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A prospective study of high resolution ultrasound in brachial plexopathies – Correlation with electrophysiological measurements

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HIGHLIGHTS

- Normative ultrasound data of the brachial plexus with acceptable limits of agreement are presented.
- Ultrasound abnormalities in brachial plexopathies are in good agreement with EDx.
- Ultrasound may supplement electrodiagnostic testing in the diagnosis of brachial plexopathies.

ABSTRACT

Objectives: To evaluate the diagnostic role of ultrasound in brachial plexopathies.
Methods: We included 59 healthy subjects (HS) and 42 patients consecutively referred with clinical suspicion of brachial plexopathy from October 2015 to May 2016. Patients underwent routine electrodiagnostic testing (EDx) as reference standard and a blinded standardised ultrasound examination of the brachial plexus as index test with cross-sectional area (CSA) as the ultrasound parameter of choice.
Results: Seventeen patients were diagnosed by EDx with brachial plexopathy, ten with mononeuropathies, and ten had normal EDx. Five had a cervical radiculopathy. In 11 (64%) out of the 17 patients with EDx diagnosed plexopathy, we found at least one abnormal level on ultrasound. Six (60%) out of ten normal EDx patients had a normal ultrasound examination at all levels. Ultrasound identified the same abnormal level(s) as EDx in eight (73%) of the 11 patients who had both abnormal EDx and ultrasound results. Mean CSA was higher in the plexopathy group compared to HS at the level of the C6 root ($p = .022$), the middle trunk ($p = .027$), and the medial cord ($p = .003$).
Conclusion: Ultrasound examination showed abnormalities in patients with brachial plexopathies in good agreement with EDx.
Significance: Ultrasound may be an important supplement to electrodiagnostics in evaluating brachial plexopathies.

1. Introduction

Evaluation of the pathology of the brachial plexus (BP) often presents a challenge to the clinicians. A thorough physical examination, electrodiagnostic testing (EDx), and various imaging modalities are required to assess the extent of pathology and determine the appropriate treatment (Brunelli and Brunelli, 1995; Tavakkolizadeh et al., 2001; Yoshikawa et al., 2006). EDx of brachial plexopathies can be used to identify the pathology, determine the severity, and evaluate the distribution of abnormalities. It can also suggest whether there are alternative diagnoses, such as nerve entrapment syndromes. EDx often includes nerve conduction studies (NCS) and needle electromyography (EMG) (Tankisi et al., 2005). Depending on the extent of EDx, the sensitivity can be as low as 10–20% (van Alfen et al., 2009; Ferrante, 2004) and the findings can be non-specific and non-localising (Jillapalli and Shefner, 2005; Martinoli et al., 2010).

Other modalities, such as magnetic resonance imaging (MRI) and computerised tomography (CT), can be used to examine the BP. MRI is good at visualising adjacent soft tissue (Zhou et al., 2004) and CT is preferred for evaluation of potential bony abnor-

Abbreviations: BP, Brachial plexus; CSA, cross-sectional area; EDx, electrodiagnostic testing; NCS, Nerve Conduction Studies; EMG, electromyography; HS, healthy subjects.

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malities. Advantages of ultrasonography include its non-invasive nature, portability, moderate pricing, and real-time imaging. However, the quality is highly operator dependent (Chen et al., 2011).

Ultrasound measurements, reported as cross-sectional area (CSA), have been proven effective at depicting normal BP anatomy (Martinoli et al., 2010) and studies on traumatic BP injury have shown that ultrasound can reliably detect root avulsion, nerve injury due to neuroma, and scar tissue formation (Haber et al., 2006). Ultrasound findings in pathology are primarily related to focal increases in hypoechogenicity and segmental CSA thickening associated with nerve entrapment and inflammation (Granata et al., 2009). Initially, only case report studies (Shafighi et al., 2003) have looked at the role of ultrasound in diagnosing brachial plexopathies. Two retrospective studies (Zaidman et al., 2013; Smith et al., 2016) have shown that ultrasound performs even better than MRI in showing abnormalities of BP. A recent retrospective study has suggested that ultrasound abnormalities such as swelling and rotational phenomena may be found in 74 percent of the peripheral nerves, rather than within the plexus itself in patients with a diagnosis of neuralgic amyotrophy (ArAnyi et al., 2017). Similar findings have been shown using MRI (Sneag et al., 2018).

