

Frontal lobe function and behavioral changes in amyotrophic lateral sclerosis: a study from Southwest China

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Abstract Despite growing interest, the frequency and characteristics of frontal lobe functional and behavioral deficits in Chinese people with amyotrophic lateral sclerosis (ALS), as well as their impact on the survival of ALS patients, remain unknown. The Chinese version of the frontal assessment battery (FAB) and frontal behavioral inventory (FBI) were used to evaluate 126 sporadic ALS patients and 50 healthy controls. The prevalence of frontal lobe dysfunction was 32.5 %. The most notable impairment domain of the FAB was lexical fluency (30.7 %). The binary logistic regression model revealed that an onset age older than 45 years (OR 5.976, $P = 0.002$) and a lower educational level (OR 0.858, $P = 0.002$) were potential determinants of an abnormal FAB. Based on the FBI score, 46.0 % of patients showed varied degrees of frontal behavioral changes. The most common impaired neuro-behavioral domains were irritability (25.4 %), logopenia (20.6 %) and apathy (19.0 %). The binary logistic regression model revealed that the ALS Functional Rating Scale-Revised scale score (OR 0.127, $P = 0.001$) was a potential determinant of an abnormal FBI. Frontal functional impairment and the severity of frontal behavioral changes were not associated with the survival status or the progression of ALS by the cox proportional hazard model and multivariate regression analyses, respectively. Frontal lobe dysfunction and frontal behavioral changes are common in Chinese ALS patients. Frontal lobe dysfunction may be related to the onset age and educational level. The severity of frontal behavioral changes may be associated with the

ALSFRS-R. However, the frontal functional impairment and the frontal behavioral changes do not worsen the progression or survival of ALS.

Keywords Amyotrophic lateral sclerosis · Frontal assessment battery · Frontal behavioral inventory · Behavioral impairment

Introduction

Amyotrophic lateral sclerosis (ALS) has traditionally been considered to be a pure motor neuron disease. However, numerous non-motor manifestations have been observed, including cognitive and behavioral impairments [1, 2]. ALS patients suffer from cognitive impairments in various domains, predominantly in the realm of executive functions and language functions [3]. Approximately, 10–15 % patients meet the diagnosis criteria of ALS-frontotemporal dementia (ALS-FTD) [4, 5], with the severity of cognition impairment ranging from mild behavioral or cognitive disturbances to frontotemporal dementia (bvFTD) [6]. Delayed diagnosis and inappropriate treatment for the non-motor manifestations of ALS may eventually hinder the compliance with medical treatments and lead to emotional disturbance both in ALS patients and their caregivers [7]. Some studies have been conducted to evaluate the association between cognitive impairment and survival of ALS patients [8–11]. However, the findings were not consistent among studies. An Irish study found that executive dysfunction was a negative prognostic indicator for ALS patients without dementia [8]. Gordon et al. [9] found that cognitively-impaired ALS patients had a shorter survival time. Another study suggested that ALS-FTD patients had shorter survival than classic ALS patients [11]. Hu et al.

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[10] reported that non-behavior cognitive impairments might impact quality of life without impacting survival.

Behavioral disturbances are important and might play a crucial role in ALS because of the overlap with ALS-bvFTD [12]. However, diagnosis of behavioral disturbances in ALS patients is not completely consistent due to different diagnostic tools are being used. And some of them are based on the information given by the patients, while others interview their caregivers. The neuropsychiatric behavioral assessments such as the frontal behavioural inventory (FBI) [13], the neuropsychiatric inventory (NPI) [14], or the Frontal Systems Behavior Scale (FrSBe) [15], are recommended to evaluate behavior changes. A study on Australian population found a substantial proportion of ALS patients manifested behavioral changes of the type seen in FTD [2]. A study on an Italian population found that 50 % of ALS patients had neurobehavioral symptoms and that the burden on the caregiver was related to the neurobehavioral symptoms of the patients [7]. A study on a small Japanese population found that frontal-lobe-related behavioral dysfunction occurred after the onset of ALS and was independent of physical impairments [15]. However, the over-diagnosis of cognitive and behavioral impairments was also potentially due to dysarthria and limb weakness of ALS patients, which might interfere with the assessment [12].

