MOTOR FUNCTION AND BEHAVIOUR ACROSS THE ALS-FTD SPECTRUM

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ABSTRACT

BACKGROUND: Behavioural/functional disturbances, characteristic of frontotemporal dementia (FTD), are also a feature of amyotrophic lateral sclerosis (ALS) and patients with combined ALS and FTD (FTD-ALS). **AIM OF THE STUDY:** To investigate the progression of behavioural disturbances in ALS and FTD using the frontotemporal dementia functional rating scale (FTDFRS). **METHODS:** Patients with ALS, FTD-ALS, and FTD were recruited from specialist clinics. Baseline assessments included the FTDFRS and the amyotrophic lateral sclerosis functional rating scale – revised (ALSFRS-R). Baseline assessments were included, as were longitudinal assessments in a proportion of patients. **RESULTS:** In total, 21 ALS, 12 FTD-ALS and 14 behavioural variant FTD (bvFTD) patients were included in the study. Moderate or severe behavioural disturbance was common in ALS patients at baseline (47.6%), although less frequent than in bvFTD patients; FTD-ALS patients displayed intermediate impairment. The ALSFRS-R showed the opposite pattern and did not correlate with the FTDFRS. During the follow-up period, significant ($p<0.05$) behavioural deterioration was demonstrated in bvFTD and FTD-ALS patients, with a trend for decline in ALS patients ($p=0.06$). **CONCLUSION:** Motor disturbance is the primary marker of disease severity in ALS, but behavioural and functional impairment are common, and may decline independently of motor function. As such, the FTDFRS may provide valuable information in the assessment and monitoring of ALS.

INTRODUCTION

Historically, amyotrophic lateral sclerosis (ALS) was considered a pure motor disorder, but cognitive and behavioural disturbances similar to those seen in frontotemporal dementia (FTD) are increasingly recognised.(1–3) Indeed, the discovery of pathological and genetic overlaps with FTD(4–6) support the concept of an FTD-ALS disease continuum. Nonetheless, the extent and impact of behavioural and functional disturbances in ALS and FTD-ALS (patients who fulfil criteria for both ALS and FTD) have not been fully elucidated.

The most common cognitive and behavioural disturbances encountered in ALS are similar to those identified in the behavioural variant phenotype of FTD (bvFTD).(3) Preliminary studies have suggested that fatigue (physical and mental), apathy, disinhibition, mood changes, and stereotyped behaviours may be more common in ALS than initially appreciated.(2,7,8) Furthermore, behavioural disturbances, which appear to be more common in the context of cognitive deficits,(9) may increase caregiver burden significantly, even more than physical disability.(10) Because the rate of functional decline in bvFTD is quite variable,(11,12) the frontotemporal dementia functional rating scale (FTDFRS) was developed to grade and track behavioural and functional decline. An initial report suggests that the FTDFRS may be useful in the assessment of ALS patients.(13)

Disease progression in ALS has traditionally been measured using the amyotrophic lateral sclerosis functional rating scale – revised (ALSFRS-R),(14) which grades patient performance on a number of everyday activities. Disability and disease severity in ALS correlate with ALSFRS-R scores,(15) but it is heavily weighted towards motor capacity and does not investigate behavioural disturbances or functional dependence in detail. The relationship between motor impairment and behavioural disturbances in ALS is yet to be determined. Moreover, very little is known about the progression of behavioural symptoms in these disorders.

The present study explored three hypotheses; first, that ALS and FTD-ALS patients demonstrate behavioural and functional disturbance, as measured by the FTDFRS, similar to that seen in bvFTD. Second, that behavioural change is independent of motor impairment, as measured by the ALSFRS-R. Finally, that the FTDFRS might offer an additional tool to track progression of ALS over time.

METHODS

Participants

Patients with ALS were recruited from a specialist, multidisciplinary ALS clinic in Sydney Australia, while bvFTD patients were recruited from an FTD-specific research clinic (Frontier). FTD-ALS patients were recruited from both clinics. All patients gave written informed consent prior to recruitment, and the study received institutional ethics approval prior to commencement. Patients were included if they 1) fulfilled criteria for ALS,(16,17) FTD-ALS,(18) or bvFTD(19); and 2) had undergone a baseline FTDFRS, ALSFRS-R and Addenbrooke's Cognitive Examination Revised (ACE-R)(20) within 2 months of each other.

