two study sites.

3.3 Statistical analysis

Descriptive statistics were used to present basic demographic data of the study population. The following parameters were calculated and presented for normal CSA values of the 14 nerve segments: mean, median, standard deviation (SD), 95% confidence intervals of the mean, and the coefficient of variation.

Normality of variables was checked by the Shapiro-Wilk test. Correlation of CSA measurements with age, gender, height and body weight was tested using the Spearman correlation coefficients. Values between genders were compared by the Kruskal-Wallis ANOVA. The general linear model (GLM) was used to test if gender remains a significant predictor of CSA when age, height and body weight are also considered. Intraclass correlation coefficients and corresponding 95% confidence intervals were calculated to define values for intra-rater, inter-rater, and inter-equipment reliability. The validity of our normal values was tested in two independent cohorts using repeated measure ANOVA for the comparison of CSA values of the 14 nerve segments. Statistica for Windows v. 11 (StatSoft, Tulsa, OK) was used for data analysis.

3.4 Ultrasonography of patients with rare neuropathies

Between January 2009 and December 2013, about 3500 predominantly outpatients were investigated with US at the Dept. of Neurology of the District Hospital in Freiberg (Germany). The vast majority of the patients were adults. The patients were referred to the outpatient consultation with a suspected peripheral nerve disease from different faculties, mostly surgeons (trauma surgeons, neurosurgeons, hand surgeons), neurologists and general practitioners. All patients were examined neurologically and by standard electrodiagnostic examination, consisting of nerve conduction studies, recording of late responses (F-waves) and needle electromyography. Demographic data (age, gender, height, and body weight) were recorded. Depending on the clinical question, either a single nerve was examined, mostly bilaterally in order to ascertain side differences, or in suspected generalized diseases several nerves were examined on different segments along the course of the nerve. Pathological alterations were documented in two planes, in longitudinal as well as in transverse scans.

Occasionally, short video sequences were recorded for better understanding of the pathology.

The CSA of the nerves was measured using the trace function of the ultrasound device by manually tracing inside the hyperechoic rim of each nerve.

4. Results

Normal CSA values and reliability measures

There was no statistically significant difference between demographic features (age, weight, height) of the German (G=31) and the Hungarian (H=25) study groups. Mean age (years) was 51.8±16.4 (G) and 48.5±15.6 (H), weight (kg) 75.4±13.0 (G) and 79.6±18.2 (H), height (cm) 171±9 (G) and 168±6 (H). The gender distribution was also similar (M:F) 15:16 (G) and 11:14 (H).

Measurements could be performed in all 56 subjects for most nerve segments with the exception of the cervical roots (4-6 invalid measurements depending of the root level) and sural nerve (6 invalid measurements) due to anatomical problems. Mean CSA values of these 14 nerve segments ranged from 2 mm^2 (sural and superficial radial nerve, both small pure sensory nerves) to 10 mm^2 (C7 root). CSA values showed mostly normal distribution in both genders and in pooled data. In univariate analyses CSA did not depend on age, body weight and height. Even without corrections for multiple comparisons, correlations at the $P<0.05$ level was rarely detected between CSA and age (in 4/14 nerve CSA segments) between CSA and weight (3/14) and between CSA and height (2/14). Males had significantly larger CSA values than females only for nerve segments in the upper arm both by univariate and multivariate testing.

CSA values of the 14 nerve segments were compared between two independent cohorts and repeated measure ANOVA revealed no significant country effect. When pairwise comparisons were done by the Mann-Whitney-

test, no significant difference was found between the CSAs in any of the nerve segments after correction for multiple comparisons.

Intraclass correlation coefficients in all three analyses of reproducibility *(*inter-rater reliability, intra-rater test-retest reliability, and inter-equipment test-retest reliability) were remarkably high (0.86 – 0.98). The intraclass correlation coefficient was the highest for inter-rater reliability with 0,98 (95% CI:0,97-0,99) followed by intra-rater test-retest reliability (0,93) and inter-equipment test-retest reliability (0,86).

Rare neuropathies

The US findings of different rare neuropathies have been presented together with data of clinical history, electrophysiology and further investigations (MRI, intraoperative findings, histology) . The presented US findings in rare neuropathies included rare tumours (intraneural lymphoma, neurofibromatosis) , focal tumour-like lesions (amyloidosis, rheumatoid arthritis), nerve torsion, rare diseases mimicking carpal tunnel syndrome (thrombosis of the persistent median artery, hyperventilation tetany, schwannoma) , thoracic outlet syndrome, Parsonage-Turner-syndrome and rare polyneuropathies (paraneoplastic multiple mononeuropathy, vasculitic neuropathy, multifocal motor and sensory demyelinating neuropathy). HRUS showed typical morphological changes in certain rare neuropathies which can be effectively used in the differential diagnosis of peripheral nerve diseases. Findings of clinical examination, electrodiagnostic tests and MRI were often insufficient in clarifying the cause of rare neuropathies. HRUS in those cases provides useful additional information with regard to the region, extent and often the aetiology of the disorder

5. Conclusions

High-resolution ultrasound (HRUS), introduced for peripheral nerve examination by Fornage in 1988, is a method that allows non-invasive imaging of numerous peripheral nerves with excellent image quality with high spatial resolution and can be modified and tailored immediately to the pathology seen by the examiner.

