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How to Assess Disease's Severity and Monitor Patients with Amyotrophic Lateral Sclerosis: Lessons from Neurophysiology

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1. Introduction

Amyotrophic Lateral Sclerosis (ALS) is a fatal, neurodegenerative disorder affecting upper and lower motor neurons; it's the commonest of the motor unit diseases in Europe and North America, characterized by a broad spectrum of clinical presentations mimicking vertebral stenosis, motor polyradiculoneuropathies and myopathies (Juergens et al., 1980; Swash, 2001). Striking asymmetry and selective involvement of individual groups of muscles, especially of hand and forearm, are typical early features of the disease. On average, delay from onset of symptoms to diagnosis is about 14 months and expected survival commonly ranges from months to a few years (Andersen et al., 2007).

Clinical neurophysiology in ALS plays a fundamental role both in the diagnosis of suspected disease and in the assessment of its severity and progression, offering a promising perspective to quantify muscle involvement and evaluate response to therapy (Brooks et al., 2000; Olney and Lomen-Hoerth, 2000; Beghi et al., 2002). Neuroimaging using magnetic resonance imaging (MRI), magnetic resonance spectroscopy (1HMRS), positron emission tomography (PET) and functional MRI may prove valuable results (Pohl et al., 2001), although they are complex, expensive and not always available. On the other hand, blood tests are necessary: hypoglycaemia insulinoma-related and autoimmune hyperthyroidism can be mistaken for ALS as they cause generalized muscle weakness, sometimes accompanied by fasciculations without a significant sensory impairment. Spinal fluid analysis could be helpful to rule out rare conditions closely mimicking ALS, such as meningeal infiltration with lymphoma, multifocal motor neuropathy (MMN) or a motor variant of inflammatory demyelinating neuropathy (CIDP). EMG investigation, usually performed with concentric needle electrodes (Daube et al., 2000), plays an essential role in the diagnosis and monitoring of ALS (Bromberg et al., 1993; Eisen, 2001; de Carvalho et al.,

2005b). Amplitude, duration, area, shape, stability on repeated discharges of motor units (MU) and activity at full effort are parameters conventionally used to evaluate disease's stage. EMG may also assess the presence of activity of the denervation-reinnervation process and number of functioning motor units by evaluating recruitment-activation pattern (Brooks et al., 2000; Finsterer and Fuglsang-Frederiksen, 2001). However, these parameters represent only indirect indicators of the number of surviving muscle fibers.

A particular method to evaluate the full MU is the so-called macro-EMG (Stålberg, 1980; Stålberg and Fawcett, 1982; Stålberg, 1983; Dengler et al., 1990). This technique provides information from a larger area of the muscle than traditional needle EMG methods. The signal is recorded by most of the fibers inside the entire MU and is often employed to follow the degree of reinnervation. That represents a quantitative technique and can be applied to follow progression and effects of putative therapies (de Carvalho et al., 2005a; de Carvalho et al., 2005b) by evaluating size of individual MU (Stålberg, 1983; Guiloff et al., 1988).

Among quantitative electrodiagnostic (EDX) techniques, the methodology of Motor Unit Number Estimation (MUNE) has been previously employed in measuring loss of functioning MU in ALS patients (McComas et al., 1971; Daube, 1995; McComas, 1995; Wang and Delwaide, 1998; Gooch and Shefner, 2004; Daube, 2006; Sartucci et al., 2007).

2. Know your enemy. The useful association of MUNE and macro-EMG

MUNE is very sensitive in documenting disease progression in ALS. Some studies combining MUNE and standard electromyography showed a highly significant correlation between motor unit loss, clinical quantitative features and variations in compound motor action potential (CMAP) amplitude over time (Liu et al., 2009). That is not surprising considering their different targets; while MUNE assesses motor unit loss, changes in CMAP amplitude and duration also account for collateral reinnervation. A few longitudinal studies using MUNE in some ALS patients have been reported that MUNE decreases as the disease progresses and that MUNE is a very reliable and reproducible method in patients with ALS (Olney et al., 2000; Kwon and Lee, 2004; Boe et al., 2007; Hong et al., 2007; Sartucci et al., 2007; Sartucci et al., 2011). Its inter-individual and intra-individual reproducibility linearly increases as disease progresses, making this technique particularly useful in the symptomatic stage of the disease (Sartucci et al., 2007; Sartucci et al., 2011). However, results from MUNE might seem contradictory or not always conclusive in view of many studies were made on animals; in comparison with transgenic mice, it's worth remembering that the majority of cases of ALS are sporadic and the SOD-1 GD^{93A} represents only about 20% of patients with hereditary ALS (Shefner et al., 2002; Zhou et al., 2007).