Diagnosis and Clinical Assessment

The diagnosis of ALS was made according to the revised El Escorial and Awaji criteria(16,17) after detailed clinical assessment. The diagnostic assessment included history, examination, nerve conduction studies, and electromyography. Alternate diagnoses were excluded on the basis of blood tests for inflammatory and autoimmune diseases, and neuroimaging of the brain and spinal cord where necessary.

The diagnosis of bvFTD was made in accordance with revised diagnostic criteria,(19) following a detailed clinical assessment, neuropsychological evaluation, and MRI of the brain. Briefly, patients were required to demonstrate early behavioural disturbance consisting of disinhibition, apathy, or

loss of sympathy/empathy, in the context of functional decline and atrophy of the frontal and temporal lobes on cerebral MRI. ALS patients underwent screening for cognitive and behavioural disturbances and, when present, underwent clinical assessment by a behavioural neurologist and formal neuropsychological assessment by a clinical neuropsychologist. Those patients who fulfilled diagnostic criteria for both FTD and ALS were classified as FTD-ALS.(18)

Motor functional status was assessed using the ALSFRS-R,(14) which grades performance on 12 every day activities using a 5-point scale (0-4 points). The ALSFRS-R gives a total of 48 points and a lower ALSFRS-R score indicates greater motor impairment. In addition to the ALSFRS-R total, the bulbar, fine motor, gross motor and respiratory sub-scores (each 12 points) were calculated. To estimate disease severity at baseline assessment, the initial rate of change in ALSFRS-R total was calculated by subtracting the patient's initial ALSFRS-R total from the maximum score (48 points) and dividing by the symptom duration in months. ALSFRS-R follow-up data was available in 28.6% of ALS, 16.7% of FTD-ALS, and 35.7% of bvFTD patients. Formal lung function tests were not performed routinely.

Behavioural and functional disturbance was assessed using the FTDFRS. The FTDFRS is a 30-item caregiver questionnaire designed to detect behavioural changes (apathy, irritability, stereotyped behaviours and impulsivity) as well as functional deficits on every day activities.(13) Several domains are assessed including behaviour, shopping, household chores/telephone use, finances, medication administration, meal preparation, eating, self-care, and mobility. As described previously,(11) the FTDFRS was developed using a Rasch analysis. Using this approach, raw FTDFRS scores were used to calculate a logit score that reflects the severity of behavioural and functional impairment in any particular patient numerically. A lower logit score indicates greater behavioural and functional impairment. The FTDFRS also defines logit score cut-offs to grade impairment as "very mild" (>4.12), "mild" (4.11 to 1.92), "moderate" (1.91 to -0.40), "severe" (-

0.39 to -2.58), "very severe" (-2.57 to -4.99) and "profound" (<-4.99). The FTDFRS was administered at baseline and at follow-up FTDFRS in a proportion of patients. Specifically, FTDFRS follow-up data was available in 23.8% of ALS, 41.7% of FTD-ALS, and 64.3% of bvFTD patients. When available, the change in logit score (i.e., final logit score – initial logit score) was used to estimate the progression in behavioural symptoms.

The ACE-R was used for baseline cognitive screening of patients. The ACE-R explores multiple cognitive domains including: attention/orientation (18 points), memory (26 points), fluency (14 points), language (26 points) and visuospatial (16 points). A score of 88/100 detects dementia with a sensitivity of 94% and a specificity of 89%, while a cut-off of 82/100 has 84% sensitivity and 100% specificity.(17)

Statistical Analysis

Statistical analysis was performed by D.D and J.R.B using the Statistical Package for Social Sciences (SPSS, IBM Corp, version 21.0). Continuous variables were analysed using analysis of variance (ANOVA) when normally distributed or the Kruskal–Wallis test when non-normally distributed. Pairwise comparisons of continuous variables were performed using the independent samples t-test when normally distributed and the Mann-Whitney test when non-normally distributed. Categorical data were analysed using the Chi-Square test. Longitudinal analyses were performed using the Wilcoxon test when non-normally distributed. All continuous data are reported as mean +/- standard deviation.

