Amyotrophic lateral sclerosis: can we predict the course of disease?

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Summary


A variety of prognostic factors have been associated with survival and disease progression in amyotrophic lateral sclerosis (ALS). With knowledge of factors that affect prognosis, clinicians can best advise their patients about their future clinical course. Moreover, the evaluation of early prognostic variables and the understanding of “at first exam” factors related to outcome may impact on the selection of patient cohorts for clinical trials. This goal is highly desirable, since the appropriate stratification of eligible patients based on the described predictors could result in reduction of sample size and study duration. It is well known that factors like age, sex, site of symptom onset and diagnostic delay, if imbalanced among treatment groups, may have a larger effect on outcome in the clinical ALS trials than the treatment itself. Thus, matching patients for established demographic and clinical parameters is particularly important in planning clinical trials. However, the randomisation for too many variables in the entry criteria may cause a large increase in the number of patients needed to balance the trial.

Based on our own data we describe here the value of prognostic factors related to outcome in patients with ALS and review the literature. The identification of younger age, limb site of onset and longer FS-FE delay as predictors of prolonged survival in an ALS clinic population is in agreement with the findings of several earlier studies that were based on smaller groups of patients. Moreover, given the well-known correlation between disease progression and survival, our finding that age at onset, time between first symptom and first examination, and site of symptom onset also act as significant and independent covariates of disease progression might be expected, although it remains at odds with certain previous reports.

Younger age at the time of symptoms onset is clearly associated with slower disease progression. In addition, younger patients survive significantly longer even after adjustment for potentially confounding factors. Patients with limb symptoms at onset survived remarkably longer than bulbar-onset patients. Moreover, in patients exhibiting limb symptoms at onset a slower disease progression was observed. We hypothesise that bulbar-onset patients may have shortened survival and faster disease progression from earlier involvement of respiratory muscles, a higher rate of respiratory complications, malnutrition and dehydration. The delay between symptom onset and first examination (FS-FE time or disease duration at diagnosis) was a robust predictor of survival and disease progression in our studies as in others. This delay was negatively related to hazard, i.e. positively related to length of survival – in other words, the longer the delay, the longer the survival and the slower the disease progression. In our patient population patients whose first examination was longer than 12 months after first symptom survived longer compared with patients who were first examined within 12 months after the onset of symptoms. Furthermore, longer time between first symptom (FS) and first examination (FE) was associated with slower disease progression. These findings support the hypothesis that the time between first symptom and first clinical examination may be a measure of the initial rate of disease progression. The more rapidly a patient initially deteriorates, the shorter the delay before the first symptom and first examination. These results suggest that fast progressing patients tend to seek medical care earlier, whereas those with slower disease progression are referred later or adapt to first symptoms for a longer time before they visit a medical care facility. In addition, we describe the prognostic
value of several “at first examination” clinical parameters – baseline value of functional rating scales such as ALSFRS and Appel score, initial progression rate and baseline value of the forced vital capacity (FVC) – all of which may have significant utility in patient management.

Keywords: amyotrophic lateral sclerosis; outcome measurement; survival; disease progression

Introduction

Amyotrophic lateral sclerosis (ALS) is a relentlessly progressive disease which usually carries a poor prognosis with a median survival of 1–3 years from diagnosis and 2–4 years from onset [1–11]. A variety of prognostic factors have been associated with survival and disease progression in ALS. The evaluation of early prognostic variables and the understanding of “at first exam” factors related to outcome may impact on the selection of patient cohorts for clinical trials. This goal is highly desirable, since ALS patients then could be stratified into smaller homogeneous groups for therapeutic trials [12]. Moreover, with knowledge of factors that affect prognosis, clinicians can best advise their patients about their future clinical course [6].

Based on our own data we describe here the prognostic factors related to survival and disease progression in patients with ALS and review the literature. Since the outcome prediction based on parameters available around the time of diagnosis provides a clinically meaningful advantage compared to a prediction based on two or more consecutive measurements, in this review we concentrated on the predictive value of clinical and demographic variables which are available at the time of first examination and diagnosis. However, we are aware of the possibility that measures taken repeatedly during the early course of the disease would likely yield improved estimates of survival and disease progression [2].

