Prognostic value of time to generalization in 71 Chinese patients with sporadic amyotrophic lateral sclerosis

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Abstract

Background: It is important to determine prognostic factors for the outcome of amyotrophic lateral sclerosis (ALS) at an early stage. The time taken for symptoms to spread from spinal or bulbar regions to both (time to generalization; TTG) is considered a strong predictor of survival; however, this has rarely been studied in Asian populations. The aim of this retrospective study was to evaluate potential factors affecting prognosis in Chinese patients with sporadic ALS, with a focus on the association between TTG and overall survival.

Methods: Seventy-one patients with sporadic ALS who were hospitalized at Chinese PLA General Hospital from 2009 to 2016 were followed up until December 2017. Survival analysis was performed using univariate Kaplan-Meier log-rank and multivariate Cox proportional hazards models. The clinical data of the patients were recorded and analyzed. Variables studied were age at symptom onset, sex, site of symptom onset, diagnostic latency, TTG, diagnostic category, ALS Functional Rating Scale-revised score, percent predicted forced vital capacity (FVC%), and disease progression rate (DPR) at diagnosis.

Results: The mean age at onset was 54 (SD = 10.2) years, and the median survival time from symptom onset was 41 months (95% confidence interval: 34–47). By univariate analysis, factors independently affecting survival were age at symptom onset (Log rank = 15.652, $P < 0.0001$), TTG (Log rank = 14.728, $P < 0.0001$), diagnostic latency (Log rank = 11.997, $P = 0.001$), and DPR (Log rank = 6.50, $P = 0.011$). In the Cox multivariate model, TTG had the strongest impact on survival time (hazard ratio = 0.926, $P = 0.01$).

Conclusions: TTG can be used as an effective indicator of prognosis in patients with sporadic ALS.

Keywords: Amyotrophic lateral sclerosis; Time to generalisation (TTG); Prognosis; Survival

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease involving the upper and lower motor neurons; its underlying cause remains unclear. Most ALS patients die of respiratory failure within 3 to 5 years, although a small percentage live longer, surviving for 10 years or more after symptom onset.[1] A staging system for ALS was explored, and the interval between symptom onset and involvement of another region was regarded as an important predictor of survival.[2] Validation of staging criteria for ALS could inform a universal and objective measure of disease progression, offering benefits for patient care, resource allocation, and clinical trial stratification. Tortelli *et al*[3,4] suggested the time from onset until symptoms spread from spinal or bulbar regions to both (time to generalization; TTG) as an early to intermediate point in the natural history of ALS, and identified a strong correlation between TTG and outcome in ALS. However, few studies on this correlation including Asian ALS patients have been reported. In this study, we evaluated clinical variables in a cohort of Chinese patients with sporadic ALS to explore the factors affecting prognosis, focusing on the correlation of TTG with overall survival.

Methods

Ethics approval

The study was approved by the Ethics Committee of the Chinese People's Liberation Army (PLA) General Hospital. Written informed consent was obtained from all participants prior to their enrolment in this study.

Subjects

Seventy-one hospitalized patients diagnosed with definite, probable, or possible ALS at the Department of

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Neurology, Chinese PLA General Hospital, between July 2009 and November 2016 were enrolled in the current study. All patients exhibited sporadic ALS. The diagnosis was made by an experienced neurologist based on the revised El Escorial criteria.[5] Clinical variables of the ALS patients were recorded, including age at symptom onset, gender, site of symptom onset, diagnostic latency (time from symptom onset to diagnosis), TTG, diagnostic category (definite, probable, or possible ALS), ALS Functional Rating Scale-revised (ALSFRS-r) score,[6] percent predicted forced vital capacity (FVC%), and disease progression rate (DPR) at diagnosis. The onset site was defined as bulbar or limb onset. The DPR was calculated according to the following formula: [(48 – ALSFRS-r score at evaluation) / (disease duration from symptom onset to evaluation in months)].[7] Follow-up for survival was carried out by phone every 3 months and ended in December 2017. Survival time was defined in months from symptom onset to death or tracheotomy. For patients who did not experience the end point, survival time was censored at the time of the last follow-up visit.

