Focused Neuromuscular Ultrasound Approach for the Diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy

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Purpose: Previous ultrasonographic studies of individuals with chronic inflammatory demyelinating polyneuropathy (CIDP) have shown nerve enlargement at several sites. This prospective study compares only the bilateral median and ulnar nerves of individuals with CIDP with reference values to determine the clinical usefulness of this focused approach as a diagnostic tool.

Methods: The cross-sectional area, echogenicity, and vascularity of the bilateral median and ulnar nerves of 25 subjects with CIDP were measured using ultrasound. Nineteen had typical CIDP based on the European Federation of Neurological Societies and the Peripheral Nerve Society guidelines, whereas six had atypical CIDP and were diagnosed based on clinical impression.

Results: Focal nerve enlargement was found in at least one segment in all subjects. Subjects with typical CIDP had larger cross-sectional areas compared with subjects with atypical CIDP.

Conclusion: A focused ultrasound study, involving only the median and ulnar nerves, is sensitive for the detection of nerve enlargement in CIDP. Measuring the cross-sectional area of the median and ulnar nerves is clinically feasible and may help establish the diagnosis of CIDP.

Key Words: CIDPNeuromuscular ultrasound, Median nerve, Ulnar nerve, CSA.

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Chronic inflammatory demyelinating polyneuropathy (CIDP) is the most common form of chronic autoimmune neuropathy, affecting approximately 30,000 people in the United States.[1] There are typical and atypical forms of CIDP, including distal acquired demyelinating symmetric neuropathy and multifocal acquired demyelinating sensory and motor neuropathy.[2] These variations in presentation, along with a lack of a single accurate biomarker,[3] can make the diagnosis of CIDP challenging.

Currently, CIDP may be diagnosed using criteria developed by the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS).[4] These criteria are based on clinical history, physical examination, electrodiagnostic testing, magnetic resonance imaging, and laboratory tests. Neuromuscular ultrasound (NMUS) has more recently been used to help physicians distinguish between CIDP and other neuropathies, such as Charcot–Marie–Tooth disease.[5] Neuromuscular ultrasound findings are not currently part of EFNS/PNS criteria, but NMUS may be a helpful complementary tool for the diagnosis and monitoring of CIDP.

This prospective study seeks to add to a growing number of publications on the use of NMUS for the evaluation of CIDP. Neuromuscular ultrasound measurements, such as nerve cross-sectional area (CSA), vary according to the subtype of CIDP, severity of disease, and treatment.[6] Peripheral nerve ultrasonography in individuals with suspected CIDP has been studied using a variety of approaches over the past decade. Several scales have been proposed to quantify upper and lower limb nerve enlargement, with some scales being more comprehensive than others. Based on previous studies, it seems that the median and ulnar nerves are typically involved in CIDP.[7] Although these comprehensive scales are informative, they may not be feasible in busy neurodiagnostic laboratories on a routine basis. This study was therefore designed to prospectively assess the sensitivity of scanning only the median and ulnar nerves bilaterally in individuals with suspected CIDP. This simplified and focused protocol was used to determine how frequently NMUS detected nerve changes in those with typical CIDP and atypical CIDP, as well as those with CIDP in remission and active disease.

METHODS

Subjects

Before initiation of this study, approval was obtained by the institutional review board. All subject in this study provided verbal and written consent. Individuals with CIDP were identified in the electronic medical record, and it was determined whether each subject met the 2010 EFNS/PNS criteria. Patients diagnosed with CIDP who presented with atypical clinical features, including significant asymmetry or limited motor involvement, were also included.

Patients were evaluated by means of a clinical assessment, ultrasound assessment, and structured clinical interview. Nineteen of 25 subjects met the 2010 EFNS/PNS criteria for definite CIDP. The other six were either probable or possible CIDP. Of note, this is not the same as those with typical versus atypical clinical phenotypes, which in this cohort was 13 versus 12. The six subjects who were not definite were mainly because of not clearly meeting the demyelinating NCS criteria for definite CIDP (five of six) but had a suggestive phenotype and/or response to treatment. The others met the NCS criteria but had a clinical

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picture that was somewhat unusual for CIDP (more monophasic without a clear response to ongoing treatment).

Clinical Assessment

Patients underwent a full neurological examination, including disability testing (Inflammatory Neuropathy Cause and Treatment disability scale)[8] and standardized muscle strength testing (Medical Research Council score)[9] in eight muscle groups bilaterally (shoulder abduction, elbow flexion, wrist flexion, first finger abduction, thumb abduction, hip flexion, knee extension, and ankle extension).

Ultrasound Assessment

The ultrasound assessment was performed with an Esaote MyLab25 (Esaote, Genoa, Italy) ultrasound device with an 18 MHz linear array transducer. The assessment was performed the same day of the neurological assessment. The transducer was aligned perpendicular to the nerves. No additional force was applied other than the weight of the transducer, and the limbs were kept in the neutral position to avoid causing any artificial nerve deformity.

