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ORIGINAL COMMUNICATION

Amyotrophic lateral sclerosis type 8 is not a pure motor disease: evidence from a neuropsychological and behavioural study

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Abstract

Objective Amyotrophic lateral sclerosis type 8 (ALS8) is a familial form of motor neuron disease, with predominance of lower motor neuron degeneration, and is caused by mutation of the vesicle-associated membrane protein-associated protein B (*VAPB*). We aimed to compare the cognitive profile of patients with ALS8 and healthy controls (HC), and to screen for behavioural features in ALS8 patients.

Methods The sample was composed of ALS8 patients ($n=22$; 14 men; median age 48 years old; median disease duration 6.5 years) and HC ($n=33$; 19 men; median age 48 years old). Patients and HC were matched for sex, age and educational level. Participants underwent behavioural, psychiatric (Hospital Anxiety and Depression Scale and Cambridge Behavioural Inventory-Revised) and neuropsychological assessments, focused on executive functions, visual memory, and facial emotion recognition.

Results ALS8 patients exhibited subtle deficits in executive functions. Compared to controls, ALS8 patients were significantly impaired in measures of flexibility and inhibitory control. ALS8 patients and HC did not differ in scores of facial emotion recognition. There was clinically relevant anxiety and depression in 36% and 27% of ALS8 patients, respectively. Behavioural disorders such as stereotypic and motor behaviours were present in more than 30% of patients.

Conclusions ALS8 patients present mild executive dysfunction and behavioural changes such as mood disorders, apathy and stereotypic behaviour. Our findings suggest that ALS8 is not a pure motor disorder and it is associated with subtle cognitive and behavioural impairments.

Keywords Amyotrophic lateral sclerosis · Cognition · Behaviour · *VAPB*

Introduction

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease (MND) in adults, and is characterized by progressive upper and lower motor neuron damage [1]. ALS can be classified in sporadic (90% of the cases) or familial (10% of cases) form. There are more than 20 identified familial ALS (FALS)-related genes: chromosome 9 open reading frame 72 (*C9orf72*), superoxide dismutase (*SOD1*), TAR DNA-binding protein (*TARDBP*), and fused in sarcoma (*FUS*) are the most frequently reported mutations among familial cases [2, 3].

ALS type 8 (ALS8), a FALS, is an autosomal dominant disorder linked to the p.P56S mutation of the vesicle-associated membrane protein-associated protein B gene (*VAPB*) mapped at the locus 20q13.3 [4]. The *VAPB* mutation was first identified in Brazilian families from the state of

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Minas Gerais (Southeast of Brazil) [5]. ALS8 was originally described as spinal muscular atrophy-type Finkel [5, 6]. In contrast to typical forms of ALS, the progression of symptoms in ALS8 is slower, and the lower motor neuron degeneration is more evident, beginning in lower limbs, with prominent fasciculations, cramps and muscle atrophy [4, 5]. Pain and tremor have also been described in ALS8 [7]. Original reports did not mention cognitive decline as a clinical feature of ALS8 [4, 5].

Although sporadic ALS was previously recognized as a pure motor system disorder, several studies have shown cognitive and behavioural changes [8–16]. The cognitive impairment affects approximately 50% of ALS patients, and up to 15% fulfil clinical criteria for frontotemporal dementia (FTD) [9, 11]. Executive dysfunction and deficits in verbal memory, language and social cognition are reported in ALS patients [9, 11, 16]. Behavioural changes such as disinhibition and apathy are mostly associated with the behavioural variant of FTD (bvFTD) [11, 12]. These findings support that there is a clinical, cognitive and behavioural continuum between ALS and FTD.

The cognitive and behavioural profile of ALS8 has not been investigated so far. Considering the predominance of lower motor neuron features associated with *VAPB* mutation, we hypothesized that individuals with ALS8 would have mild to moderate cognitive deficits, especially in executive functions as described in sporadic ALS. We aimed to investigate the cognitive profile of patients with ALS8 comparing them to healthy controls (HC) and screening for possible behavioural changes in these patients.

