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ORIGINAL RESEARCH

Frequency and risk factor analysis of cognitive and anxiety-depressive disorders in patients with amyotrophic lateral sclerosis/motor neuron disease

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Objectives: To examine the frequency and risk factors of cognitive and anxiety-depressive disorders in patients with amyotrophic lateral sclerosis/motor neuron disease (ALS/MND).

Methods: This was an observational study of 100 ALS/MND patients treated at our hospital outpatient and inpatient departments between January 2009 and April 2010 and 100 matched healthy controls. Subjects were surveyed using Mini Mental State Examination (MMSE), Zung Self-Rating Anxiety Scale (SAS), and Zung Self-Rating Depression Scale (SDS). Patient neurological status was graded by the ALS Functional Rating Scale (ALSFRS). Multivariate linear regression was used to identify factors associated with the MMSE, SAS, SDS, and ALSFRS scores.

Results: Patients had significantly lower MMSE scores than controls ($P<0.05$). MMSE score did not differ by sex or age ($<50/\geq50$ years) ($P>0.05$). Patients with higher educational level (college and above), shorter disease course (<2 years), and lower ALSFRS score (<20) had significantly higher MMSE scores (all $P<0.05$). Multivariate analysis revealed that higher education, shorter disease course, and lower ALSFRS score were independent predictors of better cognitive function (higher MMSE score). Patients had significantly higher mean SAS and SDS total scores than controls (both $P<0.05$), indicating higher subjective anxiety and depression. Female patients, patients with higher education, and those with higher ALSFRS scores had significantly higher SAS and SDS scores (all $P<0.05$). Age, occupation, diagnostic classification, disease duration, and disease awareness did not influence SAS or SDS scores. Multivariate analysis indicated that lower education and lower ALSFRS were protective factors against anxiety and depression.

Conclusion: The frequency of anxiety-depressive disorders was high among patients with ALS/MND. High educational level, short course of disease, and lower ALSFRS were associated with preserved cognitive function. Female sex, higher education, and lower ALSFRS score conferred a greater risk of anxiety and depression. Tailored pharmacotherapy and psychological interventions may help in reducing anxiety and depression in these patients.

Keywords: motor neuron disease, amyotrophic lateral sclerosis, cross-sectional study, anxiety, depression

Background

The motor neuron diseases (MNDs) are a group of neurodegenerative disorders of unknown etiology that selectively destroy motor neurons in spinal cord, brain stem, and cerebral cortex, with considerable heterogeneity among MND types.[1] Loss of motor neurons results in progressive amyotrophy, amyasthenia, and pyramidal signs, finally

evolving to fatal dysphagia and respiratory muscle weakness. Amyotrophic lateral sclerosis (ALS; or classical MND) is often used interchangeably with MND. MND/ALS tends to progress more rapidly than other neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. While the incidence is only approximately 3.9/100,000, 80%–90% of MND/ALS patients die within 3–5 years of disease onset.[2] According to Chancellor et al,[3,4] mean survival was only 2.5 years in half of MND patients, and 5-year overall survival was only 28%. Respiratory failure induced by respiratory muscle paralysis is the major cause of death.[5]

In 1896, Charcot reported the first case of MND, but the etiology still remains unclear more than 100 years later. Most recent studies have focused on the contributions of excitotoxicity,[6] gene mutations,[7] oxidative stress, inflammation, and/or hypermetabolism,[8] but no theory of MND etiology has yielded effective therapies for substantially slowing disease progression.[9] Investigated strategies include antiexcitotoxic agents like riluzole, neurotrophic agents, antioxidants, free radical scavengers,[10] and gene therapy.[7] In addition, supportive and symptomatic treatments have also been examined.[11] Still, riluzole is the only drug approved by the USA and European Union for MND treatment, and it merely prolongs survival time by about half a year.[12]