Ultrasound Sites

The entire median nerve from the wrist to axilla was scanned to identify the minimum and maximum CSA. Five fixed sites were measured—the distal wrist crease, the midforearm 15 cm proximal to the flexor retinaculum, the elbow next to the brachial artery, the upper arm at the midhumerus, and the axillary fossa. The entire ulnar nerve was also scanned from the wrist to axilla, with five fixed sites measured—Guyon canal, the midforearm 15 cm proximal to the flexor retinaculum, the elbow between the medial epicondyle and olecranon, the upper arm at the midpoint from the medial epicondyle to the axillary fossa, and the axillary fossa.

Cross-sectional area measurements of the median and ulnar nerves were taken bilaterally from transverse/axial images, measuring at the inner border of the hyperechoic epineural rim using the continuous tracing technique. Nerve CSA measurements were labeled as "increased" if they were above the upper limit of normal according to laboratory-derived normal values.[10,11] Moderate enlargement was defined as CSA >1.5 times the upper limit of normal. Echogenicity was assessed on a three-point scale: decreased echogenicity (no clear fascicles, score = 3), slightly decreased (1–2 clear fascicles, score = 2), or normal (greater than two clear fascicles, score = 1). Vascularity was assessed by slowly increasing the gain until signal was seen either in the nerve or the surrounding bones or tendons. Vascularity was also assessed on a three-point scale: normal (no signal, score = 1), slightly increased (signal in 1–2 aspects of the nerve, score = 2), or increased (signal in greater than two aspects of the nerve, score = 3). A three-point scale was used to measure echogenicity and vascularity rather than quantitative analyses as the former are more conducive to clinical visits.

Statistical Analyses

Descriptive statistics (mean, SD, and range) were used for continuous variables. A linear regression model was used to estimate the influence of remission on CSA values and the impact of CSA values on Inflammatory Neuropathy Cause and Treatment/Medical Research Council scores. Analyses were performed using Microsoft Excel.

RESULTS

Of the 25 individuals studied, all had at least one abnormality on ultrasound, as determined by focal nerve CSA enlargement. The sensitivity of this approach was therefore 100%. Twenty-three of the 25 subjects had ≥4 enlarged nerve segments. Subjects who fulfilled the 2010 EFNS/PNS criteria for definite CIDP had more enlarged segments than those with probable/possible CIDP, as presented in Table 1. Subjects with definite CIDP were also twice as likely to have at least one nerve segment that exceeded 1.5 times the upper limit of normal. In addition, the average segment CSA was larger in all segments for the definite CIDP subjects, as reported in Table 2. Changes in echogenicity were especially prominent at the median nerve at the wrist, which were hypoechoic in 66% of subjects with definite CIDP, and at the ulnar nerve at the elbow, which were hypoechoic in 92% of those subjects. Changes in vascularity were not frequently abnormal in either population; the most likely place to find vascular changes was at the median nerve at the forearm, with only 18% of subjects showing changes at this location. No patterns or associations between ultrasound

TABLE 1. Subject Demographics

	All Subjects (n = 25) Mean (Range) [STD]	Definite CIDP (n = 19) Mean (Range) [STD]	Probable/Possible CIDP (n = 6) Mean (Range) [STD]
Sex	52% female	58% female	33% female
Age	56.96 (23–84) [13.04]	57.37 (23–84) [14.51]	55.67 (46–65) [7.50]
BMI	31.41 (18.49–49.23) [7.83]	31.85 (18.49–49.23) [8.01]	30.04 (22.10–39.56) [7.78]
2 + abnormal nerve segments	100%	100%	100%
3 + abnormal nerve segments	96%	100%	83%
4 + abnormal nerve segments	92%	100%	67%
Presence of a segment >1.5x upper limit of normal	60%	68%	33%

BMI = body mass index; CIDP, chronic inflammatory demyelinating polyneuropathy.

TABLE 2. Median and Ulnar Nerve Cross-sectional Area

Nerve/Site	All Subjects ($n = 25$, mm^2) Mean (Range) [STD]	Definite CIDP ($n = 19$, mm^2) Mean (Range) [STD]	Probable/Possible CIDP ($n = 6$, mm^2) Mean (Range) [STD]	Upper Limit of Normal CSA[10,11] (mm^2)
Median nerve/wrist	15.74 (8.0–39.5) [6.86]	16.87 (9.5–39.5) [7.32]	12.17 (8.0–18.5) [3.55]	13.0
Median nerve/forearm	10.70 (5.5–27.0) [4.15]	11.05 (5.5–27.0) [4.62]	9.58 (8.0–12.5) [1.80]	10.7
Median nerve/elbow	15.52 (7.0–38.5) [6.34]	16.24 (10.0–38.5) [6.64]	13.25 (7.0–22.5) [5.11]	13.2
Median nerve/arm	16.26 (8–76) [13.18]	17.58 (8–76) [14.93]	12.08 (9–14) [1.93]	13.1
Median nerve/axilla	15.15 (7.5–51.0) [9.79]	16.37 (7.5–51.0) [11.11]	11.50 (11.0–12.5) [0.61]	11.7
Ulnar nerve/wrist	8.90 (4.5–21.0) [3.25]	9.26 (5.5–21.0) [3.42]	7.75 (4.5–11.0) [2.54]	8.1
Ulnar nerve/forearm	10.12 (5–34) [5.58]	10.95 (6–34) [6.14]	7.50 (5–10) [1.61]	8.3
Ulnar nerve/elbow	12.90 (6.0–24.5) [4.86]	13.95 (7.0–24.5) [5.01]	9.58 (6–13) [2.35]	8.8
Ulnar nerve/Arm	13.14 (4.0–56.5) [10.06]	14.11 (4.0–56.5) [11.25]	10.08 (5.5–17.5) [4.02]	8.3
Ulnar nerve/axilla	12.21 (7.0–44.5) [8.84]	13.37 (8.0–44.5) [9.67]	7.88 (7–9) [0.85]	8.6

