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● *Original Contribution*

MONITORING PROGRESSION OF AMYOTROPHIC LATERAL SCLEROSIS USING ULTRASOUND MORPHO-TEXTURAL MUSCLE BIOMARKERS: A PILOT STUDY

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Abstract—The need is increasing for progression biomarkers that allow the loss of motor neurons in amyotrophic lateral sclerosis (ALS) to be monitored in clinical trials. In this prospective longitudinal study, muscle thickness, echointensity, echovariation and gray level co-occurrence matrix textural features are examined as possible progression ultrasound biomarkers in ALS patients during a 5-mo follow-up period. We subjected 13 patients to 3 measurements for 20 wk. They showed a significant loss of muscle, an evident tendency to loss of thickness and increased echointensity and echovariation. In regard to textural parameters, muscle heterogeneity tended to increase as a result of the neoformation of non-contractile tissue through denervation. Considering some limitations of the study, the quantitative muscle ultrasound biomarkers evaluated showed a promising ability to monitor patients affected by ALS. (E-mail:) **© 2017 World Federation for Ultrasound in Medicine & Biology. All rights reserved.**

Key Words: **Amyotrophic lateral sclerosis, Motor neuron disease, Neuromuscular diseases, Biomarkers, Ultrasonography, Disease progression, Image processing computer-assisted.**

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disorder affecting both upper motor neurons (UMNs) and lower motor neurons (LMNs), leading to gradual muscle weakness and wasting (Wijesekera and Leigh 2009). The variable degree of impairment of UMN and LMN results in pathologic and clinical heterogeneity, which hinders diagnosis, prognosis and the monitoring of progression (Kinsley and Siddique 1993). Electromyography allows LMN impairment to be detected before the onset of overt symptoms and consequently has been incorporated in successive diagnostic criteria (Brooks et al. 2000). However, despite some promising new neurophysiological techniques such as motor unit number index (MUNIX) (Neuwirth et al. 2015) and electrical impedance myography (Rutkove et al. 2012), clinical tools such as Medical Research Council (MRC) (Florence et al. 1992) and the revised ALS functional rating scale (ALSFRS-r) (Simon et al. 2014), remain the gold standard biomarkers for progression monitoring in clinical trials or clinical practice.

Muscle ultrasonography (MUS) is an accessible, painless and easy-to-perform method to detect structural muscle changes in ALS (Mayans et al. 2012). More specifically, MUS reveals marked diminished muscle thickness (MTh), increased echointensity (EI) and fasciculations (Arts et al. 2012; Martínez-Payá et al. 2017a). However, in a longitudinal study, Arts et al. (2010) observed that these ultrasound changes found in ALS patients were highly variable and did not show evident correlation with functional measures like muscle strength or disability during 6 mo of monitoring (Arts et al. 2011a).

We have previously described a new first-order ultrasound biomarker, echovariation (EV), which distinguished the muscles of ALS patients from healthy control subjects, with higher effect sizes than MTh or EI and correlating better with other clinical variables (Martínez-Payá et al. 2017a).

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Although EV is a quick and easy method to obtain information on tissue homogeneity (Aggarwal and Agrawal 2012), it does not provide information concerning the relative positions of the various grey levels within the image. This issue can be resolved by a second-order statistics feature that is based on the gray-level co-occurrence matrix (GLCM), where the pixels are considered in pairs. GLCM detects the relationship between neighboring pixel intensities and provides information about gray-level patterns (Haralick et al. 1973). Moreover, GLCM parameters showed reduced granularity in the muscles of ALS patients in comparison with control subjects and a similar discrimination capacity to EV (Martínez-Payá et al. 2017b).

However, the usefulness of the textural features of EV and GLCM as progression biomarkers has not been analyzed. Hence, we designed a prospective longitudinal study in patients with ALS to evaluate these new biomarkers and compare them with MTh and EI, during a follow-up period of 20 wk.

