Role of peripheral nerve ultrasonography in neurological diagnosis

Thesis

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INTRODUCTION

The first publication on ultrasound (US) of peripheral nerves was published in 1988, which opened a new field of sonographic imaging. The advent of the technical developments led to the widespread use of musculosceletal and peripheral nerve ultrasound-diagnostics. High resolution linear transducers (15-18 MHz) are reccommended for investigation of smaller, superficial peripheral nerves, while for deep lying nerves (e.g. sciatic nerve) transducers of lower frequency are more suited. Artifact reduction softwares installed on the ultrasound device improve image quality. MRI is an appropriate tool for the investigation of larger nerves surrounded by fat, as the brachial and sacral plexus, however, subtle contrast-difference between smaller nerves and surrounding tissues makes MR-imaging difficult. A further advantage of the ultrasound is that many nerves can be easily and quickly tracked along their whole course. Dynamic investigation is also possible, which may may detect abnormalities such as pathological dislocation or luxation of a nerve, compression exerted on the moving nerve by another structure in its surrounding or decreased mobility of a compressed nerves. Furthermore, as opposed to MRI which is costly, time-consuming and not feasibel in all patients, US is inexpensive, quick and well tolerated by patients.

On the upper limb, the median, ulnar and radial nerves can be tracked by US over long segments without difficulty. With a high-resolution US-device and high-frequency transducer also smaller

nerves (e.g. deep and superficial radial nerves, digital nerves) are detectable. The investigation of the nerves on the lower extremities is technically more complicated, it depends on constitutional and technical conditions. The sciatic, femoral, tibial and peroneal nerves are easily identified at certain segments of their course, and the sural, saphenus and superficial peroneal nerves can also be examined under ideal conditions. Well-trained examiners can also investigate the supraclavicular part of the brachial plexus, including the C5, C6 and C7 cervical roots (ventral branches of the spinal nerves) immediately after their exit from the cervical foramina. High resolution ultrasound delineates the fascicular structure of the normal peripheral nerves. Transverse scanning is better suited to identifying enlarged fascicles of the edematous, compressed nerves. The cross sectional area (CSA) of a nerve can be measured on transverse scans with a resolution of one tenth of a square millimeter. According to the literature, CSA is the most valuable quantitative nerve size parameter. Longitudinal scans are suitable for detection of focal caliber changes due to compression or other reasons along the course of the peripheral nerves.

Clinical applications of high-resolution nerve ultrasound

Traumatic nerve lesions

In traumatic nerve injuries, ultrasound is able to localize the exact site of the lesion and differentiate between neurotmesis (total nerve transsection) and nerve lesions in continuity (varying degree of axonotmesis and injury to the internal nerve sheath elements),

indicating the necessity of surgical intervention and determining the prognosis. Electrophysiological investigation is unable to differentiate between these types of nerve injuries, and accurate localisation may also be a problem for some nerve segments. US allows visualisation of lesions related to the trauma in the vicinity of the nerve, such as scar tissue formation, bone-fragment or hematoma, which may thwart nerve regeneration with an unfavorable clinical outcome.

Tumors of the peripheral nerves

For the investigation of the peripheral nerve tumors, contrast-US highly is recommended. Inhomogeneous contrast-enhancement may suggest malignancy. Final diagnosis is reached by histological examination of tissue obtained by US-controlled biopsy.

Nerve ultrasonography in compression neuropathies

According to the literature, in the most frequent compression neuropathies (carpal tunnel syndrome and ulnar neuropathy at the elbow) sensitivity of high resolution nerve ultrasound is 86-89% and specificity is 87-90%, which is similar to those of electrophysiological assessment, however, with the combination of these two methods sensitivity approches 100%. Ultrasound shows nerve swelling due to venous congestion proximal to the site of compression and also depicts a change in echotexture: edematous nerves have indistinct outer margins and show a homogeneous hypoechoic appearance due to the loss of the normal