We routinely use the standard incremental technique, known as the McComas technique. Despite some limitations in comparison with statistical MUNE (alternation of motor unit, inability to recognize small motor units, small sample size), it is more reliable and less complex; in addiction, statistical MUNE cannot identify instable MUPs since it is based on the assumption that variability is due solely to the number of motor units responding in an intermittent manner (Shefner et al., 2007).

On the other hand, use of Macro-EMG is limited to muscles from which electrical activity can be elicited without any interference from other muscles (de Koning et al., 1988); moreover, it's difficult to perform it in the hands during the course of the disease due to the strong wasting of the intrinsic hand muscles. Because of these limitations, our twenty-years experience led us to combine the two techniques in order to improve diagnostic accuracy.

3. Methodological and technical considerations

The most used MUNE technique relays on manual incremental stimulation of the motor nerve, known as the McComas technique (McComas, 1995), modified by Ballantyne and Stålberg. The following test settings were used: sweep duration 50 ms, gain 2 mV/Div for M wave, 0.5 mV/Div for each step; filters 20 – 10 KHz (Keypoint Clinical Manual, 1999). The use of specific software for MUNE detects "alternation", eliminates subjectivity and the sampling of artifactually small motor units in ALS patients (McComas, 1995; Hong et al., 2007); ten incremental steps are commonly recorded (Sartucci et al., 2007).
Percutaneous stimuli were delivered over musculocutaneous nerve immediately below axilla, recording from BB muscles, and ulnar nerve at the wrist by recording from the ADM muscle of the same upper limb (Sartucci et al., 2007; Sartucci et al., 2011). Signals are detected with common surface electrodes, Ag/AgCl type, tapered on the cutis over the target muscles with a common muscle-belly tendon montage. In those patients who underwent follow-up after several months, each test was performed exactly on the same side with the same electrode position (spatial coordinates have been annotated in patients schedule).
At least two consecutive MUNE measures are usually performed on each patient to verify the consistency of our results; when required, further estimation was made until the MUNE was clearly stable. The mean of the two or more tests was calculated (Henderson et al., 2007). The results showed an excellent reproducibility with test-retest correlation coefficients ranging from 0.75 to 0.86 (Sartucci *et al.*, 2007).
The standard macro-EMG method is routinely applied in our patients (Stålberg, 1983). We employ a recording electrode, consisting of a modified single fibre EMG (SFEMG) electrode with the cannula Teflon insulated except for the distal 15 mm. The SFEMG recording surface is exposed 7.5 mm from the tip and the recording is made using two channels: the first one in whom the SFEMG activity is displayed (using the cannula as reference) and used to identify the MU and trigger the averaging procedure (band-pass filter for this channel: 500-10 kHz); fiber density (FD) of the triggering single fibre electrode is recorded. The second channel averaged the activity from the cannula until a smooth baseline and a constant macro MUP was obtained (Filter pass-band: 5-10 kHz).
Total area between the curve and the baseline, the maximal peak-to-peak amplitude (macro-MUP) during the total sweep time of 70 ms are measured (Bauermeister and Jabre, 1992). Results are expressed as individual area values from at least 20 recordings. The relative macro amplitude is expressed as the obtained mean value (Stålberg, 1983). Fibre density is expressed as number of time locked spikes obtained on the SFEMG channel (Sanders and Stålberg, 1996).

4. Our experience

Compared with previous studies (Bromberg et al., 1993; de Carvalho et al., 2005b), our idea was taking into consideration simultaneously Macro-EMG and MUNE changes, both in proximal and distal muscles, in the same sample of patients with a one-year follow-up.
Sixty-one ALS patients (34 male: mean age ± SD 60.0 ± 15.5, range 20-82 yrs; 27 female: mean age ± SD 62.0 ± 9.2 yrs, range 30-82 years), were enrolled in the study and examined basally (T0) and every 4 months (T1, T2 and T3). Macro Motor Unit Potentials (macro MUPs) were derived from Biceps Brachialis (BB) muscle; MUNE was performed both in BB and Abductor Digiti Minimi (ADM) muscles of the same side. Thirty-three healthy volunteers (13 women and 20 men, mean age: 57.7 ± 13.8 years, range 28 - 77 years) served as controls.