Functional neuroimaging and neuropathology of MND have demonstrated structural and functional impairments beyond motor regions.[13] Epidemiological studies have also found cognitive changes in a subgroup of patients, and MND patients generally demonstrate attenuations of attention, alertness, psychomotor speed, and memory compared to education- and age-matched controls. In many cases, MND coexists with other neurodegenerative diseases, particularly frontotemporal dementia (FTD).[14] Cognitive impairment is now regarded as a common component of MND progression, ranging from mild to marked FTD.[1,15] Many studies have proposed a strong association between classical MND, MND associated with dementia, and MND associated with FTD. For instance, over 100 cases of MND associated with FTD have been reported in Japan since 1964,[16] and another study has shown that approximately 15% of FTD patients showed MND symptoms.[17] Thus, MND is now recognized as a multisystem degenerative disease characterized by motor system degeneration and often associated with functional impairment induced by frontotemporal lobar degeneration.[18] The most frequent early behavioral/cognitive changes are apathy and reduced executive function. Insight and executive function deficits may help in the diagnosis of FTD in patients with ALS. These patients are negatively affected when they know that their cognitive functions are affected, and they are often seeking help.[19] Therefore, cognitive function in MND and MND symptoms in FTD should be carefully evaluated for improved treatment and to better understand the clinical and etiological relationship between MND and dementia.

Study of patients with ALS and their caregivers found that anxiety is common at the diagnostic stage.[20] Recent studies have revealed that depressive symptoms in patients with ALS will negatively affect their quality of life[21] and that higher depressive scores are associated with faster disease progression.[13] In addition, depression has been shown to influence the cognitive functions in a number of diseases.[22,23] Therefore, it is necessary for physicians to evaluate and treat patient anxiety when diagnosing MND/ALS. Surveyed caregivers of ALS patients using the Cambridge Behavior Scale found that cognitive and emotional disorders were frequently reported. Moreover, many lacked awareness of disease-related problems such as amyasthenia and dysphrasia. Once diagnosed, most MND/ALS patients present anxiety-depressive disorders, even suicidal ideation, because ALS/MND is a rapidly progressive disease with a low survival rate and short survival time. Moreover, motor dysfunction impairs socialization, which may further compound psychiatric effects.[24] Rabkin et al[25] reported that 44%–75% of ALS patients suffer from depression and approximately 10% reach the criteria for major depressive disorder. Nevertheless, in Western studies, the association between ALS and depression and the risk factors for depression vary between studies and remain controversial.[26–28] A South Korean study revealed that decreased physical functioning was associated with depressive symptoms.[29]

Until now, no large-sample studies of anxiety-depressive disorders in ALS/MND have been conducted in the People's Republic of China. To this end, we assessed the frequency and characteristics of cognitive impairments and anxiety-depressive symptoms in 100 patients with MND/ALS, and performed multiple linear regression analysis to identify clinical and demographic factors associated with low cognitive and psychiatric function. These results might help in tailoring interventions that are specific to these patients.

Methods
Study population
One hundred ALS/MND Chinese Han patients diagnosed at our outpatient or inpatient departments between January 2009 and April 2010 met the following inclusion criteria: 1) consistent with the El Escorial criteria revised by the World Federation of Neurology in 1998;[30,31] 2) no history of sedatives, psychotropic drugs, or agents affecting the central nervous system; and 3) not complicated with other diseases that may hamper the emotional expression of

anxiety-depressive disorders such as severe dementia other than ALS-related FTD, aphasia, or deafness.

One hundred healthy Chinese Han volunteers matched for sex ratio, age, and educational level were enrolled as the control group. All controls were neurologically normal as shown by examination and without past history of neuropsychiatric diseases. Normal cognitive function and the absence of anxiety or depressive symptoms were confirmed by designated physicians.

Data collection

Clinical and demographic data including age, sex, occupation, educational level, site of neurodegeneration, course of disease, diagnostic classification, anxiety score, and depression score were entered into a medical records database. The study was approved by the ethics committee of Chinese PLA General Hospital, Beijing 100853, China. All procedures performed in studies involving human participants were in accordance with the ethical standards of Chinese PLA General Hospital and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

The Mini Mental State Examination (MMSE)[32] was used to evaluate orientation to time, orientation to place, registration, attention, calculation, short-term memory, object naming, repetition, reading comprehension, language comprehension, language expression, and figure drawing ability. Total score ranges from 0 to 30 points. Cutoff values separating normal and abnormal correlate with educational levels: 17 points for the illiterate subgroup (no education), 20 points for the primary school subgroup (6 years of education), and 24 points for the middle school/higher subgroup ($>$6 years of education). Scores below the cutoff are indicative of cognitive dysfunction, while scores above the cutoff are indicative of normal cognitive status.

