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Review

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The Diagnostic Role of Neuromuscular Ultrasound in Chronic Inflammatory Demyelinating Polyneuropathy

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ABSTRACT

The immune-neuropathies are a heterogenous group of peripheral nerve disorders. Their diagnostic classification is mainly based on the documentation of the distribution pattern of peripheral nerve impairment and the results of nerve conduction studies.

Nerve conduction studies remain nowadays fundamental not only for the diagnosis of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), but also for the follow-up and measurement of response to immune-treatment. The challenge though of acquiring the best static and dynamic image of the relevant nerve structures, led to the development of high frequency ultrasound technology. Neuromuscular ultrasound has been able to detect thickened or swollen roots, peripheral nerves or plexus, findings that are consistent with ongoing inflammation, especially in cases of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Similar findings have been described also in other immune-mediated neuropathies such as Guillain–Barré Syndrome (GBS), Multifocal Motor Neuropathy (MMN) and Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM).

This review provides a timely update on the ultrasound findings of chronic inflammatory demyelinating polyneuropathy.

INTRODUCTION

Vascular ultrasound has gained a key role in the diagnostics of vascular lesions of the central nervous system. The recent development of high frequency ultrasonography (> 12MHz) provided the neurologist with a valuable tool to study peripheral nerve structures in detail.

The first pathological ultrasound findings on peripheral nerve structures have been published in 1985 by Solbiati et al.[1] On the other hand, Fornage and Rifkin reported for the first time the pathological findings of carpal tunnel syndrome.[2] Immune-mediated neuropathies are a heterogenous group of disorders, with a frequency of 13% on consecutive patients with neuropathy seen at neuromuscular reference centres.[3] The diagnosis and classification is based, in typical cases, on the time course, distribution pattern of nerve impairment (predominant involvement of motor/sensory fibers or/and autonomic nerve system), and paraclinical parameters [such as nerve conductions studies and serum antibodies]. On cases, with a typical clinical presentation, an extended diagnostic work-up, including cerebrospinal fluid examination, nerve conductions studies, sural nerve biopsy, laboratory testing, may be needed.

The role of neuromuscular ultrasound in the diagnostic workup of CIDP remains in the literature less well defined and parallels the beginning of research on entrapment neuropathies. Only a few studies in the literature have used ultrasound to examine the pathological changes

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in immune-mediated neuropathies and their correlation with the clinical and electrophysiological findings. The already published case reports/series provide the scientific society with the hope of using neuromuscular ultrasound as a helpful tool in addition to nerve conduction studies and clinical examination for the classification of immune-mediated neuropathies.

In this manuscript we provide a timely update on the pathological ultrasound findings of CIDP.

QUANTIFICATION OF ULTRASOUND FINDINGS

Cross Sectional Area (CSA) reference values for peripheral nerves and brachial plexus have been reported in various studies in the literature.[4,5] The difficulty to differentiate a normal from a pathological heterogeneity of cross sectional area changes in peripheral nerves, especially in the case of immune-mediated neuropathies, remains an important limitation of neuromuscular ultrasound in clinical practice.

Four novel ultrasound measures, aiming to quantify pathological ultrasound changes of peripheral nerves, have been recently introduced from Padua et al.[6] 1) the intranerve cross sectional area variability (for each nerve), defined as maximal cross sectional area/minimal cross sectional area and 2) the internerve cross sectional area variability (for each patient), defined as nerve with maximal intranerve cross sectional area variability/nerve with minimal intranerve cross sectional area variability. In addition, our study group introduced two other ultrasound measures: 3) the Side to Side Difference ratio of the Intranerve cross sectional area Variability (SSDIVA) (for each nerve), defined as side with maximal intranerve cross sectional area variability/side with minimal intranerve cross sectional area variability,[7] 4) the intraplexus cross sectional area variability, defined as maximal cross sectional area/minimal cross sectional area of brachial plexus.[5]

Using the intranerve cross sectional area variability the sonographer may differentiate in immune-mediated neuropathies focal (higher values) from diffuse (lower values) peripheral nerve or brachial plexus enlargement, while the internerve cross sectional area variability may reveal possible distribution patterns of peripheral nerve impairment.[5-7] On the other hand the side to side difference ratio of the intranerve cross sectional area variability may be useful in detecting any lateralization of pathological changes and the intraplexus cross sectional area variability in differentiating focal (higher values) from diffuse (lower values) brachial plexus enlargement.[5,7]

ULTRASOUND FINDINGS IN CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

The Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is an acquired immune-mediated inflammatory disorder of the peripheral nerve system. Its estimated prevalence is about 9 per 100,000 adults.[8,9,10] It is clinically characterized by the progressive or relapsing occurrence of symmetrical weakness in both proximal and distal muscles, impaired sensation, absent or diminished tendon reflexes, an elevated cerebrospinal fluid protein level, demyelinating nerve-conduction studies, and signs of demyelination in nerve-biopsy specimens. The most widely used treatments for CIDP consist of intravenous immunoglobulin, plasma exchange, corticosteroids and immunosuppression.