To our knowledge there have been no prospective studies on ultrasound in brachial plexopathies nor have correlation of ultrasound measurements to EDx been investigated. The aim of this prospective study was to evaluate the diagnostic yield of ultrasound in a consecutive cohort of patients routinely referred under the suspicion of brachial plexopathies. Moreover, we aimed to examine the correlation of the ultrasound measurements with the electrophysiological findings.

2. Methods

2.1. Study design

The study was designed as a prospective, controlled, and single blinded study, and was approved by the local ethics committee. Results are reported in accordance with guidelines on diagnostic neuromuscular ultrasound (Hobson-Webb and Boon, 2013).

We used ultrasound as the index test and EDx as the reference standard (Bossuyt et al., 2015).

2.2. Participants

Between October 2015 and May 2016 we invited 68 consecutive patients, each referred to the Department of Clinical Neurophysiology at Aarhus University Hospital on clinical suspicion of BP lesion. The patients were identified based on written clinical assessment by the referring physician. The exclusion criteria were: medical history of operation to the neck or axillary region, severe pain conditions, or a recent diagnosis of terminal disease. Ultrasound was performed prior to EDx in all but 16 patients due to logistic reasons. All ultrasound examinations were done blinded to the EDx results.

Forty-two of the 68 patients were enrolled. Twenty-six patients were not included for the following reasons: 14 did not meet for their scheduled EDx, 11 declined to participate, and one was excluded due to a Cloward operation of the cervical spine.

Sixty healthy subjects (HS) equally distributed in age-groups of one decade were recruited through advertisement at Aarhus University, Aarhus University Hospital, on the website www.forsøgsperson.dk, and among the hospital staff. The requirements for participation were: minimum age of 20 years no medical record of neuropathy, diabetes mellitus, rheumatoid arthritis, acute psychiatric illness, drug addiction or pregnancy. One healthy subject was excluded due to an unrecognised carpal tunnel syndrome. The HS received a fee for participation.

All subjects answered a baseline questionnaire on demographics, personal and family related medical history, and everyday activity. The patients were questioned on initial and current upper extremity symptoms in the form of pain, paraesthesia, and muscle fatigue. The patients also underwent a neurological examination prior to the EDx. The HS were not examined further.

2.3. Ultrasound examination (index test) (Bossuyt et al., 2015)

We used a Siemens ACUSON S2000 device with a high-frequency linear array transducer (18L6 HD). B-mode was used to visualise the nerves with a probe frequency ranging from 12 to 17 MHz. The typical scanning depth was between one to three centimetres with focus adjusted accordingly. We applied a systematic scanning technique to allow reliable ultrasonographic visualisation of 13 anatomically well-defined locations of the BP. Our assessment was an adapted version of the one described by Martinoli et al. (2010). As it is shown in Fig. 1, CSA was consistently measured just inside the hypoechoic rim using the direct tracing function on the ultrasound device.

The subject was placed in supine position with a slight extension in the neck. At first, the posterior tubercle of the transverse process of the C7 vertebra was located. The root of C7 was visualised as a circular hypoechoic structure (Fig. 1). From this position the probe was moved cranially to visualise the roots of C6 and C5. Moving caudally the nerve roots were visualised and measured between the anterior and middle scalene muscles (Fig. 2). Exiting through the interscalene triangle the roots form the superior (C5-C6), middle (C7), and inferior (C8-T1) trunk which can be visualised in a sagittal-oblique plane just above the clavicle (Fig. 3). Owing to the interposition of the clavicle, the visualisation of the infraclavicular portion of the plexus is compromised, rendering this segment of the plexus unsatisfactory with regards to quantitative assessment of the individual vesicles. Finally, the distal part of the cords is visualised using retrograde tracking of the radial, ulnar, and median nerve to the axillary area where the cords are shown surrounding the axillary artery (Fig. 4).

During ultrasound examination, the examiner was not blinded to the status of the subject (patient or control) as this was not logistically possible. However, the patients were asked not to

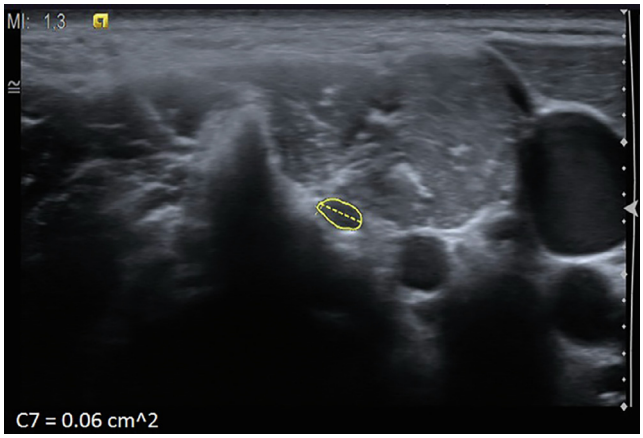

Fig. 1. Root of C7 with anterior tubercle of vertebra. A 0.06 square centimeter CSA measurement (marked in yellow) of the right C7 root exiting the central nervous system in front of the posterior tubercle of the C7 vertebra. Superficially the root is covered by muscle and to the right the jugular vein is visualized above the carotid artery. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