fascicular pattern. Perineural vascularisation may increase as well. On longitudinal scans, an abrupt caliber change and a spindle-like swelling of the compressed nerve segment can be seen. Evaluation of the anatomical background of compression neuropathies and visualisation of postoperativ and posttraumatic changes provide useful information for planning therapy. Ulnar nerve is easily accessible for US during its entire course, whereas electrophysiological assessment on the forearm and at the proximal part of the nerve is difficult. The most common site of compression of the ulnar nerve is the sulcus ulnaris at the elbow due to chronic irritation or compression under the Osborne-ligament. In case of focal demyelination with or without conduction block, neurography is able to show the exact site of compression, however, axonal lesion may preclude precise electrophysiological localization. In these cases, US helps in visualising the compressed nerve segment. Normal values may depend on many factors, therefore distal-to proximal CSA-swelling area ratios (e.g. cubital to humeral nerve area ration-CHR) are also frequently used parameters. The main significance of US is in identifying the anatomical background of the ulnar nerve compression, providing useful help in planning surgical therapy.

Nerve ultrasound in polyneuropathies

Previous studies described diffuse and/or multifocal enlargement of certain peripheral nerves and the brachial plexus in some hereditary and acquired demyelinating polyneuropathies. Little

is known about nerve size changes in axonal polyneuropathies. According to some authors, nerve enlargement is more characteristic in demyelinating than axonal polyneuropathies. Presently, the diagnosis and differentialdiagnosis of polyneuropathies is based on the clinical symptoms and detailed electrophysiological and laboratory examinatons. However, diagnosis may be difficult in the early stages of some immune-mediated polyneuropathies, whereas early immunological treatment is crucial to avoid long-term disability in these disorders.

OBJECTIVES

The aim of our prospective studies was to evaluate the role of peripheral nerve ultrasound in compression neuropathies and the differential diagnosis of polyneuropathies with consideration of the electrophysiological studies. Our results can contribute to determining the exact role of nerve ultrasonography in the modern neurological diagnostics.

The pathophysiological type of nerve lesion in compression neuropathies (focal demyeliniation or axonal loss) has a prognostic significance and contributes to the planning of patient management. In the first part of our study, we aimed to evaluate the correlation between nerve size parameters measured by ultrasound and the electrophysiological type of nerve lesion in patients with ulnar neuropathy at the elbow.

Only few reports are available on the use of peripheral nerve ultrasound in the diagnosis of polyneuropathies. Our goal was to explore whether the systematic evaluation of peripheral nerves by ultrasound provides complementary information to electrophysiological data, helping in the differential diagnosis and perhaps in the non-invasive screening of polyneuropathies.

We examined one quantitative nerve size parameter (CSA) by high-resolution ultrasound at multiple sites of upper limb nerves, in the brachial plexus, and in lower limb nerves, in patients with diffuse acquired sensorimotor demyelinating and axonal polyneuropathies and in healthy subjects, to see how the pathologic nature of polyneuropathy affects nerve size and distribution of nerve enlargement.

METHODS

Ulnar neuropathy at the elbow

Fifty elbows of 46 patients were diagnosed with ulnar neuropathy at the elbow (UNE) and included in the analysis. All patients were investigated by electrophysiological means and high resolution nerve ultrasound. Diagnosis was based on typical clinical signs and symptoms and electrophysiological findings. All patients had complaints lasting for less than 6 months, but for more than 4 weeks. Patients with previously operated UNE, UNE due to trauma, complaints or signs suggesting the presence of polyneuropathy or conditions potentially associated with polyneuropathy, and

complaints or signs suggesting lower trunk plexopathy or C8-Th1 radiculopathy were excluded from the study. Based on the electrophysiological findings, patients were classified into groups of predominantly demyelinating nerve lesion (n=21), and axonal nerve lesion (n=29). 87 ulnar nerves of 50 control subjects were also investigated by ultrasound.