Currently 16 studies (evaluating a total of 155 cases) on nerve sonography in CIDP patients have been published (Table 1). The first description of the sonographic findings of CIDP was published from Taniguchi et al.[11] In this report, the authors documented a brachial plexus hypertrophy on both sides and peripheral nerve hypertrophy at several sites. Similar findings had only been reported in MRI studies until then.[12-14] A possible explanation of this finding could derive from the classical "onion-bulb" histological appearance of the nerves in CIDP, as a result of recurrent episodes of demyelination and remyelination.[15]

After this initial publication, several years passed until the first systematic ultrasound study of CIDP patients was published. In 2004, Matsuoka et al. reported the ultrasound findings of the cervical roots in 13 patients with CIDP and 35 healthy individuals.[16] The authors demonstrated a hypertrophy of the cervical roots in 9 out of 13 patients with CIDP, a finding that seems to correlate with the elevated levels of protein in CSF. Similar findings have been reported in several case reports in the following years.[16-19] In further ultrasound studies of CIDP patients, diffuse nerve enlargements could be demonstrated.[20] These findings seem to correlate with the disease duration, but don't seem to show any significant correlation with functional disability or NCS findings.[21-23]

Another important aspect in the field of sonography in CIDP, is the possible use of this method for identifying nerve conduction blocks. The localization of the nerve conduction block is often difficult to be made in the nerve conduction studies, especially when dealing with proximal parts of the nerves. By overlooking this typical NCS finding of CIDP, a delay in the diagnosis and therefore treatment can occur. In three CIDP cases in the literature, a correlation between the site of hypertrophy detected with ultrasound and the site of conduction block detected with NCS could be demonstrated.[24,25] Although this seems to be a promising development, it is worth noting that Zaidman et al. failed to confirm these findings in a later study.[21] Systematic studies are therefore required to proof the sensitivity and specificity of this finding.

A novel approach to the quantification of the pathological findings in CIDP was recently published from Padua et al.[6] Using two new measures, the intranerve and internerve cross sectional area variability, in a small group of immune-mediated neuropathies, the authors were able to demonstrate

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Authors	Patients (n)	Control group (n)	Median nerve	Ulnar nerve	Radial nerve	Brachial plexus	Fibular nerve	Tibial nerve	Sural nerve
Taniguchi et al. 2000	1	-	X	X	-	-	-	-	-
Matsuoka et al. 2004	13	35	-	-	-	X	-	-	-
Granata et. al. 2009	1	-	X	X	-	-	-	-	-
Imamura et al. 2009	1	-	X	-	-	-	-	-	-
Zaidman et al. 2009	36	90	X	X	-	-	-	-	-
Rajabally et al. 2011	14	14	X	-	-	-	-	-	
Padua et al. 2012	2	63	X	X	-	-	X	-	N
Kerasnoudis et al. 2012a	4	30	X	X	-	-	X	-	-
Kerasnoudis et al. 2012b	1	30	X	X	-	X	X	X	-
Jang et al. 2012	1	-	X	X	-	-	X	X	-
Kerasnoudis et al. 2013a	48	75	X	X	X	X	X	X	X
Kerasnoudis et al. 2013b	34	74	X	X	X	X	X	X	X
Goedee et al, 2013	11	-	X	X	N	-	X	X	-
Jang et al, 2014	10	18	X	X	X	X	X	X	X
Zaidman et al, 2013	55	-	X	X	-	-	X	X	-
Sugimoto et al, 2013	16	-	X	X	-	X	-	-	-

Table 1: Overview of the nerve ultrasound studies on CIDP. Nerves, which were studied and showed pathological ultrasound changes are marked with "X", nerves which showed no pathological changes are marked with "N" and nerves, that were not studied at all are marked with " - ".