All patients had probable or definite ALS, according to the criteria of the World Federation of Neurology (Brooks et al., 2000).
The sample group of patients included cases with a disease duration from clinical onset of symptoms to the time of the first examination less than 48 months (mean ± 1SD: 12.2 ± 11.0 months); only few cases had a disease duration behind this limit (11 patients; about 14.3 %). Twenty-two patients presented a bulbar onset and the remaining a spinal one (Brooks et al., 2000). Muscle strength over time was evaluated by MRC score for all muscles (0-5 grading system). Forty patients were in treatment with riluzole (Rilutek® 50 mg), at a mean daily dosage of 100 mg (50 mg BID) throughout the entire period of EDX follow-up.
In twenty-nine patients (subgroup 1, SG1: 19 males and 10 females; mean age ± 1SD: 60,0 ± 11,8 years; range 30-78 years; spinal/bulbar onset: 22/7; mean disease duration 29,7 months) macro EMG was repeated after 4 months (T1). Among the second subgroup, eleven patients (subgroup 2, SG2: 8 males and 3 females; mean age ± SD: 57,0 ± 12,8 years; range 30–72 years; spinal/bulbar onset: 10/1; mean disease duration 31 months) were re-tested after 8 months (T2) and in 8 (Subgroup 3, SGP3; 7 males and 1 female; mean age ± SD: 58,0 ± 13,6 years; range 31-82 years; spinal/bulbar onset: 7/1; mean disease duration 37 months) after 12 months from the first examination.
Both patients and controls gave their written informed consent prior to participation in the study that had been approved by the local ethical Committee and followed the tenets of Helsinki.

5. Results

Macro-EMG in control subjects showed a mean area 1139.9 ± 182.8 μVms, a mean amplitude of 168.0 ± 63.7 μV, and a FD 1.24 ± 0.13 (a summary of results is given in *Figures 1* and *2*).

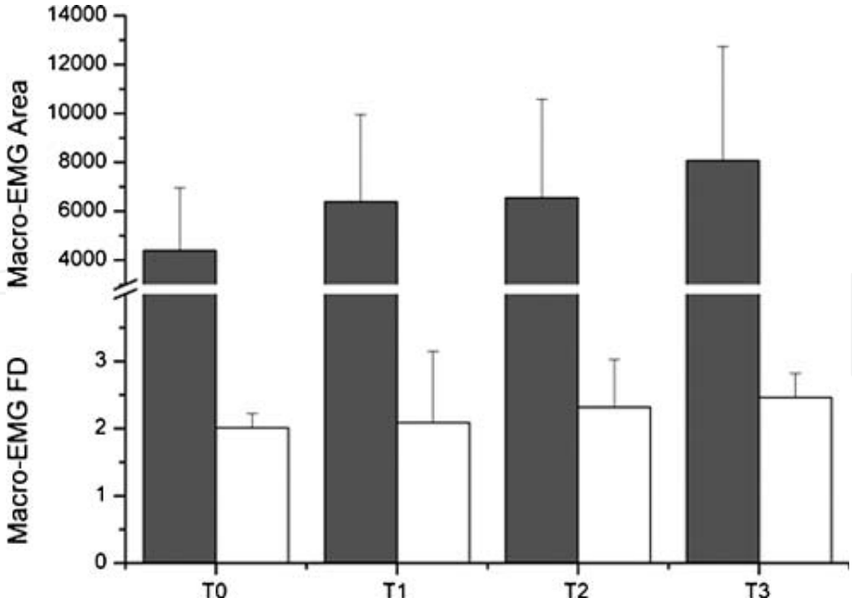

Fig. 1. Time evolution of macro-EMG FD (white columns) and of macro EMG area (gray columns; note the break and the different scale in ordinate) in ALS pt. The macro EMG area increase continuously with the time, paralleled by FD value, up to T2 (modified from Sartucci et al., 2011).

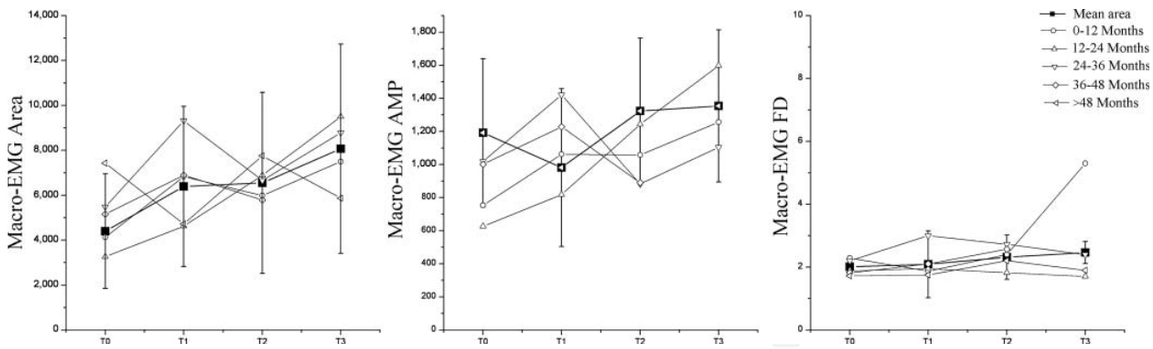

Fig. 2. Time evolution of each macro EMG parameters (area, amplitude and FD) with the time, keeping in the consideration disease duration at the beginning of the observation. Sample with a disease duration of 12-24 months exhibited a more steep slope (modified from Sartucci et al., 2011).