Electrophysiological studies were performed using a Nicolet Viking EMG device. Electrophysiological investigation of UNE patients included motor and antidromic sensory nerve conduction studies of the ulnar nerve, inching across the elbow, and electromyography (EMG) of one or two ulnar-innervated hand muscles, such as the abductor digiti minimi (ADM) and the first dorsal interosseous (FDI) muscle according to standard techniques. Patients were classified as having predominantly focal demyelinating type UNE (demyelinating group) when significant slowing of motor conduction velocity (>10 m/s) in comparison to the forearm was seen across the elbow or at any site in the inching study across the elbow, with or without motor conduction block (amplitude reduction :>20% of the compound muscle action potential [CMAP] across the elbow), and the amplitude of the sensory nerve action potential (SNAP) and the CMAP was within normal limits with distal (wrist) stimulation. Patients were classified into the axonal group if the SNAP amplitude was low (<10 μV, indicating sensory axonal lesion) or both SNAP and CMAP amplitudes were low (<10 μV and <4 mV, respectively, indicating sensorimotor axonal lesion) when stimulated at the wrist. Reference values for nerve conduction studies were normal data

collected earlier and established for our electromyography laboratory based on serial studies performed within our laboratory. These are used in routine daily practice in our laboratory; the mean ± 2.5 SD (standard deviation) was used for limits of normality. The axonal group of patients was further divided into subgroups of pure sensory axonal and mixed sensorimotor axonal involvement.

For *ultrasound examinations*, a Philips HD11XE ultrasound device with a small part imaging software and a 15 MHz 3 cm linear array transducer were used. Ultrasound examination was performed within 10 days after the electrophysiological assessment. The CSA of the ulnar nerve was then determined with manual tracing on transverse scans at three levels around the elbow (at the level of the medial epicondyle and 2 cm distal and proximal to this point), and on the mid-upper arm. Measurements were taken with the resolution of one tenth of a square millimeter. Three measurements were averaged at each nerve site. The largest CSA out of the three values around the elbow (CSA_{max}) was used for statistical analysis. The ratio of CSA_{max} of the ulnar nerve around the elbow and the CSA on the mid-upper arm (CHR) was also determined in each patient. The same measurements were carried out also in the control group.

Investigation of polyneuropathies

Thirty-eight patients with the clinical diagnosis of acquired diffuse symmetric sensorimotor polyneuropathy were systematically investigated by electrophysiology and ultrasound in our prospective study. Diagnosis was based on the signs and symptoms of the disease

and electrophysiological workup in our laboratory. Thirty-four healthy controls were also investigated by ultrasonography. Patients were classified into the following categories based on electrophysiological criteria: diffuse sensorimotor axonal (n=26) and diffuse sensorimotor primary demyelinating (n=12) polyneuropathies. Within the latter group, 9 patients were diagnosed with CIDP and 3 patients with demyelinating polyneuropathy of other origin.

Electrophysiological studies were performed in all patients using a Viking electromyography device and included median and ulnar nerve motor and sensory nerve conduction studies and F-wave studies, peroneal and tibial nerve motor nerve conduction studies and F-wave studies, sural sensory nerve conduction study and electromyography of at least two muscles (generally abductor digiti minimi and tibial anterior muscles), according to standard techniques. The left side was examined in all patients. Axonal and primary demyelinating polyneuropathy was diagnosed using standard criteria. Reference values for nerve conduction studies were normal data used in routine daily practice in our laboratory; the mean ± 2.5 SD (standard deviation) was used for limits of normality.

For *ultrasound examinations*, a Philips HD15 XE Pure Wave ultrasound device with small part imaging software and 15 MHz 3-cm linear array transducer was used. The time interval between ultrasound and electrophysiological investigation did not exceed 10 days. Nerve size measurements were made on the same side subjected to the electrophysiological examination, which, in all

patients, was the left side. On transverse scan, the CSA of the following upper limb nerves was measured: cervical nerve roots (C5–C7) immediately after their exit from the cervical foramina; the median nerve on the mid-upper arm, on the distal third of the forearm (just above the pronator quadratus muscle) and at the wrist (at the level of the pisiform bone); the ulnar nerve on the mid-upper arm, at the elbow (in the condylar groove at the level of the medial epicondyle) and on the mid-forearm; the radial nerve at the mid-upper arm (at the level of the spiral groove); and the superficial radial nerve 7–8 cm proximal to the styloid process of the radius. On the lower limbs, the CSA of the peroneal at the fibular head, the tibial nerve behind the medial malleolus, and the sural nerve on the distal leg was measured. Measurements in all control subjects were also unilateral (left side). Three measurements were averaged at each nerve site, and the resulting average value was used to calculate group mean values and standard deviations for each nerve site.