Materials and methods

Participants

This research was conducted from July 2017 to March 2018, in two Brazilian university hospitals, at Federal University of Minas Gerais (Belo Horizonte, Minas Gerais, Brazil) and at Federal University of Juiz de Fora (Juiz de Fora, Minas Gerais, Brazil). The Local Ethics committees approved the study and all participants signed a written informed consent before participating.

Fifty-five participants were included, with 22 ALS8 patients (14 male/08 female; median age 48 years old; median formal education 7.5 years) and 33 healthy controls (HC) (19 male/14 female; median age 48 years old; median formal education 8 years). Table 1 presents clinical and demographical data of enrolled subjects.

All ALS8 patients had positive genetic testing for the p.P56S *VAPB* mutation. Molecular tests were performed according to protocols described elsewhere [17]. Importantly, we did not include asymptomatic carriers. All ALS8 patients had a history of progressive neurological symptoms, with muscle atrophy, weakness, and fasciculations. One patient was under non-invasive ventilation. At the time of the assessment, patients did not present significant dysarthria. One patient had upper limb disability severe enough to limit writing; therefore, he did not undergo tests that required motor skills [drawing and writing from the Mini-Mental State Examination (MMSE), and from the Addenbrooke's Cognitive Examination-Revised (ACE-R)-visuospatial].

HC were composed of community volunteers recruited by convenience at Belo Horizonte. HC were matched with the ALS8 group for age, sex and education level. As inclusion criteria, HC did not have cognitive complaints and had normal performance on the MMSE, according to educational level [18]. Moreover, they scored below 9 out of 21 either in anxiety or depression subscales from the Hospital Anxiety and Depression Scale (HADS), indicating absence of anxiety or depressive disorders [19]. We did not include participants with severe neurological or psychiatric history such as epilepsy or bipolar disorder, uncorrected hearing or visual problems, hypothyroidism or in use of antipsychotic medications.

Table 1 Demographic and clinical data

	Healthy controls ($n=33$) Median (P25–P75)	ALS8 ($n=22$) Median (P25–P75)	p value
Age (years)	48 (43–56)	48 (43–54)	0.963[a]
Schooling (years of education)	8 (6–11)	7.5 (5.5–13)	0.781[a]
Sex (male/female)	19/14	14/8	0.781[b]
Disease duration (years)	N/A	6.5 (2.5–12)	–
Age at onset of symptoms (years)	N/A	40.5 (39–46)	–

ALS8 amyotrophic lateral sclerosis type 8, *P* Percentile, *N/A* not applicable

[a]Mann–Whitney test

[b]Chi-square test

Instruments

All participants underwent a semi-structured clinical interview and the following tests: MMSE [18], ACE-R [20], Letter Fluency Test-FAS [21], Similarities subtest from Wechsler Adult Intelligence Scale-Third edition (WAIS-III) [22], Digit Span (WAIS-III) [22], the Brazilian version of the Five Digit Test (FDT) [23] and the Hayling Sentence Completion Test (Hayling Test) [24], which evaluates the inhibition of prepotent response. The FDT assesses inhibitory control, in a non-verbal Stroop-like condition, suppressing a prepotent answer in counting numbers rather than saying the stimuli, and cognitive flexibility, alternating two different rules in the same task [23]. The Facial Emotion Recognition Test (FERT) was employed to investigate the ability of emotion recognition. It consists of a set of 35 pictures showing facial expressions of basic emotions: happiness, surprise, disgust, fear, anger, sadness or neutral [25]. Episodic memory was evaluated with the Episodic Visual Memory Test from Brief Cognitive Screening Battery (BCSB) [26]. Briefly, the memory test from the BCSB evaluates visual memory with ten figures (e.g. house, airplane). Subjects have to name the figures and then he/she is asked to recall them (incidental memory). Then, figures are presented for 30 s and subjects are asked to memorize them; another recall (immediate memory) is requested. This procedure is repeated (learning score). The delayed recall is requested after interference tasks (5-min duration). Last, the recognition task requires the subject to recognize the ten original figures among ten distractors.

