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Clinical Study

Prognostic factors for survival in patients with amyotrophic lateral sclerosis: analysis of a multi-centre clinical trial

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ABSTRACT

Information regarding factors influencing prognosis and quality of life (QoL) in patients with amyotrophic lateral sclerosis (ALS) is useful for clinicians and also for patients and their carers. The aims of this study are to identify prognostic factors for survival in ALS and to determine the physical factors influencing QoL. This study is a retrospective analysis of a cohort of 512 patients who participated in a phase II/III clinical trial of olesoxime. Cox multivariate regression analysis found older age, bulbar onset disease, low baseline forced vital capacity, low baseline manual muscle test (MMT) scores and a shorter diagnostic delay to be independently associated with poor survival outcome. Physical factors shown to have the strongest correlation with poor QoL were low weight and a reduced ability to climb stairs. Therapeutic interventions including gastrostomy and non-invasive ventilation had no positive impact on QoL in this cohort. The prognostic factors for survival identified here are consistent with other studies of ALS patients, with the additional identification of baseline MMT score as another predictor of prognosis. Furthermore, the correlation between both weight and poor lower limb function with QoL is novel and underlines the importance of careful nutritional management in this hypercatabolic condition.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressive and ultimately fatal neurodegenerative disease with an average life expectancy of 3–5 years from symptom onset. However, survival of more than 10 years has been reported in 5–10% of the patients [1].

Numerous prognostic factors have previously been proposed as predictors of survival in ALS. Clinical factors consistently reported to be associated with a worse outcome include older age at disease onset [2–16], bulbar as opposed to limb onset disease [3–7,10,11,14–17] and a shorter delay between symptom onset and diagnosis [7,8,10,13,15–17]. Other documented factors include respiratory and nutritional status. Studies have consistently demonstrated that a reduced baseline forced vital capacity (FVC) [3,8,13,18,19], faster rate of FVC decline [11,20], low Body Mass Index (BMI) [18] and rapid weight loss [8,21,22] are significant poor prognostic factors. Less established factors include sex [4,6,10,16], El Escorial Criteria (EEC) category [14–16] and the ALS Functional Rating Scale (ALSFRS) score [17,23].

Being aware of the specific clinical factors which significantly influence survival and quality of life (QoL) would help clinicians in scheduling appropriate interventions and also advising patients as to what to expect as their disease progresses [9]. The aims of this study are: 1) to determine the characteristics of ALS patients with better survival and 2) to determine which physical factors are associated with poor QoL and what impact supportive interventions have on QoL.

2. Materials and methods

2.1. Study population

This is a prospective observational cohort study using the clinical database of a multicentre phase II/III clinical trial of olesoxime (TRO19622) in ALS [24]. The cohort consisted of 512 patients recruited across 15 European centres (2009–2011).

2.2. Data collection

All patients were assessed at inclusion and every 3 months thereafter for a total of 18 months during which various clinical, biochemical and haematological parameters were measured and recorded. The revised ALSFRS (ALSFRS-R) was used to functionally

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evaluate the severity and progression of the disease. ALSFRS-R is a disease specific functional rating scale that provides information about bulbar function, limb function and respiratory function of patients with ALS in a single scale [25]. Patient QoL as assessed by a modified McGill quality of life (MQoL) questionnaire [26] was monitored every 3 months. This visual analogue scale of 0 to 10 assesses physical and psychological aspects of patient health in addition to existential well-being and support. Values closer to zero indicate poor QoL.

Diagnostic delay was defined as the recalled date of symptom onset to diagnosis. The anatomical region (bulbar, cervical or limb) where symptoms were first experienced was considered as the site of onset. Survival time was defined as time from date of disease onset until date of ALS related death or last known to be alive. Deaths which were not related to ALS (n = 8) were excluded from survival analysis.

2.3. Ethics and governance

All sites obtained approval from the appropriate ethics and regulatory authorities. Prior to trial inclusion all patients provided written informed consent.

2.4. Statistical analysis

The effects of individual baseline demographic, clinical and metabolic factors on survival were firstly analysed using Kaplan–Meier survival curves. These factors included sex, age of disease onset, site of disease onset, EEC category, BMI, FVC% predicted, ALSFRS-R score, manual muscle test (MMT) score, diagnostic delay and levels of blood creatinine, cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL) and creatine phosphokinase (CPK). In order to recode any continuous variables into categorical variables the mean value of the dataset was used as a cut-off point to predict survival. Log-rank chi-squared tests were subsequently performed to determine whether differences in survival times between the groups studied were significant, with significance accepted at $p < 0.05$. Univariate Cox proportional hazards regression analysis was performed for each prognostic factor of interest with the relative risk of death represented as a hazard ratio (HR) and 95% confidence interval (95% CI). Any factors which were shown to be associated with survival ($p < 0.1$) were then entered into a multivariate Cox proportional hazards regression analysis to provide an adjusted HR and 95% CI. Factors were subsequently considered to be significant independent prognostic factors when $p < 0.05$. A logistic regression analysis was also performed to assess the impact of clinical and metabolic factors at each follow-up visit (up to and including month 12) on overall survival outcome. The relative risk of death for each factor is represented as an adjusted odds ratio (OR) and 95% CI.

