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ORIGINAL COMMUNICATION

Cognitive and behavioral status in Japanese ALS patients: a multicenter study

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Abstract

Objectives Amyotrophic lateral sclerosis (ALS) patients may present with cognitive and behavioral abnormalities similar to frontotemporal dementia (FTD). In this multicenter study we examined Japanese ALS patients with and without FTD in order to characterize the full extent of cognitive and behavioral abnormalities, including associations with functional motor status, anxiety and depression.

Methods Patients were evaluated using the Montreal Cognitive Assessment (MoCA), Frontal Assessment Battery (FAB), Hospital Anxiety and Depression Scale, ALS Functional Rating Scale-Revised, spirometry, and verbal fluency tests. Caregivers were asked to complete the ALS-FTD-Questionnaire (ALS-FTD-Q), a behavioral screen. We defined severe cognitive impairment (MoCA < 21 or FAB < 11), mild impairment (11 ≤ MoCA ≤ 25 or 11 ≤ FAB ≤ 15), and normal cognition (MoCA > 25 or FAB > 15). Severe and mild behavioral impairments and normal behavior were defined by the ALS-FTD-Q scores.

Results In 145 ALS patients, better cognitive scores were correlated with earlier age at onset, whereas a worse behavioral score was associated with a longer disease duration and higher level of anxiety and depression. Around seventy percent of all ALS patients showed mild (40–45%) or severe cognitive impairment with cognitive impairment outnumbering behavioral impairment fivefold. Cognitive functions were more impaired in patients with age of onset over 65 years, while behavioral scores were not related to age.

Conclusions Considering the high prevalence of in particular cognitive impairment, and the diversity of impairments, the cognitive and behavioral aspects of Japanese ALS patients should be given more attention clinically.

Keywords Amyotrophic lateral sclerosis · Frontotemporal dementia · Cognitive and behavioral impairment

Introduction

Frontotemporal dementia (FTD) is the second most frequent form of pre-senile dementia following Alzheimer's disease (AD) [29]. Disease onset usually occurs before age 65 with a mean age of approximately 58 years [17]. Amyotrophic lateral sclerosis (ALS) is defined by progressive loss of upper and lower motor neurons [7]. A growing body of evidence suggests that ALS and FTD share common clinical, pathological and genetic backgrounds [3, 19, 30]. About 10–15% of ALS patients meet the criteria for FTD [14, 21, 24] and 30–50% of ALS patients exhibit cognitive impairment predominantly in executive and language functions [4, 21, 24].

The ALS subpopulation that has distinct cognitive impairment but does not meet the criteria for FTD is termed ALS with cognitive impairment (ALSci), while the ALS subpopulation that predominantly exhibits behavioral

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changes that do not fulfil criteria for FTD is termed ALS with behavioral impairment (ALSbi) [31]. Determining the cognitive and behavioral status of ALS patients is important as ALS patients with cognitive or behavioral impairment, especially when severe, have a worse prognosis than those without [15, 33].

The Japanese ALS population has a different genetic background as compared to other populations, with a lower frequency of the C9ORF72 mutation, which is strongly associated with frontotemporal dysfunction [20]. Related to this, the presence and clinical characteristics of non-motor symptoms in ALS in Japan may be different from previous reports from Western countries.

In the present report, we first aimed to characterize the full extent of cognitive and behavioral abnormalities in Japanese ALS(/FTD) patients, including the mild cases. Second, because we expected to include a relatively large number of patients, we aimed to corroborate previous findings from smaller studies in terms of associations of cognitive and behavioral changes with other clinical features (functional motor status, depression and respiratory impairment) in ALS patients [4]. Finally, since FTD is considered to represent pre-senile dementia, we examined the cognitive and behavioral status of ALS patients in two different age groups (below and over 65 years of age).