Frontal lobe functional and behavioral changes are poorly characterized in Chinese ALS populations. In addition, no study was focused on the influence of frontal lobe dysfunction and frontal behavioral changes on the progression and survival of ALS patients in Chinese populations. Therefore, the aims of this study were: (1) to explore the frequency and features of frontal lobe dysfunction and frontal behavioral changes at a cross-sectional level using two brief screening measures, i.e., the Chinese version of the frontal assessment battery (FAB) and the FBI, in Chinese ALS patients; and (2) to determine the impact of frontal lobe dysfunction and frontal behavioral changes on the progression and survival of ALS patients in a cohort of Chinese ALS patients.

Patients and methods

The study was conducted in a tertiary referral center in Southwest China (Department of Neurology, West China Hospital of Sichuan University). All ALS patients were recruited between July 2012 and May 2014. A total of 222 sporadic ALS patients who had clinical and electrophysiological evidence of combined upper and lower motor neuron involvement and who fulfilled the El Escorial revised criteria for definite or probable ALS were included [16]. Twenty-nine patients with severe dysarthria, 21

patients with severe hand weakness, and 10 patients with severe anxiety and depression were excluded. Thirty-six patients were also excluded due to incomplete assessments. Finally, a total of 126 ALS patients were included in the analyses. The demographic characteristics of all patients, including age, gender, and years of education, were recorded. The time from first symptom onset to first evaluation of the screening measures was defined as the disease duration. Young-onset ALS was defined as an ALS onset age of younger than 45 years. The onset forms were classified into spinal (upper limb, lower limb) and bulbar onset, according to the site of onset. The ALS Functional Rating Scale-Revised (ALSFRS-R) scale was applied to assess the severity of the disease during the baseline visit. The bulbar involvement was defined as a total score less than 12 on the three bulbar items (speech, swallowing, and salivation) in the ALSFRS-R scale [12].

The severity of depression was evaluated using the 24-item Hamilton Depression Rating Scale (HDRS), with a score of >20 indicating depression and a score of >35 corresponding to severe depression [17]. The severity of anxiety was evaluated using the Hamilton Anxiety Rating Scale (HARS), with a score of ≥ 14 indicating anxiety and a score of ≥ 29 corresponding to severe anxiety [18]. Mini mental status examination (MMSE) was used to screen the cognition.

Frontal lobe function was assessed using the FAB, which contains six subtests including similarities, lexical fluency, motor series, conflicting instructions, inhibitory control, and prehension behavior [19]. The FAB was proposed as a short and reliable screening tool for detecting frontal lobe function in neurodegenerative diseases such as mild cognitive impairment (MCI) [20], Parkinson's disease (PD) [21], and Alzheimer's disease (AD) [22]. However, different cut-off scores were chosen in previously published studies. For example, a score of 12 was used as a cut-off score in one study [21], whereas a score of 16 was used in another study [19]. In the current study, the cut-off score of the FAB was defined as a total score of less than 1.5 standard deviations (SD) away from the mean score of healthy controls on the FAB.

The personality and behavioral disturbance were assessed by the 24-item FBI, which was completed by the caregivers [23]. The FBI contains two subscales for negative (FBI-A) and positive behaviors (FBI-B) [23]. The quantitative measure for each item was determined using a 0 to 3 Likert-type scale. The total FBI score ranges from 0 to 72. Higher scores indicate more severe frontal behavioral disorders. A total score of ≥ 27 indicates frontal lobe dementia [23]. Based on the criteria of a previous study, a total score of zero indicates no behavioral changes, a total score from 1 to 3 corresponds to mild behavioral changes, a total score from 4 to 15 corresponds to moderate behavioral

changes, and a total score of >15 corresponds to severe behavioral changes [24].

Patients were followed with phone calls or face-to-face interviews. The rate of ALS progression was evaluated by the changes of the ALSFRS-R per month (Δ ALSFRS-R/m) (formula: ALSFRS-R score at the last visit – ALSFRS-R score at the baseline visit/month intervals between the two assessments) [25].

Age-, gender- and education-matched healthy controls from the same region were recruited to perform the FAB test. None of the healthy controls had any neurological diseases, psychiatric disorders, or other disorders. Informed written consent was obtained from all participants prior to being recruited. This study was approved by the Ethics Committee of West China Hospital of Sichuan University.