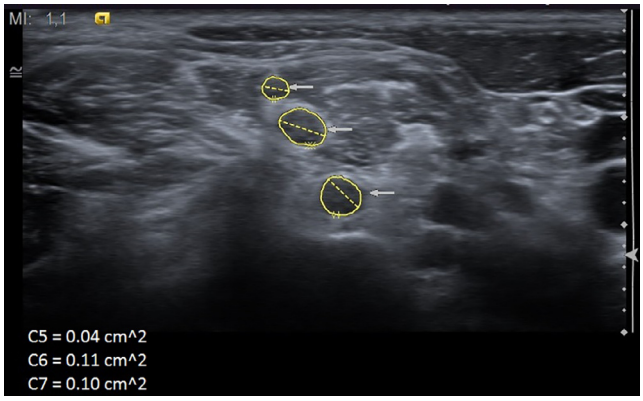

Fig. 2. Roots in the right intercalene triangle. Starting with the most superficial root, C5, C6, and C7 are marked with white arrows. The roots are seen passing between the anterior and middle scalene muscles.

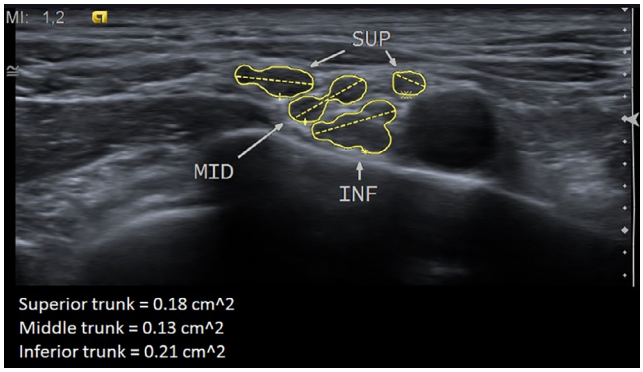

Fig. 3. Supraclavicular trunks. Posterior to the subclavian artery, lying on top of the first rib, the trunks are visualized in a sagittal-oblique plane just before running behind the right clavicle. The middle trunk, consisting of two large fascicles, is seen interposed between the superior trunk which, at this point, has started separating into its posterior and anterior divisions.

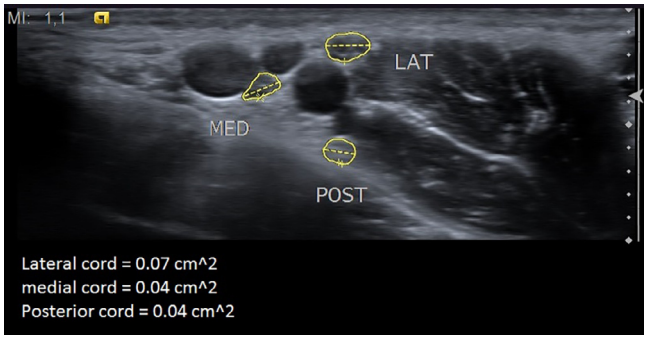

Fig. 4. Axillary view of the brachial plexus cords. Shortly before differentiation into peripheral nerves the cords of the plexus are seen circumventing the brachial artery in the axillary region. The lateral, medial and posterior cord is denoted and shown with CSA measurements.

expose their symptomatic side. A binary randomiser from www.random.org was used to decide which side to begin with. Ultrasound data was collected by RLJ but was not analysed immediately. Careful marking of the structures was performed using arrows, text, and videos. Data were then anonymised (EQ) and the CSA measurements were made (RLJ) in a blinded fashion and using direct tracing methods.

For normative data, 59 HS underwent bilateral examination of the described ultrasound protocol resulting in a maximum of 26 data points per healthy subject. Data underwent statistical examination for side dependent differences in CSA after which the mean normative values were calculated.

To assess method consistency and reproducibility, 12 HS were examined twice. For intra-rater assessment, RLJ performed two successive examinations within one week. For inter-rater assessment, RLJ and EQ performed one examination each on the same day. The last assessment performed by RLJ was used for inter-rater reliability. In-depth analysis of method variability will be published in a separate article.