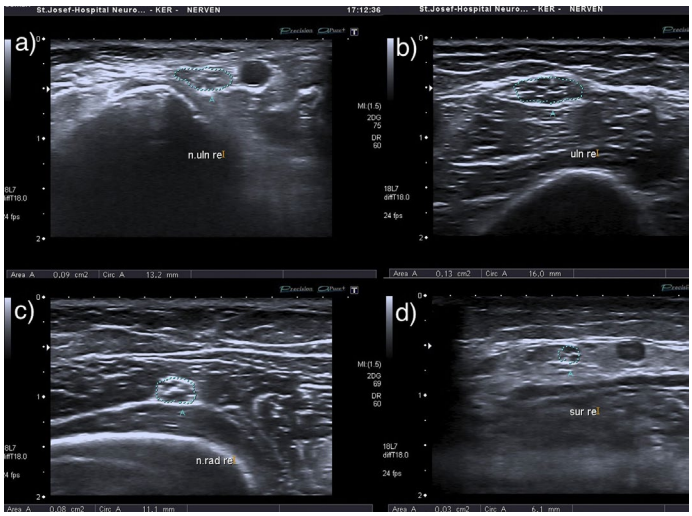

Figure 1: Overview of the "Bochum ultrasound score" for distinguishing CIDP from AIDP. Cross sectional area of the ulnar nerve in Guyon's canal (a), upper-arm (b), of the radial nerve in spiral groove (c) and of the sural nerve between the gastrocnemius muscle (d) in a patient with CIDP. The patient showed in all anatomic sites a pathological cross sectional area enlargement, when compared to controls (5), receiving a maximum sum score of 4 points

that the CIDP shows preferably a diffuse pattern of nerve enlargement (lower values of intranerve cross sectional area variability), when compared to other immune-neuropathies, such as the Multifocal Motor Neuropathy (MMN) (higher values of intranerve cross sectional area variability). These findings have been confirmed in a later study from our ultrasound lab.[26]

Recent reports on ultrasound findings in CIDP have highlighted the differerent patterns of pathological echogenity[27,28] and the increased vascularisation.[29] In addition, nerve ultrasound findings do not seem to correlate with electrophysiological findings or functional disability.[23]

DIFFERENTIATION OF CIDP FROM AIDP USING NEUROMUSCULAR ULTRASOUND

The typical CIDP is characterised by a progressive, symmetric, proximal and distal muscle weakness, paresthesias, sensory dysfunction and impaired balance, which may evolve slowly over at least 2 months.[29,30] Although CIDP symptoms do not usually reach their most severe until at least 2 months from disease onset,[31] about 16% of the patients may have a subacute onset, with monophasic course.[30]

The diagnostic challenge of distinguishing these two immune-mediated polyradiculoneuropathies during the subacute phase remains high, as in case of CIDP convincing data from randomised controlled trials indicate, that corticosteroids, Intravenous Immunoglobulines (IVIg) and plasmapheresis exert short term or long term clinical improvement in about two-third of patients.[32] Recent clinical criteria have been proposed in order to distinguish sub- acute CIDP from AIDP. According to these criteria, sub- acute CIDP should be considered when a patient thought to have AIDP deteriorates again after 8 weeks from onset or when deterioration occurs 3 times or more. Especially when the patient remains able to walk independently and has no cranial nerve or autonomic nerve system dysfunction, maintenance treatment for CIDP should be considered.[33,34]

Nerve conduction studies with respect to sural nerve sparing pattern, sensory ratio >1, or the presence of A-waves are not always helpful in distinguishing these two immune-mediated polyradiculoneuropathies during the sub- acute phase.[33]

Although the role of neuromuscular ultrasound in the diagnostic workup of immune-mediated polyneuropathies remains less well defined, the recent introduction of a new ultrasound score (Bochum Ultrasound Score-BUS) allowed the differentiation of sub- acute CIDP from AIDP[35] (Figure 1).

In view of our recent report, the anatomical sites summarised under the "Bochum Ultrasound Score" included the cross sectional area of: a) the ulnar nerve in Guyon's canal, b) the ulnar nerve in upper arm, c) the radial nerve in spiral groove and d) the sural nerve between the lateral and medial head of the gastrocnemius muscle (Figure 1). The scoring system included two simple rules 1) the patient received 1 point, for each of the above anatomic sites, where he showed a pathological cross sectional area enlargement, compared the reference values of our lab,[5] 2) if the patient showed on both sides of the body a pathological cross sectional area nerve enlargement of the concrete nerve, he also received only 1 point.[35] Considering the above, each patient could receive a minimum sum score of 0 points and a maximum sum score of 4 points. Following the previous report in the literature we used as a cut-off value for differentiating a sub- acute CIDP from AIDP a sum score of ≥ 2 points.

Among the advantages of the Bochum ultrasound score are a) easy administration, as it summarizes 4 anatomical sites that can be easily sonographically examined, b) economy of time, as it can be performed quickly (about 10 mins), c) high sensitivity and specificity in patients with no difference in disease duration, and d) lack of side effects or pain for the patients, while performing nerve ultrasound. "Bochum Ultrasound Score" should undergo multicentre, prospective evaluation in a larger sample of patients presenting with an (sub-)acute or chronic polyneuropathy to prove its specificity for CIDP

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