Statistical analysis

Comparisons of continuous variables between groups were analyzed using Student's *t* test or Mann–Whitney *U* tests. The Chi-square test was used to compare categorical variables. Continuous variables are presented as the mean \pm SD. Spearman's correlation test was used to analyze the association between the total FAB score, the total FBI score and clinical variables including age of onset, the site of onset, disease duration, educational level, ALSFRS-R score, MMSE score, HDRS score, and HARS score. The relational coefficient (r_s) described the correlations to varying degrees, i.e., $r_s \geq 0.80$ is considered a very strong correlation, $r_s = 0.60$ – 0.79 corresponds to a strong correlation, $r_s = 0.4$ – 0.59 is considered a moderate correlation, $r_s = 0.20$ – 0.39 indicates a weak correlation, and $r_s \leq 0.20$ is considered a negligible correlation [26].

The binary logistic regression model and ordinal logistic regression analysis were used to analyze the relationship between the behavioral screening tests and potential determinants such as the age of onset, gender, educational level, ALSFRS-R score, the site of onset, disease duration, and MMSE, HDRS, and HARS scores. The association between the frontal lobe dysfunction, frontal behavioral disturbances and the survival of ALS was conducted using a cox regression hazard ratio model. The association between the frontal lobe dysfunction, frontal behavioral disturbances and the progression of ALS was conducted by a multivariate regression analysis. Data analysis was performed using SPSS 18.0 statistical software. $P < 0.05$ was considered as statistically significant.

Results

A total of 126 ALS patients, including 77 males and 49 females, and fifty healthy controls were recruited. The

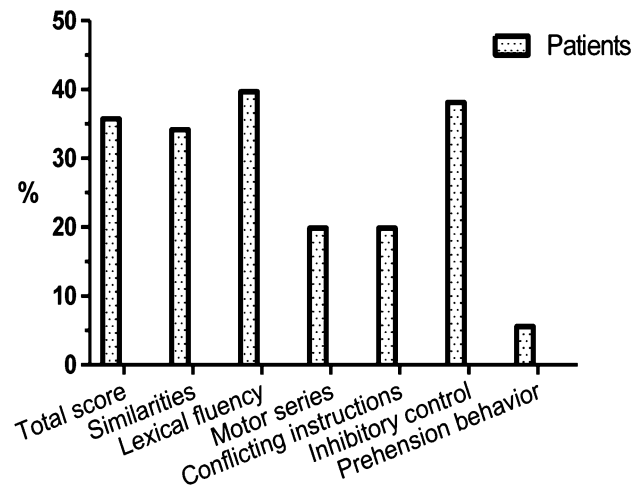


Fig. 1 The frequencies of each subscore less than 3 in FAB scale in ALS patients

mean age of the patients was 55.5 ± 13.3 years, which was not different from the mean age of the healthy controls (52.9 ± 9.0 , $P = 0.44$). The median disease duration at the baseline visit was 10.5 months. Sixty-one patients had an upper limb onset, 37 patients had a lower limb onset, and 28 patients had a bulbar onset. Bulbar involvement was found in 71 patients (56.4 %) at the baseline visit. The mean educational level was 8.7 ± 4.6 years, which was not different from the healthy controls group (9.7 ± 2.9 , $P = 0.17$). The mean ALSFRS-R score of patients was 40.9 ± 4.8 and the mean MMSE score was 26.2 ± 2.8 . The mean score of HDRS was 6.3 ± 4.8 and the mean score of HARS was 3.2 ± 3.5 . The mean FAB score of patients was 15.8 ± 2.6 , and the mean FAB score of the control group was 17.2 ± 1.0 . Therefore, the cut-off score of the FAB was set as 16 in the current study.

The frequencies of an FAB score less than 3 in each subscale in ALS patients are presented in Fig. 1. The percentage of patients was highest in lexical fluency (39.7 %) and lowest in prehension behavior (5.6 %). Based on the cut-off score of 16, ALS patients were classified into the FAB-abnormal (41 patients, 32.5 %) and FAB-normal (85 patients, 67.5 %) groups (Table 1). The FAB-abnormal group had an older age of onset, a lower educational level, lower scores for the MMSE, and higher scores for the HDRS and HARS, but had no differences in the disease duration, gender ratios, site of onset, and ALSFRS-R and FBI scores, compared with the FAB-normal group.