For *statistical analysis* normality of variables was checked with the Shapiro-Wilk test. Analysis of variance (ANOVA) was used to compare variables with a normal distribution among groups. The post-hoc Tukey test was used for pairwise comparisons. For variables with a non-normal distribution, the Mann-Whitney U-test or Kruskal-Wallis ANOVA was employed to compare groups. For multivariate analysis, the general linear model (GLM) was used. A p-value < 0.05 was considered to indicate statistical significance. Statistica for Windows Version 9.0 (StatSoft, Tulsa, OK, USA) was used for data analysis.

RESULTS

Ulnar neuropathy at the elbow

UNE was considered to be of idiopathic origin in most of our patients. In some patients, the following conditions were identified: pathological luxation of the ulnar nerve in five cases, heterotopic ossification and arthrosis signs in two patients, marked valgus position of the elbow in one patient, narrow condylar groove in two cases, and pathological fibrous band compressing the ulnar nerve in flexed elbow position in one patient. Abnormal nerve segments had a hypoechoic appearance with loss of normal fascicular pattern in all patients. In the majority of elbows (n = 46; 92%), the largest CSA was found at the level of the medial epicondyle; 2 cm below in 3 cases (6%), and 2 cm above the epicondyle in only 1 case (2%). Electrophysiological localization of the lesion was uncertain in some patients with axonal involvement (8/29), where ultrasound examination confirmed the site of compression and the diagnosis of UNE based on the focal enlargement and echostructural change of the nerve at the elbow. In patients where electrophysiological localization was possible, the site of focal nerve enlargement on ultrasonography coincided with the electrophysiological site in all cases.

In the control group, CSA_{max} did not depend on age, height and body mass index, but there was a significant positive correlation with weight (Spearman R=0.22, p=0.042), and men had significantly larger CSA_{max} than females (p = 0.038). In the control group, CHR

showed a negative association with height (Spearman R =-0.28, $p<0.01$), but was not related to other demographic parameters.

With univariate analysis, significant differences were found in nerve size parameters (CSA_{max} and CHR) among the three groups (*Table 1*). When pairwise comparisons were carried out by the Tukey-test, significantly higher CSA_{max} and CHR- values were found in the axonal group than in the control and demyelinating groups ($p<0.001$ in both comparisons); the demyelinating group also differed significantly from the controls ($p<0.01$ and $p<0.00$, respectively).

Table 1. Ulnar nerve size parameters in the control and the main patient groups.

Parameter	Control (mean±SD)	Demyelinating (mean±SD)	Axonal (mean±SD)	p-value
CSA (mm^2)	7.6±1.7	10.1±2.6	15.2±5.8	<0.001
CHR	1.2±0.24	1.7±0.3	2.1±0.6	<0.001

CSA=cross sectional area at the elbow; CHR= cubital-to-humeral CSA-ratio; p denotes the level of significance among groups by Kruskal–Wallis ANOVA

We used multivariate analysis using the general linear model to test for independent predictors of CSA^{max} and CHR in UNE. For CSA^{max} and CHR, the type of electrophysiological nerve

lesion was found to be the only significant independent predictor. ($p<0.001$).

A separate analysis was performed within the axonal group to compare those with sensorimotor damage (n = 16) to those with pure sensory lesion (n = 13). CSA^{max} differed significantly between these subgroups ($17.2 \pm 6.2 mm^2$ and $12.8 \pm 4.5\ mm^2$ in the mixed and the sensory group, respectively (Mann–Whitney test, $p = 0.012$), but the difference in CHR did not reach the level of statistical significance (2.2 ± 0.7 and 1.9 ± 0.4, Mann–Whitney test, $p = 0.33$).

Polyneuropathies

When CSA values of individual nerves were tested for differences among the two patient groups and controls, highly significant differences were found for all nerves with the exception of the sural nerve. In general, mean CSA values were the smallest in healthy controls, and polyneuropathy was associated with nerve enlargement.

In a detailed analysis, post hoc pairwise comparisons revealed the following patterns:

- Similar enlargement of CSA was found in patients with demyelinating and axonal polyneuropathies for the ulnar nerve both in the sulcus and on the forearm, the radial nerve on the upper arm, the superficial radial nerve on the forearm, the peroneal nerve at the fibular head and the tibial nerve at the ankle.