All participants were also assessed with HADS, which provides separate subscales for anxious (HADS-Anxiety) and depressive (HADS-Depression) symptoms. A score above eight in each subscale is indicative of anxiety or depression [19].

We used the Cambridge Behaviour Inventory-Revised (CBI-R) for functional and behavioural assessment of patients [27]. The CBI-R is a revised informant-based questionnaire composed of 45 items designed to assess behavioural changes and daily activities in neurodegenerative diseases [27]. The CBI-R has been previously employed in studies with ALS patients [28–30]. Here, we considered the following domains from CBI-R: abnormal eating habits, motivation, beliefs, stereotypical and motor behaviours, and abnormal challenging behaviours. We also considered the following domains as measures of functional abilities: self-care and everyday skills. The answers are chosen according to frequency of the behaviour rated on a scale of 0–4 (0 = no impairment; 4 = constant occurrence). We classified patients according to the severity of impairment, as described elsewhere [28]. The scores were calculated on each behaviour conforming to the proportions: 0–25%, mild impairment; 26–50%, moderate; 51–75%, severe, and more than 75%, very severe. The CBI-R was not available for healthy controls.

Statistical analysis

Data analyses were performed using the software Statistical Package for Social Sciences (SPSS), version 25.0. The assumption of normality was tested with Kolmogorov–Smirnov test. The statistical assumption of normality was refuted. The groups were compared using Mann–Whitney *U* Test and chi-square test. The Bonferroni correction for multiple comparisons was applied ($p < 0.002$). To measure the effect size, we calculated the value of r (for non-parametric data) using z values obtained in the comparisons. Thus, Cohen's guidelines were used to interpret this measure [31]. Correlations between variables were carried out with Spearman test.

Results

There was no statistical difference in age, sex, and education level between patients and HC (Table 1). The median disease duration of ALS8 patients was 6.5 years. Considering the ALS8 group, six (6/22 patients; 27%) and seven patients (7/22; 32%) had moderate to very severe impairment in the self-care and everyday skills domains from CBI-R, respectively.

Global cognitive functioning

There was non-significant differences between ALS8 patients and HC in the MMSE ($p = 0.015$; $r = -0.33$) and in the total score of ACE-R ($p = 0.005$; $r = -0.38$), with a trend for worse performance of patients compared to HC (Table 2).

Episodic memory

There was no difference between ALS8 patients and HC in the incidental and immediate memory, learning, and delayed recall from the Episodic Visual Memory Test (BCSB) (Table 2).

Executive function

ALS8 patients had lower performance in the forward Digit Span ($p = 0.015$; $r = -0.32$), but without significant difference. There were also non-significant differences between groups in the backward span and in the total score of the test (Table 3).

Patients and HC did not differ in the Letter Fluency Test (F, A, S). There was non-significant statistical difference

Table 2 Global cognitive efficiency and visual episodic memory test

	Healthy controls ($n=33$) Median (P25–P75)	ALS8 ($n=22$) Median (P25–P75)	p value (MW)	Effect size (r)
MMSE (/30)	29 (28–30)	29 (26.5–29)	0.015	− 0.33[a]
ACE-R—total (/100)	89 (84.5–94.5)	84 (69–90.5)	0.005	− 0.38[a]
Orientation/attention	17 (17–18)	17 (15–18)	0.069	− 0.25
Memory	23 (19–25)	19.5 (14.75–23)	0.011	− 0.34
Verbal fluency	11 (9.5–12)	9.5 (7.75–11.25)	0.113	− 0.21
Language	25 (23–25.5)	23 (20.75–25)	0.024	− 0.30
Visuospatial	15 (14–16)	14 (11.5–15)	0.004	− 0.39[a]
BCSB				
Incidental memory	6 (5–7)	5 (4–7)	0.359	− 0.13
Immediate memory	9 (7–9)	8 (7–9.25)	0.627	− 0.07
Learning	10 (9–10)	9 (8.75–10)	0.126	− 0.21
Delayed recall	8 (8–10)	8 (7–9)	0.082	− 0.24
Recognition	10 (10–10)	9 (9–10)	0.003	− 0.40
Intrusions	0 (0–0)	0 (0–1)	0.011	− 0.34