Subjects and methods

Subjects

Patients from 19 neurology or psychiatry facilities in Japan were enrolled in this cross-sectional study (2013–2019). The ethical committees of the participating hospitals approved this study and informed consent was obtained from all subjects. Patients with ALS were diagnosed using the revised El Escorial criteria (possible, probable or definite) [7]. A diagnosis of FTD was made according to the Rascovsky criteria [28]. Only patients with a proxy were included in this study. A proxy can be a partner, parent, sibling, adult child, or other caregiver who is able to assess the patient's behavior. Patients who met the revised El Escorial criteria and Rascovsky criteria were categorized as ALS/FTD. Patients with ALS with AD, ALS with progressive non-fluent aphasia, and ALS with semantic dementia were excluded. Patients with a positive family history (i.e., having relative(s) with ALS or FTD) were excluded. A minority of patients were genetically tested, and we also excluded patients with a known ALS- or FTD-associated mutation. Demographic and disease characteristics (sex, age and site of onset, years of education, presence or absence of bulbar involvement, and disease duration) were obtained from all participants.

Patients who showed bulbar symptoms as the initial sign of ALS were defined as bulbar-onset ALS, while cases with initial limb onset were classified as limb-onset ALS. There were no respiratory-onset patients in this cohort. Disease onset was defined as the time of the earliest signs of motor weakness, dysarthria, or FTD symptoms. In the ALS/FTD group, cases in which symptoms started with motor impairment were categorized as ALS-FTD, whereas cases with initial FTD symptoms were categorized as FTD-ALS. During patient enrollment, physicians at each facility were asked to categorize patients as either ALS or ALS/FTD (specified as ALS-FTD or FTD-ALS) based on individual criteria, although further classification (e.g., ALSci or ALSbi) was not required.

Methods

Patients were administered the following assessments by physicians or clinical psychologists during one of the outpatient clinic visits: the Montreal Cognitive Assessment (MoCA) [22], Frontal Assessment Battery (FAB) [12], Hospital Anxiety and Depression Scale (HADS) [34], and the ALSFRS-R. It is important to control for motor impairments in ALS patients. We therefore used scores that are corrected for motor impairment for the MOCA and FAB. Consistent with previous reports [27, 32], for items that required manual dexterity (e.g., the first item of the MoCA and four out of six items of the FAB), a note was made when these tasks could not be performed. We extrapolated the MoCA and FAB scores by taking the missing values into account. The corrected scores were calculated with the following formula: extrapolated score = (actual points scored/maximum attainable score for individual patient) × maximum score of the test. With these extrapolated scores, the normal cut-off values of the FAB and MOCA can still be applied. For the FAB, this adjustment has shown to be valid in ALS and ALS-bvFTD [26]. The anxiety and depression subcategories of the HADS were analysed separately in this study. The vital capacity (upright, in most of the cases) as a percent of the predicted value (%VCpred) was also included in the analyses. Verbal fluency was determined according to a previous report [32].

A proxy assessed the behavior of the patient using the ALS-FTD-Questionnaire (ALS-FTD-Q) [27, 32]. Previously, we translated and clinimetrically validated the ALS-FTD-Q (internal consistency, and construct and clinical validity) for use in Japan [32]. The Japanese version is posted on the official website for the Research Committee of CNS Degenerative Diseases, the Ministry of Health, Labour and Welfare of Japan (https://plaza.umin.ac.jp/neuro2/pdffiles/ALS-FTD-Q-J.pdf). We defined severe cognitive impairment (MoCA < 21 or FAB < 11), mild cognitive impairment (11 ≤ MoCA ≤ 25 or 11 ≤ FAB ≤ 15), and normal cognitive functioning (MoCA > 25 or FAB > 15). Severe

and mild behavioral impairments, and normal scores of the ALS-FTD-Q were defined as > 28, 22 ≤ ALS-FTD-Q ≤ 28 and < 22.

Statistical analysis

Comparisons between demographic and disease characteristics and clinical scores (MoCA, FAB, ALS-FTD-Q, HADS, ALSFRS-R, %VCpred, and verbal fluency) between subgroups were carried out using the Kruskal–Wallis test for continuous variables, with a Pearson's chi-squared test (χ^2) for comparison of proportions. A Spearman's rank correlation-coefficient test was conducted to examine correlations among the cognitive, behavioral, and motor assessments and the clinical features in the total group of ALS patients. We calculated effect sizes (η^2 in one-way ANOVA) or r values in the other analyses).

