Journal of Neurology (2019) 266:2277–2285
https://doi.org/10.1007/s00415-019-09392-z

ORIGINAL COMMUNICATION

Comparison of high-frequency and ultrahigh-frequency probes in chronic inflammatory demyelinating polyneuropathy

Angela Puma[1,2] · N. Azulay[3] · N. Grecu[1] · C. Suply[1] · E. Panicucci[1] · C. Cambieri[1,4] · L. Villa[1,5] · C. Raffaelli[3] · S. Sacconi[1,6]

Received: 26 March 2019 / Revised: 17 May 2019 / Accepted: 20 May 2019 / Published online: 7 June 2019
© Springer-Verlag GmbH Germany, part of Springer Nature 2019

Abstract

Objectives High-frequency ultrasound (HFUS 18–20 MHz) performed on patients with chronic inflammatory demyelinating polyneuropathy (CIDP) shows a focal enlargement, particularly in the proximal segments of upper-arm motor nerves. Ultrahigh frequency ultrasound (UHFUS 30–70 MHz), having a higher spatial resolution, enables a better characterization of nerve structures. The aim of this study was to compare the two ultrasound probes in the evaluation of motor nerve characteristics in CIDP patients.

Methods Eleven patients with definite or probable CIDP underwent an ultrasound evaluation of median and ulnar nerves, bilaterally. Nerve and fascicle cross-sectional area (CSA), vascularization, and echogenicity were assessed.

Results Nerve and fascicle CSA were increased in the proximal segments, especially in the median nerve, in 9/11 patients and in 10/11 patients at the HFUS and UHFUS evaluations, respectively. A statistically significant difference between CSA values obtained with the two probes was found only for fascicle values. UHFUS allowed for a more precise estimation of fascicle size and number than the HFUS. We were able to identify nerve vascularization in 4/11 patients at UHFUS only.

Conclusion UHFUS gives more detailed information on the changes in the internal nerve structure in CIDP patients. In particular, it permits to better characterize fascicle size and morphology, and to have a precise estimation of their number. Its frequency range also allows to evaluate nerve vascularization.

Significance Ultrasound evaluation could become an adjunctive diagnostic tool for CIDP. Further studies are needed to validate the examined parameters as biomarkers for the evaluation and follow-up of CIDP patients.

Keywords CIDP · Ultrasound · CSA · Nerve · Fascicle · Vascularization

Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an immune-mediated demyelinating neuropathy [1]. The diagnosis is based on clinical and electrophysiological criteria and, when necessary, supportive criteria, such as albumino-cytologic dissociation in the cerebrospinal fluid (CSF), hypertrophy and/or gadolinium enhancement of nerve roots or plexuses at the MRI and, ultimately, nerve biopsy [2, 3]. However, the diagnosis is sometimes not straightforward to perform. To this end, in recent years, nerve ultrasound (US) assessment has been increasingly used in centers of expertise. Evaluation using a transducer with a frequency between 15 and 20 MHz (high-frequency ultrasound—HFUS) is a common practice to diagnose dysimmune neuropathies [4–8]. HFUS shows a non-homogeneous nerve enlargement, especially in proximal median

✉ Angela Puma
puma.ar@chu-nice.fr

1 Peripheral Nervous System, Muscle and ALS Department, CHU Nice, Université Côte D'Azur, Nice, France

2 UMR7370 CNRS, LP2M, Labex ICST, Faculty of Medicine, Université Nice Côte d'Azur, Nice, France

3 Ultrasound Department, CHU Nice, Université Côte d'Azur, Nice, France

4 Department of Human Neuroscience, Centre of Rare Neuromuscular Diseases, Sapienza University of Rome, Rome, Italy

5 Pathology Department, CHU Nice, Université Côte d'Azur, Nice, France

6 Institute for Research on Cancer and Aging of Nice (IRCAN), INSERM U1081, CNRS UMR 7284, Faculty of Medicine, Université Côte d'Azur (UCA), Nice, France

nerve segments and the brachial plexus [9–11] and variable echogenicity patterns depending on the stage of the disease [8, 12]. More recently, a US probe equipped with a transducer operating at an upper frequency from 50 to 70 MHz has been approved for human use by the United States Food and Drug Administration. Earlier studies have shown that this probe allows for a better identification of nerve fascicles in the median nerve at wrist level [13], thus possibly providing detailed information on the structure and possible alterations of diseased peripheral nerves. We compared the results obtained with two transducers, a HFUS (18–20 MHz) and an ultra-high frequency US (UHFUS 30–70 MHz) one, to assess whether there are substantial differences in upper limb nerve evaluation in a cohort of definite or probable CIDP patients.

