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ORIGINAL COMMUNICATION

Progression in ALS is not linear but is curvilinear

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Abstract The aim of the study is to determine the shape of the progression curve in ALS, assess the impact of clinical variables on the rate of progression, and evaluate the association between functional decline and survival. Data were prospectively collected and entered into a clinical database from all patients seen in 2002–2008 at the Centre SLA, Hôpital de la Salpêtrière, Paris. Variables analyzed were demographic and baseline information, the ALS functional rating scale (ALSFRS-R), strength testing (MMT), and survival. Generalized additive mixed models characterized changes in ALSFRS-R and MMT scores over time. Linear mixed effects assessed the impact of demographic and clinical measures on rate of progression and Cox models examined their effect on survival. Of 2,452 patients with ALS identified, 1,884 had adequate data for analysis. The ALSFRS-R and MMT declined in a curvilinear way; a quadratic fit described the trends but a linear fit did not. The total ALSFRS-R score was negatively associated with age-of-onset ($p < 0.001$), and positively associated with baseline ALSFRS-R ($p < 0.001$) as well as more severe bulbar features ($p < 0.001$). Higher rate of decline in ALSFRS-R and MMT, older age-at-onset and bulbar-onset predicted shorter survival. Deterioration in ALS is non-linear. The early and late phases of the illness show the most rapid rates of decline. Older age and bulbar signs are associated with a steeper decline, and along with more rapid initial rate of decline, but not current functional status, also predict survival.

Keywords Amyotrophic lateral sclerosis · Natural history · Survival · Rate of progression · Clinical trials

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Introduction

Most patients with ALS survive three to five years after the first symptoms appear, but a portion have a more rapid course that is measured in months and approximately 10% of patients survive 10 years or more [1]. Although data are conflicting [2, 3], many authorities consider that ALS follows a linear course [4–6] and research indicates that functional status might predict survival [7], but the true shape of the progression curve as well as the best means to identify patients with similar survival rates are not known; some of the most severely disabled patients are among the longest survivors. Defining the shape of the progression curve and phenotypes with distinct survival patterns has implications for clinical care and study design. Improved ability to prognosticate could allow patients and their physicians to more effectively plan for future interventions. Similarly, statistical designs for research are formulated based on a predetermined anticipated rate of decline. Better understanding of the course of decline would improve the

efficiency of clinical research through refined modelling, reduced outcome variability and smaller sample sizes. Previously we showed that death rate alone, irrespective of the use of non-invasive ventilation was the most robust outcome for trials that use a survival endpoint [8]. We undertook the current study to describe the trajectory of functional deterioration in ALS and to determine which factors most reliably predict the rate of decline as well as survival.

Methods

All patients with motor neuron disease seen at the Hôpital de la Salpêtrière since 1989 have had clinical data entered prospectively into the center database at each of their clinic visits, typically every 3 months. For the current study, data from patients seen between 2002, the year that the ALS functional rating scale (ALSFRS-R) [9] was first implemented, and 2008 were extracted. Variables entered include demographic information, the ALSFRS-R, manual strength testing (MMT) [10] of 30 muscles, and survival status. The diagnosis of ALS was made according to the El Escorial World Federation diagnostic criteria [11]. Of the patients analyzed, 250 had autopsy at the time of death. The diagnosis was confirmed in all cases at postmortem examination. Patients were excluded who did not have adequate follow-up or who had a diagnosis other than ALS. Participants did not sign a consent form because the anonymized natural history data contained in the database have received exemption from the Commission Nationale Informatique et Liberté; analysis of data from this database can be reported so long as the patients cannot be identified. The goals of the study were to determine the shape of the progression curve in ALS using ALSFRS-R and MMT scores, and to assess which disease features most influence the rates of decline and survival.

Statistical methods

The specific objectives of the study were: 1. To determine whether decline in ALS is linear; 2. If non-linear, describe the shape and point(s) of change as well as the most and least rapid phases of decline; 3. Determine if slope changes apply to both ALSFRS-R and strength testing; and 4. Assess the impact of different clinical features on the rate of decline and survival.