To examine whether demographic and clinical variables contribute to the presence of cognitive (MOCA), frontal (FAB) and behavioral (ALSFTD-Q) impairment we performed multivariate logistic regression analyses. Explanatory variables with a p values < 0.25 in univariate analyses were included. We used age of onset, sex, school education, site of onset, bulbar involvement, HADS anxiety and HADS depression, ALSFRS-R, and %VCpred as explanatory variables. For the logistic regression analyses, we used the following cut-offs for abnormal scores on MOCA (≤ 25), FAB (≤ 15) and ALSFTD-Q (≥ 22).

A p value of < 0.05 was considered statistically significant. We used Bonferroni corrections to adjust for multiple comparisons. Analyses were performed using PASW statistics, version 18 (SPSS).

Results

Participants

In total, 174 patients were enrolled in the study (Table 1). Out of these patients, 165 were diagnosed with ALS whereas 9 patients (5.4%) were clinically classified as ALS/FTD. In the ALS/FTD cases, symptoms started as motor disturbances in two patients (ALS-FTD) and cognitive and/or behavioral abnormalities in seven patients (FTD-ALS). The mean age at onset, years of education, and disease duration did not differ between the ALS and ALS/FTD groups. ALS patients

Table 1 Clinical characteristics of registered ALS patients with or without FTD

	ALS			ALS/FTD		
	Total	Bulbar-type	Limb-type	Total	ALS-FTD	FTD-ALS
Number	165	43	122	9	2	7
Age at onset (years)	68.5 (9.5)	69.6 (9.4)	68.1 (9.5)	67.4 (5.3)	69.0 (8.0)	67.4 (4.1)
Sex, M/F	98/67	22/21	76/46	3/6	1/1	2/5
School education (years)	12.5 (2.4)	12.6 (2.3)	12.5 (2.4)	11.6 (2.7)	12.0 (0.0)	11.4 (3.1)
Bulbar involvement *	68.5%	100%	56.6%	89%	50%	100%
Disease duration (months)	17.0 (3–593)	17.0 (4–121)	20.0 (3–593)	39.0 (7–68)	26.5 (7–47)	39.0 (7–68)
MoCA	23.1 (4.1)	23.2 (4.5)	23.1 (3.9)	13.2 (7.3)$^{¶¶¶¶,####,!!!!}$	17.0 (4.0)	10.7 (7.8)$^{¶¶¶¶,####,!!!!}$
FAB	13.4 (3.3)	13.5 (3.4)	13.3 (3.3)	5.1 (4.0)$^{¶¶¶¶,####,!!!!}$	5.5 (0.5)$^{¶¶,#,!}$	5.0 (4.5)$^{¶¶¶,##,!!}$
ALS-FTD-Q	9.2 (9.2)	10.2 (10.2)	8.9 (8.8)	30.1 (15.4)$^{¶¶¶,###,!}$	22.5 (1.5)	32.7 (17.0)$^{¶¶,#,!}$
HADS anxiety	4.4 (4.4)	4.6 (4.1)	4.4 (4.6)	5.7 (4.0)	6.6 (6.6)	5.6 (2.9)
HADS depression	4.7 (4.2)	4.3 (3.6)	4.8 (4.4)	8.7 (5.3)	4.4 (4.4)	10.6 (4.5)
ALSFRS-R	35.8 (8.8)	37.0 (6.9)	35.4 (9.4)	30.0 (11.2)$^{¶,#,!}$	24.0 (13.0)	32.0 (9.7)
%VCpred (%)	80.8 (26.2)	73.4 (25.2)	83.2 (26.0)	62.5 (17.2)	54.8 (14.4)	67.7 (16.9)
Verbal fluency	9.8 (6.0)	9.9 (5.2)	9.8 (6.3)	28.9 (27.7)	16.6 (3.0)	34.0 (31.3)

The patients registered as ALS and who showed bulbar onset was defined as the bulbar-type ALS, while the limb type means limb onset ALS. The ALS-FTD group presented initially with motor symptoms and subjects presented with behavioral changes was categorized as FTD-ALS

ALS Amyotrophic Lateral Sclerosis, *FTD* Frontotemporal Dementia, *MoCA* Montreal Cognitive Assessment, *FAB* Frontal Assessment Battery, *ALS-FTD-Q* Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire, *HADS* Hospital Anxiety and Depression Scale, *ALSFRS-R ALS* Functional Rating Scale-Revised, *%VCpred* Predicted Vital Capacity Percentage

