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Editorial

The 'neurophysiological index' predicts survival in amyotrophic lateral sclerosis

See Article, pages 1730–1733

Planning care in amyotrophic lateral sclerosis (ALS), as well as designing clinical trials of putative therapies, requires measurement of disease severity, and rate of change. For some such purposes an overall measure of disease severity is required, such as the amyotrophic lateral sclerosis functional rating scale (ALS-FRS) which takes account of various domains of disease-related difficulty, including dressing, washing, taking food, swallowing, standing and walking, breathing and coughing. However, for testing a response to a therapeutic a measurement sensitive to the disease process is needed. This need not be an overall measure but could be quite focused. Measurements of strength, whether using a hand-held dynamometer, or a clinical rating scale such as the MRC scale have been deployed, but there is a wide range of variance in such measures, and their inter-rater variability is suspect. In clinical practice, measures of ventilatory capacity are particularly important, but patient cooperation and marked facial weakness often undermine their sensitivity.

The main features of ALS are progressive neurogenic muscular weakness and atrophy. With early diagnosis there is an opportunity to follow the lower motor neuron change, initially in scarcely affected muscles, to more advanced stages of muscular involvement. In such assessments, clinical neurophysiological measurement has a potentially important, if currently neglected, role. Conventionally, combined scores of measurements in multiple muscles have been recommended but close follow-up of changes in an individual nerve-muscle system, as a means of observing progress or therapeutic efficacy, is likely to be far more sensitive (de Carvalho et al., 2003; Cheah et al., 2011, Escorcio-Bezarra et al., 2018). A contemporary focus on motor unit number counting (MUNE), using techniques that require either special equipment or training (de Carvalho et al., 2018), has tended to over-ride conventional electrophysiological techniques despite the availability of the latter in every neurological department, and the concomitant high level of expertise among clinical neurophysiologists. In studying an approach to re-introduce conventional electrophysiology into ALS studies we considered that careful testing of a single nerve-muscle system would be sufficient to detect change in the course of the disease, and possibly a putative therapeutic effect in a simple, short Phase 1 clinical trial. Such a sensitive methodology would enormously reduce trial costs, if used to select suitable therapies for pivotal Phase 2/3 studies. Indeed, the latter would, in turn, be simplified since the pharmacokinetics of the trial compound in human ALS would be then at least partly understood (de Carvalho et al., 2003; Swash and de Carvalho, 2004).

The Neurophysiological Index (NI) fulfils this need. The NI uses conventional clinical electrophysiological studies in a single nerve-muscle system – the ulnar nerve and the abductor digiti minimi muscle (ADM) – to construct a simple mathematical relation between the compound muscle action potential (CMAP - in mV), the distal motor latency (DML - in ms) and F-wave frequency % (in 20 consecutive recordings), using the formula (CMAP/DML) × F-wave frequency % (de Carvalho and Swash, 2000, de Carvalho et al., 2003). Since the data used to calculate the NI are different, the resulting number is an index, without sign. Measurements of CMAP, DML and F-wave frequency in clinical neurophysiology laboratories are within the competence of all clinical neurophysiologists and are accurate and replicable. Little or no extra time is required in performing these measurements since they are virtually routine in the neurophysiological assessment of suspected ALS. The three components comprising the NI reflect residual contractile muscle mass in the ADM, motor conduction in the distal part of the ulnar nerve and motor endplates innervating this muscle, and the level of excitability of motor neurons in the spinal cord from which the ulnar nerve's motor fibers originate. The ulnar nerve is stimulated just proximal to the wrist. Nerves with abnormal ulnar sensory nerve action potential or signs of ulnar nerve compression at the elbow are excluded. Standard filter settings, electrode placements and stimulus settings are used and the limb temperature controlled, since ALS limbs are often cold. Since the objective is to study change in a single nerve-muscle system no additional nerve is studied for NI measurements, although the method could, of course, be applied to other nerve-muscle systems, provided coincidental nerve pathologies, such as carpal tunnel compression, are excluded.

The NI was first described as a standardized neurophysiological assessment of function in the ulnar nerve/ADM nerve-muscle system in a study of 137 patients with ALS and 35 age, gender and height-matched normal subjects (de Carvalho and Swash, 2000). In ALS the CMAP is decreased, and the DML increased in hands with weak ADM muscles, causing a reduction in the NI, which correlated with MRC strength in the ADM muscle. F-wave excitability varies during the course of the disease (de Carvalho et al., 2002). In

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a clinical and neurophysiological comparison of rapidly and slowly progressive ALS using maximal voluntary isometric contraction of the limb and trunk muscles, the ALS functional rating scale (ALS-FRS), forced vital capacity and the NI in the ulnar nerve-muscle system, the NI was the most sensitive measure of change, with the smallest coefficient of variation, suggesting that the NI should be useful for testing efficacy in small, short trials of putative new therapies in ALS as well as in clinical practice (de Carvalho et al., 2003). This finding was replicated in a second study, in which a very low intra-rater variability was confirmed (Swash and de Carvalho, 2004). Subsequently a linear reduction in NI was reported during 12 months follow-up in ALS (de Carvalho et al., 2010). Cheah et al. (2011), in a study of mixed effects models, confirmed that the NI was a valid biomarker for measurement of ALS progression. There was a more rapid decline in NI over a short period than in other, conventional measures of disease progression, such as ALS-FRS, with a moderate correlation to functional deterioration. Importantly, they found similar changes in NI in limb-onset and bulbar onset ALS. They noted, however, that a low initial baseline F-wave frequency, e.g., 0.1–0.4, could lead to a floor effect, with NI reaching zero if F-waves were absent later during the period of observation, although in our experience this is unusual. A Brazilian group has reported that MUNIX and NI were equally sensitive in detecting change in slow-progressing or early ALS (Escorcio-Bezarra et al., 2018). Nonetheless, the NI has the major advantages of simplicity and universal availability.

In this issue of *Clinical Neurophysiology*, in a study of 191 patients with ALS from China, Cao et al. (2019) report the NI can also be used to predict outcome. Patients with NI < 2.4 (the mean value in their study) at first assessment survived a shorter period (30.3 months) that those with NI > 2.4 (40.5 months) ($p = 0.019$). As in other studies, using a Cox analysis, they noted that a shorter diagnostic delay ($p < 0.0001$), bulbar onset ($p = 0.01$), and a low ALSFRS-R ($p = 0.042$) also implied a shorter disease course. In conclusion, therefore, the NI, which requires no special technology and no new clinical or technical skill, and which is calculated from data commonly routinely acquired in the clinical neurophysiology laboratory, is a simple, reliable and replicable measure for detecting change during the course of ALS and also for predicting outcome. Since all neurology departments can provide this measurement without special training, we suggest that it's time the NI was adopted more widely in clinical practice and, especially, in short, economical Phase 1 clinical trials to assist in the selection of the most promising compounds for pivotal Phase 2/3 trials (De Carvalho et al., 2010; Escorcio-Bezarra et al., 2018).

Declaration of Competing Interest

Neither author has any conflict of interest to disclose.

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