Methods

Patients

Patients were recruited from the Peripheral Nervous System and Muscle Centre of the Nice University Hospital. The only inclusion criterion was a diagnosis of definite or probable CIDP as per the European Federation of Neurological Societies/Peripheral Nerve Society's (EFSN/PNS) diagnostic criteria [2]. Patients having concomitant diseases implicated in the pathogenesis of CIDP (e.g., diabetes mellitus, dysglobulinemia) were excluded. We selected 11 consecutive patients presenting to our department in a 4-week interval from June to July 2018 and fulfilling the inclusion and exclusion criteria. All patients had been receiving immunomodulatory treatment with intravenous immunoglobulins for at least 3 months prior to study commencement. None had received other prior treatment for their CIDP (e.g., corticosteroids, immune suppressors, plasma exchange). Electroneuromyography (ENMG) (Keypoint, Medtronic) was performed on all patients between 1 and 3 months prior to the US as part of our follow-up protocol.

Ultrasound assessment

Ultrasound evaluations of peripheral nerves were performed on each patient both with a high-resolution probe (18–20 MHz, Acuson S3000, Siemens, Erlangen, Germany) and an ultrahigh-resolution probe (50–70 MHz, Vevo, VD, Visualtronics, Toronto, Canada). The median nerve (MN) and ulnar nerve (UN) were screened from wrist to midforearm and in the distal arm segment. The probes were adjusted to be perpendicular to the nerves, no pressure was applied, and neutral position was adopted for each member, except for the examination of the ulnar nerve at elbow which was performed with the elbow flexed at 90°. The nerve ultrasound examination was performed bilaterally and with both probes in one session by the same rater, who was blinded to the clinical and electrophysiological data of all patients. The protocol took in total between 40 and 60 min for each patient.

CSA for the MN was measured at 5 cm (cm) from the distal wrist crease and, on the medial side of the upper arm, 5 cm proximal to the elbow crease. CSA for the UN was measured at 6 cm from the pisiform bone and at 7 cm proximal to the medial epicondyle. We used reference values previously published by other authors. We considered nerve CSA values as abnormal if greater than the upper limit for axonal neuropathies as described by Goedee et al. [14]. For fascicle CSA, the values were considered abnormal if they were equal to or greater than those proposed by Grimm et al. for patients with acquired demyelinating neuropathy [15].

The predetermined measurement sites and the cutoff values for abnormality are shown in Table 1.

Nerve CSA assessment was performed on transversal images using the manual tracing method by placing the cursor inside the hyperechoic rim of the nerves. Depth function was not standardized but adjusted individually depending on nerve anatomy at the site of examination and patient characteristics (amount of subcutaneous tissue) so as to permit the viewing of the nerve in its entirety on transversal sections; for the UHF probe, depth could not exceed 15 mm, due to technical limitations. The zoom function was not used during acquisition of images, but could have been used afterwards to facilitate measurements after the examination, and only if the nerve appeared too small on the device screen.

Fascicle identification, counting and CSA measurement were performed on the same transversal images used for nerve CSA measurement. Fascicles were defined as hypoechoic ovoid-shaped areas surrounded by hyperechoic rims within the nerve and CSA measurement was performed with the cursor placed inside of this hyperechoic margin, in a similar fashion to nerve CSA measurement. The largest fascicle CSA was used for statistical analysis.

Nerve echogenicity was evaluated by means of a visual method. Nerves were defined as mainly hypoechoic if the fascicular echogenicity was similar to the lumen of blood vessels (e.g., the radial artery), and as hyperechoic if the grayscale was comparable to lymph node echotexture. Echogenicity alterations associated with low CSA values were not considered. For the assessment of fascicle echogenicity, we used a classification previously proposed by Padua et al. [8], who described three patterns using US probes of up to 18 MHz: class 1—enlarged nerves with hypoechoic fascicles; class 2—enlarged nerves with hypo/hyperechoic fascicles; class 3—normal nerve CSA with fascicle dedifferentiation. Class 1 (early stage) is associated with acute edema and inflammation, whereas class 3 (end stage) refers to chronic and predominantly axonal damage.

Table 1 US examination protocol and CSA cut-off values

	Site of measurement	Abnormal nerve CSA cut-off value (mm^2)[a]	Abnormal fascicle CSA cut-off value (mm^2)[b]
Median nerve	Distal site 5 cm proximal to wrist crease	> 21	≥ 8.1
	Proximal site 5 cm proximal to elbow crease	> 13	≥ 16.7
Ulnar nerve	Distal site 6 cm proximal to pisiform bone	> 17	≥ 7.5
	Proximal site 7 cm proximal to medial epicondyle	> 11	≥ 10.7

[a]Values taken from Goedee et al. [14]; for the median nerve, axonal "carpal tunnel" and "upper arm" values were used for distal and proximal sites, respectively; for the ulnar nerve, axonal "distal sulcus" and "upper arm" values were used for distal and proximal sites, respectively

[b]Values taken from Grimm et al. [15]; for the median nerve, multifocal motor neuropathy "forearm" and "upper arm" values were used for distal and proximal sites, respectively; for the ulnar nerve, multifocal motor neuropathy "forearm" and "upper arm" values were used for distal and proximal sites, respectively

All assessments of nerve and fascicle CSA, fascicle count, and echogenicity were done qualitatively by the radiologist performing the examination and by a neurologist experienced in nerve ultrasound. A qualitative method was chosen for the examinations as we did not possess a specific software for the UHF probe.