Outcome measurement in amyotrophic lateral sclerosis

Since the approval of riluzole, survival has been the principal primary outcome measure used in ALS clinical trials [13]. However, as an outcome measure, survival has a number of limitations. Although it seems unequivocal as an endpoint, its definition may be problematic [14]. In clinical trials the time to death or tracheostomy is commonly used to define survival. However, with the advent of non-invasive ventilation (NIV), defining survival has become more difficult. The identification of survival may also be affected by factors other than disease-modifying therapies, including variable standards of care and management in different countries [13]. Moreover, survival in ALS is known to vary among individuals and considered to be difficult to predict in individual cases [15].

Most importantly, the median survival from first symptom in ALS ranges from 2 to 4 years [1–11], necessitating long trial durations and the enrollment of large numbers of patients to reliably measure treatment effect. Therefore, ALS studies of survival are large, long and expensive, and there is a clear need for alternative clinical trial endpoints with a particular view toward improving study design.

In recent years several endpoints other than survival have gained favour as primary outcome measures. Muscle strength, measured by using maximum voluntary isometric contraction (MVIC) or manual muscle testing (MMT), is a clinically relevant measure of disease progression in ALS and has been used as the primary outcome measure in a number of trials [14, 16]. However, difficulties in assessing muscle strength in patients with ALS, such as the need for complex and expensive equipment for MVIC testing or the need for well-trained evaluators to perform MMT, are limitations of these methods. Forced vital capacity (FVC) has also been used as the primary endpoint in several clinical studies [17, 18] and FVC was proven to be a sensitive measure of disease progression and predictor of survival [3, 4]. However, FVC assesses only a single aspect of ALS. The measurement may be associated with increased variability in patients with significant bulbar involvement and may have limited accuracy at later stages of disease [19, 20]. In addition to muscle strength testing and FVC several functional rating scales are commonly used in ALS clinical trials. The ALS Functional Rating Scale (ALSFRS) which measures activities of daily living is easy to administer, sensitive, clinically meaningful and reliable and has been proven to correlate with survival. Thus, it seems to be a much more attractive primary outcome measure than muscle strength or FVC [7, 8, 13, 14, 19]. Similarly, the Appel ALS Score (AALS score) may also be useful as a primary outcome measure in clinical studies [2, 21–23]. Consequently, outcome measures other than survival seem to be gaining increasingly broad acceptance for use as primary endpoints in clinical ALS trials. However, in contrast to well-analysed covariates of survival, little is known about predictors of disease progression in ALS despite the potential relevance of disease progression in the design of clinical trials.
Outcome predictors

Age at the time of disease onset or at the time of diagnosis belongs to the most consistently reported prognostic factors in ALS [2–8, 12, 14, 15, 24–27]. Younger age at the time of symptoms onset is clearly associated with slower disease progression. In addition, younger patients survive significantly longer even after adjustment for potentially confounding factors. In our patient population [9–11] the prognosis worsened with older age groups: patients who exhibited the first symptom at an age of 40 or younger had a median survival time of 6.01 years (95% CI 4.67–7.34), compared with 3.23 years (95% CI 3.03–3.43) for patients with onset between 40 and 70 and 2.85 years (95% CI 2.47–3.23) for patients above 70 years. In the hazards analysis patients in the age group between 40 and 70 years had a 2.65-fold increased risk of death or tracheostomy compared to patients younger than 40 years (p <0.001). This effect was even stronger for the group of eldest patients who were characterised by a 3.86-fold increased risk of death in comparison to the group of youngest patients [10]. Moreover, patients younger than 40 years progressed more slowly (12 months to 20-point change in Appel score, 95% CI 9–14) than patients in the age group above 40 years (9 months, 95% CI 8–9, p <0.001) [11]. The mechanism underlying this phenomenon is unknown. Younger patients may compensate better for declining motor function and older patients may have fewer motor neurons to compensate. However, such explanations provide little insights as to the mechanisms involved. The faster progression of the disease and shorter survival in older patients have also been related to the less intensive symptomatic care received by older individuals and their greater psychological distress, which is linked to a poorer prognosis [5].