CIDP, chronic inflammatory demyelinating polyneuropathy; CSA, cross-sectional area.

parameters and Inflammatory Neuropathy Cause and Treatment or Medical Research Council sum scores were found.

Eight of the individuals in this study were in remission and 17 were not. A t-test showed no significant association between remission status and median or ulnar CSA, echogenicity, or vascularity at any segment.

DISCUSSION

This study was conducted prospectively to show that a focused ultrasound study using only the median and ulnar nerves can detect CIDP. Although there are other sonographic methods of detecting CIDP, they are complicated and time-consuming. Scanning the median and ulnar nerves is a quick and efficient way to aid in the diagnosis of CIDP. Changes are seen at common compression sites, but patients with CIDP nearly always have more nerve enlargements, especially in the proximal median and ulnar segments. In subjects who fit the 2010 EFNS/PNS criteria for definite CIDP, multiple nerve segments were enlarged, and the mean segment sizes were larger than the upper limit of normal in all segments (Table 2).

A limitation in the study was the relatively small sample size ($n = 25$). Nerve segment sizes were not normalized for weight, height, sex, or body mass index, although previous studies have shown a positive correlation between nerve CSA and body mass index.[12] This approach can be cumbersome in a busy diagnostic laboratory, which is why it was not used in this study. In addition, there was one outlier who had significantly larger CSA measurements than any other subject, for example, this subject had an ulnar nerve CSA of 54 mm^2 at the arm, and the average CSA at that site for all other subjects was 11.33 mm^2. We presented the bilateral CSA measurements as a mean of the left and right sides to simplify data presentation, but it is important to note that there may not be statistical independence using this approach. Six subjects did not fit the EFNS/PNS criteria but were previously diagnosed with CIDP. These subjects were not excluded in the data analysis because in clinical practice, it is common for patients to be diagnosed with and treated for CIDP outside of the EFNS/PNS criteria. Therefore, including these subjects yielded clinically relevant results. The European Federation of Neurological Societies and the Peripheral Nerve Society criteria may not encompass all individuals with CIDP, especially those with atypical subtypes.[13] Finally, a control group was not used in this study design, so specificity of this approach could not be assessed. It might be expected that controls could have some areas of asymptomatic enlargement, particularly at common sites of entrapment. However, enlargement at multiple nerve sites would not be expected in controls. It is also worth noting that some sites, such as the ulnar nerve at the elbow and median at the wrist, can have reduced echogenicity even in healthy individuals. This likely explains the high rate of hypoechoic ulnar nerves at the elbow (92%) and median nerves at the wrist (66%) in this study. We included common entrapment sites because these areas are frequently imaged, have the most robust data regarding reference values, and are some of the least technically challenging sites to image. Finally, multifocal nerve enlargement does not only occur in CIDP because it has been reported in other immune-mediated polyneuropathies, sarcoidosis, amyloidosis, leprosy, and even some inherited polyneuropathies, such as hereditary polyneuropathy with predisposition to pressure palsies.[14]

Previous studies have used NMUS to measure the median and ulnar nerves of individuals with CIDP. These studies have shown that subjects with demyelinating polyneuropathies have enlargement of these upper limb nerves compared with axonal polyneuropathies.[15] Nerve size variability, particularly of the median and ulnar nerves, may be characteristic of CIDP.[16,17] This study supports that NMUS may be used as a diagnostic tool for CIDP and its variants. With its ease of use, especially along the median and ulnar nerves, NMUS has the potential to be a clinically useful tool for monitoring disease progression. Additional data are needed to show the prognostic value of NMUS because the relationships between symptom severity, duration of symptoms, treatment type, and ultrasonographic features are unclear. Future studies may reveal these relationships.

Despite the establishment of EFNS/PNS criteria, CIDP remains challenging to diagnose. A focused ultrasound study,

involving only the median and ulnar nerves, is sensitive for the detection of nerve enlargement in CIDP. Therefore, measuring the CSA of the median and ulnar nerves may help establish the diagnosis of CIDP in routine clinical practice.

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