2.4. Electrodiagnostic testing (reference standard)

NCS and EMG were performed with the EMG equipment Keypoint version 2.11 (Alpine, Denmark). EDx was performed by certified neurophysiologists and the strategy for diagnosing and localisation of a BP complied with the guidelines of the Danish Society of Clinical Neurophysiology, www.dskn.dk, developed by the Danish National Consensus Group (Fuglsang-Frederiksen and Pugdahl, 2011).

The EDx diagnosis of BP was made using EDx findings (sensory, motor, and EMG) together with the clinical presentation. The localisation of the lesion was established when a minimum of one sensory nerve, one motor nerve, and one to two muscles from the symptomatic portion of the BP were abnormal and all other measurements outside this portion were normal. In case of radiculopathies, MRI was used as the diagnostic reference standard.

NCS and EMG were performed following the department's routine methods. A quantitative analysis of the motor unit potentials was performed as described (Buchthal and Pinelli, 1953). In case of clinical symptoms or findings suggesting a polyneuropathy, NCS of nerves in lower extremities were performed.

2.5. Statistical methods

Statistical analysis was performed in STATA 13 and SPSS 20. Continuous data is presented as mean CSA plus two standard deviations (SD). To investigate side dependent difference in CSA, a paired t-test with equal variances was done. For comparison of three groups or more, an Analysis of Variance with Tukey post hoc test was performed. Multiple regression analyses for age, gender, height and weight were performed. Two-tailed p-values of <0.05 were considered statistically significant.

Upper and lower reference values in each anatomical location were defined as the mean value ± 2 SD. For reproducibility testing, right- and left-sided data was evaluated with Bland-Altman plots with 95% limits of agreement. Bland-Altman plots were examined for violating a priori cut-off estimates for reference values of ± two standard deviations. A qualitative assessment of the plots was done to reveal systematic bias in the variance.

To compare ultrasound to EDx we looked at a paired contingency table for sensitivity and specificity.

3. Results

3.1. Demographics

In the study population, we included 59 HS and 42 patients divided into four groups; brachial plexopathies (n = 17), mononeuropathies (n = 10), EDx normal (n = 10), and cervical radiculopathies (n = 5) (Fig. 5).

A baseline comparison of demographics between patients and HS was performed (Table 1). The patients were heavier and had a higher BMI compared to HS. The duration of symptoms was on average 19.8 (1–96) months, the distribution of the symptomatic

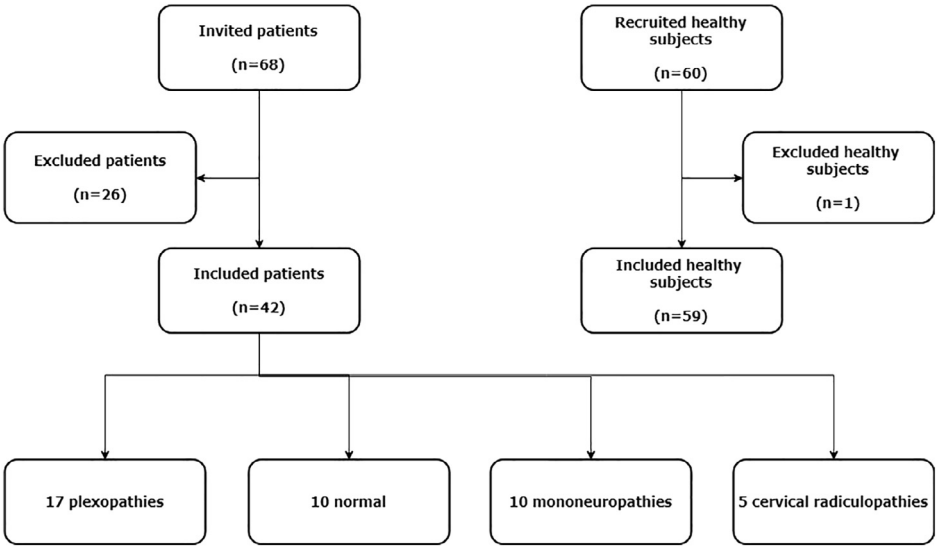

Fig. 5. Flowchart of study population. The flowchart shows the inclusion of study participants and distribution of the final diagnosis. EDx was used as the diagnostic reference standard. In the cervical radiculopathy group MRI was used as diagnostic reference standard.

Table 1
Demographic characteristics of the study population.