The analyses investigated the trend of total ALSFRS-R and MMT scores with respect to time from symptom onset. There is no well-accepted time trend for these scores, so generalized additive mixed models were used in the initial exploration. Random subject effects were included in the models to account for within-subject correlations. Once the time trend was characterized, the impact of clinical variables, including age-at-onset, site-of-onset, gender, weight at the first visit, height, and baseline ALSFRS-R and MMT on the above outcomes was further examined using a linear mixed effects model. The analyses focused on the first 5 years of the illness, but the changes during the first 10 years and in those surviving longer than 10 years were also described. Finally, the impact on survival of the clinical variables was assessed using Cox models. The analyses were performed in R, version 2.8.1. The generalized additive mixed model analyses were conducted using the "gamm" function in the R library "mgcv", the linear mixed model analyses were conducted using the "lme" function in the R library "nlme", and the survival analysis were conducted using the "coxph" function in the R library "survival". A p value of 0.05 or smaller was considered statistically significant.

Results

Clinical features and course of progression

The sample's demographics are displayed in Table 1. Of 2,452 patients entered into the database after 2002, 608 were excluded due to the diagnosis not being confirmed as ALS, absence of ALSFRS-R, or inadequate follow-up, leaving 1,844 for the analyses. The mean number of visits was 3.7 (SD = 3.0), and average length of follow-up was 2.7 (SD = 3.0) years. Analysis of clinical variables showed that the ALSFRS-R declined in a curvilinear way in the first 5 years. The statistical test indicated that a quadratic fit was adequate to describe the trend but a linear fit was not ($p < 0.001$). The rate of progression was most rapid in the early and late phases of the illness. Figure 1 shows that the initial rapid decline slowed approximately 18 months after symptom-onset. The curves were similar during the first 5 and 10 years and for those patients surviving longer than 10 years. The ALSFRS-R subscales, Bulbar, Arm, Leg and Respiratory, were also analyzed individually. Each was significantly curvilinear, and shaped similarly to the curve for the overall scale; except the respiratory subscale, which trended toward linear, but did not meet statistical significance for linearity.

We fit several models to examine the impact of the clinical variables on decline in ALSFRS-R. Gender, weight at first visit, and height were not significant and were excluded from subsequent models. In the final model (Table 2), the decline in the total ALSFRS-R score followed a quadratic curve; the total ALSFRS-R score was negatively associated with age-of-onset, and positively associated with baseline ALSFRS-R as well as more severe bulbar features as measured by the bulbar subscale of the ALSFRS-R ($p < 0.001$).

Table 1 Demographic data

Variable	Sample size	Mean ± SD or Count (%)
Height, cm	1,822	165.4 ± 27.4
Weight, kg	1,821	71.4 ± 41.1
Age, years	1,841	59.7 ± 13.2
Site of onset	1,822	
Bulbar		516 (28)
Limb		1,306 (72)
Sex	1,844	
Female		789 (43)
Male		1,055 (57)

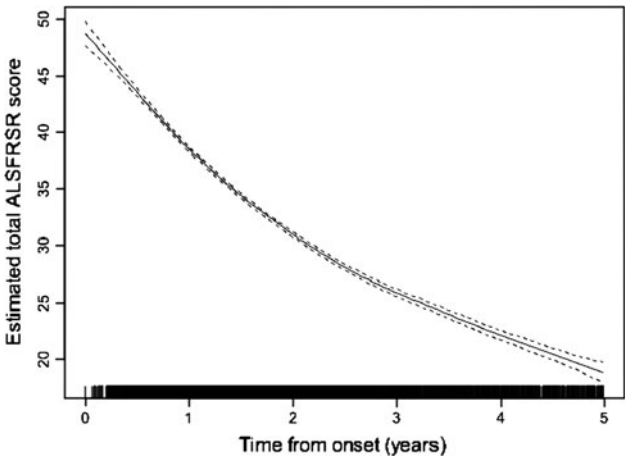

Fig. 1 Effect of time from symptom onset on total ALSFRS-R score in the first 5 years based on linear mixed effects additive model

Table 2 Estimated effects in predicting ALSFRS-R score based on linear mixed model