In ALS patients at T0, both Macro-MUP area and FD were above upper normal limits: macro-MUP area was 4397.6 ± 2554.9 μVms (+ 285.8%; $p < 0.001$), mean FD 2.01 ± 0.2 (+62.1%; $p < 0.005$).

The macro EMG MUP area was abnormal in 57 (93.4%). and normal in 4 (6.6%) patients, the FD resulted increased in 55 pt. (90%) and normal in 6 (10%). Macro EMG MUP area and peak-to-peak amplitude exhibited a good correlation (Spearmann coeff. of correlation = 0.888) at every time of testing (Gan and Jabre, 1992).

Macro MUPs area (*Figure* 2) resulted progressively increased at every time, especially at T3 compared with T0: Area: + 45.3% (T1); + 49.0% (T2); + 83.6% (T3); FD showed a trend to increase up to T3: +3.5% (T1); +15.4% (T2); +22.4% (T3) (Fig 2).

FD resulted increased in cases with longer disease duration (*Figure 2*). Anyway, the FD was generally increased when macro EMG amplitude was also increased in the first stage of disease; after less than one year (about 8 months) they showed a large dispersion of value.

MUNE (*Figure 3*) in controls resulted in BB muscle 91.9 ± 18.9, with a mean step area of 2.09 ± 0.7 μV/ms and a Mean Maximal M wave of 131.9 ± 36.0 mV; for the ADM muscle 87.7 ± 14.6, with a mean step area of 1.05 ± 0.4 mV/ms and Mean Maximal M wave of 61.3 ± 21.2 mV. In ALS patients, values were behind normal limits in 56 (91.8%) and within normal limits in 5 (8.2%) in BB muscle; in 60 (98.4%) and in 1 (1.6%) in ADM muscle. Functioning MUs number progressively decreased in both muscles throughout the entire follow-up period. The Pearson's correlation coefficient was 0,61, suggesting the rate and amount of MU decrease was approximately similar in both muscles (Cuturic et al., 2005). In ALS MUNE exhibited a parallel trends in proximal and distal muscles (BB and ADM), independently of disease duration (see *Figures 3 and 4*); mean step area, instead, increased more in BB, especially in patients with longer disease duration. MUP amplitude at T0 did not show any significant difference between females and males, even if a bit higher in males ($p>0.05$, Figure 5).

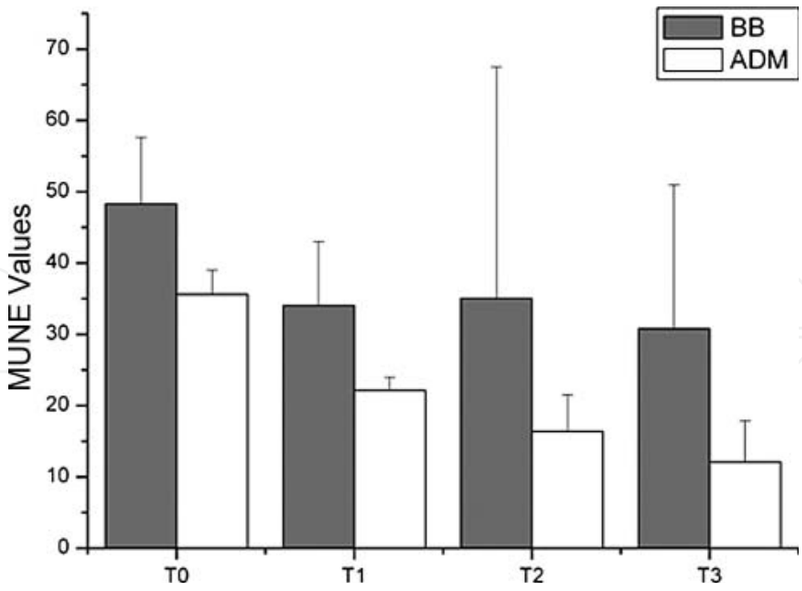

Fig. 3. Histogram showing MUNE values in both BB (gray columns) and ADM (white columns) muscles at every time of measurement. The trends is similar even if more evident in ADM (modified from Sartucci et al., 2011).

