Changes in Motor Unit Number Estimate and Forced Vital Capacity as Predictors of ALS Progression

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ABSTRACT

Background. An independent measure of lower motor neuron function that can be monitored over time is essential in evaluating the effect of drugs or stem cell transplantation and in determining prognosis in amyotrophic lateral sclerosis (ALS). Longitudinal changes in forced vital capacity-percent of predicted (FVC%) and motor unit number estimate (MUNE) may identify patient groups with more rapid disease progression.

Objective. We attempted to define cutoff values for 3-month changes in FVC% and MUNE that identify ALS patients with rapidly progressive disease defined as survival of 30 months or less from symptom onset.

Design. Cohort study.

Subjects. We report data from 26 ALS patients, 10 patients reported previously, and 16 patients not reported previously, except for the reproducibility of their MUNE data.

Results. Of the 26 patients, 7 had rapid progression. Either a 40% decrease in statistical MUNE or a 20% decrease in FVC% over 3 months identified 6 of 7 rapid progressors (Sensitivity=86% 95% confidence interval [CI] 42.1% - 99.6%). Of the 19 patients without rapid progression, 18 met neither the FVC nor MUNE criterion (Specificity = 94.7% CI 95% 74.0% - 99.9%). In a proportional hazards model, 3-month change in both FVC and MUNE were significantly predictive of decreased survival.

Conclusion. We suggest the use of a three-month change in MUNE or FVC% as a secondary enrollment criterion in therapeutic trials or to identify a subgroup of rapid progressors that may respond differently to treatments.

Keywords: *ALS, amyotrophic lateral sclerosis, FVC, MUNE, EMG.*

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease with loss of both upper and lower motor neurons. Patients live an average 3-5 years after symptom onset and ultimately die due to involvement of the diaphragm causing respiratory failure. Survival depends on the degree of lower motor neuron involvement, which is why stem cell trials for ALS have been targeting the spinal cord. An independent measure of lower motor neuron function that can be monitored over time is essential to evaluating the effect of drugs or stem cell transplantation and to determining prognosis. Various measurements have been used to monitor progression in ALS including forced vital capacity (FVC), compound muscle action potential (CMAP), and manual muscle testing (MMT), but these techniques do not specifically measure lower motor neuron loss. The most sensitive marker of disease progression in ALS, and the only measure of lower motor neuron loss, has been found to be motor unit number estimation (MUNE) using a variety of techniques.[1,2]

The concept of motor unit number estimation was developed in 1971 by McComas, who estimated MUNE as the ratio of the maximal CMAP divided by the average single motor unit (SMUP): $MUNE = CMAP_{max}/SMUP_{mean}$. To determine the average single motor unit, he developed the incremental stimulation technique, which is used less frequently than other techniques due to the problem of alternation in the number of axons activated at a particular stimulation current.[3] To avoid the problem of alternation, the multiple point stimulation technique was developed. Single axons are activated by moving the stimulator along different points of the nerve and stimulating just enough to activate single axons. These are then averaged together and used in the equation above to calculate MUNE.[4] Spike triggered averaging and decomposition MUNE also collects one SMUP at a time by using low levels of muscle contraction and applying decomposition algorithms to the interference pattern.[5] The amplitude is influenced by the force of contraction and this needs to be accounted and adjusted for.[6] An alternative technique, the statistical method, which does not involve moving the stimulator or collecting individual SMUPs, was developed by Daube.[7] This technique uses Poisson statistics to determine the variance at different set stimulation intensities and thus estimate the single motor units. A direct comparison of the multiple point method and the statistical method demonstrated greater reproducibility with the statistical method but systematically lower MUNE values.[8]

MUNIX is a relatively newly developed technique by Nandedkar[9] in 2003 using surface interference patterns recorded during voluntary contractions to extract the average SMUP. Preliminary results suggest it is more reproducible, at least when compared to incremental stimulation.[10]

Three studies have reported longitudinal changes in motor neurons over time using MUNE.[11, 12,13] Results show more rapid loss of motor neurons in patients with shorter survival. This loss happens even before clinical weakness, as demonstrated in SOD 1 mutation carriers.[14]