*Bulbar involvement was defined as a score ≦11 on the 3 bulbar items of the ALSFRS-R. Disease duration was expressed median month (range), other factors are expressed mean (SD)

$^{¶}p < 0.05$, $^{¶¶}p < 0.01$, $^{¶¶¶}p < 0.001$, $^{¶¶¶¶}p < 0.0001$ vs ALS (total), respectively

$^{#}p < 0.05$, $^{##}p < 0.01$, $^{###}p < 0.001$, $^{####}p < 0.0001$ vs ALS (Bulbar), respectively

$^{!}p < 0.05$, $^{!!}p < 0.01$, $^{!!!!}p < 0.0001$ vs ALS (Limb), respectively

performed significantly better in terms of MoCA, FAB and ALS-FTD-Q scores compared with ALS/FTD patients. Among the 165 ALS cases without FTD, 43 had bulbar-type ALS (26.1%) and 122 had limb-type ALS (73.9%). Demographic, clinical (ALSFRS-R) and cognitive or behavioral data did not differ between bulbar- and limb-onset patients. Frequencies of severe and mild cognitive impairment are 25.2% and 39.6% by MoCA and 21.5% and 45.6% by FAB, respectively. Frequencies of severe and mild behavioral impairment are 4.7% and 8.0%.

Associations between cognitive, behavioral and clinical variables in ALS patients without FTD

Demographic, clinical, and cognitive and behavioral data for ALS patients and ALS/FTD patients are shown in Table 1. Below, we selectively present data of ALS patients without FTD. Out of 145 patients, 10 (6.9%) and (9.7%) patients, respectively, had impairments necessitating the use of extrapolated scores for the MoCA and FAB. Among the items of the MoCA and FAB, language and delayed recall categories of the MoCA, and similarities, motor series, and inhibitory control of the FAB showed relatively lower scores (as compared to the other items) in ALS patients (Supplementary Table 1). The correlation coefficients (r) of cognitive (MoCA and FAB), behavioral (ALS-FTD-Q), motor assessments (ALSFRS-R), and other clinical features are shown in Table 2. Cognitive scores (MoCA and FAB), but not the behavioral score (ALS-FTD-Q) showed moderate correlations ($0.3 \leq r < 0.5$) [10] with age of onset, years of education, and verbal fluency. Since fluency is included in the FAB, we examined FAB scores without the fluency score which correlated with verbal fluency scores ($r = -0.317$, $p < 0.001$). The behavioral score (ALS-FTD-Q) showed moderate correlations with HADS (which did not survive correction for multiple comparisons). ALSFRS-R was highly correlated ($0.5 \leq r$) [10] with %VCpred, moderately with HADS anxiety and depression, and with disease duration. Overall, associations were not different between the bulbar- and limb-onset groups (data available upon request), and most of the associations survived correction for multiple corrections (Table 2).

Logistic regression analyses

To identify demographic variables (including age) and clinical variables that contribute to the presence of cognitive (MOCA), frontal (FAB) and behavioral (ALSFTD-Q) impairment we performed multivariate logistic regression analyses (Table 3) for these three outcomes.

Table 3 Multivariate logistic regression analyses

	Variable	Significance	Exp (B)
MoCA	Sex	0.026	3.034
	School education	0.048	1.242
	Age at onset	0.000	0.898
	ALSFRS-R	0.008	1.100
FAB	HADS depression	0.002	1.174
	Age at onset	0.000	0.890
	Disease duration	0.010	0.984

Exp(B) odds ratio, *ALSFRS-R* ALS Functional Rating Scale-Revised, *MoCA* Montreal Cognitive Assessment, *FAB* Frontal Assessment Battery

Table 2 Associations between cognitive and behavioral impairment and clinical variables

	MoCA	FAB	ALS-FTD-Q	ALSFRS-R
Age at onset	−0.457****	−0.430****	−0.071	0.021
School education	0.410****	0.425****	0.112	0.018
Disease duration	0.148	−0.128	0.352****	−0.293***
MoCA		0.684****	−0.009	0.015
FAB	0.684****		0.082	−0.033
ALS-FTD-Q	−0.009	0.082		0.015
HADS anxiety	0.223**	0.226**	0.507****	−0.307***
HADS depression	0.252**	0.277***	0.483****	−0.341****
ALSFRS-R	0.015	−0.033	−0.279***	
%VCpred	0.056	0.046	−0.230**	0.612****
Verbal fluency	−0.383****	−0.445****	0.028	0.034