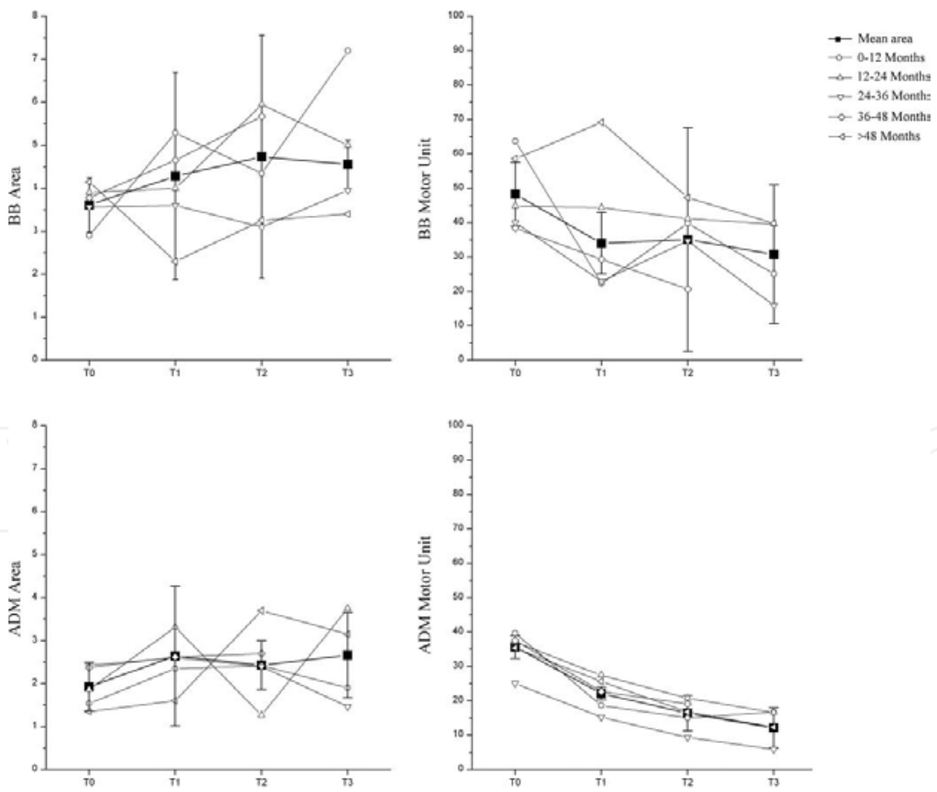

Fig. 4. MUNE values in both BB and ADM muscles at every time of evaluation in pt. with different disease duration and their mean value (filled circles) (modified from Sartucci et al., 2011).