As mentioned above, we previously compared two popular MUNE methods, the multiple point stimulation method and the statistical method. In our hands the statistical method had better reproducibility than the multiple-point stimulation method.[8]

A single measurement of the FVC% has long been recognized as a strong predictor of survival in ALS patients.[15] In fact, the usual criterion for admission to hospice, denoting the expectation of less than six months to live, is the FVC% value. Vender and colleagues demonstrated that the half of their patients who had more rapid rates of change in FVC had survivals half as long.[16]

In this study, we attempted to identify specific cutoffs for 3-month decrease MUNE and FVC% to identify rapidly progressive ALS.

Methods

Subjects. The patient population for this study consisted of 26 patients with probable or definite ALS who participated in the phase 3, placebo-controlled, low-dose, brain-derived neurotrophic factor (BDNF) trial at UCSF. All 26 patients had initial and 3-month measurements of both MUNE and FVC which were technically satisfactory. Testing was performed after patients gave written and informed consent. This study was approved by the UCSF Institutional Review Board.

Electrophysiological Studies. Electrophysiological studies were performed using methods that have been described previously.[11,17] At the baseline visit, bilateral compound muscle action potentials (CMAPs) were recorded from the hypothenar muscles with stimulation of the ulnar nerve at the wrist. Subsequent electrophysiological studies were performed on the side with the larger amplitude, if this limb had signs of upper or lower motor neuron involvement clinically. If the upper limb with the larger ulnar CMAP amplitude did not have signs of upper or lower motor neuron involvement clinically, then subsequent electrophysiologi-

cal studies were performed on the side with the smaller amplitude. The statistical method of MUNE was performed three times on each occasion, as we have described previously.[11,17] For longitudinal analysis, the three MUNE counts of each day were averaged.

Forced Vital Capacity. Forced vital capacity was measured with a Renaissance spirometer (Puritan Bennett, Boulder, Colorado). This spirometer calculates the forced vital capacity, percent of predicted (FVC%) based on the age and height of the patient. Three measurements were required to be within a ten percent range for acceptance. The highest of these values was used for analysis.

Statistical Analysis. The primary focus was to identify patients who had rapidly progressive ALS. Rapidly progressive disease was defined as survival from symptom onset to death of no more than 30 months. The need for ventilator support for more than 23 hours a day would have been considered equivalent to death, but this was not applicable for any of the included patients.

The rapid progressors were compared to non-rapid progressors regarding age, site of onset, 3-month percent change in MUNE and FVC%. Means were compared using t-tests with unequal variance and proportions were compared using the Fischer exact test. Both 3-month percent change in MUNE and FVC% were incorporated into a Cox proportional hazards survival model. Individual ROC curves with areas under the curve were constructed for 3-month percent change in MUNE and FVC% as tests for rapid progression. We based our choice of cut points to identify rapid progressors on visual inspection of the ROC curves. We calculated the sensitivity and specificity of a rule combining the two cut-points. We compared the Kaplan-Meier survival curves of the rule-positive to the rule-negative patients using the log-rank test. All statistical analyses were performed using STATA (Stata Corp., College Station, TX).

Results

Of the 26 patients, 7 had rapid progression as defined by survival from symptom onset of 30 months or less. The rapid progressors did not differ from the other patients regarding age or site of onset (Table 1).

The mean 3-month decrease in MUNE was almost 3 times greater among the rapid progressors than in the other patients, and the mean 3-month decrease in FVC% was more than 3.5 times greater. However, because of the small number and high variability in the rapid progression group, these differences did not reach statistical significance.

Table 1. Comparison of Rapid Progressors to Other Patients

	Survival from Symptom Onset				Total		P
	≤30 months		> 30 months				
N	7		19		26		
Mean Survival (range)	22.7	(19 - 25)	87.3	(39 - 277)	69.9	(19 - 277)	
Age (SD)	55.1	(11.6)	54.4	(10.0)	54.9	(11.0)	0.901
Males (%)							
Site of Onset							0.922
Bulbar	2	28.6%	4	21.1%	6	23.1%	
Upper Extremity	2	28.6%	6	31.6%	8	30.8%	
Lower Extremity	3	42.9%	9	47.4%	12	46.2%	
3-month % decrease							
MUNE (SD)	40.8	39.3	14.3	20.6	21.4	28.7	0.132
FVC% (SD)	22.6	22.0	6.1	6.5	10.6	14.2	0.096

In the Cox survival model, the 3-month changes in both MUNE and FVC% were statistically significant (Table 2).

