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ABSTRACT

We assessed the prognostic value of muscle ultrasonography in 31 patients with amyotrophic lateral sclerosis (ALS) and compared it with accepted prognostic variables like functional capacity (measured with the ALSFRS-R rating scale) and muscle strength. Each patient was examined once. The following ultrasonography parameters were determined: muscle thickness, echo intensity (EI) and the presence of fasciculations. Correlations between baseline measurements, preslope values and survival were calculated. EI, disease duration, muscle strength preslope and ALSFRS-R preslope correlated with survival. Using a stepwise multivariate analysis, the combination of EI preslope and ALSFRS-R preslope was shown to have the best predictive value for survival.

INTRODUCTION

Survival is an important and frequently used outcome measure for clinical trials in amyotrophic lateral sclerosis (ALS).[1,2] The median survival time from diagnosis is estimated to be around 15 months.[3] However, more than 25% of patients live longer than 4 years.[3] Due to this large interindividual variation, the use of survival as a primary outcome measure leads to studies with large sample sizes and long duration.[3-6] One possible solution to compensate for population heterogeneity is the use of prognostic variables for stratification. Examples of such variables are age, time from symptom onset to diagnosis, and functional capacity as measured with the revised ALS Functional Rating Scale (ALSFRS-R).[3,5-7]

Ultrasonography, a painless and relatively simple technique, can be used to visualize structural muscle changes caused by a neuromuscular disorder.[8] Affected muscles show a diminished muscle thickness and appear whiter (i.e. have an increased echo intensity; EI).[8] Aging also results in diminished muscle thickness and increased EI.[8] By quantitative analysis, with use of age and gender based normal values, it is possible to discriminate between neuromuscular and non-neuromuscular diseases with high sensitivity and specificity.[8] Furthermore, due to its capability to register movements, ultrasonography is a highly sensitive tool to reveal fasciculations. Recently we showed that even in an early stage of ALS, atrophy, increased EI and fasciculations could be detected.[9]

Here, we studied whether muscle ultrasonography can be used as an additional prognostic tool to predict survival in patients with ALS.

METHODS

Subjects

We included 31 patients with probable, possible or definite ALS according to the El Escorial Criteria.[10] Patients were examined once. Recordings included measurements of muscle strength, ALSFRS-R and muscle ultrasonography. Outcome was retrieved from the medical records. The survival time, defined as the time from symptom onset, was estimated using medical records. The local ethical committee approved the study and all patients gave written informed consent.

Ultrasonography

Using a standard protocol,[9] transverse ultrasound scans were made of the following muscles or muscle groups on both sides: sternocleidomastoid, biceps brachii including the underlying brachialis muscle, forearm flexor group, quadriceps femoris and tibialis anterior. Measurements were performed using either a Philips IU22 with a 5-17 MHz linear broadband transducer or a HP Sonos 2000 phased-array real-time scanner with a 7.5-MHz transducer. The system settings and conversion procedure to combine results from the two scanners have been described elsewhere.[11] Thickness and EI of each muscle were determined using standardized procedures.[9] Furthermore, each muscle(group) was screened for fasciculations during 10 seconds.[9]

Muscle strength and ALSFRS-R

Muscle strength of 10 different muscle groups of the neck, upper and lower limbs was manually tested on both sides, and scored with the modified scale of the Medical Research Council.[12] The total sum score was calculated, with a maximum score of 100. The

ALSFRS-R was used to quantify activities of daily living.[13] The ALSFRS-R consists of 12 items with scores ranging from 0 to 4, with a maximum achievable score of 48 (0 = total disability, 48 = normal).

Analysis

Data were analyzed using SPSS V16.0. Data are shown as mean ± SD (range). Muscle thickness and EI were corrected for age, gender and handedness and transformed into z-scores, which were then summed to yield a composite z-score (with a normal value of 0). The prognostic value of each variable was expressed in terms of a hazard ratio using univariate analysis. For the factors reaching significance in this test, adjusted hazard ratios were estimated by multivariate analyses (forward conditional method) using a Cox proportional hazards regression model. Tested variables included age, disease duration, number of muscles with fasciculations, and baseline values of EI, muscle thickness, ALSFRS-R and strength. In addition, preslope values of EI, muscle thickness, ALSFRS-R and strength were calculated and tested as prognostic variable. Preslope values – the estimated rate of change of outcome measures prior to first examination- have shown to be good predictors of survival in various studies.[5,6,14] Preslope values were computed as follows: (measured value – normal value) / disease duration. The relation between the different variables was assessed using Spearman's correlation coefficients.

RESULTS

A total of 31 patients were included (19 males), with an age of 60.4 years ± 12.4 (37-80) and weight of 77.1 kg ± 10.7 (53-93). Six patients were classified as possible, 22 as probable, 2 as definite and 1 patient as familial ALS. They all used riluzole. The diagnosis was established 13.8 months ± 8.6 (3-39) after symptom onset. Ultrasonography examination was performed 21.2 months ± 10.4 (5.2-51.4) after presenting symptoms. At that time the mean ALSFRS-R score was 35.4 ± 6.8 (18-46) and the mean muscle strength 84.7 ± 11.6 (57-99). At the time of analysis -approximately 6 months after inclusion of the last patient- 16 out of 31 patients (51.6%) were deceased.