The mean FBI score was 3.3 ± 7.3 . Based on the FBI score, 68 patients (54.0 %) showed no frontal behavioral changes, 36 patients (28.6 %) exhibited mild behavioral changes, 11 patients (8.7 %) exhibited moderate behavioral changes, and 11 patients (8.7 %) showed severe behavioral changes. Five of the eleven patients exhibiting severe behavioral changes had frontal lobe dementia. The

Table 1 Demographic and clinical characteristics of ALS patients in terms of frontal functional status and frontal behavioral changes

	Frontal functional status			Frontal behavior change				
	FAB-abnormal (score <16)	FAB-normal (score ≥16)	<i>P</i> value	FBI score (0)	FBI score (1–3)	FBI score (4–15)	FBI score (>15)	<i>P</i> value
Number	41	85		68	36	11	11	
Men: women	21:20	56:29	0.114	39:29	24:12	8:3	6:5	0.638
Age of onset (years)	58.0 ± 11.3	50.3 ± 13.2	0.002*	54.9 ± 13.5	50.3 ± 11.6	49.2 ± 15.7	51.7 ± 10.9	0.250
Disease duration (months)	12.8 (3–161)	11.3 (3–168)	0.553	11.2 (3–168)	12.7 (3–162)	13.3 (9–49)	11.3 (5–129)	0.163
Site of onset (UL/LL/bulbar)	17/14/10	44/23/18	0.547	39/15/14	14/15/7	5/2/4	3/5/3	0.192
Bulbar involvement (%)	28 (68.3 %)	43 (50.6 %)	0.060	34 (50 %)	23 (63.9 %)	7 (63.6 %)	7 (63.6 %)	0.490
Years of education	6.7 ± 4.6	9.7 ± 4.3	<0.001*	8.8 ± 4.7	8.5 ± 4.7	10.7 ± 3.7	7.3 ± 4.1	0.350
ALSFRS-R	41.1 ± 4.8	40.8 ± 4.8	0.722	42.1 ± 3.4	40.3 ± 5.3	40.7 ± 4.5	35.5 ± 7.0	<0.001*
MMSE score	24.0 ± 3.3	27.3 ± 1.7	<0.001*	26.5 ± 2.9	25.9 ± 2.8	26.7 ± 2.2	24.9 ± 2.8	0.277
FAB score	–	–	–	15.9 ± 2.7	15.7 ± 2.6	16.1 ± 2.1	15.2 ± 2.6	0.829
Similarity	–	–	–	2.6 ± 0.6	2.6 ± 0.8	2.7 ± 0.5	2.1 ± 0.8	0.108
Lexical fluency	–	–	–	2.5 ± 0.6	2.6 ± 0.6	2.9 ± 0.3	2.5 ± 0.5	0.211
Motor series	–	–	–	2.8 ± 0.6	2.7 ± 0.7	2.5 ± 1.0	2.3 ± 1.0	0.130
Conflicting instruction	–	–	–	2.7 ± 0.7	2.7 ± 0.7	2.6 ± 0.7	2.7 ± 0.5	0.985
Go-no-go task	–	–	–	2.4 ± 0.9	2.3 ± 0.9	2.4 ± 1.0	2.5 ± 0.7	0.810
Prehension behavior	–	–	–	2.9 ± 0.3	2.9 ± 0.5	3.0 ± 0.0	3.0 ± 0.0	0.693
FBI score	4.5 ± 9.4	2.7 ± 6.0	0.285	–	–	–	–	–
FBI positive symptoms	1.0 ± 2.5	0.9 ± 2.3	0.857	–	–	–	–	–
FBI negative symptoms	3.5 ± 7.2	1.8 ± 4.0	0.178	–	–	–	–	–
Mean score of HDRS	7.5 ± 4.6	5.7 ± 4.7	0.021*	6.0 ± 4.6	6.2 ± 5.0	5.01 ± 3.7	9.9 ± 4.8	0.058
Mean score of HARS	4.2 ± 3.7	2.7 ± 3.3	0.020*	2.2 ± 2.8	4.2 ± 3.8	2.5 ± 1.8	6.5 ± 4.5	<0.001*

ALS amyotrophic lateral sclerosis, UL upper limb, LL lower limb, ALSFRS-R ALS Functional Rating Scale-Revised, MMSE mini-mental state examination, FAB frontal assessment battery, FBI frontal behavior inventory, HDRS Hamilton Depression Rating Scale, HARS Hamilton Anxiety Rating Scale

* Significant difference

ALSFRS-R and HARS scores were significantly different among the groups with different severities of frontal behavioral changes (Table 1), whereas no differences were found in other parameters, such as disease duration, the site of onset, gender, educational level, and MMSE, FAB and HDRS scores. The patients had different proportions of neurobehavioral symptoms based on the FBI score (Fig. 2). The most common impaired neurobehavioral domain was irritability (32 patients, 25.4 %), followed by logopenia (26 patients, 20.6 %) and apathy (24 patients, 19.0 %).