	Healthy subjects, n = 59 (mean ± 95% confidence internal)	Patients, n = 42 (mean ± 95% confidence internal)	P-value
Age (year)	45.4 (41.2–49.5)	48.7 (43.1–54.2)	0.33
Weight (kilo)	72.3 (68.5–76.2)	80.9 (75.0–86.7)	0.01
Height (meter)	1.73 (1.70–1.75)	1.74 (1.71–1.77)	0.49
BMI (kg/m^2)	24.1 (23.1–25.2)	26.6 (24.9–28.2)	0.01
Gender (n)	(m:w) 30:29	(m:w) 25:17	n.s.*
Hand dominance (n)	(right:left) 52:7	(right:left) 39:3	n.s.
Occupationn (n)	White collar n = 18, blue collar n = 14, retired n = 14, student n = 13	White collar n = 24, blue collar n = 5, retired n = 5, student n = 8	n.s.

Demographics table comparing age, weight, height, BMI, gender, hand dominance, and occupation in the healthy control group to the whole patient group.
* n.s. = non significant.

side was 25:17 (right:left) and the distribution of the aetiology was 19:22 (idiopathic:traumatic). Three of the plexopathy patients had a diagnosis of diabetes mellitus.

3.2. Electrodiagnostic data

3.2.1. Brachial plexopathy patients

Out of the 42 patients, 17 were diagnosed with a BP lesion; eight with a traumatic plexopathy, five with a brachial neuritis (Parsonage-Turner syndrome), three in relation to surgery around the plexus, and one following local radiation treatment after a breast cancer resection.

Out of the 17 patients, five patients were diagnosed with a panplexopathy, two with a superior trunk lesion, two with an inferior trunk lesion, one with medial cord lesion, one with posterior cord lesion, and one with lateral cord lesion. In five cases EDx could not localise BP damage to a single location; in two patients EDx suggested a lesion of the posterior and medial cord, in one lesion to the lateral cord and the lower plexus, in one lesion to the posterior and medial cord, and one was suspected of having a radiculopathy in which lesion to the posterior cord could not be excluded.

3.2.2. Mononeuropathy patients

Ten patients were diagnosed with mononeuropathies classified into three traumatic axillary nerve injuries, two entrapment mononeuropathies (one ulnar nerve at Guyons channel and one median nerve at the carpal tunnel), one median neuritis presumably on vasculitis basis, two suprascapular neuropathies (one traumatic and one traction traumatic), and two traumatic lesions of the long thoracic nerve.

3.2.3. Normal EDx

In ten patients, all EDx were normal.

3.3. Ultrasound data

3.3.1. Reproducibility

The limits of agreement derived from Bland-Altman plots are shown in Table 2. No systematic bias in the variance was found. Compared to the reference values (Table 3), in nine out of 13 locations the upper limit of the mean difference between two examiners does not exceed the upper limit (1.96SD) of the reference value for the respective locations. At the level of the C8 root, the C6 interscalene root, the axillary medial cord and the axillary posterior cord the upper limit of agreement exceeds the 1.96SD. These results warrant caution when interpreting results in these anatomical locations.

In 43 out of the 59 HS, one or both C8 measurements could not be obtained. For this group an average BMI of 25.2 was found. For the HS in which both C8 were visualised an average BMI of 21.5 was found. For our patient group, we were only able to visualise both C8 roots in 10 individuals. This group had an average BMI of 22.8. The remaining 32 patients with one or both C8 roots hidden had an average BMI of 27.6.

Table 2
95% Limits of agreement using Bland-Altman plots.

Anatomical location	Mean difference (Lower and upper limit)
C5 root	−0.005 cm^2 (−0.03 to 0.02)
C6 root	−0.005 cm^2 (−0.03 to 0.02)
C7 root	0.002 cm^2 (−0.02 to 0.03)
C8 root	−0.002 cm^2 (−0.04 to 0.04)
C5 root (interscalene region)	−0.006 cm^2 (−0.03 to 0.02)
C6 root (interscalene region)	0.004 cm^2 (−0.02 to 0.03)
C7 root (interscalene region)	−0.007 cm^2 (−0.03 to 0.01)
Supraclavicular superior trunk	−0.006 cm^2 (−0.06 to 0.05)
Supraclavicular middle trunk	−0.011 cm^2 (−0.06 to 0.04)
Supraclavicular inferior trunk	−0.004 cm^2 (−0.04 to 0.03)
Axillary lateral cord	−0.003 cm^2 (−0.03 to 0.03)
Axillary medial cord	−0.004 cm^2 (−0.03 to 0.02)
Axillary pasterior cord	−0.014 cm^2 (−0.06 to 0.04)

Mean CSA difference of the second rater (EQ) is compared to that of the first rater (RLJ). Lower and upper limits, shown in brackets, indicate the extent as to which a measurement recorded by the first rater may be recorded different by the second rater. N = 59 healthy subjects.