RESULTS

Patient demographics and clinical features

In total, 47 patients were included in the study; 21 patients with ALS, 12 with FTD-ALS, and 14 with bvFTD. At the time of the diagnostic evaluation, 10 of 12 FTD-ALS patients had a

combination of motor symptoms and mixed cognitive/behavioural deficits, including language deficits in some patients. Only 2 patients had established FTD diagnoses prior to the onset of ALS (one patient had progressive non-fluent aphasia and one had behavioural variant of FTD). Detailed demographic data are presented in Table 1. Of the ALS patients, 42.9% were male, compared to 91.7% of FTD-ALS cases and 100% of bvFTD cases ($p<0.001$). There was no significant difference in mean age or years of formal education between the ALS, FTD-ALS, and bvFTD groups. The mean symptom duration prior to initial assessment did not differ significantly between groups. In addition, the initial rate of change in ALSFRS-R score (see *Methods*) did not differ between the ALS and FTD-ALS groups (ALS 4.3 +/- 4.8, FTD-ALS 4.0 +/- 4.3, P=0.68).

Interestingly, FTD-ALS patients performed worse on baseline cognitive screening than bvFTD and ALS patients (Table 1). The mean ACE-R total was significantly ($p<0.05$) reduced in FTD-ALS compared to bvFTD and ALS. In particular, FTD-ALS patients performed significantly ($p<0.05$) worse on the attention/orientation and verbal fluency ACE-R subtasks compared to the other patient groups.

Motor dysfunction and behavioural disturbance at baseline

As may be expected, ALS and FTD-ALS patients had more motor functional impairment than the bvFTD group, reflected in significantly lower mean ALSFRS-R total scores ($p<0.001$), as illustrated in Figure 1A. Both the ALS and FTD-ALS groups had more bulbar and fine motor dysfunction compared to the bvFTD group, demonstrated by significantly ($p<0.001$) reduced bulbar and fine motor ALSFRS-R subscores (Table 1). In addition, the FTD-ALS group demonstrated significantly impaired gross motor function compared to the bvFTD group.

In contrast, the FTDFRS demonstrated an inverse pattern for behavioural/functional impairment, with the most impairment in bvFTD, the least in ALS, and intermediate impairment in FTD-ALS

(Figure 1B). Specifically, the mean FTDFRS logit score differed significantly ($p<0.05$) between disease groups, with post-hoc tests demonstrating a reduced logit score in bvFTD compared to ALS. The mean FTDFRS logit score for the FTD-ALS group did not differ significantly from either the bvFTD or the ALS groups. The proportion of patients with moderate or severe behavioural/functional impairment on the FTDFRS differed ($p<0.05$) between groups. Specifically, 85.7% of bvFTD patients had moderate or severe behavioural/functional disturbance at baseline according to the FTDFRS, compared to 47.6% of ALS patients ($p<0.05$). Of FTD-ALS patients, 75% had mild-moderate behavioural/functional disturbance according to the FTDFRS, but this was not significantly different to either the bvFTD or ALS groups. Importantly, correlational analyses showed no association between the mean ALSFRS-R total and the mean FTDFRS logit scores at baseline ($p=0.84$).

Motor dysfunction/behavioural disturbance at follow-up

Unfortunately, follow-up data was available for only a minority of patients, and FTDFRS data was more complete than ALSFRS-R data. Importantly, there was no significant intergroup difference between the duration of follow-up, which varied on average between 9-17 months for both the ALSFRS-R and the FTDFRS. Furthermore, there was no significant difference within each group between the duration of follow-up for the ALSFRS-R and the duration of follow-up for the FTDFRS.

Notwithstanding these considerations, when pairwise comparisons of the ALSFRS-R at baseline and follow-up were performed within each group, a trend for decline in the ALSFRS-R total was only detected in the ALS group ($p=0.06$). No significant change in ALSFRS-R total or subscores was detected in the bvFTD or FTD-ALS groups.

All patient groups demonstrated deterioration in behavioural/functional disturbance over the period

of follow-up, as reflected in a decline in mean FTDFRS logit scores (data not shown). In addition, pairwise comparisons revealed a significant decline in mean FTDFRS logit score from baseline to follow-up in bvFTD and FTD-ALS ($p<0.05$), and a trend for decline in ALS ($p=0.06$). As with the baseline data, there was no correlation between the mean ALSFRS-R total and mean FTDFRS logit scores at follow-up for those patients who had completed both assessments.

DISCUSSION

The present study demonstrated that behavioural and functional deficits are common in ALS and FTD-ALS, but the degree of impairment is less dramatic than that seen in bvFTD. Conversely, the degree of motor impairment was most marked in ALS and FTD-ALS. There was no significant correlation between the degree of motor impairment and the severity of behavioural/functional disturbance across the disease groups. Importantly, significant changes in behaviour and function were detected in all patients groups over time. As such, the FTDFRS may prove a useful adjunct in the measurement of ALS and FTD-ALS disease progression.