Statistical analysis

Normally distributed data are expressed as mean and standard deviation, and non-normally distributed data as median and interquartile range. Categorical variables are expressed as frequencies (percentages). Survival analysis was performed using univariate Kaplan-Meier log-rank and multivariate Cox proportional hazards models. Variables included in the Cox models were TTG, age at symptom onset, diagnostic latency, and DPR at diagnosis. Spearman rho correlation analysis was conducted to analyze the relation between TTG and other clinical variables. Analyses were performed using SPSS software (ver. 20.0; SPSS Inc., Chicago, IL, USA). The statistical significance level was set at $P < 0.05$.

Results

Seventy-one patients with sporadic ALS were enrolled in this study, including 37 males (52%) and 34 females (48%), for a male-to-female ratio of 1.09. The mean age at onset was 54.12 years (SD = 10.20; range: 25–72 years). Of these, 18 (25%) were classified as bulbar onset, and 53 (75%) as limb onset ALS. The median diagnostic latency was 11 months (range: 2–77 months). Of these patients, 51 had definite, 12 probable, and eight possible ALS. ALSFRS-r score and DPR were recorded for 60 patients; the mean ALSFRS-r score was 38 (SD = 6; range: 15–47), and the mean DPR was 0.54. The FVC%, which was obtained from all patients, ranged from 26.2% to 129.0%, with a mean value of 80.1% (SD = 21.6%). All of these patients progressed to generalized ALS. The median time for symptoms to become generalized (TTG) was 10 months (range: 1–69 months). At the end of the follow-up period, survival data were complete for all cases. At that point, 45 (63%) patients had died or undergone tracheostomy, and 26 were alive; the proportion of patients alive at censoring was 37%. The median survival time by Kaplan-Meier analysis was 41 months [95% confidence interval (95% CI): 34–47].

To examine correlations between clinical variables (age at onset, gender, site of onset, diagnostic category, diagnostic latency, ALSFRS-r score, FVC, DPR at diagnosis) and survival, we split the ALS patients into two groups for each continuous variable using a median cut-off. Significant prognostic variables in the univariate Kaplan-Meier analysis were age at onset, diagnostic latency, and DPR at diagnosis. Gender, site of onset, diagnostic category, ALSFRS-r score, and FVC% at diagnosis were not found to be significant prognostic factors [Table 1]. For TTG, ALS patients were stratified into two groups using the median value of 10 months as a cut-off. The Kaplan-Meier analysis showed that patients with TTG < 10 months had a significantly shorter survival time (median survival = 27 months) than patients with TTG > 10 months, who had a median survival time of 70 months (Log rank = 14.728, $P < 0.0001$). Dividing patients into TTG quartile groups (5, 10, 20 months) yielded similar survival analysis results; as TTG increased, median survival time also increased (21, 27, 45, and 74 months, respectively; Log rank = 21.418, $P < 0.0001$) [Table 1, Figures 1 and 2].

After inclusion of these variables in the Cox proportional hazards model, we observed that factors independently affecting survival within the model were TTG and age at symptom onset [Table 2]. Compared with age at symptom

Table 1: Kaplan-Meier analysis of clinical variables of ALS patients.

Variables	Median survival time (months)	Log-rank value	*P*
Sex (male/female)	38/48	1.493	0.222
Age at onset (≤55/ > 55 years)	83/27	15.652	<0.0001
TTG (≤10/ > 10 months)	27/70	14.728	<0.0001
TTG (≤5/ > 5 and ≤10/ > 10 and ≤20/ > 20 months)	21/27/45/74	21.418	<0.0001
Diagnostic latency (≤12/ > 12 months)	27/70	11.997	0.001
Onset site (bulbar/limb)	34/52	4.855	0.028
Diagnostic category (definite/probable/possible)	38/60/83	3.729	0.155
ALSFRS-r score (≤38/ > 38)	45/55	2.109	0.146
FVC% (≤70%/ > 70%)	43/52	1.688	0.194
DPR (≤0.54/>0.54)	102/39	6.500	0.011

ALSFRS-r score: ALS Functional Rating Scale-revised score; DPR: Disease progression rate; FVC: Forced vital capacity; TTG: Time taken for symptom spread from spinal or bulbar regions to both.

