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Editorial

Reading the palm with MUNIX: A 'reversed split hand' in spinal muscular atrophy

See Article, pages 315–319

The split hand phenomenon in amyotrophic lateral sclerosis (ALS), first reported by Wilbourn and Sweeney (1994) and Wilbourn (2000), has proved a resilient clinical sign, although it is not always present in ALS (Wilbourn, 2000; Menon et al., 2004), and it is occasionally found in other neuromuscular disorders (Wilbourn, 2000; Kuwobara et al., 2008). It consists of marked atrophy of the thenar eminence (APB) and first dorsal interosseous (FDI) muscles with relative sparing of the abductor digiti minimi (ADM). Its cause is uncertain. Although there has been a great deal of speculation that in some way the phenomenon is consistent with a cortical origin for muscle atrophy in ALS no absolute experimental support for this suggestion is available, the argument depending on an association of ideas about the evolved function of the human thumb rather than on any objective, experimentally testable evidence (Weber et al., 2000; Eisen et al., 2017).

In this issue of *Clinical Neurophysiology*, Günther et al. (2018) report a study using the motor unit number index (MUNIX) technique for quantifying functional motor units in a muscle. MUNIX uses surface recorded electromyography (EMG) during graded isometric voluntary activity to generate the surface recorded interference pattern and compound muscle action potential (CMAP) used in the calculation of the index – MUNIX is not a directly recorded calculation of the actual number of motor units in a muscle, but it is a convenient and validated method for recording from many different muscles in the limbs (de Carvalho et al., 2018). The study was carried out in two German centers and one Swiss center by practiced investigators, specifically trained in the technique. Thenar and hypothenar small hand muscles were studied in the right hands of 38 genetically confirmed adults with 5q spinal muscular atrophy (SMA) types 2 and 3, and in 65 ALS patients and 24 normal control subjects. All the studied subjects were of similar age. The primary objective of the study was to test the sensitivity and specificity of neurophysiological markers for treatment trials and disease monitoring in SMA. In the SMA patients, in comparison with control subjects, CMAP and MUNIX were reduced in APB (MUNIX 103.1 ± 63.1 in SMA vs. 184.8 ± 52.3 in controls), and even more strikingly reduced in ADM (MUNIX 49.2 ± 44.1 in SMA vs. 183.3 ± 40.6 in controls). The FDI muscle was also markedly affected in SMA, similarly to the ADM (MUNIX 65.7 ± 56.0 in SMA vs. 293.0 ± 61.8 in controls). In some SMA type 2 patients, insufficient motor units remained for assessment. A MUNIX index, defined as the product of APB and FDI MUNIX divided by ADM MUNIX was found to reliably discriminate SMA and ALS hands from normal hands. Further analysis using another index – that the investigators termed the Preserved Thenar Index (APB MUNIX divided by the sum of FDI and ADM Indexes) – differentiated SMA hands from ALS hands with sensitivities and specificities greater than 90%, although other measures, e.g., CMAP values, proved non-discriminatory (Günther et al., 2018). Strong correlations were also found of MUNIX in APB and FDI with functional rating scores, but there was less strong correlation with ADM MUNIX. The investigators note a surprising result. In SMA, MUNIX studies of small hand muscles showed a "reversed split hand" phenomenon; that is, there was more marked loss of motor unit in hypothenar than in thenar muscles. This surprising finding discriminated SMA and ALS. It was found in less severely affected hands as well as in more severe cases. It did not correlate with disease progression, and thus seems to be a potentially useful diagnostic tool, that could therefore be used as a biomarker of this disease (Günther et al., 2018).

In future studies, it will be important to ascertain whether this "reversed split hand" phenomenon is unique to SMA or whether it also occurs in other motor neuronal disorders. More detailed studies are needed of motor unit loss in the APB, FDI and ADM muscles, assessed by MUNIX, at different stages of all these disorders, especially in ALS, SMA, bulbospinal muscular atrophy, Hirayama disease, Machado-Joseph disease and in normal aging, perhaps using motor neuropathies as neurogenic controls. How soon in the natural history of these disorders does this selective loss of motor units become evident? Why does it not occur in all cases? In ALS only about half of patients have the split hand distribution of atrophy of small hand muscle when tested (Menon et al., 2013), a finding that itself casts doubt on the 'cortical hypothesis' for this finding, although, it does of course not invalidate a cortical abnormality, especially cortical hyperexcitability, as a factor in the disease (Kiernan and Petri, 2012). However, physiological factors in the peripheral motor system, such as innate differences in motor endplate characteristics, for example, neuromuscular transmission, have not so far been thoroughly considered as causative factors conferring susceptibility to denervation in these motoneuronal disorder (de Carvalho M, Swash M. The split hand in amyotrophic lateral sclerosis: a role for the neuromuscular junction; in preparation). Increased excitability in motor axons innervating

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these three muscles in ALS have been reported in differing distributions by different investigators, but there are no similar relevant studies in SMA. In addition, studies of the corticomotoneuronal innervation likewise seem to differ between different investigators (Shibuya et al., 2013; Bae et al., 2014).

If one looks back 50 years ago or more, to studies of lower motor neuronal susceptibility in acute poliomyelitis, an acute viral lower motor neuronal disorder affecting spinal and brainstem motor neurons, it was a well-known clinical phenomenon that motor neurons that were active at the time of viremia were particularly susceptible; i.e., during the first 48–72 hours after the initial gastrointestinal infection (Russell, 1949). This led to much speculation about the nature of focal initial involvement in ALS, a disorder that often affects small hand muscles or other focal spinal segments (Ravits and La Spada, 2009), especially in the cervical enlargement of the cord. However, there is no evidence that ALS is an acute infectious illness and this notion of homology regarding the phenomenon of focal onset in the two disorders has not withstood the test of later critical studies. Nonetheless, the problem of focal denervation at onset in ALS, exemplified by the focality of Wilbourn's split hand syndrome in the disease, remains unexplained. In 5q SMA, focal involvement has not been much remarked on, since proximal weakness is the major clinical feature, but the discovery of a reversed split hand phenomenon in this disorder places this question of specific focality in motor neuron disorders in the forefront of phenomena requiring answers.

Conflicts of interest

None.

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