Before discussing the results of the present study in further detail, several limitations are acknowledged. Firstly, the number of patients in each group was relatively few, even though detailed baseline data were available. Furthermore, follow-up patients were even fewer, particularly for the ALSFRS-R, suggesting caution when interpreting the results. The FTDFRS is focussed on behaviour and instrumental activities of daily living (e.g. shopping independently, meal preparation, managing finances, and taking medications) and there was no significant correlation between ALSFRS-R and FTDFRS scores at baseline or follow-up. Nonetheless, it is possible that some components may have been influenced by ALS motor symptoms, rather than just behavioural disturbances. Finally, the detection of cognitive deficits relied on the ACE-R, rather than on a formal neuropsychological assessment.

Previous studies have attempted to quantify behavioural symptoms in ALS.(21) In the present study, 47.6% of ALS patients had moderate or severe behavioural/functional deficits at baseline. A systematic review of cohort studies by Raaphorst et al(22) found that 17 to 88% of ALS patients reported mild to moderate behavioural changes. The wide range of behavioural symptoms reported in previous studies of ALS is most likely due to methodological variations in detecting and grading behavioural deficits. Several studies have used the Frontal Systems Behaviour Scale (FrSBe), to assess behaviour in ALS.(2,23–25) Using the FrSBe, one study found behavioural disturbance in a quarter of patients, and 39.6% showed impairment in at least one domain, particularly apathy.(9)

Consistent with a previous study,(24) baseline FTDFRS and ALSFRS-R scores did not correlate in the present study. One potential explanation for the lack correlation between the ALSFRS-R and the FTDFRS in the present study is that these two measures presumably measure different deficits encountered within the FTD-ALS disease spectrum. In keeping with this interpretation, a preliminary report suggests that patients with mild physical impairment may still have severe behavioural deficits as measured by the FTDFRS, and conversely, patients with severe physical disability may have little if any behavioural disturbance.(13) The two instruments differ significantly; for example, the ALSFRS-R is heavily weighted towards motor function (fine and gross), bulbar dysfunction, and the impact of motor deficits on basic activities. In contrast, the FTDFRS is geared towards behavioural disturbances and more complex tasks such as managing finances, shopping independently and taking medications appropriately. ALS specific assessments, such as the MiND-B,(26) have been developed recently to document behavioural symptoms.(26,27) However, one advantage of the FTDFRS is that it also includes functional items, addressing disease severity from both functional and behavioural perspectives.

The fact that motor and behavioural deficits do not correlate in ALS has important implications for clinical practice and research. From a clinical perspective, reliance on motor assessment only may

underestimate disease impact. In fact, behavioural disturbances in ALS may have a greater influence on carer burden than motor deficits.(10) Clear documentation of behavioural changes and cognitive impairment may improve patient care, especially when considering involvement of other family members in complex decision-making. From a research perspective, behavioural and functional disturbances, documented using measures like the FTDFRS or the MiND-B, should be considered for future drug trials in conjunction with the ALSFRS-R.

Little is known about the progression of behavioural/functional disturbance in ALS. Using a conservative approach to analysis, significant changes in the FTDFRS were demonstrated in FTD-ALS over time, with a trend for change in ALS. No significant change in ALSFRS-R scores was detected in any of the disease groups, although there was a trend for decline in the ALS group. Given that ALSFRS-R follow-up data was insufficient, this finding may simply reflect small sample size, although differences in patterns of disease progression cannot be excluded. As such, it is difficult draw firm conclusions about whether the ALSFRS-R is more or less sensitive to change than the FTDFRS. Given the wide variability in motor presentation, rate of motor decline, and patient survival in ALS, more accurate markers of prognosis are urgently required for clinical and research use. Further studies should examine the utility of the FTDFRS in prognostication and tracking of behavioural changes as ALS progresses.

The results of the present study indicate that the pattern of motor symptoms in ALS, FTD-ALS and bvFTD are not congruous with behavioural and functional impairment. While motor dysfunction was less severe in the bvFTD group than in ALS or FTD-ALS, the opposite was true of behavioural disturbance. All three groups displayed behavioural and functional impairment at baseline as well as deterioration over the follow-up period, as measured by the FTDFRS. As such, the present study suggests that the FTDFRS offers important additional information in the assessment of ALS and FTD-ALS patients. Further study is required to determine whether the FTDFRS is helpful in

monitoring progression of behavioural changes in ALS and FTD-ALS.