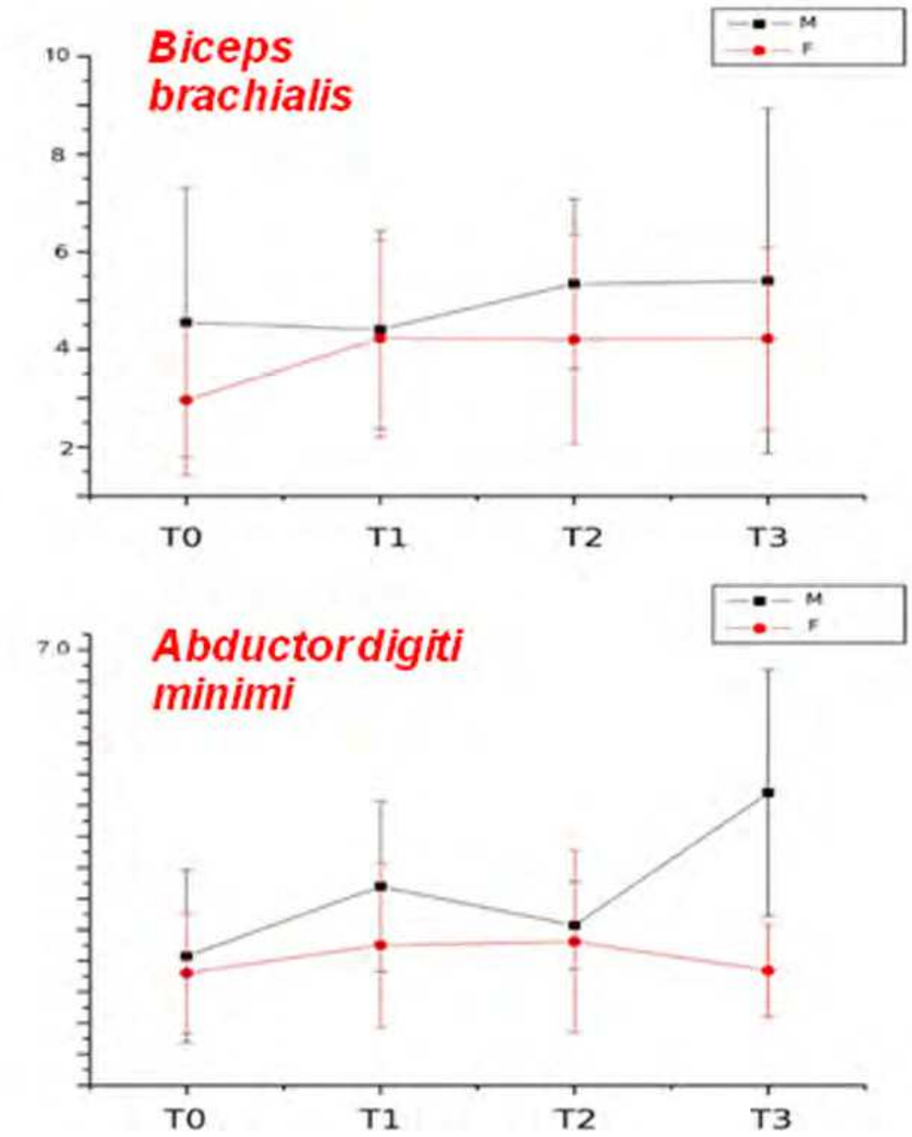

Fig. 5. MUP amplitude at T0 did not show any significant difference between females and males, both in spinal and bulbar form, even if a bit higher in males ($p>0.05$; Sartucci et al., personal data).

5.1 Correlation between macro-MUP and MUNE

All main macro-EMG parameters (area, amplitude and FD), as well as MUNE features (number of MUPs and mean step area either in the BB and ADM), did not disclose any significant difference between patients intaking the drug for both disease type (spinal or bulbar) at any time during the follow-up period (*Figure* 6). As concerns as Macro-EMG area, the difference in the mean values among the different levels of treatment is not great enough to exclude the possibility that the difference is just due to random sampling variability. There is not a statistically significant difference between riluzole vs. control ($p = 0.321$), as confirmed by FD measures over time ($p = 0.588$).

6. Conclusions and unanswered questions

Our study design was a prospective study to evaluate ongoing denervation/reinnervation process. Main aim was to objectively measure the extent of MU loss and the accompanying changes in innervation pattern during the time in ALS patients (Stålberg, 1983; Jabre, 1991), and therefore is often impossible to perform it in a hand muscle in the course of ALS due to the strong wasting of the intrinsic hand muscles; consequently to evaluate distal time disease evolution and its behaviour compared with proximal district we had to use only MUNE.

Area and amplitude of the Macro-MUP reflect number and size of muscle fibers in the motor unit (Schwartz et al., 1976; Stålberg et al., 1976). MUNE instead is the ideal tool for the assessment of disease in which primary defect is MU loss (Strong et al., 1988; Gooch and Shefner, 2004; Daube, 2006; Sartucci et al., 2007).

ALS is featured by repetitive cycles of denervation/reinnervation and the mechanism lead to a variation of fibre density within a given motor unit (Stålberg, 1983; de Carvalho et al., 2005a; de Carvalho et al., 2005b). If this rearrangement is interrupted by new processes of denervation, following further motor neuron loss, this will lead to areas of grouped atrophy and loss of muscle fibers. Reinnervation process are strictly interwoven with lower motor neuron loss; quantization and tracking of MU loss with simultaneously gauging countervailing collateral dynamic innervation may be assessed by combining MUNE and macro-EMG (Gooch and Shefner, 2004; Pouget, 2006). The macro-EMG gives a global view of the MU. First, the physical length of the electrode (15 mm), cover the entire diameter of an average sized MU; the large electrode surface suppresses the contribution of the closest action potentials and favours the relative influence of slow components so including distant fibers (Sanders and Stålberg, 1996).

Macro-EMG parameters in controls were in agreement with data of others authors (Stålberg and Fawcett, 1982; Stålberg, 1983; Jabre, 1991). Both macro-MUP area, amplitude and FD were beyond upper normal limits, as expected, in ALS (Bauermeister and Jabre, 1992; Gan and Jabre, 1992). Macro-EMG parameters progressively increased, at least in the first eight months compared with baseline as proved by coefficient of correlation at each time displaying a progressive increment of correlation up to 8 months, suggesting the process of MU rearrangement begins to fail after 8 months of disease course. Also when macro EMG area and amplitude were increased, FD was parallely increased.