ALS8 amyotrophic lateral sclerosis type 8, *P* percentile, *MW* Mann–Whitney test, *MMSE* Mini-Mental State Exam, *ACE-R* Addenbrooke's Cognitive Examination-Revised, *BCSB* Brief Cognitive Screening Battery (Visual Episodic Memory Test)

[a]ALS8 ($n=21$)

between patients and HC in the Category Fluency Test (animals—ACE-R), with a trend for worse performance of patients compared to HC ($p=0.007$; $r=-0.36$). Patients underperformed in comparison with controls in the Similarity WAIS subtest ($p=0.021$; $r=-0.31$), but with no statistical significance (Table 3).

There was significant difference between groups in the Part A (Time) from the Hayling Test—Time A ($p=0.001$; $r=-0.45$)—indicating that patients were slower than controls (Table 3). There was a trend for worse performance of ALS8 patients in Correct Answers Part B ($p=0.007$; $r=-0.36$), Quantitative Errors Part B ($p=0.009$; $r=-0.35$), and Qualitative Errors Part B ($p=0.008$; $r=-0.35$).

ALS8 had significantly lower scores than HC in the two tasks of the FDT: reading ($p<0.001$; $r=-0.56$) and counting ($p<0.001$; $r=-0.48$). There was a trend for worse performance of ALS8 patients in other FDT steps: choosing ($p=0.007$; $r=-0.36$) and shifting ($p=0.014$; $r=-0.33$).

Emotion recognition

There was no statistical difference between groups in the recognition of facial emotions (Table 3).

Behaviour and mood

According to HADS, clinically significant anxiety and depressive symptoms were observed in 36.4% and 27.3% of patients, respectively (Fig. 1a, b). To check the relation between mood symptoms and cognitive deficits, we classified ALS8 patients according to the presence of depression or anxiety. The following subgroups were then composed of ALS8 subgroup without depression ($n=16$; score on HADS-Depression ≤ 8) and ALS8 subgroup with depression ($n=6$; score on HADS-Depression ≥ 9), and ALS8 subgroup without anxiety ($n=14$; score on HADS-Anxiety ≤ 8) and ALS8 subgroup with anxiety ($n=8$; score on HADS-Anxiety ≥ 9). We compared subgroups (ALS8-depression vs. ALS8-no depression; ALS8-anxiety vs. ALS8-no anxiety). These subgroups did not differ on neuropsychological measures.

Figure 1c presents behavioural changes according to CBI-R. Stereotypical behaviours (e.g., mental rigidity, checking time repeatedly), lack of motivation (e.g., loss of interest, reduced affection), alterations on eating habits (e.g., sweet food preference, to eat more than before), and abnormal behaviours (e.g., disinhibition, impulsivity, loss of decorum) were the most frequent behavioural disorders among ALS8 patients.

Correlations

We investigated correlations in the ALS group. We did not find correlations between cognitive variables and HADS-A or HADS-D. There was no significant correlation between disease duration and cognitive variables. There were no significant correlations between executive tests and episodic memory test (5-min recall-BCSB).