Predictor	Estimated coefficient	Standard error	*p* value
Time from onset	−10.441	0.269	<0.001
Difference in limb and bulbar onsets	−0.874	0.465	0.060
Square of time from onset	0.834	0.048	<0.001
Age at onset	−0.046	0.013	<0.001
Baseline ALSFRS-R	0.660	0.024	<0.001
Interaction of time from onset and limb-bulbar onset difference	1.579	0.190	<0.001

ALSFRS-R revised version of the ALS functional rating scale

The total MMT score also declined in a curvilinear way, and a quadratic, but not a linear, fit described the trend ($p = 0.01$). Age, gender, weight, height, and baseline ALSFRS-R were not significant predictors of decline. In the best-fit model (Table 3), the total MMT score followed a linear curve only after controlling for baseline MMT score; the decline was deeper in the limb onset group, and was positively associated with baseline MMT score.

Table 3 Estimated effects in predicting MMT score based on linear mixed model

Predictor	Estimated coefficient	Standard error	*p* value
Time from onset	−9.714	0.613	<0.001
Difference in limb and bulbar onsets	−0.693	1.473	0.638
Baseline MMT	0.776	0.022	<0.001
Interaction of time from onset and limb-bulbar onset difference	−1.713	0.683	0.012

MMT = manual muscle testing of 30 muscles

Table 4 Estimated hazard ratio in predicting survival using 5-year decline rates in ALSFRS-R and MMT based on Cox model

Predictor	Estimated hazard ratio	95% confidence interval	*p* value
5-year decline rate in ALSFRS-R	1.036	1.030, 1.042	<0.001
5-year decline rate in MMT	1.008	1.006, 1.010	<0.001
Age at onset	1.023	1.016, 1.030	<0.001
Difference in limb and bulbar onsets	0.713	0.603, 0.842	<0.001

ALSFRS-R revised version of the ALS functional rating scale

MMT manual muscle testing

We examined the impact of sites-of-onset on decline in the ALSFRS-R using several approaches. In the initial analyses, decline trended more steeply in patients with bulbar-onset than limb-onset ($p = 0.06$). In subsequent analyses, decline in function was found to be steeper in those with onset in the legs than in the arms ($p = 0.02$), and in those with proximal limb-onset compared to distal limb-onset ($p = 0.004$).

Survival

At the time of analysis, 1,144 (74%) patients had died. In Cox models (Tables 4, 5), higher rate of decline in both the first 18 months and the first 5 years from symptom onset in either the ALSFRS-R or MMT, older age-at-onset and bulbar-onset were associated with shorter survival. Baseline ALSFRS-R, baseline MMT score, the decline of ALSFRS-R or MMT in the first year, gender, height, and weight did not predict survival. When age and rate of decline in ALSFRS-R and MMT were examined as dichotomous variables about their medians (median

Table 5 Estimated hazard ratio in predicting survival using 18-month decline rates in ALSFRS-R and MMT based on Cox model

Predictor	Estimated hazard ratio	95% confidence interval	*p* value
18-month decline rate in ALSFRS-R	1.016	1.007, 1.030	<0.001
18-month decline rate in MMT	1.008	1.004, 1.010	<0.001
Age at onset	1.024	1.012, 1.040	<0.001
Difference in limb and bulbar onsets	0.852	0.618, 1.170	0.450

ALSFRS-R revised version of the ALS functional rating scale

MMT manual muscle testing

Table 6 Estimated hazard ratio in predicting survival using dichotomized versions of 18-month decline rates in ALSFRS-R and MMT based on Cox model

Predictor	Estimated hazard ratio	95% confidence interval	*p* value
18-month decline rate in ALSFRS-R above median	1.635	1.188, 2.250	0.003
18-month decline rate in MMT above median	2.122	1.521, 2.960	<0.001
Age at onset, above median	1.832	1.351, 2.480	<0.001
Difference in limb and bulbar onsets	0.773	0.568, 1.050	0.100

ALSFRS-R revised version of ALS functional rating scale

MMT manual muscle testing

age = 61.5 years, 18-month decline in ALSFRS = 14.64 points, 18-month decline in MMT = 20.87 points), each also significantly predicted survival (Table 6).