The time elapsed from disease onset plays a fundamental role, since patients included with a diseases duration between 12 and 24 months showed largest changes in Macro EMG features, suggesting a higher efficiency of compensatory mechanisms at least in early stages of disease. Evidence of some MU loss at baseline compared with controls and its trend over time, together with a broader mean step area, yields novel insights into the pathophysiology of MU loss and its relationship to motor function in patients with ALS (Daube et al., 2000; Sartucci et al., 2007). Fluctuation of MU estimates between separate time could suggest reversible motoneurons dysfunction (Gooch and Shefner, 2004). The coefficient of correlation for MUNE – macro EMG mean area regression line was not significant (= - 0.17) in BB muscle, suggesting that both processes go on in some way independently. In more advanced stages, a decline of the strength of the surviving MUs, especially those with higher thresholds, seems to contribute to the progressive muscle weakness, in addition to both corticospinal degeneration and reduction in motoneurons

number (Dengler et al., 1990). Our study also showed a significant correlation between MRC scores and EDX measurements throughout the whole course of the disease only for ADM muscle. The absence of a significant correlation between MUNE and MRC values ($p > 0.05$) for BB could confirm the specificity of EDX investigations to track over time changes in muscle MU features and number. Muscle strength seems to decline more linearly than MUNE values: that could be explained, as recently suggested by Liu et al. (2009) with the persistence of a small proportion of lower motor neurons long-term surviving.

6.1 Gender and amyotrophic lateral sclerosis. Lessons from motor unit estimation

Another interesting result is about gender differences (*Figure 5*); in fact, some studies have reported a significant male predominance until the sixth decade of life and an older average age at onset for females, sometimes explained with a possible protective effect of estrogen. In our experience, MUP amplitude at T0 did not show any significant difference between females and males, even if a bit higher in males: MUP amplitudes were 86.9 ± 21.2 μV and 84.1 ± 17.5 μV for the biceps brachii and abductor digiti minimi muscle, respectively, in females, 90.7 ± 17.3 μV and 88.2 ± 16.8 μV in males ($p>0.05$). This is only a trend, as gender don't influence motor unit loss neither corresponding decline in MRC values over time. The lack of significant differences between females and males in both spinal and bulbar form, as emerged from our sample, is consistent with results reported by Hegedus (Hegedus et al., 2009): the antioxidant effects of estrogens and their proved role in preventing glutamate-related toxicity *in vitro* (Kruman et al., 1999; Nakamizo et al., 2000) could not delay both the early retraction of nerve terminals from neuromuscular end-plates and the dying-back of the axons during asymptomatic phase *in vivo*, as well as the denervation/reinnervation process in later stages. However, there is a substantial lack of studies describing the contribution of gender in progression of ALS; that's likely due to the discrepancy between humans patients and animal models, in terms of disease and presymptomatic phase duration, absence of sensitive biological markers and different pathogenesis (sporadic vs. SOD1-related; Zhou et al., 2007).

6.2 MUNE and Macro-EMG in evaluating response to treatment

Our investigation was aimed to evaluate also the EDX effects of one of the most common drug employed in the ALS, riluzole (Leigh et al., 2003), on the fundamentals process of ALS: the primary process of motorneurons loss and denervation, and the secondary process of reinnervation. Riluzole is a benzothiazole derivative with a wide range of effects on glutamate pathways including inhibition of presynaptic glutamate release; it is relatively safe and well tolerated. Prescription of riluzole is restricted to patients with probable or definite ALS. At the moment, there is no convincing evidence that treatment at 100 mg daily is associated with a significant increase in survival (Miller et al., 2007); its effects on quality of life and survival are weak especially in older patients (over 75 years), in those with bulbar onset and at more advanced stages (Miller et al., 2003). We did not detect any significant electrophysiological difference between patient intaking the drug and those who didn't (see *Figure 6*), but considering the high attrition rate it's quite difficult to draw any conclusion about the effect of pharmacological treatments on neurophysiological parameters. Future studies are then required to solve this dilemma.