ALS Amyotrophic Lateral Sclerosis, *FTD* Frontotemporal Dementia, *MoCA* Montreal Cognitive Assessment, *FAB* Frontal Assessment Battery, *ALS-FTD-Q* Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire, *HADS* Hospital Anxiety and Depression Scale, *ALSFRS-R ALS* Functional Rating Scale-Revised, *%VCpred* Predicted Vital Capacity Percentage

$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$. Except for the coefficients with, all statistically significant findings survive Bonferroni correction (adjusted p value = 0.00113)

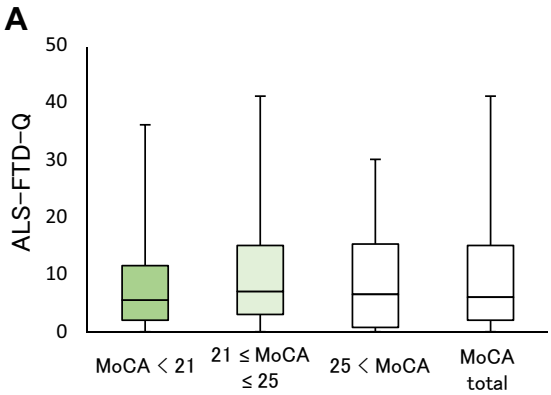
Sex (males performing worse), education, age at onset, and ALSFRS-R explained some variation (Cox and Snell $R^2 = 0.344$ and Nagelkerke $R^2 = 0.473$) of cognitive impairment (MOCA). HADS depression, age at onset, and disease duration explained some variation in FAB (Cox and Snell $R^2 = 0.233$ and Nagelkerke $R^2 = 0.322$). For behavioral impairment (ALS-FTD-Q) no explanatory variables were found in a model which included bulbar involvement, site of inset and HADS-subscale anxiety.

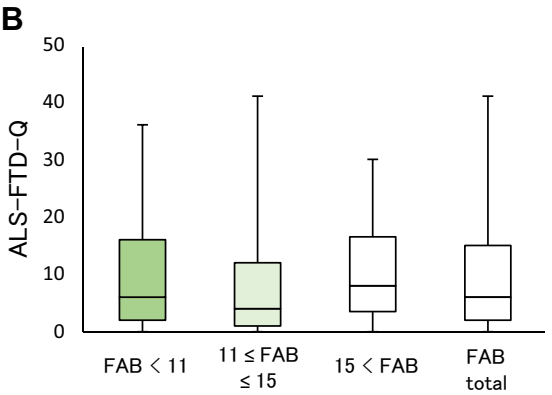
Relationships between cognitive and behavioral decline

No associations were found between cognitive and behavioral disturbances as measured by either MoCA or FAB with the ALS-FTD-Q (Table 2). When ALS patients were analysed according to severity of cognitive impairment (groups based on either MoCA or FAB scores indicating severe or mild impairment, or normal), ALS-FTD-Q scores did not differ in relation to MoCA or FAB severity (Fig. 1a and b), suggesting that cognitive decline and behavioral alterations are at least partly unrelated.

When the cognitive status of ALS patients was analysed in different groups based on ALS-FTD-Q scores (severe or mild impairment, or normal behavior (Fig. 1c and d), severe cognitive impairment, which occurred in 27.6% (based on MoCA) and 22.8% (based on FAB) of the patients, was most often present in patients with normal behavior. Figure 1c and d show that in our cohort of Japanese patients, there are approximately 5 times more cognitively impaired patients than patients with behavioral impairment (e.g. 66.7% vs. 12.4% when patients with mild and severe cognitive and behavioral impairment are included; 27.6% vs. 4.1% when only patients with severe cognitive and behavioral impairment are included).

Two out of 145 patients showed severe cognitive impairment as well as severe behavioral abnormalities (1 patient had a MoCA score of 21 and a FAB score of 10; another patient had a MoCA score of 13 and a FAB score of 8).