Table 3 Neuropsychological data: executive functions and emotion recognition

	Healthy controls ($n=33$) Median (P25–P75)	ALS8 ($n=22$) Median (P25–P75)	p value (MW)	Effect size (r)
Letter fluency FAS—total	38 (29.5–47.5)	34 (23.75–44.5)	0.254	− 0.16
Letter fluency F	13 (10–16.5)	12.5 (9.75–17.25)	0.605	− 0.07
Letter fluency A	12 (8–15.5)	10 (5.75–12.75)	0.185	− 0.18
Letter fluency S	12 (9.5–16.5)	11 (7–15)	0.282	− 0.15
Category fluency (animals)	17 (14–20.25)	12.5 (10.75–17)	0.007	− 0.36
Digit span—total	13 (11–15)	12 (8.75–13.5)	0.062	− 0.25
Forward	8 (7–9)	7 (6–8.25)	0.015	− 0.32
Backward	5 (3.5–6)	4 (3–6)	0.387	− 0.12
Similarities (WAIS)	23 (14–28)	14 (8.75–21)	0.021	− 0.31
FDT				
Reading	25 (23–30)	35 (28.75–38.5)	<0.001	− 0.56
Counting	28 (26–31)	35 (28–43.5)	<0.001	− 0.48
Choosing	43 (38.5–50)	52 (46–64.5)	0.007	− 0.36
Shifting	64 (48–69.5)	77 (54.75–97.5)	0.014	− 0.33
Hayling test				
Time A	14.52 (11.6–17.45)	23.08 (15.29–31.88)	0.001	− 0.45
Correct answers A (/15)	15 (15–15)	15 (15–15)	0.674	− 0.07
Errors A	0 (0–0)	0 (0–0)	0.674	− 0.07
Time B	65.17 (37.26–84.97)	78.06 (38.34–97.99)	0.352	− 0.13
Correct answers B (/15)	10 (7.5–13.5)	7.5 (4–9)	0.007	− 0.36
Quantitative errors B (/15)	5 (1.5–7.5)	7.5 (5.75–11)	0.009	− 0.35
Qualitative errors B (/45)	6 (3–14.5)	11.5 (8–21.5)	0.008	− 0.35
Time B – A	48.49 (24.93–68.35)	58.15 (16.95–66.89)	0.939	− 0.01
FERT—total (/35)	27 (24–29)	26.50 (23.75–27.25)	0.280	− 0.15
Happiness (/5)	5 (5–5)	5 (5–5)	0.400	− 0.17
Surprise (/5)	5 (4–5)	4 (3–5)	0.093	− 0.23
Disgust (/5)	4 (4–5)	4 (3–5)	0.689	− 0.06
Fear (/5)	2 (1–3)	1.5 (0.75–3)	0.139	− 0.20
Anger (/5)	4 (3–4)	3 (2–4)	0.254	− 0.16
Sadness (/5)	3 (2–4)	3.5 (3–4.25)	0.295	− 0.14
Neutral (/5)	5 (4–5)	5 (4–5)	0.675	− 0.06

ALS8 amyotrophic lateral sclerosis type 8, *P* percentile, *MW* Mann–Whitney test, *FDT* Five Digit Test, *FERT* Facial Emotion Recognition Test

Discussion

In the current study, we investigated cognitive and behavioural features of ALS8 patients through a comprehensive assessment. To the best of our knowledge, this is the first investigation of cognitive functions and behavioural profile of patients with *VAPB*-related ALS.

As expected, we did not observe major cognitive decline in ALS8. The results of the neuropsychological tests showed mild cognitive dysfunction, particularly involving executive dysfunction, similar to the findings described in sporadic ALS [11, 12, 16]. On the other hand, some results differ from typical cognitive profile observed in sporadic ALS, such as preservation of emotion recognition and letter fluencies.

The executive functions were the most prominent cognitive impairment in our sample. There was a trend for worse performance of ALS8 patients in all subscores of the Hayling Test—Part B, indicating deficits in inhibitory control and cognitive flexibility. However, ALS8 patients did not differ from HC in Hayling Test—Part A, except in the subscore "Time". The performance of ALS8 patients in the Hayling Test—Part A indicates that the syntactic comprehension and the semantic linguistic process are not impaired. Although we did not correct verbal responses for motor performance, our sample did not present clinically relevant dysarthria, and slower reaction time may have occurred due to decreased processing speed. These findings in the Hayling test are concordant with the results from FDT in ALS8, which demonstrated reduced