3.3.2. Normative data

We did not find any side difference in CSA measurements. Therefore, right sided measurements were arbitrarily selected to represent normative data so as to avoid an artificial decrease in variance.

Multiple regression analysis predicting CSA from age, sex, height, and weight did not reveal any relation, i.e. $p > .05$. Upper reference values of the 2% and 5% cut-off were calculated and are presented in Table 3.

3.3.3. Ultrasound comparison of groups

Comparing our brachial plexopathy group to the other groups, we found five locations with a difference in the mean CSA; at the C6 root ($F(4,95) = 4.27$, $p = .003$), at the C6 root in the interscalene region ($F(4,83) = 2.50$, $p = .049$), at the supraclavicular middle trunk ($F(4,87) = 2.55$, $p = .045$), at the axillary lateral cord ($F(4,92) = 2.65$, $p = .038$), and at the axillary medial cord ($F(4,91) = 3.84$, $p = .006$) (Table 4).

A post-hoc test showed that the mean CSA was higher in the plexopathy group compared to the healthy subject group at the level of the C6 root ($p = .022$), at the middle trunk ($p = .027$), and at the axillary medial cord ($p = .003$). It also showed that CSA was higher in the plexopathy group compared to the mononeuropathy group at the level of the C6 root ($p = .017$). No other differences were found between these two groups. We found no differences in the mean CSA at any level in the healthy subject group when compared to both the EDx normal group and the mononeuropathy group.

In the plexopathy patients, we found a total of 22 abnormal (according to the normative data) measurements in the symptomatic side compared to only eight measurements above the upper limit in the asymptomatic side (Table 5).

3.3.4. Sensitivity and specificity of ultrasound compared to EDx in EDx diagnosed plexopathy group

Eleven out of the 17 plexopathies presented with both EDx and ultrasound abnormalities resulting in a sensitivity of 64%. The 11 patients had a minimum of one abnormal (above our upper reference value) ultrasound finding on the symptomatic side. We found no ultrasound measurements below the lower reference value. Six patients out of ten in the EDx normal group had a normal ultrasound examination at all levels giving us a specificity of 60% (Table 6).

Six patients with abnormal EDx and normal ultrasound examination included three traumatic, two neuritis, and one radiotherapy induced plexopathy.

In eight out of 11 patients in which EDx and ultrasound were abnormal, ultrasound identified the same abnormal level(s) as EDx corresponding to a 73% agreement between the two methods. Three out of five (60%) brachial neuritis patients and five out of seven (71%) traumatic plexopathy patients had an abnormal ultrasound examination.

Table 4
Ultrasound comparison of groups (n = 101).

Anatomical location	One-way ANOVA significance level (P-value)
C5 root	0.6476
C6 root	0.0032
C7 root	0.6288
C8 root	0.5674
C5 root (interscalene region)	0.8514
C6 root (interscalene region)	0.0488
C7 root (interscalene region)	0.4992
Supraclavicular superior trunk	0.7660
Supraclavicular middle trunk	0.0451
Supraclavicular inferior trunk	0.3607
Axillary lateral cord	0.0383
Axillary medial cord	0.0062
Axillary posterior cord	0.1298

One-way Analysis of Variance p-values for each anatomical location. P-values below 0.05 are considered significant, suggesting a difference in mean CSA between groups. N = 101 is the number of healthy subjects and all patient groups.

Table 3
Normative reference values (n = 59).