MATERIAL AND METHODS

Patients

Patients were recruited from the ALS Association (ADELA) of Valencia, Spain, September 2013–April 2014. We included 26 patients diagnosed with ALS, according to the revised El Escorial Criteria (Brooks et al. 2000) by an experienced neurologist (J.F.V.C.). The same cohort had been used previously to assess changes in EV and GL among patients (at recruitment) and controls (Martínez-Payá et al. 2017a, 2017b). For this longitudinal study, each patient was evaluated twice more within an interval of 10 wk ± 7 d.

Standard protocol approval, recruitment and patient consent. This study was approved by the Ethics Committee of the Universidad Católica de Murcia, Guadalupe, Spain. All participants provided written informed consent.

Recorded variables

Demographic and clinical characteristics (gender, age, weight, height, body mass index and time since diagnosis) were recorded. Muscle strength was measured using the MRC global score with a maximum value of 100 (Florence et al. 1992), as described and segmented by upper limbs, (maximum 50), lower limbs (maximum 30) and neck muscles (maximum 20). The ALSFRS-r rating scale (Cedarbaum et al. 1999) was assessed by the same investigator (J.M.P.) on the same day the MUS was performed.

Ultrasonography

MUS was performed in four muscle groups of each side by the same experienced examiner (J.M.P.), blinded for the diagnosis, with a phased array real-time scanner LOGIQe BT12 (General Electric Healthcare, Beijing, China) and a 5 – 13 MHz linear array transducer (12 L – RS) as previously published (Martínez-Payá et al. 2017a, 2017b).

Applying the standardized protocol described (Arts et al. 2011a; Martínez-Payá et al. 2017a), bilateral transverse ultrasound images of the biceps and brachialis, forearm flexors group, quadriceps femoris and tibialis anterior were obtained and measured. Three images were taken of every muscle to minimize variation in measurement parameters (Arts et al. 2008).

The resulting images had a resolution of 820 × 614 pixels (with a scale of 99.5 px/cm for tibialis anterior muscle and 83.5 px/cm for other muscles) involving 256 gray levels, and were stored as tag image file format (TIFF) files without compression or loss (Wiggins et al. 2001).

Image analysis

MTh was measured with electronic calipers as previously described (Arts et al. 2010; Martínez-Payá et al. 2017a, 2017b). This parameter was measured in all three images of each muscle group by an expert ultrasonographer (J.M.P.) and the mean of the three values was used for the corresponding analysis.

The image processing and analysis was performed by one researcher (J.R.D.), blind to diagnosis, using the ImageJ software (v.1.48 [2015], National Institutes of Health, Bethesda, MD, USA). The region of interest (ROI) was selected with the ROI Manager application for ImageJ, with a size of 71 × 40 pixels for tibialis anterior and 73 × 73 pixels for other muscle groups on an 8-bit gray-scale. The ROI was defined as the muscle region without bone and fascia with the best reflection (Martínez-Payá et al. 2017a, 2017b) (Fig. 1). This ROI selection method was found to be reproducible and valid in a previous study (Martínez-Payá et al. 2017a). From the ROI we obtained EI, EV (Martínez-Payá et al. 2017a) and GLCM (Martínez-Payá et al. 2017b) textural features.

The texture analysis based on a GLCM is derived from the angular relationship between neighboring pixels (Nanni et al. 2013), among which five parameters were selected: energy or angular second moment (ASM); textural correlation (TC); homogeneity or inverse difference moment (IDM); contrast (CON) and entropy (ENT). A homogeneous image would be the result of a greater ASM, TC and IDM and a smaller CON and ENT.

Statistical analysis

Data were analyzed using IBM SPSS Statistics for Windows 19.0, 2010 (IBM Corp. Armonk, NY, USA). Data were summarized by mean, standard deviations, range and 95% confidence intervals for continuous variables and absolute and relative frequencies for categorical variables. Significance was fixed at 0.05 in all the statistical tests.

The follow-up group with 3 measurements (initial, 10th wk and 20th wk) was compared with the lost to

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