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Editorial

Nerve ultrasound in dorsal root ganglion disorders: Smaller nerves lead to bigger insights

See Article, pages 568–572

After decades of having to make do with electric stimulation and recording (i.e. nerve conduction studies, electromyography and evoked potentials), nerve ultrasound now provides the opportunity to improve neurodiagnostic patient care by deploying a powerful tool to detect neuromuscular pathology in an accurate and patient-friendly way (Mah et al., 2018; Walker et al., 2018). Nerve ultrasound is also increasingly providing neurologists and clinical neurophysiologists with the opportunity to increase their insight in the pathophysiology of peripheral nervous system (PNS) pathology. In this issue of *Clinical Neurophysiology*, Leadbetter and coworkers (Leadbetter et al., 2019) describe the results of their study on nerve ultrasound for diagnosing sensory neuronopathy in spinocerebellar ataxia type 2 and CANVAS syndrome. Their main finding, which may come as a surprise, is that the peripheral nerves in these dorsal root ganglion (DRG) disorders become visibly *smaller* in size. This is a novel finding in nerve ultrasound, as up till now virtually any nerve pathology, such as entrapment, trauma or inflammation, has been found to lead to (multi-)focal or generalized size increases in fascicles and whole nerves (Telleman et al., 2018). The study by Leadbetter et al. is important, as the finding that this specific group of DRG disorders, that is, peripheral sensory neuron disorders, behaves completely different, helps us understand better what to expect of morphological nerve changes in different PNS disorders.

To understand why nerve size changes in PNS disorders, we first need to look at the morphological characteristics of peripheral nerves. The general building plan of a nerve will probably be quite familiar, with the bundling of myelinated and unmyelinated axons, Schwann cells and endoneurial matrix material in nerve fascicles, that are ensheathed by the connective tissue layer of the perineurium that contains the blood-nerve barrier and vasa and nervi nervorum. These fascicles then bundle together as a nerve root, plexus element or peripheral nerve bundle proper, surrounded by another connective tissue layer, the epineurium, that transits into the surrounding connective tissue layers of muscle fascia or subcutis (Sunderland et al., 1970). Ultrasonographically, this gives the characteristic transverse nerve appearance of a cut high-voltage cable, with small black dots surrounded by thin white layers representing the fascicles, bundled together in a large outer cable sheath (van Alfen et al., 2018).

Next, it is important to realize what the ratio between axon/myelin and connective tissue in a given nerve segment is, and how that ratio changes from the proximal root to the distal end branches (Schraut et al., 2016). Connective tissue elements of the perineurium and epineurium are relatively sparse at the very proximal root and plexus levels, with an average connective tissue content of around 25–30%. Ultrasonographically, this means that roots will always look rather black in appearance without much discernible fascicular architecture, as the sparseness of connective tissue elements provides relatively few reflectors to create an image on screen. Going more distally, the amount of connective tissue increases, and is estimated to be around 40–50% for the median or ulnar nerve at the level of the wrist, and even higher up to 60–70% for the peroneal and tibial nerves in the lower leg. Ultrasonographically, this translates into the typical honeycomb appearance of the distal limb nerves. Another important feature of peripheral nerves, also mentioned in the current paper, is the ratio between sensory axons versus motor axons in a given nerve bundle. In a landmark histological study by Gesslbauer et al. it was shown that sensory axons, that innervate both skin receptors and muscle spindles, represent more than 90% of the total axon number in any mixed upper limb nerve (Gesslbauer et al., 2017).