Physical factors influencing patient QoL at each visit were determined via a backward elimination one way analysis of covariance (ANCOVA). Preliminary correlation and linear regression analysis were performed to ensure that the correlation among covariates and linearity assumptions for ANCOVA were met. The dependant variables investigated were weight (kg), FVC% predicted, total MMT score and the scores of the following 8 ALSFRS-R sub-domains: salivation (ALSFRS-R Sa), speech (ALSFRS-R Sp), swallow (ALSFRS-R Sw), climbing stairs (ALSFRS-R C), walking (ALSFRS-R W), turning in bed and adjusting bed clothes (ALSFRS-R T), handwriting (ALSFRS-R H) and dressing and hygiene (ALSFRS-R D). Each domain is scored on a scale of 0-4; a score of 4 implies normal function.

A paired-samples t-test was performed to assess the impact of gastrostomy and non-invasive ventilation (NIV) on patient QoL. Initial comparisons were made between the mean MQoL score pre- and post-intervention. Further analysis was performed using the MQoL score obtained pre-intervention and the MQoL score recorded at the first and then second follow-up visit post-intervention. Significance was accepted when $p < 0.05$.

All statistical analysis was performed using the IBM SPSS for Windows version 21.0 software package (IBM, Armonk, NY, USA).

3. Results

3.1. Cohort demographics and clinical features at baseline

The study population (n = 512) consisted of 331 (65%) males and 181 (35%) females. The mean age of disease onset was 55 years; ranging from 25–78 years. Males presented at an earlier age than females with average ages of 54 and 58 years respectively. In total 406 patients presented with limb onset disease (79.3%), 106 had bulbar onset (19.7%) and the remaining five patients had cervical (neck) onset ALS (1%). As per the El Escorial criteria 108 cases (21.1%) had definite ALS, 286 (55.9%) probable and 118 (23%) probable ALS—laboratory supported. Diagnostic delay; defined as date of symptom onset till the date of diagnosis, ranged from 0 to 1078 days with a mean of 288 days.

3.2. Survival analysis

During the course of the study 159 patients died of which 151 deaths (95%) were ALS related. Mean disease duration (date of symptom onset until date of death) was 814 days, ranging from 310 to 1557 days. The mean cumulative survival time from symptom onset for the entire cohort was 1400 days (95% CI 1344–1455).

Differences in survival rates and Kaplan–Meier estimates of survival times for each baseline factor are shown in Table 1. As demonstrated by the log-rank chi-squared statistics, survival differed significantly in 8 of the 15 variables analysed. Factors conferring both better survival rates and survival times were: younger age of disease onset ($\leqslant$55 years), limb onset disease, lower EEC category, higher FVC (>93%), higher ALSFRS score (>39), higher MMT score (>127), elevated serum creatinine (>64) and a longer diagnostic delay (>288 days).

3.3. Prognostic factors at baseline

Each factor of interest was individually assessed using Cox's univariate analysis to determine its prognostic value. (Table 2) The following factors were identified as potential predictors of survival outcome ($p < 0.1$): sex, age and site of disease onset, EEC category, BMI, FVC% predicted, ALSFRS-R and MMT scores, blood creatinine and CPK levels and diagnostic delay. These factors were fed into a multivariate Cox regression model to ascertain their independent effects on survival. (Table 2) Subsequently female sex ($p = 0.563$), EEC category ($p = 0.076$), BMI ($p = 0.225$), total ALSFRS-R score ($p = 0.299$), blood creatinine level ($p = 0.729$) and blood CPK level ($p = 0.497$) were eliminated from the final model. As such, the baseline factors shown to be significant independent predictors of better survival in this cohort were: younger age of disease onset, limb onset disease, higher FVC% predicted, higher MMT score and longer diagnostic delay ($p < 0.001$ for all variables).

3.4. Prognostic factors during follow-up

The predictive value of demographic and clinical variables obtained at the first five follow-up visits (Table e1) on overall patient survival was assessed via direct logistic regression. The same exploratory variables as used in Cox's regression were used with the exception of total cholesterol level which was excluded