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	MoCA < 21	21 ≤ MoCA ≤ 25	25 < MoCA	Total
28 < ALS−FTD−Q	1 (0.7%)	4 (2.8%)	1 (0.7%)	6 (4.1%)
22 ≤ ALS−FTD−Q ≤ 28	3 (2.1%)	4 (2.8%)	5 (3.4%)	12 (8.3%)
ALS−FTD−Q < 22	36 (24.8%)	50 (34.5%)	41 (28.3%)	127 (87.6%)
Total	40 (27.6%)	58 (40.0%)	50 (32.4%)	145 (100%)

D

	FAB < 11	11 ≤ FAB ≤ 15	15 < FAB	Total
28 < ALS−FTD−Q	2 (1.4%)	2 (1.4%)	2 (1.4%)	6 (4.1%)
22 ≤ ALS−FTD−Q ≤ 28	4 (2.8%)	3 (2.1%)	5 (3.4%)	12 (8.3%)
ALS−FTD−Q < 22	27 (18.6%)	60 (41.4%)	40 (27.6%)	127 (87.6%)
Total	33 (22.8%)	65 (44.8%)	40 (32.4%)	145 (100%)

Fig. 1 Relationship between cognitive and behavioral abnormalities. ALS patients were divided into severely impaired, mildly impaired, and normal MoCA groups. The ALS-FTD-Q scores between groups are expressed as box plots (**a**). The same procedure was performed for FAB scores (**b**). Data show that the severity of cognitive impairment and behavioral impairment is unequal. Effect sizes (η^2) are 0.00 (**b**) and 0.03 (**b**)

Relationship between age of onset and cognitive or behavioral abnormalities

ALS patients were divided into two groups according to age of onset: ≤ 65 years ($n = 65$) or > 65 years ($n = 80$), and cognitive and behavioral status was compared between groups (Fig. 2a–c). Age of onset was related to cognitive scores, i.e., disease onset at higher age was associated with worse performance on the MOCA and FAB (Fig. 2a and b). Behavioral scores did not differ between these two age groups. (Fig. 2c). We further divided ALS patients into four groups according the age of onset which showed a relation of age at onset with cognitive decline (Fig. 2d).

Discussion

Cognitive and behavioral assessments in ALS

In the current study we examined cognitive and behavioral functions in a large cohort of sporadic ALS patients. Behavioral abnormalities were less frequent in ALS patients compared to cognitive impairment. Cognitive abnormalities were also more frequent in elderly patients with age of disease onset over 65, while behavioral abnormalities did not show an age-related trend.

We used the MoCA and FAB to assess cognitive impairment in the current study. The Edinburgh Cognitive and Behavioural Amyotrophic Lateral Sclerosis Screen (ECAS), which is currently the most widely used screening test for cognitive impairment in ALS patients, is not yet available in Japan and could therefore not be used [2]. We chose to include the MOCA, and not the MMSE which was often used in previous ALS studies, as it covers more cognitive domains, in particular executive dysfunction, and has a higher sensitivity and specificity, as compared to the MMSE. We have previously shown that the FAB, when adjusted for motor impairment, does differentiate between ALS patients with and without FTD [26].

The MoCA assesses short-term memory, visuospatial abilities, attention, concentration and working memory, time and place orientation, executive function, and language [22].