Some investigators have reported male sex as a favourable prognostic factor even after adjustment for previously established outcome covariates [1, 6, 25]. However, in our series no association between gender and prognosis was found [10, 11]. This finding agrees with the vast majority of previous studies [3, 4, 7, 15, 28–30].

Most previous studies have reported that disease onset in the limbs rather than in the bulbar muscles is predictive of longer survival time [3, 4, 6, 7, 15, 24–26]. Bulbar-onset patients may have shortened survival from earlier involvement of respiratory muscles, a higher rate of respiratory complications, malnutrition and dehydration [15]. Studies prior to 1995 suggested that the negative prognostic effect of bulbar onset could be explained by the older onset age of these patients [2, 31, 32]. In our more recent analysis a clear association between site of onset and survival has been shown. Patients with limb symptoms at onset survived remarkably longer than bulbar-onset patients (3.74 vs 2.80 years, p <0.001) [9, 10]. Moreover, in patients exhibiting limb symptoms at onset a slower disease progression (measured as a time to 20-point change in Appel score) was observed (9 months to 20-point change in limbs-onset patients, versus 7 months for bulbar-onset patients, p <0.001) [11]. In the hazards analysis the presence of bulbar symptoms at onset increased the risk of death and disease progression even after adjustment for several well-established prognostic factors (i.e. age). We attempted to investigate limb onset more extensively by creating several subcategories for the extremity-related sites: proximal versus distal, first symptom in upper extremity versus lower extremity, but there was no statistically significant correlation between those factors and survival or disease progression in our series. However, the symptom progression rate in the lower limbs, but not lower limbs onset, has been shown to be significantly related to outcome by others [5].

The delay between symptom onset and first examination (FS-FE time or disease duration at diagnosis) was a robust predictor of survival and disease progression in our studies as in others [2, 3, 6, 14]. This delay was negatively related to hazard, i.e. positively related to length of survival – in other words, the longer the delay, the longer the survival and the slower the disease progression. In our patient population patients whose first examination was longer than 12 months after first symptom survived longer (4.04 years, 95% CI 3.75–4.32) compared with patients who were first examined within 12 months after the onset of symptoms (2.61 years, 95% CI 2.38–2.84, log-rank p <0.001) [10]. Furthermore, longer time between first symptom (FS) and first examination (FE) was associated with slower disease progression (FS-FE >12 months, 10 months to 20-point change in Appel score, 95% CI 9–12; versus 8 months, 95% CI 7–9, for patients with FS-FE time <12 months), (p <0.001) [11]. Most importantly, in all performed multivariate models FS-FE delay remained significantly and independently associated with survival and disease progression. Of note is that the previously reported relationship between FS-FE time and the disease progression rate between first symptom and first examination supports the hypothesis that the time between first symptom and first clinical examination may be a measure of the initial rate of disease progression [2]. The more rapidly a patient initially deterio-
rates, the shorter the delay before the first symptom and first examination. These results suggest that fast progressing patients tend to seek medical care earlier, whereas those with slower disease progression are referred later or adapt to first symptoms for a longer time before they visit a medical care facility [2, 15, 24].

In a large prospective population-based study by Chio et al. El Escorial Diagnostic Criteria (EEDC) status at diagnosis was directly related to outcome [5]. Definite ALS at presentation was significantly associated with survival and resulted in a median survival of 23 months, compared with 34 months for probable ALS, 35 months for possible ALS and 58 months for suspected cases. However, the only other prospective study to analyse survival according to EEDC category found no significant difference [33].