Patients showed a reduced muscle thickness, total z-score: -11.6 ± 13.1 (-38.8 – 12.2) and increased EI: total z-score 22.0 ± 13.9 (5-68.5). The average number of muscles showing fasciculations was 6.6 (range 1-10).

Table 1 displays the results of the univariate and multivariate analysis to predict survival. As reported before,[3,5,6] shorter disease duration, and lower ALSFRS-R preslope were individually associated with a shorter survival. Furthermore, lower muscle strength preslope was correlated with a worse prognosis. Of the ultrasound measures, higher EI preslope values significantly predicted shorter survival as well.

Table 1. Cox proportional hazard analysis to predict survival

	Univariate		**Multivariate**	
	Hazard ratio (95% CI)	p	Hazard ratio (95% CI)	p
Age	1.02 (0.97 - 1.06)	0.471		
Gender	1.27 (0.47 -3.38)	0.637		
Weight	0.98 (0.93 - 1.02)	0.318		
Disease onset - diagnosis	0.93 (0.86 - 1.00)	0.052		
Disease onset - ultrasound	0.94 (0.89 - 0.99)	0.020		
Number of muscles with fasciculations	1.09 (0.89 – 1.33)	0.388		
Total muscle thickness	1.00 (0.96 - 1.06)	0.830		
Total EI	1.01 (0.98 - 1.05)	0.574		
Total strength	0.98 (0.94 - 1.01)	0.171		
Total ALSFRS-R	0.96 (0.90 - 1.02)	0.162		
EI preslope	4.72 (2.02 – 11.03)	0.001	4.88 (1.06 – 22.44)	0.042
Muscle thickness preslope	0.89 (0.38 – 2.07)	0.774		
Strength preslope	0.08 (0.03 – 0.25)	< 0.001		
ALSFRS-R preslope	0.021 (0.003 – 0.15)	< 0.001	0.019 (0.002 – 0.23)	0.002

Stepwise multivariate analysis revealed a predictive model that only included the EI preslope and ALSFRS-R preslope as prognostic variables. Although being an individual predictor of survival, muscle strength preslope was not of additional value to the multivariate predictive

model. This may be due to the strong correlation between muscle strength and ALSFRS-R preslope (correlation coefficient 0.74, p <0.001). The correlation between EI and ALSFRS-R preslope was relatively weak (correlation coefficient -0.41, p = 0.05), indicating that these are independent predictors. The correlation coefficients of the other preslope parameters were as follows: ALSFRS-R - muscle thickness: 0.18 (p = 0.344), muscle thickness - EI: -0.45 (p = 0.011) and EI - strength preslope: -0.51 (p = 0.004).

The prognostic value of both EI and ALSFRS-R preslope is further illustrated by Kaplan-Meier plots, showing clear differences in survival when stratified using EI or ALSFRS-R preslope or the combination of both (Figure).

DISCUSSION

Our study shows that an increased muscle EI preslope predicts survival in patients with ALS. Moreover, increased EI had additional prognostic value when combined with the ALSFRS-R preslope, an already accepted predictor for survival.[1,5,6] The independent value of both measures is supported by their rather low correlation, suggesting they represent different aspects of the disease process in ALS. The number of fasciculations did not predict survival.

Although muscle strength preslope was strongly predictive for survival in the univariate analysis is, it did not emerge as an additional predictive parameter in the stepwise multivariate analysis. Most likely, this was due to the strong correlation between muscle strength and the ALSFRS-R preslope, so adding muscle strength to the model did not increase its predictive value.

Preslope values were better predictors of survival than baseline values or disease duration. Preslope values combine these two aspects, probably making these a better indicator of the rate of “preclinical” disease progression. A practical advantage of preslope values is the fact that they are based on just one evaluation point that can be routinely acquired during the diagnostic process. In addition, preslope values are convenient in clinical trials, since these do not require a lead-in period.[4] However, it would be useful to directly compare preslope ultrasonography measures with a longitudinal repeated measures design as a final 'validation'.

EI preslope was a good predictor of survival, in contrast to muscle thickness. This may be due to the fact that EI is the result of intramuscular fatty or fibrous tissue, an irreversible consequence of denervation.[15,16]. In contrast, muscle atrophy is not only caused by denervation but is also the result of other factors like disuse. Training and reinnervation can temporarily prevent muscle atrophy, but will not have considerable effects on the amount of intramuscular fatty or fibrous tissue.

The significant results in this relatively small study further show the strength of EI preslope as a predictor for survival. However, precise cut-off values need to be established in a large follow-up trial.