Anatomical location	Upper reference values (mean (SD))	5% cutoff values	2% cutoff values
C5 root	0.09 cm^2 (0.06 (0.015))	0.08 cm^2	0.09 cm^2
C6 root	0.14 cm^2 (0.10 (0.02))	0.13 cm^2	0.14 cm^2
C7 root	0.14 cm^2 (0.10 (0.02))	0.13 cm^2	0.14 cm^2
C8 root	0.13 cm^2 (0.10 (0.015))	0.13 cm^2	%*
C5 root (interscalene region)	0.08 cm^2 (0.06 (0.01))	0.08 cm^2	0.09 cm^2
C6 root (interscalene region)	0.12 cm^2 (0.10 (0.01))	0.12 cm^2	0.12 cm^2
C7 root (interscalene region)	0.14 cm^2 (0.10 (0.02))	0.13 cm^2	%*
Supraclavicular superior trunk	0.25 cm^2 (0.19 (0.03))	0.24 cm^2	0.27 cm^2
Supraclavicular middle trunk	0.16 cm^2 (0.12 (0.02))	0.18 cm^2	0.20 cm^2
Supraclavicular inferior trunk	0.24 cm^2 (0.16 (0.04))	0.23 cm^2	0.28 cm^2
Axillary lateral cord	0.13 cm^2 (0.10 (0.015))	0.13 cm^2	0.13 cm^2
Axillary medial cord	0.08 cm^2 (0.07 (0.005))	0.08 cm^2	0.08 cm^2
Axillary posterior cord	0.09 cm^2 (0.07 (0.01))	0.09 cm^2	0.09 cm^2

Upper reference values were calculated and are presented as CSA plus 2 standard deviations, as 5% cut off values, and as 2% cut off values. Numbers in parenthesis denote values for mean CSA and two standard deviations respectively. N = 59 healthy subjects.

* Percentile could not be calculated due to insufficient data points.

Table 5
CSA difference in plexopathy group.

Anatomical location	Symptomatic side	Asymptomatic side
C5 root	1	0
C6 root	3	1
C7 root	3	1
C8 root	0	0
C5 root (interscalene region)	2	1
C6 root (interscalene region)	3	2
C7 root (interscalene region)	1	0
Supraclavicular superior trunk	1	0
Supraclavicular middle trunk	4	2
Supraclavicular inferior trunk	1	1
Axillary lateral cord	0	0
Axillary medial cord	3	0
Axillary posterior cord	0	0
Total	22	8

The table shows values above our a priori normative reference values for each anatomical location. N = 17 representing the brachial plexopathy group.

Table 6
Paired contingency table of EDx findings compared to ultrasound.

	EDx +	EDx −	
Ultrasound +	11	4	15
Ultrasound −	6	6	12
	17	10	27

Vertically, EDx positive BP patients and EDx no-abnormality patients are listed. Horizontally, these are compared patients with a positive or negative ultrasound examination respectively.

3.3.5. Sensitivity of ultrasound and EDx in the referred group

In the overall group, EDx identified abnormalities in 32 (76%) of the patients while ultrasound identified abnormalities in only 20 (45%) of patients. On the other side, ultrasound identified pathology in 10% of patients with normal EDx.

4. Discussion

4.1. Findings and implications

In this prospective study we examined the value of high-resolution ultrasound in identifying pathology of the BP in patients with symptoms of brachial plexopathies. Moreover this is one of the first studies to compare high-resolution ultrasound findings with EDx.

We found that ultrasound measurements of CSA at various levels of the brachial plexus were abnormal in 64 % percent of patients who were diagnosed with brachial plexopathy by EDx. Ultrasound agreed with EDx on the level of the lesion in 75% of the patients. The mean CSA at the level of the C6 root, the middle trunk, and at the axillary medial cord differentiated the plexopathy group from the HS group. At the level of C6, the plexopathy group also had a higher mean CSA value compared to the mononeuropathy group. We did not find any differences in CSA between the HS group and the patients diagnosed with mononeuropathies or symptomatic patients with normal EDx.

In two out of five (40%) patients with neuralgic amyotrophy, and in three out of eight (37%) patients with traumatic lesion of the plexus, we could not find ultrasound abnormalities at the brachial or axillary level.

When evaluating the findings of our study and the apparent low performance of ultrasound in diagnosis of BP compared to EDx some extrinsic and intrinsic issues of the study should be addressed.

First, one should bear in mind that ultrasound and EDx are examining different aspects of nerve pathology. When the nerve lesion is followed by inflammation and oedema (Granata et al., 2009), the nerve CSA will increase and the pathology will be visible on ultrasound but may not be evident on EDx. However, when the pathology is axonal loss and thus evident in EDx, there may not be any increase in CSA and ultrasound will fail to identify an abnormality.

Second, the examiner performing the ultrasound was blinded to the clinical information of the patients which was not the case for the clinical neurophysiologist, who had access to clinical information and was able to tailor the examination accordingly Obviously, this was done in order to increase the certainty of the results of the index test (ultrasound), but may have hindered the ultrasound to perform with its full potential and may have artificially lowered the sensitivity compared to the EDx. We tried to minimise this effect by examining as many levels as possible within the brachial plexus and by standardising the scanning method. Nevertheless, we do believe that ultrasound would have performed better if the examiner had interviewed and examined the patient and integrated the findings with the ultrasound examination.