Doppler sonography was used for the assessment of nerve vascularization.

Acquisition was performed at 90° to skin surface and no steer was applied. Dynamic range of both devices was 65 dB and only concerned the B-mode acquisition. Comparatively to the HF US probe, for the UHF Doppler examination we used an inferior scale (4.8 cm/s for UHF, 8 cm/s for HF) and a higher global gain (38 dB for UHF, 30 dB for HF), to comply with the higher frequency (40 MHz for UHF, 6.25 MHz for HF) of the Doppler mode. There was no difference concerning Doppler settings comparatively to its use for non-nerve tissues using these probes.

Statistical analysis

For statistical analysis, IBM SPSS Statistics, version 20 (Chicago, IL, USA) was used. Because the distribution of values was normal, Student's *t* test was used for means comparisons between both US probes. The level of statistical significance was set as $p < 0.01$.

Results

Patients

Eleven patients (eight men and three women, mean age 64.09 years, range 38–76 years) with definite or probable CIDP were included in the present study. Their demographical and clinical data are summarized in Table 2.

Ultrasound assessment and measurements

Nerve CSA was increased in at least one of the examined segments in 10/11 (90.9%) patients at the UHFUS and in 9/11 (81.8%) patients at the HFUS. This increase was found mostly in the proximal median nerve segment. No statistically significant difference was found in the absolute or mean CSA values obtained with the two transducers, although CSA values appeared to be higher with the UHF probe; mean nerve CSA values are summarized in Table 3. Fascicle CSA was increased in 1/11 (9%) patients using the UHF probe, while such a change was found in 5/11 (45.4%) patients using the HF probe, a difference which was statistically significant. Similarly to nerve CSA, higher fascicle CSA values were obtained in the proximal segments and with the HFUS probe, but more so in the ulnar nerve. We found a statistically significant difference between the mean size values of the fascicles obtained with the two probes, with greater values obtained using the HF probe ($p < 0.01$); mean fascicle CSA values are summarized in Table 3. We observed an increase in fascicle CSA without a corresponding increase in nerve CSA in three patients using the HF transducer (ulnar nerve in the distal arm segment for patients 1, 7 and 10), whereas only patient 10 had similar changes at the UHFUS.

The number of fascicles displayed with the UHF probe was statistically higher than that displayed using the HF probe ($p < 0.01$) (Table 4). We also found a gradient with respect to fascicle number, with higher values in the distal segments (Table 4 and Fig. 1).

Table 2 Patient characteristics

Patient no.	Gender	Age (years)	CIDP category	Disease duration (years)	Treatment duration (months)
1	M	68	Definite	2	3
2	M	65	Probable	3	1
3	M	60	Definite	8	2
4	F	69	Definite	7	4
5	F	38	Definite	1	2
6	M	76	Definite	2	1
7	M	75	Probable	1	9
8	M	53	Definite	5	9
9	F	66	Definite	31	36
10	M	63	Probable	2	10
11	M	72	Probable	3	9

M male, *F* female

The echogenicity of the nerve was assessed with a focus on areas of nerve enlargement. Using the UHF probe, six patients were classified as class 1, four patients as class 2 and one patient as class 3 (Fig. 2). No difference in echogenicity was found between examination with the two probes in all but three patients (patients 2, 6 and 9) in whom the nerves appeared more hyperechoic with the HF probe. Furthermore, in these patients the UHF probe enabled to better identify the fascicles, some of which kept a hypoechoic aspect (Fig. 2).

On Doppler examination, we found epineural/endoneural vascularization in 5/11 (45.4%) patients (patients 1, 2, 3, 5 and 6) using only the UHFUS (Fig. 3).

Discussion

The available literature data suggest that upper limb nerve enlargement, as evidenced by ultrasonography, occurs in 90% of CIDP patients, either treated or not; however, with long duration of disease, these changes tend to disappear [10]. Structural nerve changes are less well characterized, and one may find discordant information in the literature. In our cohort, we found focal increases in nerve diameter, particularly in the proximal segments of the median nerve, in 10/11 (90.9%) and in 9/11 (81.8%) patients using the UHFUS and HFUS probes, respectively. We did not find any increase in nerve CSA in patient 9; this may be due to either the limited nerve segment we explored, or to the patient's longstanding disease at the moment of the evaluation (31 years) versus the rest of the examined patients (between 1 and 8 years' disease duration).

Overall, nerve CSA values obtained with the UHF transducer were higher than those obtained with the standard probe (Table 3). Studies on ulnar and median nerve anatomy have already shown that nerve CSA is indeed greater in biopsy specimens [16, 17] compared to the values obtained through HFUS [7, 14, 18, 19], mainly because echography is less sensitive in detecting epineural edges compared to the optical microscope [20]. The resolution offered by the UHFUS, which is three to five times higher than that of the standard US probe [21], allows for a better identification of the hypoechoic margin of the nerves and thus probably accounts for the values we obtained in our study. Literature data are relatively scarce with respect to the fascicle size in neuropathies, and the available studies were done using the standard probe. Interestingly, in our study we found a statistically significant difference between the number of patients with fascicle CSA increase between the two probes. The highest values were found with the HF probe. Furthermore, we found segments of increased fascicle CSA without corresponding nerve CSA increase in three patients using the HF probe; all patients had such changes in the distal arm segment of the ulnar nerve. Of the three identified patients, only one had similar changes when examined with the UHF probe. These findings are probably related to the fact that this is a segment in which the ulnar nerve is subject to frequent, albeit minor, trauma.