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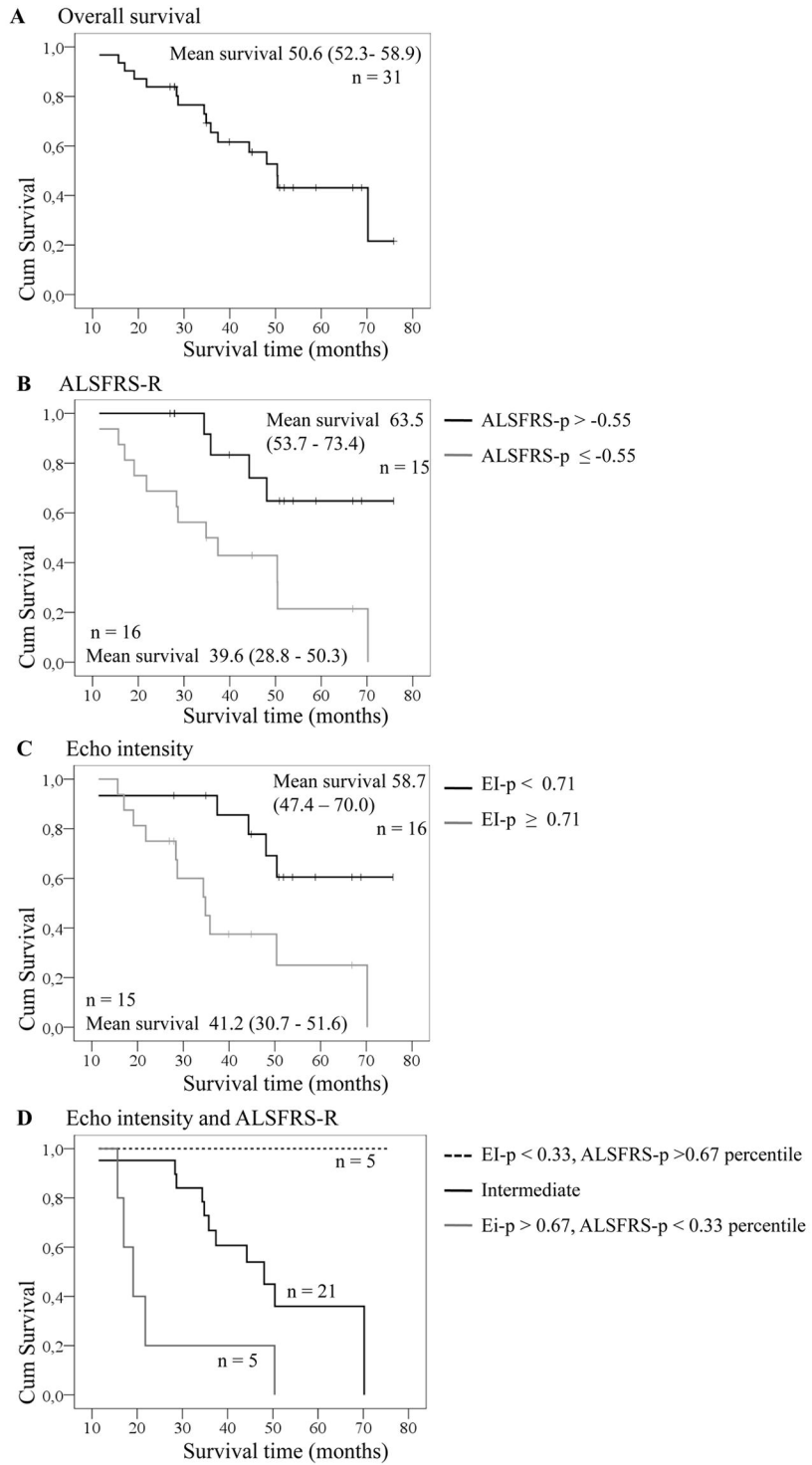
FIGURE LEGEND

Figure

Kaplan-Meier plot describing overall cumulative survival (A) and cumulative survival after stratification by ALSFRS-R preslope (B), EI preslope (C) or the combination of EI and ALSFRS-R preslope (D). The small vertical lines represent censored cases. In plot B and C median values of ALSFRS-R and EI preslope were used as cut-off values respectively. In plot D, 33th and 67^{th} percentiles were used as cut off. Abbreviations: EI-p - EI preslope, ALSFRS-p - ALSFRS-R preslope.


A
Overall survival
Mean survival 50.6 (52.3- 58.9)
n = 31
Cum Survival
Survival time (months)
B
ALSFRS-R
Mean survival 63.5
(53.7 - 73.4)
n = 15
n = 16
Mean survival 39.6 (28.8 - 50.3)
ALSFRS-p > -0.55
ALSFRS-p ≤ -0.55
C
Echo intensity
Mean survival 58.7
(47.4 – 70.0)
n = 16
n = 15
Mean survival 41.2 (30.7 - 51.6)
EI-p < 0.71
EI-p ≥ 0.71
D
Echo intensity and ALSFRS-R
n = 5
n = 21
n = 5
EI-p < 0.33, ALSFRS-p >0.67 percentile
Intermediate
Ei-p > 0.67, ALSFRS-p < 0.33 percentile