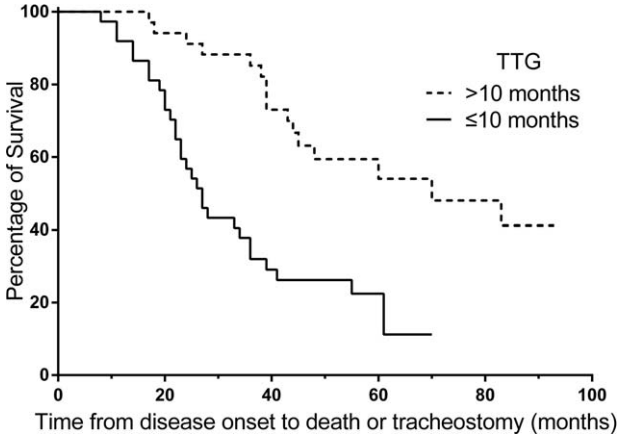

Figure 1: Comparison of survival of patients with ALS stratified by the median of TTG (10 months). ALS: Amyotrophic lateral sclerosis; TTG: Time taken for symptom spread from spinal or bulbar regions to both.

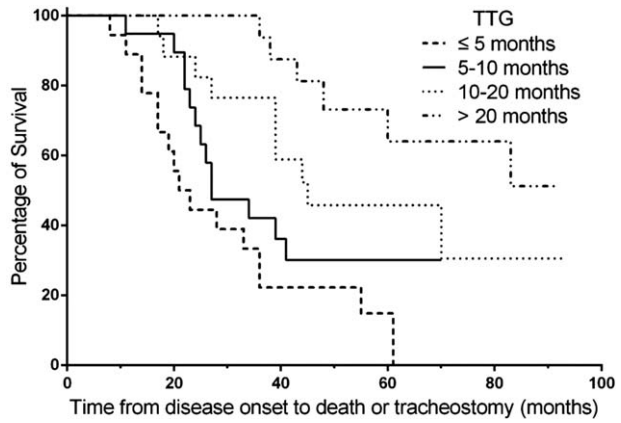

Figure 2: Comparison of survival of patients with ALS stratified by TTG quartile groups (cut-off values are 5, 10, 20 months). ALS: Amyotrophic lateral sclerosis; TTG: Time taken for symptom spread from spinal or bulbar regions to both.

onset [hazard ratio (HR) = 1.079, $P = 0.021$], TTG was the stronger prognostic factor (HR = 0.926, $P = 0.01$).

Spearman rho correlation analysis was used to evaluate the correlation between TTG and other clinical variables. TTG was inversely correlated with ALSFRS-r score and DPR at diagnosis ($r = -0.288$, $P = 0.004$ and $r = -0.620$, $P < 0.0001$, respectively), and positively correlated with diagnostic latency ($r = 0.705$, $P < 0.0001$). No correlation was observed between TTG and age at onset, sex, diagnostic category, or FVC% at diagnosis [Table 3]. A shorter TTG was found in bulbar onset patients (mean: 9.29 months, SD: 10.50 months) than in limb onset patients (mean: 14.19 months, SD: 12.69 months).

Discussion

This clinical research has shown that shorter TTG is related to adverse prognosis in Chinese patients with sporadic ALS. Compared with diagnostic latency, age at symptom onset, and rate of decline in ALSFRS-r score at diagnosis, TTG had the strongest impact of any factor on overall survival, indicating that TTG has the potential to offer prognostic information to ALS patients at an early stage.

Table 2: Independent variables considered as risk factors for patient mortality (or tracheotomy).

Variable	Wald Chi-squared	Hazard ratio	*P*
Age at onset	5.352	1.079	0.021
Diagnostic latency	2.159	3.438	0.142
TTG	6.553	0.926	0.010
DPR at diagnosis	0.973	0.943	0.324

DRP: Disease progression rate; TTG: Time taken for symptom spread from spinal or bulbar regions to both.

Table 3: Spearman correlation coefficient values for the relationships between TTG and other clinical variables.

Variables	r_s	*P*
Age at onset	−0.099	0.177
Sex	−0.012	0.869
Onset site	0.217	0.003
Diagnostic latency	0.705	<0.0001
Diagnostic category	0.108	0.145
FVC at diagnosis	−0.096	0.270
ALSFRS-r score at diagnosis	−0.288	0.004
DPR at diagnosis	−0.620	<0.0001

ALSFRS-r score: ALS Functional Rating Scale-revised score; DPR: Disease progression rate; FVC: Forced vital capacity; TTG: Time taken for symptom spread from spinal or bulbar regions to both.