Spearman's correlations between ALS-related variables and the neurobehavioral test results are shown in Table 2. The total FAB score was correlated with the age of onset ($r_s = -0.296$, $P = 0.001$), educational level ($r_s = 0.441$, $P < 0.001$), MMSE score ($r_s = 0.647$, $P < 0.001$), and HARS score ($r_s = -0.192$, $P = 0.031$). The total FBI score was correlated to the site of onset ($r_s = 0.179$, $P = 0.044$), bulbar involvement ($r_s = -0.180$, $P = 0.044$), ALSFRS-R ($r_s = -0.250$, $P = 0.005$), and HARS score ($r_s = 0.340$, $P < 0.001$) (Table 2).

The binary logistic regression model revealed that an onset age >45 years (OR 5.976, 95 % CI 1.939–18.417, $P = 0.002$), and lower educational level (OR 0.858, 95 % CI 0.778–0.945, $P = 0.002$) were potential determinants of an abnormal FAB in ALS patients. Ordinal logistic regression analysis showed that a lower ALSFRS-R score (OR 0.127, 95 % CI 0.051–0.204, $P = 0.001$) was a potential determinant of the frontal behavioral status in ALS patients (Table 3).

At the end of follow-up, 107 patients were alive, 12 patients were deceased, and 7 patients were lost to follow-up. Seven patients died of respiratory failure and 5 died of dysphagia. The mean follow-up time between the two visits was 10.3 ± 4.3 months and the mean ALSFRS-R score was 32.7 ± 9.0 at the last visit. Finally, a total of 107 patients were included to investigate the association between frontal lobe function, frontal behavioral changes and disease progression. After adjustment for the age of onset and the site of onset, the cox proportional hazard model showed that the disease duration and ALSFRS-R score were significantly

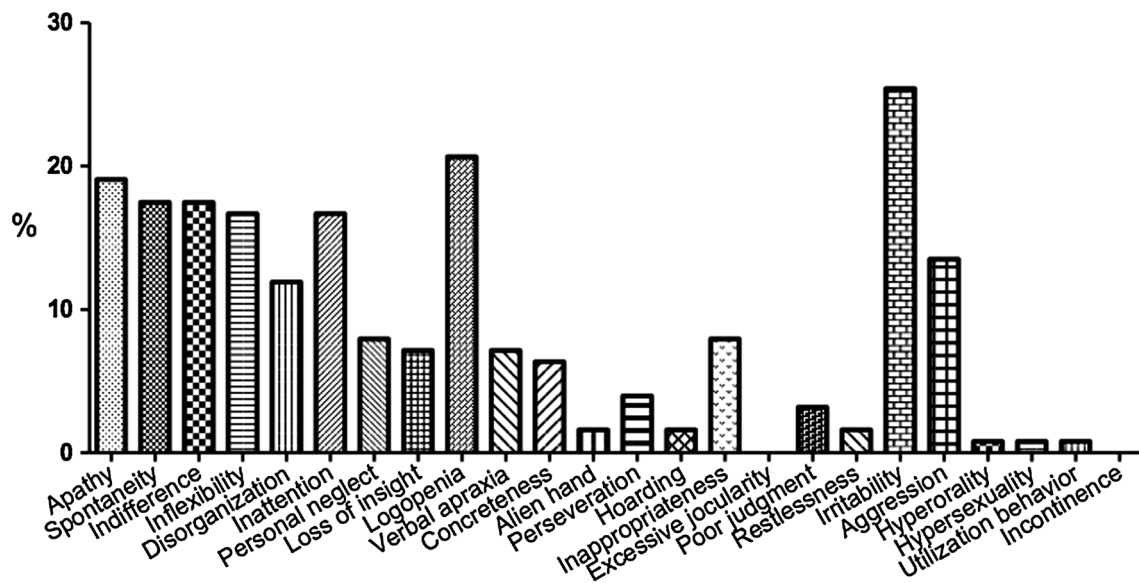


Fig. 2 Histogram shows the proportion of ALS patients with changes of each frontal behavior domain of the FBI

