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High resolution ultrasound in peripheral neuropathies

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Nerve Ultrasound: a brief introduction

High-resolution ultrasonography (HRUS) is a diagnostic tool that is increasingly used in the work-up of peripheral nerve disease. As many peripheral nerves run a superficial course, they can be studied over a long tract, especially in the arms. This is a big advantage over Magnetic Resonance Imaging (MRI) when multiple nerves have to be studied, as MRI is relatively expensive, time consuming and not readily available everywhere. Different aspects of nerve morphology can be studied with HRUS. Nerve cross-sectional area (CSA) can be determined at multiple sites along the nerve. CSA can be measured at entrapment sites (e.g. the carpal tunnel, cubital tunnel, Guyon’s canal and the fibular head), but also at non-entrapment sites. Apart from nerve CSA vascularization, echogenicity, fascicular pattern and endoneurial thickness can be investigated as well. All those modalities can give critical insight in the origin and development of various peripheral neuropathies.

The additional value of HRUS in determining diagnosis and cause of different types of mononeuropathy, like carpal tunnel syndrome and ulnar neuropathy at the elbow, has been established in the past years. In recent years research into applications of HRUS in assessing polyneuropathies has vastly expanded as well. This lecture summarizes the most important findings of those studies.

Increased Nerve CSA: an important diagnostic finding in polyneuropathies?

Discriminating axonal and demyelinating polyneuropathies can be very difficult when using only clinical and electrodiagnostic testing. The clinical picture can overlap, electrodiagnostic testing can be inconclusive, and misdiagnosis of demyelinating neuropathies like chronic inflammatory demyelinating polyneuropathy (CIDP) is common. It is, however, important to adequately discriminate these types of polyneuropathy, as acquired demyelinating polyneuropathies can be treated, whereas no treatment is usually available in axonal polyneuropathy. Several studies showed that HRUS can accurately discriminate an axonal from a demyelinating polyneuropathy, when investigating nerve CSA at non-entrapment sites. Zaidman et al. found that demyelinating polyneuropathies (Charcot-Marie-Tooth disease (CMT) and CIDP) had significantly enlarged nerve CSA compared to healthy controls and patients with axonal polyneuropathy. Other studies, including those performed by Scheidl et al., Grimm et al., and Goedee et al., also showed nerve enlargement in demyelinating polyneuropathies, while this could not be found in axonal polyneuropathy.
These findings clearly indicate that HRUS can be a useful tool to identify patients with a treatable demyelinating polyneuropathy.

Apart from discriminating axonal and demyelinating polyneuropathy it is also important to discriminate different subtypes of demyelinating polyneuropathy, because not all demyelinating polyneuropathies can be treated. Acquired inflammatory demyelinating polyneuropathies (e.g. CIDP) can be treated with corticosteroids, intravenous immunoglobulins (IVIg) and plasmapheresis, but no treatment options are available for hereditary demyelinating polyneuropathies (e.g. CMT1). Several studies show that HRUS can aid in making the distinction. Zaidman et al. found that patients with CMT1 often showed massive nerve enlargement, while moderately increased CSA was found in CIDP and only very mildly increased CSA in Guillain-Barré Syndrome (GBS). Sugimoto et al. also found that nerve CSA in CMT was significantly higher in CMT than in CIDP. HRUS can additionally help to discriminate several subtypes within the group of hereditary polyneuropathies. In several studies most nerve enlargement was observed in CMT1A, while a much lesser degree of enlargement was seen in CMT1B and CMTX. In CMT2, an axonal subtype of CMT, no significant nerve enlargement was found at all. All these findings show that HRUS can have an important role in determining (sub)types of demyelinating polyneuropathies and that it also may direct genetic research in the future in case of suspected hereditary neuropathy.

Another important, frequently encountered clinical dilemma is distinguishing motor neuron disease (MND, e.g. amyotrophic lateral sclerosis (ALS)) from multifocal motor neuropathy (MMN). These diseases can have very similar clinical features, but prognosis and treatment are very different. HRUS can be of aid in such cases. Nerve enlargement can be observed in MMN, while this isn’t found in MND. Grimm et al. found that HRUS could discriminate MMN and ALS with a sensitivity of 87.5% and a specificity of 94.1%, and a recent study by Goedee et al even found a sensitivity of 99% (95%-CI 78-99%) and specificity of 100% in a cohort of treatment naïve.