Thus far, no effective drug treatment for ALS has been developed. Defining an effective early stage prognostic marker usually facilitates estimation of the progression and outcome of the disease, which is of great value for patient care planning and phase III clinical trials in ALS. Chiò *et al*[8] reported that the rate of symptom progression in early ALS was a reliable indicator of the subsequent course of the disease in a population-based, prospective study. Furthermore, flail arm and flail leg syndromes, which often progress relatively slowly compared with typical ALS in the early phase, with symptoms confined to the upper or lower limb region for more than 1 year, often have a better prognosis.[9] Fujimura-Kiyono *et al*[10] proposed that, in ALS, the interval between onset and involvement of a second region is a significant predictor of survival. Nevertheless, it is usually not easy for patients to recall the precise interval between onset and involvement of a second region. Tortelli *et al*[3,4] suggested that the interval from spinal or bulbar involvement to the involvement of both regions (ie, TTG) is a crucial intermediate point in the disease process and can typically be well recognized by the patient. In addition, the combined presence of spinal and bulbar involvement over a short interval dictates wider expansion of the disease process and a more aggressive course, which can be used as a comprehensive and effective prognostic indicator for ALS.

Using TTG median and quartile cut-offs, the Kaplan-Meier survival curve showed that survival was reduced with a short TTG, supporting the suggestion that TTG is a sensitive and reliable predictor of survival, consistent with results of research by Tortelli *et al*.[3,4] Moreover, we found that DPR at diagnosis and diagnostic latency were also associated with survival, and that survival was shorter in bulbar *vs*. limb onset, and in older *vs*. younger patients; there was no significant difference in survival between males and females. The most commonly reported predictors of shorter survival in ALS thus far are bulbar onset, older age at symptom onset, rapid early rate of progression based on functional measures, and shorter diagnostic latency; our observations corroborate these findings of previous studies.[11-13] After adjusting for age at onset, DPR at diagnosis, and diagnostic latency, the results of the present study showed that TTG was the most useful prognostic factor overall. As for diagnostic latency, earlier diagnosis by a specialist in ALS generally predicts worse prognosis, as it indicates rapid disease progression and typical symptoms that can be differentiated from other diseases more easily. However, later diagnosis may be influenced by other factors, such as the patient's medical condition and the form of clinical onset; delayed diagnosis may occur due to a lack of sufficient attention and timely medical treatment. With regards to DPR at diagnosis, it commonly reflects a rapid rate of progression of functional decline in the early stage of ALS; a high score predicts a better outcome. Nevertheless, DPR is also influenced by diagnostic latency. We consider that the greatest value of TTG in predicting survival lies in its objectivity, accuracy, and simplicity.

Our study showed a positive correlation between TTG and diagnostic latency, and revealed that TTG is shorter with bulbar onset ALS. These results are in line with the observation that bulbar onset ALS and shorter diagnostic latency predict a worse prognosis,[13] further confirming the reliability of TTG as a prognostic factor. TTG showed negative correlations with ALSFRS-r scores and DPR at diagnosis, perhaps because patients with shorter TTG were more likely to present with bulbar and spinal involvement at an early stage, and to have had a timely physical examination; hence, ALS functional scores had yet to decrease significantly at the time of diagnosis.

The time of disease spread was considered a reflection of the progression rate of neuroaxonal damage.[14] Neurofilament heavy chain and light chain in body fluids, including cerebrospinal fluid (CSF) and plasma, have been recognized as biological markers of neuroaxonal degeneration, reflecting disease activity and progression in ALS.[15-17] In previous studies, Tortelli *et al*[18] demonstrated that high levels of neurofilament light chain in CSF were predictive of a short TTG. Likewise, a short TTG was found in patients with high plasma and CSF Phosphorylated Neurofilament Heavy Chain (pNF-H) levels.[19] These observations confirm the role of TTG as an external expression of neuroaxonal degeneration in ALS.

In summary, the present study further supports the conclusion that the time taken for symptom generalization after onset is a primary predictor of overall survival in Chinese ALS patients, suggesting that it as an important milestone in the course of disease development. The main limitation of our study was the relatively small number of subjects. During follow-up, patients or their relatives generally remember the time of tracheotomy or death, but it is not easy for them to recall the exact TTG, especially for deceased cases. Therefore, the TTG in our study was obtained from medical history data based on patient recall on hospitalization. We collected clinical notes on a large cohort of 435 ALS patients hospitalized in our department between July 2009 and November 2016, but complete notes on survival and TTG were available for only 71 patients. Moreover, poor compliance with patient follow-up in China is another reason for the small sample. A prospective population-based study is required.

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Conflicts of interest

None.

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