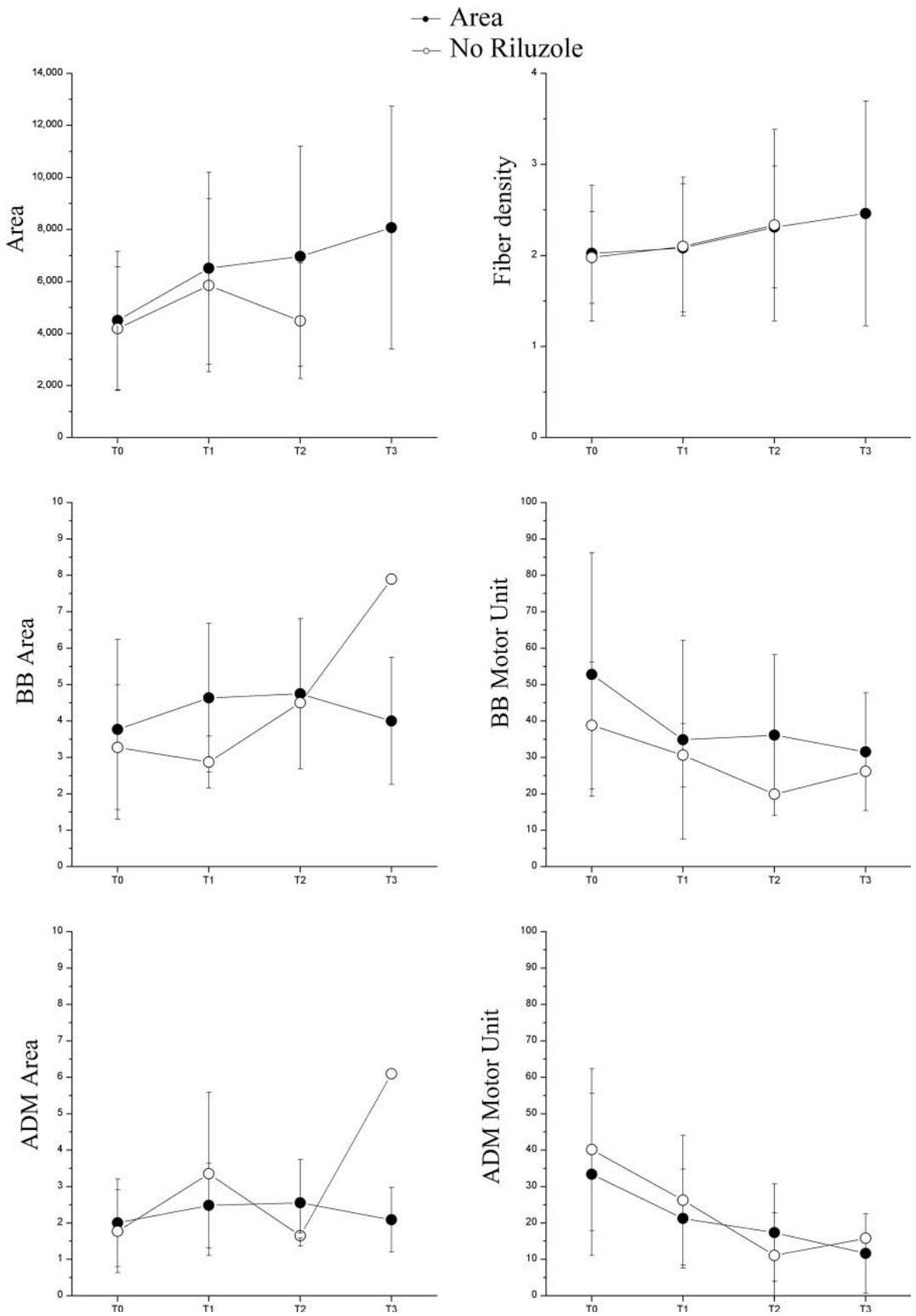

Fig. 6. Effects of Riluzole on the macro EMG and MUNE parameters with the time, in patients intaking (filled circle) or not (empty circle) the drug (modified from Sartucci et al., 2011).

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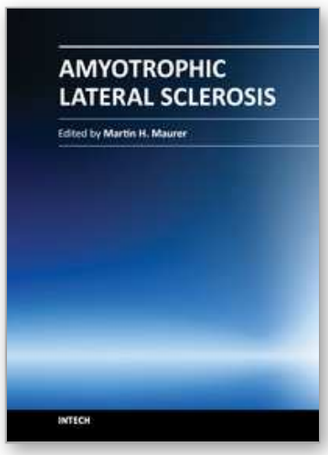

Amyotrophic Lateral Sclerosis

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Though considerable amount of research, both pre-clinical and clinical, has been conducted during recent years, Amyotrophic Lateral Sclerosis (ALS) remains one of the mysterious diseases of the 21st century. Great efforts have been made to develop pathophysiological models and to clarify the underlying pathology, and with novel instruments in genetics and transgenic techniques, the aim for finding a durable cure comes into scope. On the other hand, most pharmacological trials failed to show a benefit for ALS patients. In this book, the reader will find a compilation of state-of-the-art reviews about the etiology, epidemiology, and pathophysiology of ALS, the molecular basis of disease progression and clinical manifestations, the genetics familial ALS, as well as novel diagnostic criteria in the field of electrophysiology. An overview over all relevant pharmacological trials in ALS patients is also included, while the book concludes with a discussion on current advances and future trends in ALS research.

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