Can survival and disease progression be accurately predicted by clinical measures at the first exam? ALS is thought to have already undergone gradual progression by the time of symptoms manifestation, involving a long preclinical period [34]. If the state of progression could be determined at the diagnostic stage, future progression might be predicted. As mentioned above, the functional rating scales like ALSFRS and Appel score are increasingly used to assess outcomes in clinic patients and clinical trials for ALS [35]. The total initial score for the ALSFRS has recently been identified as a strong predictor of prognosis [7, 8, 36]. Similarly, we investigated the association between total AALS score at the time of first examination and survival or disease progression by comparing patients with total AALS score below and above 60 points [9–11]. A 60-point level was chosen because it is indicative of a clinically evident impairment in a patient’s clinical status and ability to perform activities of daily living. The median survival time for patients with baseline total AALS score below 60 points was 3.94 years (95% CI 3.57–4.31), compared to 3.02 years (95% CI 2.80–3.23, log-rank p <0.001) for those with baseline AALSS above 60 points. Patients with first exam total score below 60 points progressed more slowly (11 months to 20-point change in AALS, 95% CI 10–12) than patients with baseline score above 60 points (6 months, 95% CI 6–7). (p <0.001).

Moreover, the total Appel score at baseline has been shown to be a significant predictor of survival and disease progression even after adjustment for several potentially confounding variables and may constitute prognostic signposts in the early stages of the disease course.

As discussed above, the duration of the prediagnostic period (FS-FE time) represents an import-
relation between the rate of decline in pulmonary function, either defined as the slope of a pulmonary score [2, 12] or the rate of FVC decline [4, 5], we showed that even a single FVC measurement value obtained at an initial visit may serve as a good predictor of survival and disease progression in the ALS clinic population [11]. We investigated the association of the FVC at baseline with (1) tracheostomy-free survival or (2) time to 20-point AALS score progression from baseline exam for two subgroups of patients with baseline FVC value above (n = 690) and below 75% (n = 344). This FVC value was the optimal cut-off point resulting in stratification into two large populations which were significantly different in terms of survival and disease progression. The median survival of ALS patients with baseline FVC >75% was 4.08 years, compared to 2.91 years for patients with baseline FVC <75% (log-rank p <0.001). In addition, patients with baseline FVC value <75% progressed faster (8.0 months to 20-AALS points progression) compared to patients with baseline FVC >75% (10.0 months to 20-AALS points progression, p <0.001). Moreover, the predictive value of this baseline FVC remained significant after including several established prognostic factors such as age, sex, site of onset and FS-FE time in the hazards analysis as well after correction for potentially effective therapies like riluzole medication or use of NIV and PEG. The results of this study not only confirm our clinical impression that patients with lower FVC values at baseline progress faster and die sooner but also provide a tool for baseline stratification for clinical trials.

The identification of younger age, limb site of onset and longer FS-FE delay as predictors of prolonged survival in an ALS clinic population is in agreement with the findings of several earlier studies that were based on smaller groups of patients. Moreover, given the well-known correlation between disease progression and survival, our finding that age at onset, time between first symptom and first examination, and site of symptom onset, well-established predictors of survival in ALS, also act as significant and independent covariates of disease progression might be expected, although it remains at odds with certain previous reports [4, 12]. In addition, we describe the favourable prognostic value of several “at first examination” clinical parameters – lower baseline value of ALSFRS or AALSS, lower initial progression rate and higher baseline FVC, all of which may have significant utility in patient management.

With knowledge of early factors that affect prognosis, clinicians can more meaningfully advise patients about their potential clinical course. Moreover, the knowledge of outcome predictors may be helpful in designing new treatment trials, ones which use survival or disease progression as the primary endpoints. The appropriate stratification of eligible patients based on the described predictors could result in reduction of sample size and study duration. It is well known that factors like age, sex, site of symptom onset and diagnostic delay, if imbalanced among treatment groups, may have a larger effect on outcome in the clinical ALS trials than the treatment itself. Thus, matching patients for established demographic and clinical parameters is particularly important in planning clinical trials. However, the randomisation for too many variables in the entry criteria may cause a large increase in the number of patients needed to balance the trial.

References