Table 2 Spearman’s correlation coefficients between the FAB, FBI and ALS-related variables

	FAB		FBI	
	<i>r_s</i>	<i>P</i> value	<i>r_s</i>	<i>P</i> value
Age of onset	−0.296	0.001*	−0.138	0.123
Site of onset	−0.089	0.319	0.179	0.044*
Bulbar involvement	0.133	0.136	−0.180	0.044*
Disease duration	0.017	0.852	0.146	0.103
Education	0.441	<0.001*	−0.028	0.757
ALSFRS-R	0.023	0.800	−0.250	0.005*
MMSE	0.647	<0.001*	−0.177	0.051
HDRS	−0.171	0.056	0.123	0.169
HARS	−0.192	0.031*	0.340	<0.001*
FAB	1	–	−0.098	0.276
FBI	−0.098	0.276	1	–

All correlations were calculated by Spearman’s correlation
ALSFRS-R ALS Functional Rating Scale-Revised, *MMSE* mini-mental state examination, *FAB* frontal assessment battery, *FBI* frontal behavior inventory, *HDRS* Hamilton Depression Rating Scale, *HARS* Hamilton Anxiety Rating Scale

* Significant difference

associated with the survival status of ALS patients ($P < 0.001$, OR 0.771; $P = 0.001$, OR 0.864, respectively). However, frontal functional impairment and the severity of frontal behavioral changes were not associated with the survival status. With the progression of ALS (Δ ALS-FRS – R/m) set as a dependent variable, multivariate regression analyses revealed that the frontal functional impairment and the severity of frontal behavioral changes were not associated with the progression of ALS ($P > 0.05$) after

adjustment for the age of onset, the site of onset, disease duration, ALSFRS-R, and treatment with riluzole.

Discussion

This study is the first to explore the frontal lobe function and frontal behavioral changes and the impact of frontal lobe function and behavioral deficits on the progression and survival of ALS patients in a Chinese population of ALS patients using the FAB and FBI. Patients with an onset age >45 years, lower educational level, and more severe motor disabilities are likely to experience more severe frontal lobe dysfunction and frontal behavioral changes. However, the frontal functional impairment and the frontal behavioral changes are not associated with the progression or survival of ALS.

In the current study, the prevalence of frontal lobe impairment was as high as 32.54 % based on the FAB cut-off score of 16, which is consistent with previous studies using different cut-off scores of the FAB (from 23 to 55 %) [14, 27, 28]. “Lexical fluency deficit” was the highest affected domain. Previous studies have also reported that the most common cognition impairment in ALS patients was verbal fluency [14, 28]. In our study, the deficit on prehension behaviour was relatively rare, which was consistent with previous reports (3–12 %) [28, 29]. Prehension behavior is more likely to be presented in patients with severe frontal lobe dysfunction, which is relatively uncommon in ALS [28]. Our finding also supports this notion. Our study found that the ALS patients with onset age >45 years or patients with lower educational levels,

Table 3 Regression analyses predicting outcome while adjusting for non-significant but clinically important covariates

Outcome variable	Independent significant covariates	OR (95 % CI)	P value	Non-significant controlled covariates
FAB	Onset age	5.976 (1.939–18.417)	0.002	The site of onset, disease duration, ALSFRS-R, HDRS, HARS, bulbar involvement
	Educational level	0.858 (0.778–0.945)	0.002	
FBI	ALSFRS-R	0.127 (0.051–0.204)	0.001	Onset age, the site of onset, educational level, disease duration, HDRS, HARS, bulbar involvement

ALSFRS-R ALS Functional Rating Scale-Revised, FAB frontal assessment battery, FBI frontal behavior inventory, HDRS Hamilton Depression Rating Scale, HARS Hamilton Anxiety Rating Scale, OR odds ratio, CI confidence interval

performed worse in the FAB test. These factors have been noted by previous studies [20, 28, 30]. In our study, the frontal lobe impairment was not correlated with the site of onset or bulbar involvement, which is consistent with the study by Sterling et al. [31]. However, Gordon et al. [4] found that bulbar-onset was possibly associated with cognitive impairment in ALS.