A 10 percent decrease in MUNE and FVC% corresponded to an increase in mortality rate of 25% and 50% respectively.

Visual inspection of the ROC curves shows high specificity cut points at 40% for MUNE and 20% for FVC (Figure 1). A rule classifying the patient as a rapid progressor for either a 3-month decrease of 40% in MUNE or 20% in FVC correctly identified 6 of 7 rapid progressors and 18 of 19 other patients. This corresponds to a sensitivity of 86% (95% confidence interval [CI] 42.1% - 99.6%) and specificity of 94.7% (CI 95% 74.0% - 99.9%). One patient with a 3-month MUNE increase of 4% and FVC% decrease of 6% survived only 23 months and would have been a false negative by this rule. Also, a patient who had a 50% decrease in MUNE and a 7.5% decrease in FVC% survived 44 months and would have been falsely identified as a rapid progressor.
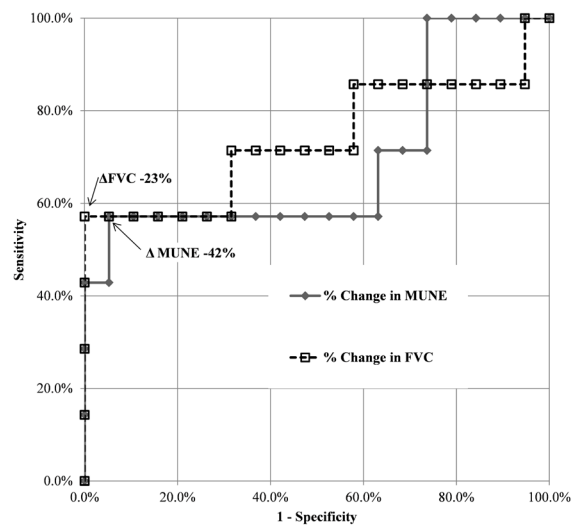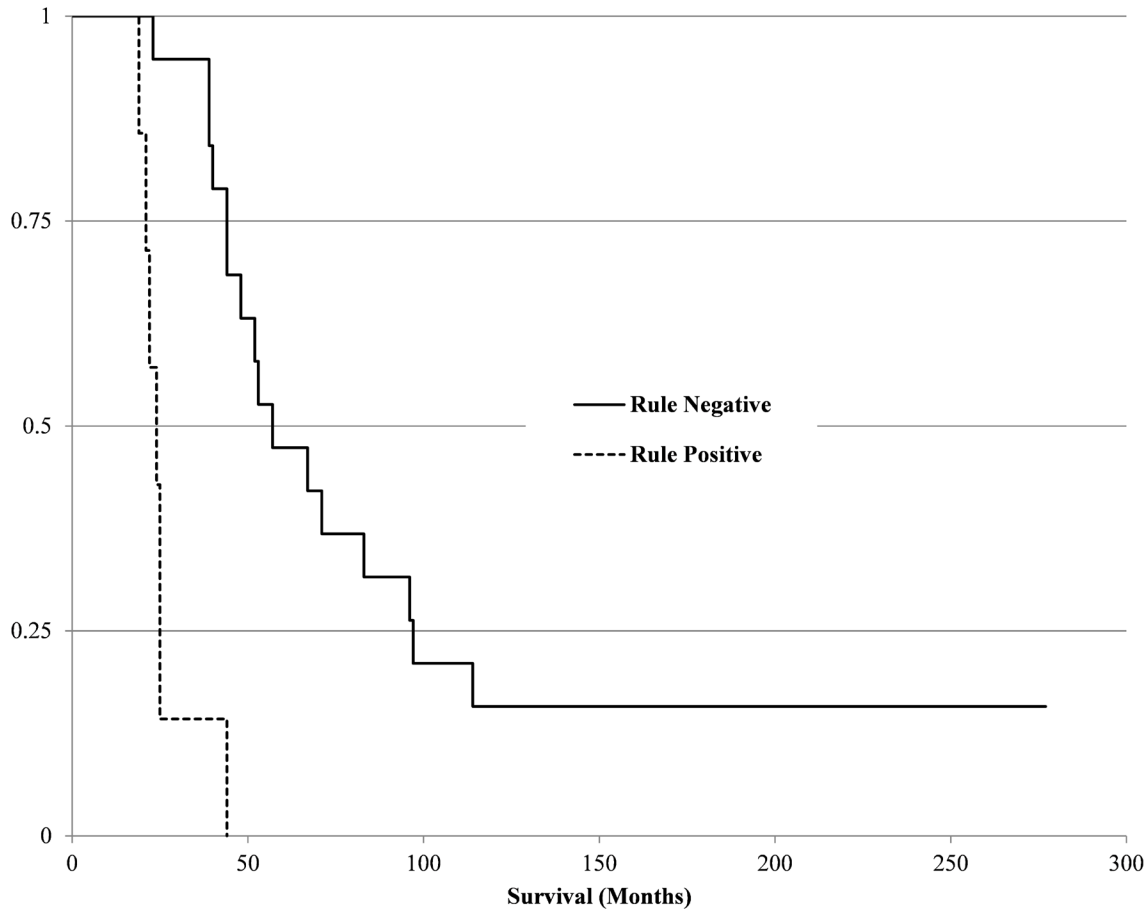