- Significantly larger CSA values were found in patients with demyelinating polyneuropathies than in those with axonal neuropathies for the C5–C7 cervical roots, for the median nerve on both the upper arm and the forearm and at the wrist and for the ulnar nerve on the upper arm.

There was a significant difference in height, age, weight and gender distribution between patient groups and healthy volunteers, but these factors did not prove to be independent predictors of CSA when tested with the general linear model. Type of polyneuropathy (i.e. none, demyelinating or axonal) was the main predictor of CSA for all roots and nerves.

In the demyelinating polyneuropathy group, qualitative morphologic analysis revealed pronounced segmental caliber changes on several nerves in 5 of 9 patients with CIDP; in some cases, fascicular enlargement was also pronounced. In the axonal polyneuropathy group, the tibial nerve was enlarged in all patients and had an inhomogeneous hyper-echoic appearance with loss of the normal fascicular pattern.

We performed also the detailed and combined sonographic and electrophysiological examination of two patients with MADSAM (multifocal acquired demyelinating sensory and motor neuropathy), as first in the literature. The data of these two patients were excluded from the main statistical analysis to avoid the heterogeneity of the patients groups. Striking concordance of electrophysiological and ultrasonographic (morphologic) findings was found: marked focal enlargement and change of echostructure of

the nerves were co-localized with existing conduction blocks of nerves clinically affected. Milder focal ultrasonographic abnormalities were seen on nerves showing subclinical electrophysiological involvement. A novel and remarkable finding of our study is the detection of persistent ultrasonographic findings on nerves which have shown complete clinical and electrophysiological recovery following treatment, at sites precisely corresponding to the previous conduction blocks.

CONCLUSIONS

In our study, we set out to assess the role of peripheral nerve ultrasound in modern neurological diagnostics in ulnar neuropathy at the elbow and in the differential diagnosis of polyneuropathies. The following conclusons were drawn.

1. Ultrasound shows pronounced focal morphological abnormalities at the site of the compression in entrapment syndromes, which may be of significant diagnostic help particularly in nerve lesions with non-localizing axonal loss. We found that focal ulnar nerve sweling in patients with ulnar neuropathy at the elbow is larger in axonal nerve lesion than in demyelinating nerve lesion, and nerve size correlates also with the severity of axonal damage. In addition to helping in the localization of nerve lesion and visualisation of the anatomical background, ultrasonography may also reflect the type and degree of nerve lesion in entrapment

neuropathies, which has a prognostic significance and contributes to the planning of patient management.

2. Polyneuropathies are characterized by nerve enlargement in comparison to controls, but the distribution of nerve enlargement in demyelinating and axonal polyneuropathies is characterized by different patterns. In acquired demyelinating polyneuropathies, an additional degree of nerve thickening appears in proximal upper limb nerves and cervical nerve roots and preferentially of the median nerve compared with axonal polyneuropathies. Diffuse enlargement of the nerves and abnormal echostructure of the tibial nerve are characteristic of axonal polyneuropathies. Qualitative analysis found a segmental/multifocal enlargement of the nerves in most of our patients with aquired demyelinating polyneuropathy as opposed to the diffuse enlargement of the nerves in hereditary demyelinating polyneuropathies reported previously in the literature. We conclude that ultrasonography may be a useful complementary tool in differentiating polyneuropathies and could have an important role especially in the diagnosis of cases where electrophysiological results are equivocal.

3. It is concluded that in certain acquired demyelinating neuropathies as in MADSAM neuropathy ultrasound examination shows morphological abnormalities, focal enlargement and change of echotexture of the nerves, which correspond precisely to the sites of conduction blocks. This may be of significant help in localizing the pathological nerve segment when the conduction block is at an electrophysiologically inaccessible site or when substantial

secondary axonal loss has occurred. A novel and remarkable finding of our study that these focal alterations are also seen on nerves that have functionally recovered after treatment, allowing even retrospective confirmation of conduction block sites and providing a significant help in differential diagnosis of immune-mediated demyelinating polyneuropathies.

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