The ALS Functional Rating Scale (ALSFRS)[33] evaluates neurological impairment of ALS from the following measures: speech, salivation, swallowing, handwriting, cutting food and handling utensils, dressing and hygiene, turning in bed and adjusting bed clothes, walking, climbing stairs, and breathing. For each measure, normal is scored as 4, while total loss is scored as 0. The total score is 40, and lower score indicates more severe neurological dysfunction.

The Self-Rating Anxiety Scale (SAS)[34] is composed of 20 items (with choices of A to D) including both positive items scored from 1 (A) to 4 (D) and negative items (questions no 5, 9, 13, 17, and 19) scored from 4 (A) to 1 (D). A gross score is obtained by adding the scores of the 20 questions, and the standardized score is obtained by the integral part of 1.25-fold of the gross score. Subjective anxiety was defined as a standard score $\geq$50. The Self-Rating Depression Scale (SDS)[35] includes 20 items, each graded from 1 to 4, for a maximum total score of 80. Subjective depression was defined as a total score $\geq$50.

Statistical methods

Quantitative data are expressed as mean $\pm$ standard deviation, and categorical data are expressed as frequency/ratio. The t-test was used to compare quantitative means between two groups, one-way analysis of variance to compare multiple quantitative means, and the chi-square test to compare two ratios. Multiple linear regression analysis was performed to evaluate candidate predictive factors for cognitive impairment and anxiety-depressive disorders. SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was applied for statistical analysis with the significance level defined as $P<0.05$.

Results

Baseline group characteristics

Fifty-two men and 48 women (male-to-female ratio 1.08:1) with age of onset between 16 and 74 years (mean 54.7$\pm$10.2 years) and symptom-to-diagnosis time from 3 to 48 months (mean 13.2$\pm$10.4 months) were enrolled in the MND/ALS group (Table 1). One hundred neurologically healthy volunteers matched for mean age, sex ratio, and education level were enrolled as the control group.

MMSE evaluation of ALS/MND patients

The MMSE total score and subscores for recall, calculation, and figure drawing were significantly lower in the patient group compared to the control group (Table 2, all $P<0.001$).

Among patients, univariate analysis indicated that the MMSE score did not differ significantly between male and female patients or between those $<$50 years and those $\geq$50 years (both $P>0.05$). In contrast, patients with higher educational level (college and higher), shorter course of disease ($<$2 years), and lower ALSFRS score ($<$20) had higher MMSE scores than those with lower education, longer course of disease, and higher ALSFRS score, respectively (all $P<0.05$, Table 3).

Among patients, multiple linear regression analysis was performed with MMSE total score as the dependent variable and sex, age, educational level, disease course, and ALSFRS score as independent variables. Educational level (β=0.335, $P<0.001$), course of disease (β=0.252, P=0.001), and ALSFRS score (β=0.568, $P<0.001$) significantly affected MMSE total score. Specifically, higher educational level, short course of disease, and lower ALSFRS score were predictive of higher MMSE scores and thus greater preservation of cognitive function (Table 4).

Table 1 Clinical and demographic characteristics of the patient group

Variable	Cases (total =100)
Sex	
Male/female	52/48
Age (years)	
<50/≥50	29/71
Occupation	
Technician	15
Director of government office/public institute	12
Office staff	2
Commercial workers	4
Service staff	3
Farmers, forestry, herdsmen, fishermen	24
Production and transportation	11
Others/nonspecified	21/8
Site of occurrence	
Medulla oblongata	21
Cervical spine	481
Thoracic spine	1
Lumbosacral spine	30
Educational level	
Senior high school and lower	73
College and higher	27
Disease course (years)	
<2/≥2	54/46
Disease classification	
ALS	82
Progressive muscular atrophy	7
Progressive bulbar paralysis	11

Abbreviation: ALS, amyotrophic lateral sclerosis.

Anxiety-depressive disorders in ALS/MND patients

The patient group also had significantly higher mean SAS standard score, mean SDS standard score, and frequencies of both anxiety and depression than the control group (all $P<0.05$, Table 5).