Determining nerve CSA has various diagnostic applications. In addition to the diagnostic applications mentioned above, nerve enlargement has also been described in multiple other conditions like multifocal inflammatory demyelinating neuropathy (Lewis-Sumner Syndrome / MADSAM), Hereditary Neuropathy with Liability to Pressure Palsies (HNLPP), diabetic polyneuropathy, anti-MAG polyneuropathy, leprosy, vasculitic polyneuropathy, POEMS syndrome, paraneoplastic neuropathy and neurofibromatosis. In GBS nerve enlargement is also found, sometimes in an early phase of the disease. As nerve conduction studies often
only reveal abnormalities in the later stages of the disease, HRUS might give additional diagnostic information. However, the enlargement in GBS is often mild, widespread, and the time to occurrence of nerve enlargement varies between patients. The role of HRUS in evaluating GBS therefore still seems limited.

Quantifying abnormalities: another tool to improve diagnostics?
Not only nerve CSA can be used to discriminate types of polyneuropathy. Several scores and protocols based on the measurement of nerve CSA have been developed to improve classification of polyneuropathies further. Padua et al. suggested the intraneur (largest CSA of nerve / smallest CSA of nerve) and interneur (largest intraneur variability score / smallest intraneur variability score) variability ratio’s as additional tools to improve classification of polyneuropathies. Kerasnoudis et al. developed the Bochum ultrasound score to discriminate CIDP from AIDP (acute inflammatory demyelinating polyneuropathy) and from MMN/MADSAM. In this score nerve CSA of the ulnar nerve at Guyon’s canal and the arm, the radial nerve at the spinal groove and the sural nerve at the level of the gastrocnemius muscle is determined to calculate the probability of having CIDP. Grimm et al. also developed a score (the ultrasound pattern sum score (UPSS)) with which acute and subacute polyneuropathies can be distinguished. In this score nerve CSA of motor nerves in the arms and legs (UPS-A), nerve roots and the vagal (UPS-B) and sural nerves (UPS-C) is calculated to determine the total sum score (UPSS). A modified UPSS could be applied as well to discriminate subtypes of hereditary polyneuropathies. Goedee et al recently introduced a limited protocol assessing the brachial plexus at truncal level (superior, medial and inferior trunk) and the median nerve at the forearm and arm. In this protocol cut-off values were developed to discriminate acquired demyelinating polyneuropathies and axonal neuropathies and to discriminate MMN and MND.

Although scores and protocols have been developed to improve diagnostics, general applicability of such tools has to be determined. A recent study by Grimm et al that validated the performance of the Bochum ultrasound score and the UPSS showed promising results, but many patients in this study had an already established diagnosis and were already on long-term treatment. Larger, prospective cohort studies in treatment naïve patients will have to be performed to determine (and validate) a standardized score or protocol that can be applied with ease in clinics worldwide.

Fascicle size, epineurium size, echo-intensity and vascularity: other important morphological characteristics?
Nerve CSA is the most easy measurable and most often studied morphological characteristic of the nerve in polyneuropathies, but several other characteristics of the nerve can be studied as well. Increased fascicle size is reported in patients with CMT and CIDP. In leprosy hypervascularization of the nerve is observed in patients with a type 1 or 2 reaction and an enlarged epineurium is also reported. Abnormal nerve echogenicity has been identified in mononeuropathies, but in polyneuropathies this feature has not yet been thoroughly investigated. Padua et al. suggested an interesting classification of sonographic abnormalities in CIDP based not only on nerve CSA but also on features like fascicle size and echogenicity. Patients with a different class of abnormalities seem to have a different disease duration and may have a different prognosis. For instance, patients with nerves with normal CSA, but hypo-echogenic appearance seem to have a worse prognosis in comparison to patients with slightly enlarged nerves and normal echogenicity. Although other features than nerve CSA can be investigated and abnormal findings have been observed data on those features are scarce at this moment. Further investigation will be needed to elaborate the exact role of those other morphological characteristics in determining diagnosis and prognosis of polyneuropathy.