ACKNOWLEDGEMENTS

This work was supported by funding to Forefront, a collaborative research group dedicated to the study of frontotemporal dementia and amyotrophic lateral sclerosis, from the NHMRC program grant (#1037746) and the ARC Excellence in Cognition and its Disorders Memory Node (#CE110001021). JRB is supported by a NHMRC Early Career Fellowship (#1072451). SH is supported by the Graham Linford Fellowship from the MNDRIA.

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TABLES

Table 1. Patient demographics

FTD-ALS patients were significantly more impaired on the ACE-R than bvFTD and ALS patients, especially on the attention/orientation and verbal fluency subtasks. ALS and FTD-ALS patients had significantly greater motor functional impairment than bvFTD patients. In contrast, behavioural and functional impairment was more significantly more common in bvFTD than in ALS. When applicable, data is presented as mean +/- standard deviation. Note: the ACE-R is scored out of 100 points; attention/orientation (18 points), memory (26 points), fluency (14 points), language (26 points) and visuospatial (16 points). ALS = amyotrophic lateral sclerosis; FTD-ALS = frontotemporal dementia and amyotrophic lateral sclerosis; bvFTD = behavioural variant frontotemporal dementia; NS = non-significant. [a]bvFTD compared with ALS ($p < 0.001$), [b]bvFTD compared with FTD-ALS ($p < 0.05$), [c]ALS compared with FTD-ALS ($p < 0.05$)

	ALS	**FTD-ALS**	**bvFTD**	**P-value**
Number of Patients	21	12	14	
Male Gender (% of patients)	9 (42.9%)	11 (91.7%)	14 (100%)	<0.001
Age (years)	63.7 +/- 11.4	63.3 +/- 7.5	61.7 +/- 8	NS
Education (years)	12.7 +/- 3.3	11.4 +/- 3.0	13.5 +/- 4.3	NS
Symptom Duration (months)	33.4 +/- 27.6	41.3 +/- 30.8	50.6 +/- 35.1	NS
ACE-R				
Attention and orientation	17.7 +/- 0.7	15.5 +/- 2.4	17.6 +/- 0.6	<0.05[b,c]
Memory	22.5 +/- 3.2	18.7 +/- 5.4	22.4 +/- 2.7	NS
Fluency	11.1 +/- 3	6.8 +/- 3.9	10.9 +/- 3.2	<0.05[b,c]
Language	23.6 +/- 2.1	20.8 +/- 3.2	22.1 +/- 3.3	NS
Visuospatial	15.4 +/- 0.9	13.8 +/- 1.8	14.6 +/- 2.3	<0.05[c]
Total	90.5 +/- 6.5	78.1 +/- 9.1	87.6 +/- 7.6	<0.05[b,c]
ALSFRS-R				
Bulbar	8.5 +/-3	8.1 +/-2.9	11.6 +/-1.1	< 0.001[a,b]
Fine Motor	8.7 +/-3.2	9.6 +/-2.3	11.4 +/-1.9	< 0.01[a,b]
Gross Motor	10 +/-2.4	9.8 +/-1.7	11.1 +/-2.2	< 0.05[b]
Respiratory	11.1 +/-2.1	11.2 +/-1.5	11.9 +/-0.4	NS
Total	38.4 +/-6.3	38.7 +/-6	46 +/-5.3	< 0.001[a,b]
FTDFRS				
Logit Score	1.7 +/-1.6	0.8 +/-2	0 +/-1.4	< 0.05[a]
Very mild or mild	11 (52.4%)	3 (25%)	2 (14.3%)	< 0.05[a]
Moderate or severe	10 (47.6%)	9 (75%)	12 (85.7%)	

FIGURE LEGENDS

Figure 1. Baseline motor and behavioural function

A: The ALS and FTD-ALS groups scored a significantly lower total ALSFRS-R at baseline than the bvFTD group ($p < 0.05$), corresponding to greater motor impairment
B: The bvFTD group had a significantly lower FTDFRS logit score (See Methods) than the ALS group at baseline ($p < 0.05$), corresponding to greater behavioural and functional impairment. The FTD-ALS group exhibited intermediate impairment, which was not significantly different to the other groups.