In the patient group, univariate analyses of candidate factors associated with anxiety and depression revealed higher

Table 2 Comparison of MMSE scores between the patient group and control group

Items	Patient group (n=100)	Control group (n=100)	P-value
Male:female	52:48	53:47	0.887
Age (mean ± SD)	54.67±10.17	52.01±18.37	0.2067
Recall (3)	1.82±0.68	2.98±0.02	<0.001
One-hundred-minus-seven test (5)	3.82±0.98	4.80±0.12	<0.001
Drawing figure (2)	1.63±0.12	1.88±0.08	<0.001
Total (30)	27.04±2.81	29.66±0.14	<0.001

Notes: The MMSE total score and subscores for recall, calculation, and figure drawing were significantly lower in the patient group than in the control group. Values in the parenthesis represent the maximal score in the score range.
Abbreviations: MMSE, Mini Mental State Examination; SD, standard deviation.

Table 3 Univariate analysis of associations between clinical and demographic variables and patient MMSE scores

Related factors	n	Mean ± SD	P-value
Sex			
Male	52	27.40±3.06	0.215
Female	48	26.67±2.49	
Age (years)			
<50	29	27.00±2.62	0.827
≥50	71	27.14±3.24	
Educational level			
High school and lower	73	26.38±2.79	<0.001
College and higher	27	28.52±2.12	
Disease course			
<2	54	28.52±3.14	<0.001
≥2	46	25.24±2.67	
ALSFRS score			
<20	78	27.64±2.23	<0.001
≥20	22	24.35±3.59	

Notes: Patients with higher educational level (college and higher), shorter course of disease (<2 years), and lower ALSFRS score (<20) had higher MMSE scores than those with lower education, longer course of disease, and higher ALSFRS score, respectively.
Abbreviations: MMSE, Mini Mental State Examination; ALSFRS, amyotrophic lateral sclerosis Functional Rating Scale; SD, standard deviation.

SAS and SDS scores in females, those with higher education, and those with lower ALSFRS scores (<20) compared to males, those with lower educational level, and higher ALSFRS scores (≥20), respectively (Table 6). In contrast, age (<50 vs ≥50 years old), occupation (mental vs physical labor), ALS diagnosis (clinically confirmed vs clinically suspected), course of disease (<2 vs ≥2 years), and disease awareness had no significant influence on SAS and SDS scores.

Multivariate linear regression analysis revealed that educational level and ALSFRS score were independently associated with anxiety (β=0.410, $P<0.001$ and β=0.268, $P=0.013$, respectively) and depression (β=0.441, $P<0.001$

Table 4 Multivariate linear regression analysis for independent predictors of patient MMSE scores

Variables	Regression coefficient	Standardized regression coefficient	P-value	95% CI	
Constant	22.269		<0.001	18.628	25.911
Sex	−0.675	−0.134	0.100	−1.483	0.133
Age	0.020	0.072	0.369	−0.024	0.065
Education	1.004	0.335	<0.001	0.498	1.51
Disease course	−1.355	−0.252	0.001	−2.171	0.232
ALSFRS score	0.180	0.568	<0.001	0.127	−0.538

Notes: Higher educational level, short course of disease, and lower ALSFRS score were predictive of higher MMSE scores and greater preservation of cognitive function.
Abbreviations: MMSE, Mini Mental State Examination; ALSFRS, amyotrophic lateral sclerosis Functional Rating Scale; CI, confidence interval.

Table 5 Comparison of SAS and SDS scores between the patient and control groups

	Patient group (n=100)	Control group (n=100)	P-value
SAS standard score	45.5±7.2	36.5±7.3	<0.05
SDS standard score	44.8±8.2	36.3±9.1	<0.05
Anxiety, n (%)	84 (87.5%)	24 (24.0%)	<0.05
Depression, n (%)	20 (20.8%)	6 (6.0%)	<0.05

Notes: The patient group had significantly higher mean SAS standard score, mean SDS standard score, and frequencies of both anxiety and depression than the control group. Data are presented as mean ± standard deviation.
Abbreviations: SAS, Zung Self-Rating Anxiety Scale; SDS, Zung Self-Rating Depression Scale.

and β=0.385, $P<0.001$, respectively). Specifically, lower educational level and higher ALSFRS scores were predictive of lower SAS and SDS scores. Thus, lower education and higher ALSFRS scores were protective factors against anxiety and depressive symptoms (Tables 7 and 8).

Discussion

The patient group had significantly lower MMSE scores for recall and calculation (the one-hundred-minus-seven test) compared to controls matched for age and education. The patient group also showed deficits in figure drawing, although this could be due to motor deficits (suggesting that the drawing item might be of little value for intellectual evaluation in this patient group). Multivariate analysis revealed that high educational level, short disease course, and lower ALSFRS scores were independently associated with higher MMSE scores, indicative of preserved cognitive function.