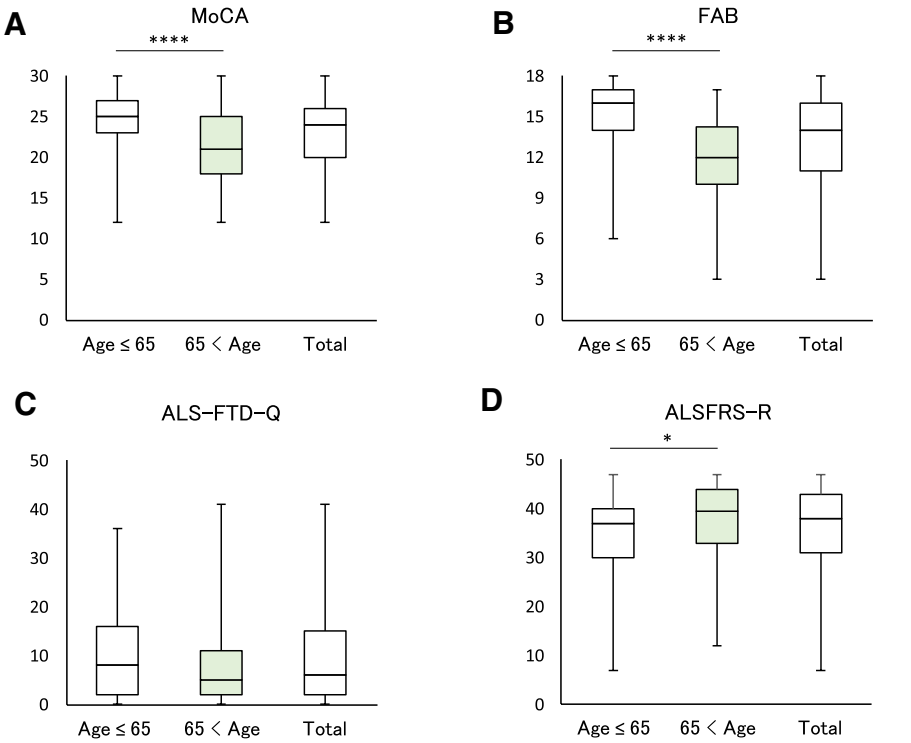

Fig. 2 Age of onset in relation to cognitive, behavioral and motor scores. Age of onset only affects cognitive (**a** and **b**) and motor (**d**) scores but not behavioral score (**c**). *$p < 0.05$, ****$p < 0.0001$. Effect sizes (r) are 0.40 (MoCA), 0.42 (FAB), 0.13 (ALS-FTD-Q), and 0.20 (ALSFRS-R). The relations of age at onset with cognitive decline, behavioral and motor scores are shown (**d**)

D

	Age ≤ 55 (n = 22)	55 < Age ≤ 65 (n = 43)	65 < Age ≤ 75 (n = 55)	75 < Age (n = 25)
MoCA	25.9 (2.3)	24.0 (4.0)	22.1 (3.8)	20.2 (4.3)
FAB	15.4 (2.7)	14.5 (3.2)	12.6 (3.2)	11.0 (3.0)
ALS−FTD−Q	8.7 (6.9)	11.2 (10.4)	8.2 (9.5)	8.0 (7.5)
ALSFRS−R	34.3 (9.4)	33.9 (9.0)	37.7 (9.1)	36.3 (5.0)

Mean (SD).

The FAB assesses frontal lobe function with tests of conceptualization, mental flexibility, motor programming, sensitivity to interference, inhibitory control, and environmental autonomy [12]. Four items, excluding conceptualization and environmental autonomy, are thought to evaluate, or at least be related to, executive function. The dysexecutive profile of our patients is further supported by a correlation in our study between both MOCA and FAB (= minus the score on the fluency item) with verbal fluency. Verbal fluency is one of the most consistent executive abnormalities in both ALS and bvFTD ALS patients [1, 5].

There are some limitations in the use of these screening instruments in ALS patients. Both tests require dexterity, which can be impaired in ALS patients. Also, these tests have not been specifically designed for ALS patients and the MoCA has not been validated for use in ALS patients. The FAB, with the adaptations previously published [26] has shown to be valid in ALS patients. The advantages of using the MOCA and FAB include the generalization of our findings to other patient populations. In addition, in the present study we demonstrated that the MoCA and FAB tests, with motor-corrected scores could be utilized to evaluate cognitive function in ALS.

Associations of cognitive and behavioral impairment with demographic and clinical variables

In this report lower MoCA and FAB scores (implicating worse cognitive performance) were associated with higher age at onset. Although we do not have any conclusive explanation for this trend, a specific characteristic of our Japanese multicentre cohort, i.e. highly aged population, might have influenced these findings. The mean age at onset in our cohort was 68.5 years (Table 1) which is considerably higher as compared to previous studies summarized in a systematic review and meta-analysis of the cognitive profile of ALS ($n = 44$) [4] in which the mean age was 59.6 varying between 51.7 to 68.3 years. It is conceivable that in our study, a higher age partly contributed to the findings of a relatively high frequency of cognitive decline.