The nerve size increase that accompanies entrapment neuropathies, inflammatory neuropathies (both demyelinating and axonal) and nerve trauma, is generally assumed to result from a combination of nerve edema, connective tissue proliferation (i.e. scarring) following local injury, and in the case of traumatic neuromas proliferating axon bundles forming the growth cone. As a large proportion of the distal limb nerves is formed by connective tissue elements, perineurial and epineurial proliferation in response to injury or mechanical friction is a very understandable mechanism, by which overall nerve size will increase in case of pathology, and the presence of edema or axon outgrowth will only increase it further. Indeed, until the publication of the work of Leadbetter's group in sensory neuron pathologies, the only condition in which nerve size has been found to *decrease* slightly at the group level was in

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patients with motor neuron disease, i.e. amyotrophic lateral sclerosis (Schreiber et al., 2016). That the nerve size decline was very small (on average 0.04 mm^2 per month) and could only be measured at the group level is not too surprising, given the relatively small fraction of motor axons of around 10% in mixed nerves. But it is with the current additional data from Leadbetter's group that we can now complete the picture, as their finding of about a 50% decrease in overall nerve size, confirms that sensory neuron loss will lead to a decrease of up to 90% of the nerves' axonal content that originally made up 50–60% of the whole tissue content of that limb nerve.

In other words, the results of this study underpin that nerve size changes that can be detected with ultrasound are to a certain extent predictable. PNS disorders that will affect both axon content as well as connective tissue elements of nerve will most likely lead to an overall increase in size. The more pathophysiological processes occur simultaneously (e.g. inflammation with edema, scarring and axonal regrowth combined), the larger the nerve size will most likely be, while for example progressing to end-stage denervation with scarring but without edema or a growth cone at a particular nerve site might again cause a relative decline in cross sectional area; something that has been found in end-stage carpal tunnel syndrome (Moghtaderi et al., 2012). Disorders that affect motor or sensory neurons without causing connective tissue changes by mechanical or inflammatory mechanisms will lead to a decrease in nerve size, which will be most likely be small for any motor neuron disorder (10% of 50% = 5% of the whole distal limb nerve size maximally) and only detectable at group level, but will be large and detectable at the individual level in sensory neuronopathies. The next step will be to further validate, and maybe refine, these predictions based on ultrasound studies in all different types of neuropathies. With further improvements in ultrasound equipment, nerve ultrasound will increasingly come to be an in-vivo replacement for simple histology at the light microscope level.

Conflict of interest statement

The author reports no conflict of interest.

References

van Alfen N, Mah JK. Neuromuscular ultrasound: a new tool in your toolbox. Can J Neurol Sci 2018;45:504–15.
Gesslbauer B, Hruby LA, Roche AD, Farina D, Blumer R, Aszmann OC. Axonal components of nerves innervating the human arm. Ann Neurol 2017;82:396–408.
Leadbetter R, Weatherall M, Pelosi L. Nerve ultrasound as a diagnostic tool for sensory neuronopathy in spinocerebellar ataxia syndrome. Clin Neurophysiol 2019;130(4):568–72.
Mah JK, van Alfen N. Neuromuscular ultrasound: clinical applications and diagnostic values. Can J Neurol Sci 2018;45:605–19.
Moghtaderi A, Sanei-Sistani S, Sadoughi N, Hamed-Azimi H. Ultrasound evaluation of patients with moderate and severe carpal tunnel syndrome. Prague Med Rep 2012;113:23–32.
Schraut NB, Walton S, Bou Monsef J, Shott S, Serici A, Soulii L, et al. What protects certain nerves from stretch injury? Anat Rec (Hoboken) 2016;299:111–7.
Schreiber S, Dannhardt-Stieger V, Henkel D, Debska-Vielhaber G, Machts J, Abdulla S, et al. Quantifying disease progression in amyotrophic lateral sclerosis using peripheral nerve sonography. Muscle Nerve 2016;54:391–7.
Sunderland S. Anatomical features of nerve trunks in relation to nerve injury and nerve repair. Clin Neurosurg 1970;17:38–62.
Telleman JA, Grimm A, Goedee S, Visser LH, Zaidman CM. Nerve ultrasound in polyneuropathies. Muscle Nerve 2018;57:716–28.
Walker FO, Cartwright MS, Alter KE, Visser LH, Hobson-Webb LD, Padua L, et al. Indications for neuromuscular ultrasound: Expert opinion and review of the literature. Clin Neurophysiol 2018;129:2658–79.

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