The prevalence of depression in patients with ALS compared to the general population is controversial. Indeed, Atassi et al[28] reported a lower frequency of depression in patients with ALS. Nevertheless, in Western studies, the association between ALS and depression and the risk factors for depression vary between studies and remain controversial.[26–28] A South Korean study revealed that decreased physical functioning was associated with depressive symptoms.[29] Most of these studies report on small groups of patients, and it is thus difficult to compare the frequency of depression with the general population.

Cognitive function, operationally defined as skillful utilization of knowledge, depends on multiple neural processes such as acquisition, recall, working memory, attention, calculation,

Table 6 Univariate analysis of associations between clinical and demographic parameters and patient SAS and SDS scores

Related factor	n	SAS		SDS	
		Mean ± SD	P-value	Mean ± SD	P-value
Sex			0.048		0.048
Male	49	42.1±8.9		41.5±11.3	
Female	47	45.6±8.2		45.9±10.1	
Age (years)			0.851		0.828
<50	29	45.3±8.4		44.5±9.1	
≥50	67	45.6±6.6		44.9±7.9	
Educational level			<0.001		<0.001
Senior high school and lower	72	44.1±5.4		42.9±7.2	
College and higher	24	49.8±9.8		50.1±8.9	
Occupation			0.175		0.625
Mental labor	34	46.2±10.6		45.2±13.7	
Physical labor	51	43.8±5.5		44.0±8.9	
Diagnostic classification			0.840		0.694
Confirmed ALS	37	43.8±7.4		44.1±7.9	
Suspected ALS	35	43.2±16.3		42.9±16.6	
Course of disease (years)			0.763		0.857
<2	57	45.8±8.5		44.7±9.2	
≥2	21	45.2±5.1		45.1±6.8	
ALSFRS score			0.033		0.002
≥20	77	44.7±6.3		43.5±7.7	
<20	19	48.6±9.5		50.0±8.4	
Disease awareness			0.184		0.079
Yes	58	44.7±7.2		43.6±7.9	
No	38	46.7±7.1		46.6±8.4	

Notes: Univariate analyses of candidate factors associated with anxiety and depression revealed higher SAS and SDS scores in females, those with higher education, and those with lower ALSFRS scores (<20) compared to males, those with lower educational level, and higher ALSFRS scores (≥20), respectively.
Abbreviations: SAS, Zung Self-Rating Anxiety Scale; SDS, Zung Self-Rating Depression Scale; ALS, amyotrophic lateral sclerosis; ALSFRS, amyotrophic lateral sclerosis Functional Rating Scale; SD, standard deviation.

Table 7 Multivariate linear regression analysis for independent predictors of patient SAS scores

Variable	Regression coefficient	Standardized regression coefficient	*P*-value	Regression coefficient 95% CI	
Constant	36.423		<0.001	23.489	49.356
Sex	0.556	0.036	0.743	−2.807	3.919
Age	−0.139	−0.168	0.117	−0.313	0.036
Education	7.189	0.41	<0.001	3.492	10.885
Disease course	−1.257	−0.073	0.501	−4.958	2.445
ALSFRS score	4.972	0.268	0.013	1.089	8.854
Disease awareness	1.652	0.108	0.311	−1.578	4.881

Notes: Lower educational level and higher ALSFRS scores were predictive of lower SAS scores. Lower education and higher ALSFRS scores were protective factors against anxiety and depressive symptoms.
Abbreviations: SAS, Zung Self-Rating Anxiety Scale; ALSFRS, amyotrophic lateral sclerosis Functional Rating Scale; CI, confidence interval.

and abstraction/generalization. Cognitive functioning in MND is traditionally considered normal, but clinical observations have revealed progressive cognitive decline and even dementia symptoms in MND patients.[36] Recent studies conducted in the People's Republic of China and elsewhere have demonstrated cortical damage associated with speech comprehension and fluency impairments, memory deficits, and decline in calculation, as well as subcortical damage associated with impairments in abstraction.[37] In addition, MND patients exhibited local reductions in cerebral blood flow and metabolic activity in frontal lobe, insular lobe, parahippocampal gyrus, and thalamic nuclei, and these reductions correlated with cognitive deficits.[38] Such cognitive impairment may be mild at early stages and may be possibly neglected by patients, caregivers, and clinicians. However, cognitive decline may be more difficult to detect at a later stage due to exacerbation of dyskinesia and bulbar paralysis-induced speech disorder. Accurate evaluation of cognitive function at the early stages may enhance treatment efficacy, thereby enhancing patient quality of life.