Pattern of Nerve Enlargement: even more useful information?
Nerve enlargement has been found in multiple types of polyneuropathy. With increasing data on the distribution of morphological abnormalities, there also seem to emerge different patterns of nerve enlargement in different types of polyneuropathy. In CMT diffuse enlargement of the nerves is found, especially in CMT1A and to a lesser degree in CMT1B and CMTX. In CIDP diffuse enlargement of the nerves is also possible, but more often symmetric enlargement of the proximal nerve segments is observed. In MMN abnormalities can be found frequently as well in proximal nerve segments, but abnormalities are more often distributed asymmetrically and more often focal enlargement is found. In contrast to CMT, in which diffuse enlargement is at non-entrainment sites, striking enlargement at entrapment sites can be found in HNLPP while enlargement at non-entrainment sites is only reported sporadically. In axonal polyneuropathies (e.g. diabetic polyneuropathy and chemotherapy induced polyneuropathy) no general nerve enlargement is found; mostly only slight enlargement at entrapment sites is observed. An exception to this is vasculitic neuropathy, in which mild enlargement of peripheral nerves is found at non-entrainment sites, though the brachial plexus seems to be spared. In leprosy most typically enlargement is not found at entrapment sites, but proximal of these sites. Especially the ulnar nerve is frequently involved proximal to the cubital tunnel in this disease. Because different types of polyneuropathy show a different distribution of sonographic
abnormalities the pattern of nerve enlargement could be an additional clue for the existence of a certain polyneuropathy. This should be explored further in future studies.

**HRUS: are there other than diagnostic applications?**

Most research on HRUS in polyneuropathies has focused on the diagnostic applications of HRUS, but there may also be a role for HRUS in predicting long-term prognosis and treatment response in polyneuropathies. A retrospective study by Zaidman et al. showed that CIDP patients with decreasing nerve CSA over time had a favourable treatment response, while patients with a stable or increasing nerve CSA had not. Another small prospective study by Kerasnoudis et al. showed that a decrease in intraneurive variability correlated with favourable outcome in CIDP. A study by Chaduvula et al, performed in 57 leprosy patients to monitor disease activity during a follow-up period of 2 years, showed that at the baseline visit and during follow up the investigated nerves were significantly thicker in patients with leprosy reactions in comparison to healthy controls (p<0.0001) and to a lesser extent also to patients without reactions. During follow-up, nerve size did not change much in patients without reactions, while it decreased significantly in patients with reactions. Furthermore hypervascularization decreased during treatment. At baseline, endoneural blood flow was present only in the 36 patients with reactions. It was present in 55% of these patients and remained present in only 1 patient after treatment at the end of the follow-up period. This disappearance of hypervascularization after treatment in leprosy reactions was also observed in another follow-up study by Lugão et al.

Although the results of those studies are promising, more prospective studies investigating the prognostic value of HRUS have to be performed and the exact role of HRUS in determining prognosis and treatment outcome has yet to be established.

HRUS may also be a useful screening tool in certain peripheral neuropathies. Recent studies showed frequent involvement of the peripheral nervous system in neurofibromatosis type 1 and 2. A pilot study we recently conducted in a group of 17 neurofibromatosis type 1 patients showed that 41.2% of patients had multiple plexiform neurofibromas, while 23.5% of patients had almost no abnormalities at all. As benign tumor load and presence of plexiform neurofibromas are risk factors for malignant transformation of a neurofibroma, which is a main cause of morbidity and mortality in this disease, HRUS may be useful to identify a subgroup of patients that benefit from more regular follow-up. It may also be useful to perform follow-up in the group of patients with multiple plexiform neurofibromas, and it may be applied as a tool to monitor treatment response in randomized controlled trials that
investigate treatment for peripheral nerve sheath tumors. However, larger prospective studies will have to be performed to determine if such applications are useful.

**Summary and Future directions**

Research into diagnostic applications of HRUS in peripheral neuropathies has vastly expanded in recent years with very promising results. HRUS is able to discriminate axonal and demyelinating polyneuropathies as well as several subtypes of demyelinating polyneuropathy. Determining nerve CSA seems to be most useful to distinguish peripheral neuropathies, but the distribution of sonographic abnormalities also seems to be an important clue to a specific diagnosis. In addition, several scores and protocols have been developed to further improve the ability of HRUS to discriminate different types of peripheral neuropathy.

Apart from the diagnostic applications HRUS may also have prognostic value in peripheral neuropathies. Both the change in nerve CSA and the change in vascularization of the nerve seem to correlate with prognosis and treatment response in specific peripheral neuropathies. Although results are promising, further research is needed to elaborate the role of HRUS in assessing peripheral neuropathies. The sonographic protocols used in different studies vary greatly and few studies investigated the role of morphological features of the nerve other than nerve CSA (e.g. vascularity, echogenicity). Furthermore most studies had relatively small sample size and/or a retrospective design, and most studies were performed in a single center, on a single device, and by only one or a limited amount of investigators. Large prospective studies investigating the diagnostic and prognostic value of HRUS in polyneuropathies in a multicenter setting are therefore needed. The influence of inter-observer variability on HRUS results should also be established in order to determine the applicability of identified cut-off values of previous and future studies in daily clinical practice.

**References**