We found overall fascicle CSA values obtained at the UHFUS to be lower than those obtained at the HFUS. While for statistical analysis we only used the largest fascicle CSA, overall impression for the examiner was that this was a general finding. Furthermore, we were able to identify focal fascicular swelling on nerve longitudinal sections, which in our opinion was an expression of focal fascicular inflammation (Fig. 4). The fascicle CSA values obtained with the UHF probe are lower than those reported by Grimm et al. [15] for inflammatory neuropathies, who performed the examinations with a HF probe. This is probably related to the fact that the UHFUS allows for a more detailed analysis of nerve fascicles, thus providing data more consistent with those

Table 3 Mean nerve and fascicle cross-sectional area values of the median and ulnar nerve

	MN-FOREARM				MN-ARM				UN-FOREARM				UN-ARM			
	N-CSA		F-CSA		N-CSA		F-CSA		N-CSA		F-CSA		N-CSA		F-CSA	
	R	L	R	L*	R	L	R*	L*	R	L	R*	L*	R	L	R*	L*
HFUS	15.7 [9.3]	12.7 [6.7]	1 [0.6]	2.1 [2.2]	18.6 [11.2]	14.1 [9.3]	2.7 [1.8]	3.4 [2.5]	8.7 [5.5]	7.4 [2.2]	1.2 [1]	1.4 [0.7]	12.7 [6.5]	11.1 [2.8]	2.5 [1.3]	1.9 [1.1]
UHFUS	16.3 [7.8]	14,9 [5.5]	0,4 [0.3]	0,6 [0.3]	21.9 [14.5]	20.3 [10.5]	1.1 [0.9]	1.2 [0.8]	9.4 [6.6]	9 [4.1]	0.4 [0.3]	0.6 [0.5]	13.6 [5.3]	12.6 [2.6]	1.1 [1.2]	1 [0.7]

Numbers in brackets represent standard deviation

HFUS high-frequency ultra sound, *UHFUS* ultrahigh-frequency ultra sound, *MN* median nerve, *UN* ulnar nerve, *N-CSA* nerve cross-sectional area, *F-CSA* fascicle cross-sectional area, *R* right, *L* left

*Statistical significance ($p < 0.01$) between CSA values obtained with the two probes at the same site

proposed by different anatomical studies [16, 21], while the mean fascicle size obtained with the standard probe is probably the sum of several indistinguishable fascicles [22]. Therefore, we propose that even though our fascicle CSA values were lower than those reported they are still to be considered as pathologic, and possibly more accurate. The fascicular diameter did not correlate with location or nerve size, but was inversely proportional to the fascicle count, which is in accordance with the anatomical studies [16].

Furthermore, we found a statistically significant difference between the number of fascicles obtained with the two probes (Table 4), with a greater number of fascicles being identified with the UHF probe. This is probably due to the greater frequency of the UHF transducer which offered better resolution images. For the UHFUS evaluation, the fascicle count was higher in the forearm compared to the arm with a total fascicle number close to the reference values provided by anatomy studies (Fig. 1) [16].

Regarding the nerve echogenicity, three patterns have been described thus far: (i) hypoechogenic nerves, associated with nerve enlargement as an expression of focal edematous inflammation of the nerve; (ii) intermediate forms, characterized by swollen hyperechoic and hypoechoic fascicles; (iii) hyperechogenic nerves, associated with nerve atrophy and nerve degeneration, which are found mainly in the advanced stages of the disease [9, 23–26]. In our study, we found a predominantly intermediate pattern of echogenicity with both probes, which was probably related to both the disease duration in most patients and their undergoing an intravenous immunoglobulin treatment [22]. The only patient in whom we found a frank hyperechoic pattern with both probes was the only one with a long disease history (> 31 years); nerve CSA in this patient was within normal values in all examined nerve segments. The hyperechoic aspect is probably due to the accumulation of amorphous substances in the endoneurium [27], suggesting fibrosis; it has been demonstrated that patients with this type of US aspect respond less well to therapy and have general worse functional prognosis[22, 24]. Our patient is responsive to treatment by intravenous immunoglobulins, but is dependent on it.