Third, we only measured the CSA at the BP level and axillary level and at predetermined levels. While the roots were scanned in the continuous manner, there is still the possibility that we could have missed nerve pathologies located elsewhere. One retrospective and not controlled study (ArAnyi et al., 2017) in patients with neuralgic amyotrophy has reported swelling of the nerve/fascicle with constriction and rotational phenomena (nerve torsion and fascicular entwinement) in the distal part of the nerves with a sensitivity of up to 74%. In this study, we aimed to examine the diagnostic yield of ultrasound in diagnosis of brachial plexopathies by visualising and measuring the supraclavicular, infraclavicular and axillar portion of the brachial plexus. However, examining the distal part of nerves could have increased the diagnostic yield and should be included in further studies, preferably prospective, blinded and with a control group.

Fourth, as we wanted to establish the diagnostic yield of ultrasound in a consecutive group of patients referred to the department under the suspicion of brachial plexopathy, the included group was heterogeneous with a wide range of aetiologies. Thus, we cannot exclude that more abnormalities could have been detected if the groups had been larger and more homogeneous.

Fifth, in this study it was not possible to visualise the BP sufficiently, neither in the infraclavicular nor in the retropectoral area. Furthermore, the C8 and TH1 were also difficult to visualise. These roots and locations showed insufficient reproducibility and in many patients no measurements could be obtained. Thus, the data from these roots and locations were not included in the analysis. Factors such as location, BMI, and cervical length may compromise accessibility due to a deeply located nerve structure with a vaguely defined circumference. Previous studies (Demondion et al., 2003; Martinoli et al., 2002, 2010) have struggled in visualising especially the root of T1, the infraclavicular cords, and the retropectoral cords. The root of T1 exits the central nervous system below the T1 vertebrae in a location which, in most cases, lies too deep to be visualised with ultrasound. The BP cannot be tracked from a cranial location in these locations due to the clavicle interfering with the ultrasound signal. Besides, locating the plexus after skipping the clavicle cannot be done in a satisfactory manner for one to sufficiently identify the different sections of the plexus. Thus, we may have missed pathologies at those levels.

Another aspect to be addressed is that we found ultrasound abnormalities also in asymptomatic sides of the BP patients. This may have been caused by a measurement error, especially at the locations in which Bland Altman plots limit of agreements warrants caution. In order to avoid these possible false positive mea-

surements, the upper reference values could be increased from mean + 1.96 SD to mean + 3SD. There may be, of course, another explanation such as the possibility that nerve pathology might be evident on ultrasound even though the patient does not report any symptoms. Van Alfen et al have recently shown that up to 38% of patients with neuralgic amyotrophy have bilateral affection of the brachial plexus (van Alfen et al., 2015).

It is also worth mentioning that our patient group was heavier than the HS group. Studies (Qrimli et al., 2016) have shown a weak positive correlation with weight/BMI, mostly for the distal portion of the nerves. Moreover, we did not find any correlation between our cohorts, thus, we believe that the differences in CSA could not be explained by differences in weight/BMI.

One strong aspect of our study is the large group of HS examined to determine the CSA reference material of the BP. Moreover, in order to define the limits of CSA pathology, an elaborate amount of normative data has been collected. Comparing our data to reference material from other authors, an apparent advantage seems a uniform distribution of age groups, assessment with regard to systematic bias, and concordance between Bland Altman limits of agreement and cut-off reference values in nine out of 13 locations (Cartwright et al., 2008).

Also, our reference material represents a more compact collection of normative data for the BP. Other authors have produced reference material for both upper and lower extremity nerves ranging from 12 to 15 individual measurements (Cartwright et al., 2008; Kerasnoudis et al., 2013), whereas our 13 locations are all within the range of the nerve root to the distal cords. As a result, individual reference values for the interscalene roots and supraclavicular trunks are available. This was done to increase the opportunity of correlating clinical assessment to pathological findings.

5. Conclusion

We conclude that ultrasound measurements can be used as a modality for anatomically identification of the BP within clinically acceptable limits of agreement. Although we found the agreement between EDx and ultrasound in plexopathy patients to be satisfying, the sensitivity and specificity of ultrasound with EDx as a diagnostic reference standard was not high. Therefore, we recommend that ultrasound is to be seen as a supplement to EDx in the diagnosis of brachial plexopathies.

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Conflict of interest

None.

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