Using HRUS, we established reference values in healthy subjects for the most frequently examined nerve segments on the upper and lower extremities and for the cervical roots and assessed different aspects of reliability. Three objectives were examined. As a first step, we established a set of normal CSA values for C5, C6, and C7 cervical roots, and several upper and lower limb nerves, including some pure sensory nerves, at pre-defined anatomical sites, and assessed whether CSAs correlated with age, gender, height, and body weight. Second, we systematically assessed the reliability of these measurements on several nerves in the upper and lower limbs, with respect to intra-rater, inter-rater and inter-equipment variation. CSA values of two independent cohorts from the two study sites were also compared in order to determine the external validity of collected normal values. Thirdly, we analysed cases of rare neuropathies assessed by ultrasonography in order to establish the role of HRUS in rare disorders of the peripheral nerves.

Based on our results, the following conclusions are drawn:

1. The mean CSA of the 14 nerve segments ranged from 2 to 10 mm^2 and there was a good correlation of these results with previously reported normal values.

2. We found no consistent correlations between CSA values and age, height, or body weight, but males had significantly larger values than females for nerve segments in the upper arm.

3. The intra-rater, inter-rater and inter-equipment reliability was high with intraclass correlation coefficients of 0.93, 0.98, and 0.86, respectively.

4. HRUS shows typical morphological changes in certain rare neuropathies, which can be effectively used in the differential diagnosis of peripheral nerve diseases.

5. Findings of clinical examination, electrodiagnostic tests and MRI are often insufficient in clarifying the cause of rare neuropathies. HRUS in these cases provides useful additional information with regard to the region, extent and often the aetiology of the disorder.

6. List of own publications

The thesis is based on the following publications:

Böhm J, Scheidl E, Bereczki D, Schelle T, Arányi Z. (2014) High resolution ultrasonography of peripheral nerves: measurements on 14 nerve segments in 56 healthy subjects and reliability assessments. ***Ultraschall in der Medizin/European Journal of Ultrasound***, DOI:10.1055/s-0033-1356385 IF: 4,116

Penkert G, Böhm J, Schelle T. ***Focal Peripheral Neuropathies. Imaging, Neurological, and Neurosurgical Approaches***. Springer-Verlag, Berlin Heidelberg , 2014. ISBN 978-3-642-54779-9

Böhm J, Schelle T. (2013) Stellenwert der hochauflösenden Sonografie bei der Diagnostik peripherer Nervenerkrankungen. ***Aktuelle Neurologie***, 40: 258-268. IF: 0,320

Böhm J, Scheidl E, Schelle T. (2013) Aktueller Stellenwert der HRUS bei der Diagnostik von Polyneuropathien. ***NeuroTransmitter***, 24:34-39.

Leypoldt F, Friese MA, Böhm J, Bäumer T. (2011) Multiple enlarged nerves on neurosonography: an unusual paraneoplastic case. ***Muscle and Nerve***, 43:756-758. IF: 2,367

Böhm J, Visser LH, Lehmann TN. (2011) High-resolution sonography of posttraumatic neuroma of the superficial radial nerve. ***Central European Neurosurgery***, 72:158-160. IF: 0,838

Böhm J. (2010) Akut carpalis alagút szindróma hyperventilatio okozta tetania következtében. ***Magyar Radiológia***, 84:1-4.

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Böhm J. (2003) Paraspastik, Polyneuropathie und „tumoröse Veränderungen" der Achillessehnen: Polyneuropathie als Begleitsymptom bei einer Systemerkrankung? ***Aktuelle Neurologie***, 30:407-409. IF: 0.269

Other publications:

Scheidl E, Böhm J, Simó M, Bereznai B, Bereczki D, Arányi Z. (2014) Different patterns of nerve enlargement in polyneuropathy subtypes as

detected by ultrasonography. ***Ultrasound in Medicine and Biology***, 40(6):1138-45. IF: 2,455

Scheidl E, Böhm J, Farbaky Z, Simó M, Bereczki D, Arányi Z. (2013) Ultrasonography of ulnar neuropathy at the elbow: Axonal involvement leads to greater nerve swelling than demyelinating nerve lesion. ***Clinical Neurophysiology***, 124:619-625. IF: 3,144

Scheidl E, Böhm J, Farbaky Z, Debreczeni R, Bereczki D, Arányi Z. (2013) A nagy felbontású ideg-ultrahang vizsgálatok jelentősége a perifériás idegek betegségeinek diagnosztikájában. ***Ideggyógyászati Szemle/ Clinical Neuroscience***, 66:4-13. IF: 0,348

Scheidl E, Böhm J, Simó M, Rózsa C, Bereznai B, Kovács T, Arányi Z. (2012) Ultrasonography of MADSAM neuropathy: focal nerve enlargements at sites of existing and resolved conduction blocks. ***Neuromuscular Disorders***, 22:627-631. IF: 3,464

Schelle T, König R, Böhm J, Dettmann S, Gruber H. (2013) Sonografische Charakteristika von Raumforderungen peripherer Nerven. ***NeuroTransmitter***, 24(11): 26.

Arányi Z, Böhm J. (2014) Unusual ultrosonographic findings after nerve trauma explained by Martin-Gruber anastomosis. ***Clinical Neurophysiology***. In press. IF: 3,144