The images obtained with the two probes suggest that the UHF probe allows for a better nerve echogenicity visualization. Even when the nerve assumes a more hyperechoic aspect compared to the evaluation with the classical probe, the UHF probe still allows for recognition of fascicles and to distinguish those that are hypoechoic. As the hyperechoic aspect is predominantly associated with nerve fibrosis, that fact that we were able to identify hypoechoic fascicles may mean that inflammation still plays a major role even if there is associated fibrosis; we concede, however, that the hypoechoic aspect of the fascicles in the hyperechoic nerves may only be due to the contrast difference as a result of the

Table 4 Mean fascicle number

	MN-FOREARM		MN-ARM		UN-FOREARM		UN-ARM	
	R*	L*	R*	L*	R*	L*	R*	L*
HFUS	8.4 [3.6]	5.4 [2.8]	4.4 [1.4]	4.4 [1.4]	4.5 [2.6]	3.9 [1.1]	4.2 [1]	4 [1.2]
UHFUS	20.4 [7.2]	22.4 [10.4]	12.1 [4.3]	10.8 [4.7]	13.9 [7.3]	11.5 [1.9]	9.9 [2.8]	9.5 [2.4]

Numbers in brackets represent standard deviation

HFUS high-frequency ultra sound, *UHFUS* ultrahigh-frequency ultra sound, *MN* median nerve, *UN* ulnar nerve, *R* right, *L* left

*Statistical significance ($p < 0.01$) between number values obtained with the two probes at the same site

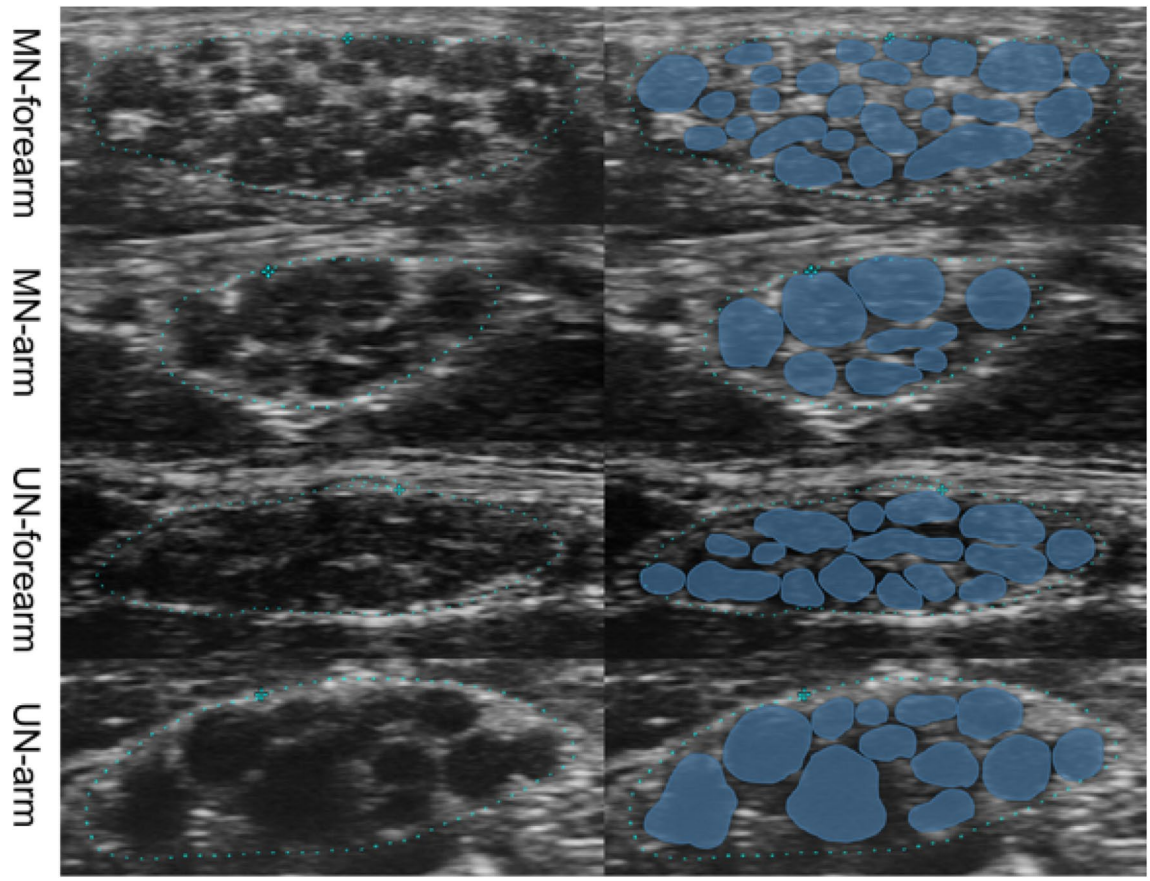

Fig. 1 Fascicle number evaluation on nerve cross sections at UHF probe evaluation, with distal–proximal gradient. Images on the right side have the fascicles highlighted. *MN* median nerve, *UN* ulnar nerve

increased hyperechogenicity of the interstitial tissue or to the better identification of additional hypoechoic fascicles with the UHF probe. If the hypoechoic aspect is proved to be a consequence of inflammation, this may aid in the therapeutic decision-making, even possibly supporting the use of combined therapies or second-line treatments.

