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Editorial

Sonomorphology of median nerve in relation to function: Important lessons from carpal tunnel but still complex

Sonographic evaluation of median nerve morphology is advancing as practical non-invasive bedside diagnostic test in a diverse spectrum of peripheral nerve disorders (Telleman et al., 2021, Walker et al., 2018). The most common and robust sonographic parameter is nerve size, assessed as cross-sectional area (CSA) on transverse images within hyperechoic rim of the epineurium (Telleman et al., 2018, Walker et al., 2018). Nerve ultrasound now frequently complements routine electrodiagnostic testing, enhancing more accurate localisation and allowing identification of alternate causes (e.g. ganglion/cyst, tumour, traumatic/iatrogenic lesions, relation with surrounding tissues), and improving detection of potentially treatable neuropathies (Herraets et al., 2020, Padua et al., 2012, Pelosi et al., 2021, Walker et al., 2018). However, nerve changes in nerve morphology should not be considered the prerequisite for functional changes as shown in physical examination or electrophysiologic tests. In fact, the functional redundancy of the human peripheral nervous system is relatively large (Henderson and McCombe, 2017, Sleutjes et al., 2019). Also, mixed nerves in human arms are mainly populated by sensory axons and only a smaller contribution of motor axons (Gesslbauer et al., 2017). In contrast, most of clinical and electrodiagnostic evaluation is primarily aimed at motor function. Therefore, it is not uncommon to find abnormal nerve morphology with ultrasound that appears to be clinically 'silent' and have normal or only nonspecific electrodiagnostic findings. Moreover, changes in morphologic domain may also be part of different pathophysiologic components of the disease and even have unique temporal evolution that differs from the electrophysiological function. Consequently, studies that have compared electrophysiologic nerve function with sonographic nerve morphology in diverse neuropathies reported mixed results, often with limited or even no clear correlation at all (Al-Hashel et al., 2015, Di Pasquale et al., 2015, Goedee et al., 2019, Goedee et al., 2016, Kerasnoudis et al., 2015, Simon et al., 2015, Telleman et al., 2017).

Although carpal tunnel syndrome (CTS) is often viewed as a singular clinical entity, the underlying pathophysiologic mechanisms are actually quite diverse (e.g. diabetes, hypothyroidism, arthritis, pregnancy, repetitive mechanical injury, hereditary and acquired polyneuropathies, mucopolysaccharidoses and amyloid) and still only partly understood (Padua et al., 2023). Consequently, most diagnostic studies on CTS have included heterogenous samples with different underlying causes, variable disease duration and clinical severity. Diagnostic test characteristics for CTS may therefore differ, depending on the pathophysiology and context, as is currently considered for ultrasound CTS tests in the elderly and more severe CTS (Gregoris and Bland, 2019, Miwa and Miwa, 2011, Moschovos et al., 2019). Also, use of the appropriate sonographic reference values for sonographic nerve size is highly warranted as these may vary between populations (BMI, ethnicity and race), local anatomy (carpal tunnel in- vs outlet, bifid median nerve), insonation frequency (i.e. <15 or >15 MHz), the use of zoom magnification, and positioning of wrist (neutral vs extended or flexed position), or may even be lacking (e.g. disease specific cut-off values for CTS in polyneuropathies, as these have been excluded in published studies). Nevertheless, evaluation of median nerve size on ultrasound (CSA carpal tunnel and ratio (CSA wrist/forearm (WFR)) is now considered an appropriate diagnostic test in patients with suspected CTS (Padua et al., 2023, Pelosi et al., 2022). Other sonographic parameters that have been suggested in CTS (e.g. echogenicity, vascularisation on Doppler, flattening ratio, elastography and nerve mobility), appear to have limited added diagnostic value.

In this volume of *Clinical Neurophysiology Practice*, Grönfors et al. report smaller nerve sizes on ultrasound in older patients (age $\geq$ 65 years) with moderate or severe CTS (Grönfors et al., 2023). Their data not only confirms that median nerve CSA in the elderly may fall below the current published disease specific cut-offs for CTS, as was previously demonstrated by others (Gregoris and Bland, 2019, Moschovos et al., 2019), but also showed that WFR may be more effective in identifying older patients with CTS. An important limitation is that the authors were not able to address the influence of several factors such as disease duration, previous non-surgical treatment, and underlying causes for CTS. Also, they excluded mild CTS, patients with bifid median nerves, signs of polyneuropathy and previous surgical carpal tunnel release, and did not evaluate median nerve size at carpal tunnel outlet. Therefore, the diagnostic yield of median nerve WFR in elderly with mild CTS and bifid median nerves remains elusive. In patients with suspected CTS superimposed on polyneuropathy, caution on use and interpretation of ultrasound is warranted and this should only be used to help identify other lesions not detected by electrodiagnostic testing (e.g. neurofibroma or cyst/ganglion at carpal tunnel). Future ultrasound studies in CTS should not only

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consider age, but also compare the diagnostic yield in distinct causes including polyneuropathy.

The authors also determined axon loss in CTS, using needle electromyography (EMG) of the m. abductor pollicis brevis, and visual grading of recruitment (normal, mildly-severely reduced, and/or motor unit potentials (MUPs) with high amplitude and increased duration/polyphasia) and amount of spontaneous muscle fiber activity (Grönfors et al., 2023). Hence, after warming (no further specification of technique or duration) the authors used sensory conduction slowing of median $\geq$ 10 m/s compared to ulnar nerve, and distal motor latency (DML) $\geq$ 4.2 ms (8 cm distance between stimulation and recording site) as cut-off for moderate CTS and absent sensorimotor responses for 'extreme' CTS. This criterion of sensory slowing may be less sensitive than the more commonly used distal sensory latency (DSL) (Padua et al., 2023), and others prefer median vs ulnar motor comparison (lumbrical respectively second dorsal interosseus muscles) or even use 7 instead of 8 cm as standardized distance (Werner and Andary, 2011). It should be noted, that the electrophysiologic grading used by the authors does not necessarily reflect clinical severity of signs and symptoms in CTS. Also, axon loss can be determined by motor unit estimation (MUNE) techniques, but both needle EMG and MUNE do not take into account the focal slowing as a result from demyelination caused by local compression of median nerve at carpal tunnel. Therefore, the correlation between electrodiagnostic findings and median nerve CSA remains complex, as there are multiple factors involved in CTS: electrophysiologic abnormalities are not limited to exclusive axonal involvement only, the contribution of motor fibers in the median nerve is small compared to sensory component and morphological changes could thus be more dependent on sensory involvement, cause and duration of compression at carpal tunnel may affect electrophysiological function and sonomorphology differently. Perhaps it is therefore not a surprise, that associations between needle EMG and median nerve CSA and WFR in the presented study are weak. However, they did report more needle EMG and nerve conduction abnormalities in the older patient group. Combined with the smaller nerve sizes on ultrasound, these electrodiagnostic findings further support concept of distinct pathophysiologic processes involved in the elderly with CTS. Consequently, the diagnostic and treatment strategies in elderly with suspected CTS may need to be tailored accordingly.

Conflict of Interest Statement

The author has no potential competing interests to disclose that are relevant to the content of the editorial and its associated manuscript.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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