Despite two recent large cohort studies, it is still debated whether the frequency of cognitive and behavioral impairment is different across disease stages of ALS, with a possible higher frequency in the latest disease stages [9, 11]. These findings may, to some extent be related to respiratory insufficiency and resulting nocturnal or daytime hypercapnia. The latter causes executive and memory impairment, which is in part reversible after the start of non-invasive ventilation [18, 23, 25]. We did not stratify our cohort according to disease stages but aimed to examine associations between demographic (age, gender), and clinical variables (including vital capacity) with measures of cognitive (including frontal dysfunction) and behavioral impairment.

For the behavioral impairment in our cohort, which was remarkably lower as compared to cognitive impairment, a weak correlation between ALS-FTD-Q scores and respiratory dysfunctioning (%VCpred) was shown, which did not survive correction for multiple comparisons. In a multivariate logistic regression none of the included variables explained the outcome behavioral impairment, which suggests that this is a separate construct within ALS patients.

Regarding cognitive impairment and respiratory dysfunction, we did not find associations between the cognitive outcome measures and vital capacity, neither in correlation analysis, nor in regression models. This is possibly related to the low proportion of patients with respiratory impairment in our cohort, which is reflected by the mean %VCpred of 80.

Depression and anxiety in ALS/FTD

The prevalence of depressive disorders in ALS ranges from 12–75% [35]. with a meta-analysis showing depression and/or depressive mood in 33.4% ALS patients [8].

Our finding of an association ($r = 0.5$, which survived correction for multiple comparison) between the scores of ALS-FTD-Q and HADS provides further insights in the construct validity of the ALS-FTD-Q, in Japanese patients. Further analyses suggested that the association between behavioral abnormalities and the HADS is primarily driven by the anxiety subscale of the HADS, which showed a trend in the multivariate regression model explaining the presence of behavioral changes, whereas the depression subscale was not an explanatory variable. As certain aspects of abnormal behavior within the FTD spectrum overlap with symptoms of anxiety and depression (restlessness, apathy, withdrawal behavior) [35] a correlation between the HADS was expected and found in previous studies on the construct validity of the ALS-FTD-Q [27, 32].

In our previous reports correlations between ALS-FTD-Q and HADS were somewhat lower ($r = 0.36$ in Japan and 0.18 in the Netherlands), as compared to the current study [27, 32]. This may be related to a different mix of patients (prevalent vs. incident) or a true transcultural difference related to affective and behavioral symptoms between Japan and the Netherlands.

Further research is needed to disentangle these relations and secondly, to examine to what extent the progression of cognitive and behavioral changes in ALS is related to a degenerative disease process in non-motor regions or related to a combination of progression of affective symptoms (as a consequence of the disease) and respiratory insufficiency, as discussed above [11, 25].

An interesting hypothesis is that depression/anxiety symptoms are primary symptoms of ALS/FTD, related to the pathological processes in frontal and temporal brain regions [16]. Consisting with this hypothesis, Bieniek et al. [6] reported

the relation between depression and the *C9ORF72* hexanucleotide repeat expansion, a major cause of ALS and FTD. Among 31 individuals with clinical diagnosis of depressive pseudodementia and without ALS nor FTD pathology by the postmortem examination, they found two individuals (6.45%) with an expanded *C9ORF72* repeat.

Limitations

Apart from its strengths (large cohort, multicentre evaluation, use of disease specific behavioral questionnaire) this study has several limitations. We did not use ALS-specific cognitive screening tools and no follow-up measurements were performed. To provide more insight in the progression of cognitive and behavioral impairment, more longitudinal studies in well-defined patient groups (i.e., short disease duration) with relevant data on respiratory function including nocturnal measures examined with ALS specific neuropsychological tests and behavioral measures are necessary [13].

Secondly, the terms we used in this study, such as ALS with cognitive impairment or with behavioral disturbance, are not necessarily equivalent to ALSci or ALSbi as defined by consensus criteria.[31]

Conclusions

Cognitive impairment and behavioral changes occur in a relatively large proportion of Japanese ALS patients with cognitive impairment being far more prevalent. Future studies should focus on appropriate evaluation of cognitive and behavioral abilities at the earliest disease stage as well as the examination of factors that contribute to the progression of cognitive and behavioral symptoms.

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Compliance with ethical standards

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