Finally, the UHFUS also appears to be a valuable tool for visualizing peri- and endoneural vascularization. Various studies, performed with the HF probe, have already described the identification of the nerve vascularization in relation to nerve inflammation [28]. We were able to identify the vasa nervorum using a standard, non-contrast-enhanced, Doppler technique in 5 of the 11 patients and only with the UHF probe. All five patients had been receiving treatment for a short period of time (less than 3 months) at the time of US evaluation. Taking into account that the remaining six patients had been receiving treatment for longer periods of time, this could imply that the immunomodulatory treatment leads to a reduction in inflammation. It would be interesting to verify this hypothesis by studying the nerve vascularization in inflammatory neuropathy patients at the time of diagnosis and as a follow-up investigation at preset intervals

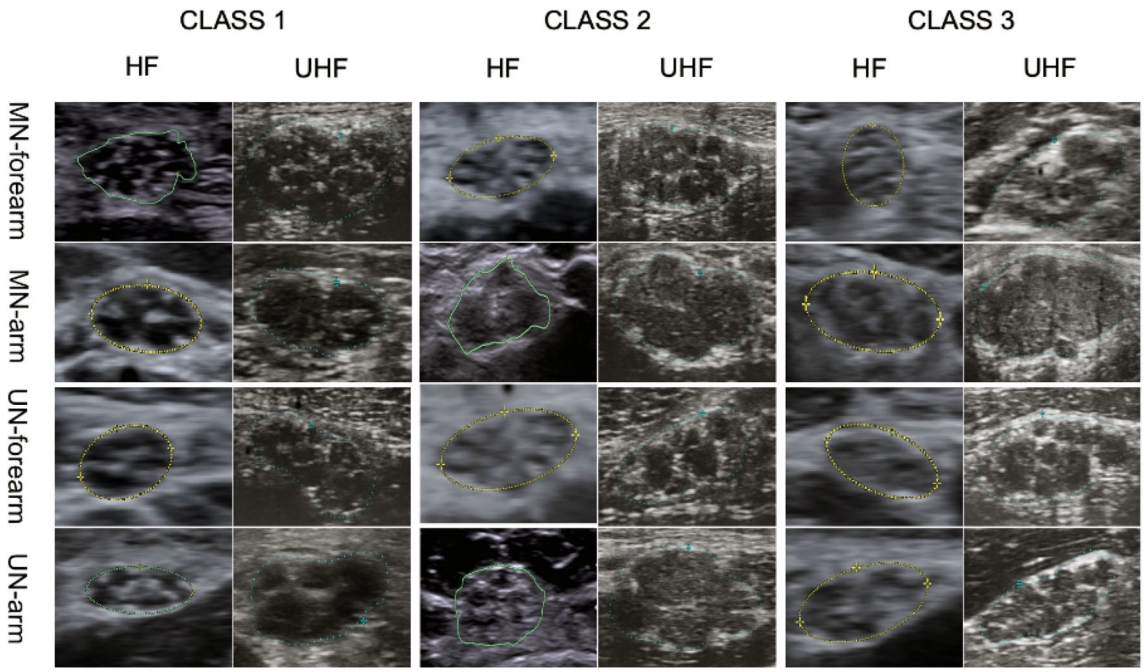

Fig. 2 Patterns of nerve echogenicity. *HF* high-frequency probe, *UHF* ultrahigh-frequency probe, *MN* median nerve, *UN* ulnar nerve

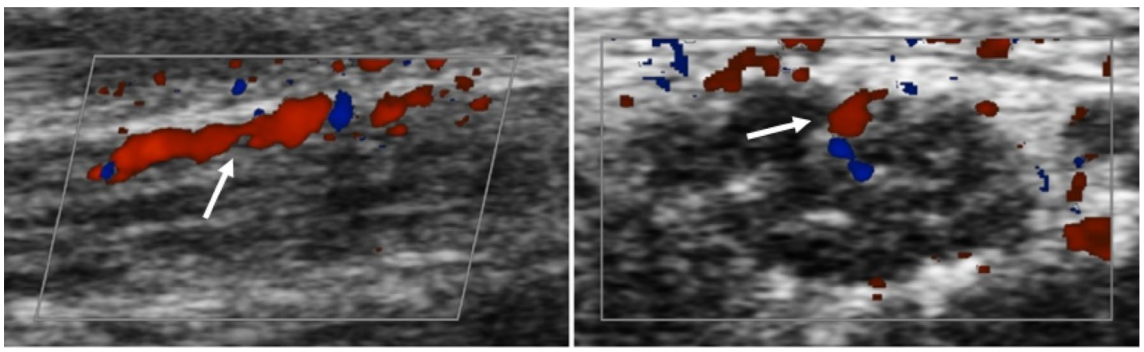

Fig. 3 Nerve vascularization. Image on the left shows the nerve in longitudinal section; image on the right shows nerve in transverse section; vasa nervorum highlighted by arrow