Higher anxiety and depressive scores were reported by females, patients of higher educational level, and those with higher ALSFRS scores. Female sex was independently associated with higher anxiety-depressive symptoms (SDS and SAS scores). Recent studies have implicated hormonal changes in female anxiety.[39] Moreover, as women play multiple roles in the family, they may worry about the family's future due to their illness. The fact that patients with college and higher educational levels also exhibited more severe symptoms of anxiety than those with senior high school and lower educational levels may be explained by greater awareness of future outcome. ALSFRS for neurological deficit evaluation shows that severe neurological impairment and poor daily living ability can induce anxiety-depressive status, which is supported by a previous study.[13] In contrast, age, occupation, disease duration, diagnostic classifications, and degree of disease awareness had no significant effects on SAS or SDS scores. The lack of effect of disease duration may reflect patient adjustment or acceptance of condition despite more severe symptoms.

In a previous report, approximately 25% of ALS patients were on antidepressants.[40] In the present cross-sectional study, only a minority of patients were receiving psychotherapy or antidepressants, underscoring a lack of attention to anxiety and depression in MND patients. No randomized, double-blind, controlled trials on drug therapy for anxiety and depression associated with MND/ALS have been conducted so far.[41] Clinically, the most commonly used agents are selective serotonin reuptake inhibitors and tricyclic antidepressants, of which the latter are also effective for anxious symptoms

Table 8 Multivariate linear regression analysis for independent predictors of patient SDS scores

Variable	Regression coefficient	Standardized regression coefficient	*P*-value	Regression coefficient 95% CI	
Variable	24.409		0.001	10.993	37.826
Sex	1.628	0.095	0.355	−1.86	5.117
Age	−0.102	−0.111	0.265	−0.283	0.079
Educational	8.617	0.441	<0.001	4.782	12.452
Disease course	−0.517	−0.027	0.789	−4.357	3.323
ALSFRS	7.95	0.385	<0.001	3.923	11.978
Disease awareness	2.493	0.146	0.142	−0.857	5.843

Notes: Lower educational level and higher ALSFRS scores were predictive of lower SDS scores. Lower education and higher ALSFRS scores were protective factors against anxiety and depressive symptoms.
Abbreviations: SDS, Zung Self-Rating Depression Scale; ALSFRS, amyotrophic lateral sclerosis Functional Rating Scale; CI, confidence interval.

and useful for salivation, pseudobulbar palsy, and insomnia. We suggest that antianxiety and antidepressive treatments should be considered upon diagnosis.

The present study is not without limitations. The sample size was small, but considering the rarity of the disease and compared to previous studies, it was quite large. Nevertheless, the patients were from a single institution in the People's Republic of China, and future multicenter studies should increase the sample size and validate the findings of this study. ALS/MND is influenced by genes such as *C9ORF72*, *SOD1*, *TDP-43*, and *FUS*;[42] however, no genetic data are available for the patients included in this study. Nutrition is also a factor that could affect ALS progression, quality of life, and depressive symptoms;[43] however, nutritional status of the patients was not available. Finally, hospitalized patients and outpatients may suffer differently from depression, but these data were not assessed in the present study. Future studies should include the assessment of polymorphisms in these genes and nutritional data as they might influence the psychological outcomes.

Conclusion

The frequency of symptoms of anxiety and depression in Chinese patients with ALS/MND was high. High educational level, short course of disease, and lower ALSFRS were independently associated with preserved cognitive function. Female sex, higher education, and lower ALSFRS score conferred a greater risk of anxiety and depression. Tailored pharmacotherapy and psychological interventions may help reduce anxiety and depression in these patients.

Author contributions

FC carried out the study design, data collection, and analysis, and wrote the manuscript. WJZ, ZBZ, YR, YFL, ML, and YYH participated in data collection, statistical analysis, and provided the critical revision. XSH conceived of the study, participated in its design and coordination, and provided the critical revision. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work. All authors approved the final version of the paper.

Disclosure

The authors report no conflicts of interest in this work.

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