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Editorial Open Access

Differences in Motor Unit Loss and Axonal Regeneration Rate between Sporadic and Familiar Amyotrophic Lateral Sclerosis: An Undervalued Field of Research?

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Editorial

Amyotrophic Lateral Sclerosis (ALS) is a clinically and genetically heterogeneous, late-onset, neurodegenerative disorder of the motor system [1]. Five to ten percent of cases are familial and about 20% of these cases have point mutations in the Cu/Zn superoxide dismutase 1 (SOD-1) gene. Since its discovery, mutations in Cu/Zn superoxide dismutase (SOD-1) have stimulated a huge amount of interest [2], but the pathogenic mechanisms underlying disease's induction in familiar cases are still elusive. The most accepted hypothesis is that familiar ALS, SOD-1 positive could be caused by a neuronal damage, due to a gradual accumulation of a toxic product SOD-1 this cumulative damage leads to a disruption of the cytoskeleton and organelle trafficking within motor neuron dendrites. Aggregates do not exclusively occur in neurons, but also in glial cells, raising the question of whether mutant SOD-1 expression in neurons is sufficient per se to induce pyramidal degeneration and sustain disease evolution over time [3]. The familial form is clinically indistinguishable from the sporadic one and to date only few studies have tried to highlight electromyographic differences between sporadic and familiar ALS forms.

In Motor Neuron Diseases (MND), standard needle electromyography often reveals evidence of chronic reinnervation (increased motor unit action potential amplitudes and duration, with reduced recruitment), eventually associated with fasciculations and signs of denervation activity in progress, but provides little information about the extent of both motor neuron loss and axonal regeneration. The supramaximal CMAP amplitude also provides little evidence of the extent of motor neuron loss and normal CMAP amplitudes might mistakenly suggest that motor neuron loss has not occurred yet [4].

A particular method to record the full motor unit potentials is the so-called macro-EMG [5]. This technique provides information from a larger area of the muscle than standard concentric needle EMG. That represents a quantitative neurophysiology method and can be applied both to follow effects of putative therapies and to assess the size of individual motor unit. Among EDX techniques, Motor Unit Number Estimation (MUNE) is a measure of a primary pathologic process of motor neuron loss and can help to identify a huge number of poorly evident cases of reduction in motor units number, even in the presence of a ambiguous or not insightful needle EMG [6].

In a previous study [7] we found that ALS patients with SOD-1 mutations have a higher number of motor units at moment of diagnosis when compared with sporadic cases, as previously emerged from the work of Aggarwal in pre-symptomatic SOD-1 mutations carriers [8]. Moreover, while in sALS the macro-EMG parameters progressively increase, displaying a gradual increment of correlation up to 8 months, in familiar form there is not a specific time interval in which the axonal regeneration and the collateral sprouting can balance the neuronal damage. In other words, despite faster loss of motor units, in fALS we have paradoxically disclosed a more effective axonal sprouting in the fewer surviving motor fibers.

These results are confirmed by several studies in G93A transgenic mice, where the total dendritic surface area, the number of branching nodes and the fiber length of mutant motor neurons are significantly increased when compared with wild-type cells [9,10]. This apparent paradox may have a quite simple solution and these all anatomical differences could account for intrinsic membrane excitability changes: in fact, mutant motor neurons show a reduction in action potential threshold and are characterized by an increase both in spike height and depolarization rate in resting membrane potential [11]. However, whether these signs of increased excitability in fALS represent a pointless neuroprotective response of nervous system or a disease mechanism is still a matter of debate. On the other hand, we cannot rule out alternative explanations: in fALS the substantial lack of a fleeting stabilization of motor unit number within eight months from clinical onset could indicate that damage of cell different from motor neurons is a critical factor to the progression of corticospinal degeneration [12] (Figure 1).

Further studies are needed to solve these dilemmas, especially in familiar forms different from those related to mutations pertaining to Cu/Zn superoxide dismutase gene.

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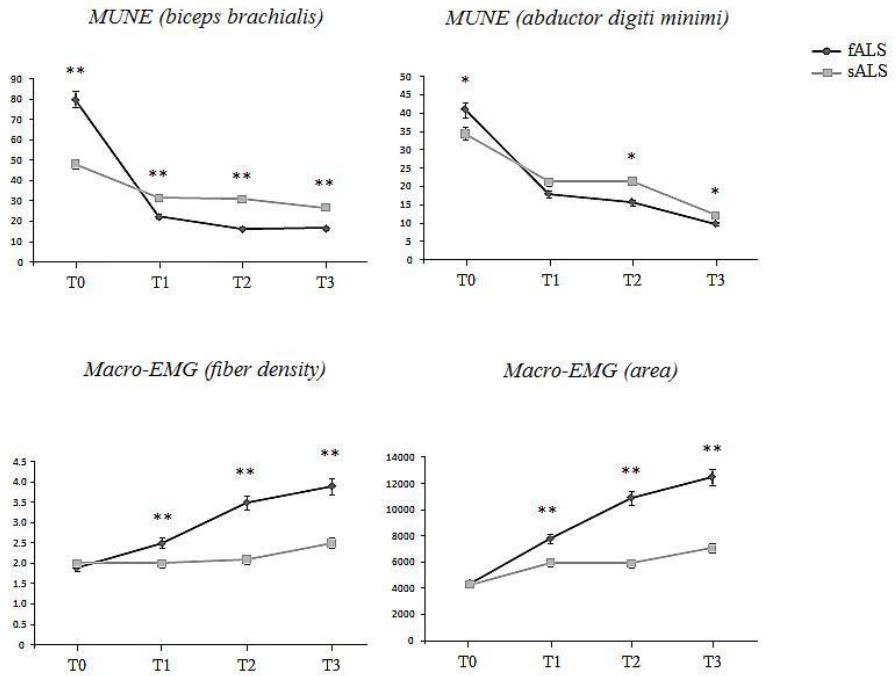

Figure 1: The top row shows MUNE values both for biceps brachialis, on the left, and abductor digiti minimi muscles, on the right, at different time points (at the moment of diagnosis and after 4, 8 and 12 months, respectively T0, T1, T2 and T3). Note that, at the moment of diagnosis, motor units number is higher for familiar cases (black lines, fALS) compared with sporadic ones (gray lines, sALS). Bottom row shows Time trend of Macro-EMG parameters (area, fiber density) over time. All the values increase more steeply in familiar than in sporadic forms (black and gray lines, respectively), strengthening the idea that in the first group there is a paradoxical more effective axonal sprouting (modified from Bocci et al. [7]; *p < 0.05; **p < 0.01).

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