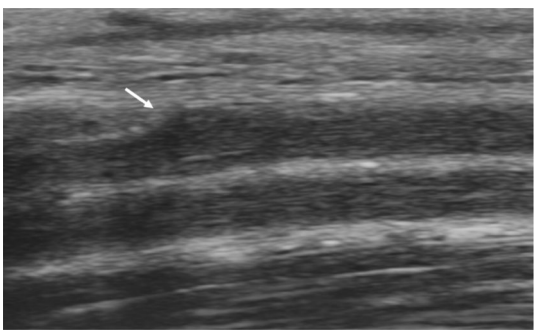

Fig. 4 Focal fascicle enlargement in nerve transversal section

of time to assess response to therapy, as it has recently been shown that other parameters such as changes in echogenicity detected by HF probe are not useful for the follow-up of CIDP because they lack sensitivity in detecting significant changes in the internal structure of the nerve, unless they are performed over a period of 10–20 years [22]. Contrast enhancement could increase the procedure sensibility. It would also be of use to conduct a trial to validate vascularization examination as a biomarker for CIDP relapse in relapsing forms of the disease.

From a technical point of view, the HF probe allowed for an assessment of the nerve from the wrist up to the

axilla, for both the MN and the UN. On the other hand, using the UHF probe, we were unable to examine the MN in the proximal thirds of the forearm and arm; for the UN, the examination was not possible in the proximal half of the forearm and arm. This is due to the difference in frequency range between the two transducers.

This study presents several limitations. With regard to the studied population, we acknowledge that the limited number of CIDP patients, their clinical heterogeneity, their rather advanced age and the fact that they had all been receiving treatment with intravenous immunoglobulins may limit the possibility to draw general conclusions regarding the ultrasonographic changes in this population. Furthermore, the lack of a control group raises the necessity of conducting a comparative study to strengthen our findings.

Because of the characteristics of the UHF probe, and mainly due to its lower tissue penetration, even though the values we obtained for nerve and fascicle CSA approach those reported in anatomical studies, it is necessary to conduct further studies to standardize reference values. While our examination protocol somewhat differed from the ones used in the studies cited for reference values, we feel that the approximations regarding measurement sites do not significantly influence the results, especially when referring to fascicle CSA values. However, we believe that having used more proximal sites than those in the referred literature permitted us to exclude possible nerve alterations secondary to compression at anatomical entrapment points, which would have influenced mainly nerve CSA values.

Conclusions

UHF ultrasound provides detailed information on the internal structure of the nerve. Internal morphology, including fascicle size and count, echogenicity and epineural/endoneural vascularization are better visualized with this probe, compared to the traditional HF probe. However, the drawbacks of the 30–70 MHz probe are the lack of availability and the limited capacity to explore deep structures, thus not allowing for proximal nerve segment examination. Even if the UHF probe will probably not replace the HF one as a tool in the daily clinical practice, it could provide additional information, with respect primarily to nerve vascularization as a possible marker for inflammation. The better characterization of the examined parameters opens up new avenues for further research in the understanding of CIDP physiopathology, disease staging and therapeutic strategy selection. Further longitudinal studies on larger CIDP patient cohorts are needed to confirm these findings.

Compliance with ethical standards

Conflicts of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical standards The study protocol was in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration.

References

1. Mathey EK, Park SB, Hughes RAC et al (2015) Chronic inflammatory demyelinating polyradiculoneuropathy: from pathology to phenotype. J Neurol Neurosurg Psychiatry 86:973–985. https://doi.org/10.1136/jnnp-2014-309697
2. Joint Task Force of the EFNS and the PNS (2010) European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society-First Revision. J Peripher Nerv Syst JPNS 15:1–9. https://doi.org/10.1111/j.1529-8027.2010.00245.x
3. Van den Bergh PYK, Hadden RDM, Bouche P et al (2010) European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society—first revision. Eur J Neurol 17:356–363. https://doi.org/10.1111/j.1468-1331.2009.02930.x
4. Di Pasquale A, Morino S, Loreti S et al (2015) Peripheral nerve ultrasound changes in CIDP and correlations with nerve conduction velocity. Neurology 84:803–809. https://doi.org/10.1212/WNL.0000000000001291
5. Kerasnoudis A, Pitarokoili K, Behrendt V et al (2015) Correlation of nerve ultrasound, electrophysiological and clinical findings in chronic inflammatory demyelinating polyneuropathy. J Neuroimaging 25:207–216. https://doi.org/10.1111/jon.12079
6. Pitarokoili K, Schlamann M, Kerasnoudis A et al (2015) Comparison of clinical, electrophysiological, sonographic and MRI features in CIDP. J Neurol Sci 357:198–203. https://doi.org/10.1016/j.jns.2015.07.030
7. Jang JH, Cho CS, Yang K-S et al (2014) Pattern analysis of nerve enlargement using ultrasonography in chronic inflammatory demyelinating polyneuropathy. Clin Neurophysiol 125:1893–1899. https://doi.org/10.1016/j.clinph.2013.12.115
8. Padua L, Granata G, Sabatelli M et al (2014) Heterogeneity of root and nerve ultrasound pattern in CIDP patients. Clin Neurophysiol 125:160–165. https://doi.org/10.1016/j.clinph.2013.07.023
9. Grimm A, Schubert V, Axer H, Ziemann U (2017) Giant nerves in chronic inflammatory polyradiculoneuropathy. Muscle Nerve 55:285–289. https://doi.org/10.1002/mus.25272
10. Décard BF, Pham M, Grimm A (2018) Ultrasound and MRI of nerves for monitoring disease activity and treatment effects in chronic dysimmune neuropathies—current concepts and future directions. Clin Neurophysiol 129:155–167. https://doi.org/10.1016/j.clinph.2017.10.028
11. Goedee HS, Brekelmans GJF, van Asseldonk JTH et al (2013) High resolution sonography in the evaluation of the peripheral nervous system in polyneuropathy—a review of the literature. Eur J Neurol 20:1342–1351. https://doi.org/10.1111/ene.12182
12. Fisse AL, Pitarokoili K, Motte J et al (2019) Nerve echogenicity and intranerve CSA variability in high-resolution nerve ultrasound (HRUS) in chronic inflammatory demyelinating polyneuropathy