Figure 1. ROC curves for 3-month change in MUNE and FVC (percent of predicted) as tests for survival of 30 months or less. AUROC = 0.69 (MUNE) and 0.74 (FVC).

Table 2. Hazard Ratios from the Cox Proportional Hazards Model

3-month decrease	Hazard Ratio	95% Confidence Interval			Mortality Increase per 10% Decrease
MUNE	1.023	1.004	-	1.041	24.9%
FVC%	1.041	1.006	-	1.077	49.6%

Figure 2. Kaplan-Meier survival curves for rule-negative (N=19) and rule-positive (N=7) groups. The rule is positive if the 3-month decrease is greater than 40% for MUNE or 20% for FVC (percent of predicted).

The 6 patients identified by the rule showed significantly decreased survival compared to the other patients (incidence rate ratio 4.0 [95% CI 1.6-9.7]). Figure 2 shows the Kaplan-Meier survival curves.

Discussion

We demonstrate that decreases in MUNE and FVC% over three months may separate ALS patients into two groups with markedly different survivals. The ALSFRS had not been validated at the time of this study and thus was not used, plus this study was looking at gathering physical measures to identify rapid progressors.

The number of sporadic ALS phenotypes is not known regarding potentially different etiologies or responses to treatment. Certainly, familial and sporadic ALS have different etiologies, although the pathogenic mechanisms seem to converge. In familial ALS, a single gene with a large effect is required for causation. In sporadic ALS, multiple genes possibly interacting with environmental or lifestyle factors

are thought to be involved with causation. Several genetic loci have been associated with susceptibility to sporadic ALS,[18-24] but those identified by genome wide studies do not always correlate with phenotypes of ALS.[25] A favorable response to treatment may be more easy to demonstrate in a subgroup of patients with rapidly progressive ALS as identified in only 3 months if changes in MUNE or FVC% are measured and using our suggested criteria.

Our choice of a decrease of 40% in MUNE or 20% in FVC% was based on inspection of survival data in this cohort, which raises the issue of "overfitting." This classification of rapid progressors is unlikely to perform as well in other cohorts. However, our data shows a strong and independent association of both MUNE and FVC% with rapid progression and this is detectable over only 3 months of observation. Given that FVC% is far less invasive than MUNE, it would be easier for FVC% to have a more ubiquitous application looking for rapid progressors. We suggest the use of a three-month change in MUNE or FVC% as a

secondary enrollment criterion in therapeutic trials or to identify a subgroup of rapid progressors that may respond differently to treatments.

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