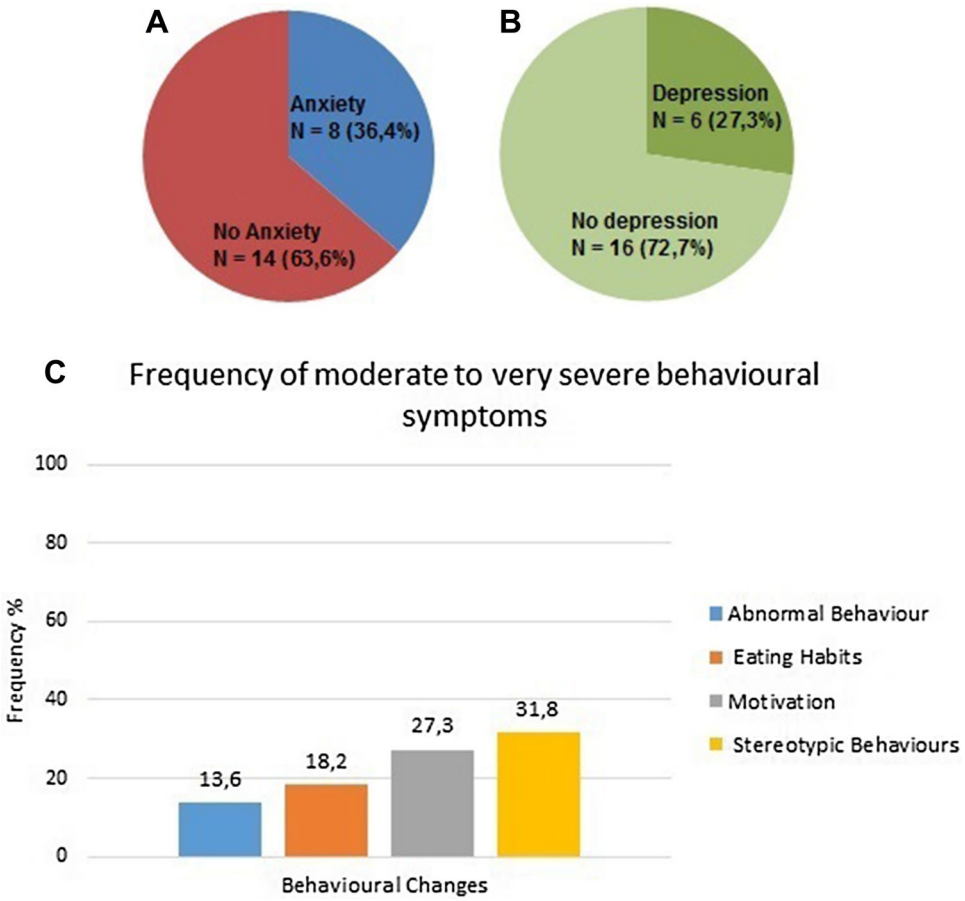

Fig. 1 **a** Proportion of patients in the amyotrophic lateral sclerosis type 8 (ALS8) group with clinically significant anxiety according to the Hospital Anxiety and Depression Scale (HADS). **b** Proportion of patients in the ALS8 group with clinically significant depression according to the HADS. **c** Behavioural symptoms measured by the Cambridge Behavioural Inventory-Revised (CBI-R) in patients with ALS8

processing speed, difficulty to maintain focused attention and to inhibit responses.

There was also a trend for worse performance of ALS8 patients in digit spans, indicating a decline in attentional capacity. Patients also underperformed in the WAIS Similarity subtest, but without statistical difference. This suggests that ALS8 may be associated with mild impairment in verbal abstract reasoning, which may be due to executive dysfunctions and not to language deficits.

Remarkably, these executive deficits seem not to be caused by mood disorders. Indeed, we did not find any difference in cognitive profiles in subgroups according to the presence/absence of anxiety or depression. Taken together, these findings suggest that ALS8 patients have a mild dysexecutive syndrome characterized by inhibition and flexibility deficits, and reduced processing speed.

Episodic memory may be impaired in ALS [32–34]. Episodic memory deficits in sporadic ALS have been mainly associated with executive decline. However, some studies indicate that episodic memory deficit in ALS may be due to involvement of medial temporal structures [33]. In our findings, the episodic visual memory seems spared in ALS8, and we did not find correlations between executive tests and memory scores. These findings suggest that episodic memory in ALS8 is not affected by the executive dysfunctions.