(CIDP). J Neurol 266:468–475. https://doi.org/10.1007/s00415-018-9158-3
13. Cartwright MS, Baute V, Caress JB, Walker FO (2017) Ultrahigh-frequency ultrasound of fascicles in the median nerve at the wrist. Muscle Nerve 56:819–822. https://doi.org/10.1002/mus.25617
14. Goedee HS, van der Pol WL, van Asseldonk J-TH et al (2017) Diagnostic value of sonography in treatment-naive chronic inflammatory neuropathies. Neurology 88:143–151. https://doi.org/10.1212/WNL.0000000000003483
15. Grimm A, Winter N, Rattay TW et al (2017) A look inside the nerve - Morphology of nerve fascicles in healthy controls and patients with polyneuropathy. Clin Neurophysiol 128:2521–2526. https://doi.org/10.1016/j.clinph.2017.08.022
16. Brill NA, Tyler DJ (2017) Quantification of human upper extremity nerves and fascicular anatomy: upper extremity fascicular anatomy. Muscle Nerve 56:463–471. https://doi.org/10.1002/mus.25534
17. Chang KS, Low WD, Chan ST et al (1963) Enlargement of the ulnar nerve behind the medial epicondyle. Anat Rec 145:149–155
18. Scheidl E, Böhm J, Simó M et al (2014) Different patterns of nerve enlargement in polyneuropathy subtypes as detected by ultrasonography. Ultrasound Med Biol 40:1138–1145. https://doi.org/10.1016/j.ultrasmedbio.2013.12.020
19. Grimm A, Heiling B, Schumacher U et al (2014) Ultrasound differentiation of axonal and demyelinating neuropathies. Muscle Nerve 50:976–983. https://doi.org/10.1002/mus.24238
20. Thoirs K, Scutter S, Wilkinson M (2003) The ulnar nerve at the elbow: an anatomic, sonographic, and histology comparison. J Diagn Med Sonogr 19:16–23. https://doi.org/10.1177/8756479302239546
21. Sunderland S (1945) The intraneural topography of the radial, median and ulnar nerves. Brain J Neurol 68:243–299
22. Fisse AL, Pitarokoili K, Motte J et al (2018) Nerve echogenicity and intranerve CSA variability in high-resolution nerve ultrasound (HRUS) in chronic inflammatory demyelinating polyneuropathy (CIDP). J Neurol. https://doi.org/10.1007/s00415-018-9158-3
23. Kerasnoudis A, Pitarokoili K, Gold R, Yoon M-S (2015) Nerve ultrasound and electrophysiology for therapy monitoring in chronic inflammatory demyelinating polyneuropathy. J Neuroimaging 25:931–939. https://doi.org/10.1111/jon.12279
24. Härtig F, Ross M, Dammeier NM et al (2018) Nerve ultrasound predicts treatment response in chronic inflammatory demyelinating polyradiculoneuropathy—a prospective follow-Up. Neurother J Am Soc Exp Neurother 15:439–451. https://doi.org/10.1007/s13311-018-0609-4
25. Grimm A, Vittore D, Schubert V et al (2016) Ultrasound pattern sum score, homogeneity score and regional nerve enlargement index for differentiation of demyelinating inflammatory and hereditary neuropathies. Clin Neurophysiol 127:2618–2624. https://doi.org/10.1016/j.clinph.2016.04.009
26. Grimm A, Rattay TW, Winter N, Axer H (2017) Peripheral nerve ultrasound scoring systems: benchmarking and comparative analysis. J Neurol 264:243–253. https://doi.org/10.1007/s00415-016-8305-y
27. Matsuda M, Ikeda S, Sakurai S et al (1996) Hypertrophic neuritis due to chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): a postmortem pathological study. Muscle Nerve 19:163–169. https://doi.org/10.1002/(SICI)1097-4598(199602)19:2%3c163:AID-MUS6%3e3.0.CO;2-C
28. Goedee HS, Brekelmans GJF, Visser LH (2014) Multifocal enlargement and increased vascularization of peripheral nerves detected by sonography in CIDP: a pilot study. Clin Neurophysiol 125:154–159. https://doi.org/10.1016/j.clinph.2013.05.025