Based on the FBI score, almost half of the ALS patients (46.03 %) had frontal behavior impairment. Mild behavioral changes in ALS were more common than moderate and severe behavioral changes. These findings are in agreement with some previous studies [6, 12, 32]. However, the point prevalence of FTD (3.97 %) in our ALS patients is lower than that in other studies (8–15 %) [2, 33]. Some possible explanations for this difference include the following: (1) the mean disease duration was shorter in our study, which may have had an impact on the severity of the frontal behavioral changes; and (2) the ethnic background may have contributed to such contrasted finding. Previous studies mainly focused on the behavioral changes in populations from Western countries [33]. There is lack of sufficient information from Asian populations; (3) also, the screening scales used among studies were different. Because of the complexity of behavioral disturbances, the diagnosis of ALS-behavioral impairment should meet at least two non-overlapping supportive diagnostic features that are determined by neuropsychological assessments from patient interviews or caregiver reports [34].

Previous studies reported that the “perseveration, apathy and disinhibition” domains were the most commonly affected domains in ALS patients [7, 33, 35]. Our study found that irritability was the most frequently affected domain. Among the three most frequent domains of neurobehavioral changes, the other two domains, logopenia and apathy, belong to the negative symptoms category, which may indicate that negative symptoms in Chinese ALS patients are more prevalent than positive symptoms.

Neurobehavioral symptoms were correlated to the site of onset and the presence of bulbar involvement, which is in accordance with a previous study [7]. There was an association between the bulbar presentation and behavioral changes, but no association with cognitive impairment,

which should be cautiously explained. A previous study also reported the debate on the relationship between cognitive and behavioral symptoms [36]. The total FBI score was weakly correlated to the ALSFRS-R score. Meanwhile, a lower ALSFRS-R score was a potential determinant of the behavioral changes in our ALS patients, which suggests that behavioral impairment in ALS may increase as the disease progresses. Thus, it is important to recognize behavioral changes early and to give targeted therapies.

Some studies have investigated the impact of fronto-temporal syndromes and behavioral changes in ALS patients, and their findings were inconsistent. Elamin et al. [8] found that executive dysfunction negatively affected survival in Irish ALS patients. Olney et al. [11] reported that FTD led to a shorter survival in American ALS patients. Hu et al. [10] found the non-behavioral cognitive impairments may impact the quality of life without impacting survival. However, our results showed that frontal functional impairment and frontal behavioral changes were not associated with the survival status and did not worsen the progression of ALS. The following may explain this difference. Although the total sample size in our study was relatively large, the number of deceased patients was very low at the end of our study. This may have influenced the cox proportional hazard model results. In addition, we should consider the impact of dysarthria, respiratory dysfunction, and motor impairments when estimating behavioral disturbances. We should also consider the potential influence of lacking of compliance with treatment recommendations on survival. Acceptance of life prolonging treatment such as PEG, NIPPV or tracheostomy in our ALS population was significantly lower than that in the developed countries because of differences in the cultural and economic factors between Chinese and Caucasian population. There was no significant difference in compliance for these life prolonging treatments between patients with and without frontal behavioral changes due to the small number of patients who chose PEG (two patients) and NIPPV (five patients). However, the ratio of acceptance of these life prolonging measures in ALS patients with abnormal cognition is significantly lower than that in patients with normal cognition in the United States, which

makes sense that survival difference between the two groups [37]. Therefore, further prospective studies with larger sample sizes from different races and with a longer follow-up time may help to verify the associations between behavioral changes and the progression of ALS.

There are several limitations of the present study that should be discussed. First, our study is a cross-sectional study. We explored the frequency and features of frontal lobe dysfunction and behavioral changes at baseline, as well as the correlations between frontal lobe dysfunction and behavioral changes at baseline and the progression and survival of ALS, not the behavioral changes between the two visits with the progression of the disease. Second, it is difficult to distinguish between the cognitive impairment caused by ALS itself and that caused by poor mobility. Third, the results may have been affected by unpredictable factors that were unknown at the time of the study. Finally, there is a sample bias because our participants were recruited from a single Chinese ALS center. Therefore, it is important to conduct multi-center prospective studies on frontal lobe functional and behavioral changes in ALS.

Conclusions

Frontal lobe functional and behavioral changes are common in Chinese ALS patients at the time of diagnosis. The age of onset and educational level are related to frontal lobe dysfunction. The ALSFRS-R score is associated with the severity of frontal behavioral changes. However, the frontal functional impairment and frontal behavioral changes do not worsen the progression or survival of ALS.

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Conflicts of interest The authors declare no conflict of interest.

Ethical standard This study was approved by the Ethics Committee of West China Hospital of Sichuan University.

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