Compared to HC, ALS8 patients had normal performance in the Letter Fluency, but there was a trend for ALS8 patients underperforming in the Category Fluency (animals). While there are consistent findings of verbal fluency impairment in ALS [16], semantic deficits are not commonly reported in ALS patients. However, semantic deficits can be found in ALS [14, 15], suggesting anterior temporal lobe involvement [15]. The cognitive battery employed in the present study was not focused on semantic memory. Further studies with more specific tools are needed to investigate semantic abilities and other language functions in ALS8.

Social cognition, including emotion recognition, is impaired in ALS patients, reinforcing the ALS-FTD continuum [11, 16, 34, 35]. On the contrary, ALS8 patients in our sample did not have deficits in emotion perception. The reasons for this observation remain unclear. The recognition of facial emotions relies in different cerebral regions, including superior frontal gyrus, amygdala, and other limbic regions [36, 37]. Our findings suggest that these regions are unimpaired in ALS8, but more studies are warranted to explore social cognition in ALS8.

Besides subtle cognitive deficits, our patients also exhibited behavioural disorders. Clinically significant depression and anxiety were observed in 27.3% and 36.4% patients, respectively. These findings are similar to those reported in sporadic ALS [38]. Apathy is the most common neuropsychiatric symptom in sporadic ALS [28]; lack of motivation was identified in 27% of our clinical sample. These observations suggest that psychiatric symptoms in ALS8 overlap with those observed in sporadic ALS.

Of note, we found changes in eating habits, abnormal behaviour, stereotypical and motor behaviour in a subset of ALS8 patients. These behavioural features are observed in behavioural variant frontotemporal dementia (bvFTD). Frontal behaviour abnormalities may occur in sporadic ALS and up to 15% patients fulfil criteria for bvFTD [11, 28]. Even though none of our patients fulfilled criteria for probable bvFTD, our findings suggest that ALS8 may share similar behavioural symptoms with sporadic ALS and bvFTD.

Our study has limitations that should be pointed out. First, we did not include a group of typical sporadic ALS patients. This would be valuable in comparing the cognitive–behavioural profile between clinical groups, and exploring specific patterns in ALS8 patients. Second, this is a cross-sectional study; longitudinal follow-up of patients will be of interest to investigate how cognitive–behavioural impairments change over disease progression. Most of our patients had mild functional impairment. It is possible that a group of more severely disabled patients would disclose more intense cognitive deficits.

We did not use a standardized measure of neurological disability such as ALS Functional Rating Scale [39]. However, severity was estimated by disease duration and by CBI, which provides measures of functional abilities (scores on self-care and everyday skills). Finally, the absence of neuroimaging assessment precludes the analysis of the cerebral correlates of the neuropsychological deficits. While our study demonstrates cognitive and behavioural dysfunctions associated with the p.P56S-*VAPB* mutation, the neural underpinnings of these findings remain unclear. Neuroimaging investigation with modern techniques may clarify the neural basis of cognitive deficits in ALS8.

Despite these caveats, this study brings clinically relevant data. Contrary to the original report [5], our findings suggest that ALS8 is not a pure motor disease and is associated with cognitive and behavioural disorders. These results should be taken into account in the assistance and management of patients. An investigation of these manifestations can provide potential improvements in the clinical management of ALS8 patients. For instance, mood disorders should be investigated and treated. Caregivers should be informed about possible cognitive and behavioural manifestations of the disease, as these may be the cause of relevant carer burden [40]. In conclusion, the present data challenge prevailing concept of ALS8 as a pure motor disorder and provide evidence of cognitive and behavioural involvement in the disease. Further studies with larger series of patients, longitudinal follow-up and neuroimaging investigation are warranted to better understand the cognitive and behavioural disorders associated with *VAPB* mutation.

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Compliance with ethical standards

Conflicts of interest The authors declare no conflicts of interest.

Ethical approval This study was approved by local ethics committee (Universidade Federal de Minas Gerais—approval number 17850513.2.0000.5149).

Informed consent Informed consent was obtained in writing from all participants.

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