Discussion

The shape of progression in ALS has not been well characterized previously. Until recently, neurodegenerative disorders, including ALS, have been considered by many authorities to progress at consistent, linear rates. Discussions with patients are conducted and trials are designed using assumptions of linearity [6, 12, 13]. Recent evidence, however, indicates that progression in other neurodegenerative disorders may be non-linear, both in animals [14] and humans [15, 16], and that genetic [17, 18] and environmental [19] factors, including cultural and spiritual influences [20], may contribute to changes in slope, independent of treatment. Quadratic models appear to fit all stages of Alzheimer's disease [19, 21], and the non-linear decline can be used to separate groups of patients from normals [22].

In ALS, some studies have indicated that the decline in ALSFRS-R may be linear, and the assumption of linearity has lead to the use of statistical methods that reduce sample size and trial duration [5, 7] as ways to improve the efficiency of drug testing. Great expense has been expended in trials that use the assumption of linear decline [6, 12, 13]. Linear estimates of progression have also been used to predict survival, and therefore to link phase II and phase III trials [23].

Our data indicate that in ALS, decline in function and strength are non-linear, with the fastest rates of decline occurring in the first 18 months of symptomatic disease and toward the end stages of the illness. The non-linear progression has implications for the testing of medications; if linear models are inaccurate, incorrect statistical assumptions could lead to spurious associations with the rate of decline [24], one possible explanation for the ongoing failure of trials of potential neuroprotective agents. In comparing decline between two groups, forcing linear fits onto two distinct quadratic curves could result in the same linear fit for both groups, leading to the inability to detect group differences that might, in theory, be shown using a better fitting quadratic model. While both analytic methods, linear or quadratic, are approximations, the more precise fit, shown as the quadratic model from these data, would result in greater power to detect group differences. Linear models, used for convenience, may result in adequate fit in some situations, for example during the mid-phase of the illness, if that phase could be predicted with precision. Most trials that use functional outcome measures, however, now attempt to enroll patients early in the course of the illness to minimize dropout [6, 13]. Enrolling patients early in the disease course increases the risk of including the initial point of non-linearity in the progression curve. In general and over the course of the illness, linear models would result in lower power and weaker ability to predict survival or decline in function than quadratic models. Further, phase II trials that examine functional outcome measures cannot necessarily be assumed to predict outcome in phase III trials that use a survival endpoint; in this study, rate of progression in the first 18 months predicted survival, but baseline function, point function in time, and 1-year progression rate did not.

The changes in slope in ALS may represent different phases of motor neuron loss due to pathophysiological evolution. Non-linearity might also reflect interventions. In Parkinson's disease, the rate of decline in rating scale scores can change after initiation of therapy, impacting sample size calculations in trials [25]. In ALS, the use of riluzole, gastrostomy, ventilatory support, and multi-

disciplinary care prolong survival. Because most patients first present to multi-disciplinary care centers about 1 year after their symptoms appear, different interventions are likely to be prescribed between 1 year and 18 months after symptom-onset, coinciding with the point in the progression curve where slowing first occurs. Eventually, the illness outpaces the currently available therapies. In our study, there was a second phase of acceleration of progression rate toward the end of the disease. Unfortunately, data were not available to examine the impact of therapy in this study. We suggest that trial designs use analytic plans that account for non-linearity and standardized approaches to applying different therapies. Death rate alone, irrespective of tracheostomy or respiratory intervention, is the most robust outcome measure for phase III trials [8], and a straightforward comparison of final versus initial ALSFRS-R scores, independent of slope, could simplify analysis of phase II trials.

Predictors of steeper rate of deterioration can be used in discussions with patients in the clinic and in trial design. The strongest predictors of more rapid functional deterioration in this study were older age, greater prominence of bulbar features and poor function at the first visit. The strongest predictors of shorter survival were higher initial rate (18 months) of decline in function, older age and bulbar-onset. In agreement with other studies [26, 27], these variables could be dichotomized to stratify patients in clinical trials in order to obtain more homogeneous groups for statistical comparisons and for discussion and planning in the clinic.

Conflict of interest statement None.

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