How common are behavioural changes in amyotrophic lateral sclerosis?

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Abstract
Our objectives were to assess the frequency of behavioural changes in patients with amyotrophic lateral sclerosis (ALS) and to compare the clinical profile of ALS patients with those with behavioural variant frontotemporal dementia (bvFTD). Ninety-two patients with ALS and their carers participated in a postal survey. ALS patients completed self-report measures of motor function and mood. Eighty-one carers of ALS patients and 25 carers of bvFTD patients completed the revised version of the Cambridge Behavioural Inventory (CBI-R). Results showed that reduced motivation was reported in more than 80% of the ALS cases, with almost 41% of them having moderate-severe apathy. Depression was present in 30% of ALS patients and did not contribute significantly to the presence of behavioural symptoms. Bulbar and limb onset ALS patients did not differ. Abnormal behaviour and stereotypical and motor behaviours were present to a moderate-severe degree in around 20%, and 11% reached the criteria for FTD. The rate of behavioural symptoms was significantly higher in the bvFTD group than ALS in all behavioural domains (p <0.001). In conclusion, apathy was the most prominent feature in ALS patients. A substantial proportion of ALS patients manifested behavioural changes of the type seen in FTD, with 11% fulfilling the criteria for FTD.

Key words: Amyotrophic lateral sclerosis, behavioural symptoms, frontotemporal dementia

Introduction
Although traditionally considered a motor disorder, it is now apparent that ALS is a multisystem disease (1), which overlaps considerably at a clinical level with frontotemporal dementia (FTD) (2–4). This overlap has been reinforced by recent pathological findings, in that TDP-43 has been recognized as the principal protein inclusion in ALS and in a subset of FTD cases (5,6).

While cognitive aspects of ALS have been explored in detail (2,4,7–10), behavioural changes have received relatively less attention, perhaps because of the overwhelming nature of the physical disability. Although a number of studies have reported behavioural changes in ALS patients, including disinhibition, irritability, emotional blunting, lack of empathy, and particularly apathy (9,11,12), these studies have typically involved rather small numbers. That apathy is a core symptom of both depression and FTD further complicates the interpretation of findings to date.

Patients with ALS, understandably, suffer degrees of mood disturbance and the contribution of depression to the apathy commonly reported in ALS has not been fully elucidated (13). Moreover, the instrument most commonly applied in ALS studies to date – the Frontal Systems Behaviour Scale (FrSBe) – groups the deficits in three categories (apathy, disinhibition and executive dysfunction), and has several items addressing apathy but is confounded by the motor impairment in ALS. In addition, the FrSBe does not assess stereotypical behaviours, which are common in FTD, or psychotic symptoms (13,14). Given claims regarding the prevalence of FTD-like symptoms in ALS, there is a surprising lack of formal comparison between ALS and FTD cohorts. Furthermore, it would be of considerable interest to
examine the profile of features across these disorders using a common instrument.

The Cambridge Behavioural Inventory-Revised (CBI-R) is a neuropsychiatric questionnaire evaluating a wide range of psychopathological symptoms as well as everyday functional ability, which is able to discriminate the behavioural profiles of the different neurodegenerative diseases including Alzheimer’s disease (AD), Parkinson’s disease (PD), and behavioural variant frontotemporal dementia (bvFTD) (15,16). Patients with FTD show a striking pattern of symptoms on the CBI-R, making it a promising instrument to employ in an ALS cohort.

There have been suggestions that patients with bulbar-onset ALS have a greater rate of cognitive impairment (17) although behavioural changes have not been systematically explored; neither has the relationship between degree of physical disability and presence of behavioural abnormalities. As such, the aims of this study were to assess the frequency of behavioural changes in a large cohort of patients with ALS using the CBI-R and to assess the impact of mood disturbance and motor function on behavioural symptoms. An additional aim was to compare the clinical profile of patients presenting with ALS versus those with behavioural variant frontotemporal dementia (bvFTD).

**Methods and subjects**

Patients diagnosed with ALS were recruited through the Motor Neurone Disease Association of New South Wales (MND NSW) who kept their identities anonymous. Of 354 ALS patients registered as members of the association, 34.5% accepted an invitation to participate in a postal survey evaluating neuropsychiatric symptoms and motor function. Of those patients who did not complete the survey, 10% cited health or personal problems and 15% died before they could participate in the study, leaving 92 ALS patients and 81 carers who returned the completed survey. Ethical approval was obtained from the Human Research Ethics Committee of South Eastern Sydney/Illawara Area Health Service. Patient or family consent was obtained from each participant.

In terms of disease controls, we identified 25 patients with clinical diagnosis of bvFTD with complete information from carers. All of them were seen in The Frontotemporal Dementia Research Group (FRONTIER) between January 2008 and December 2009, diagnosed by a senior neurologist, had neuropsychological assessment, met current consensus criteria for FTD (3) and did not manifest features of ALS.

**Instruments**

We designed a clinical questionnaire enquiring about demographic details, past medical and family history, symptom onset and distribution, date of onset and diagnosis by a neurologist (18), plus subsequent clinical course (available from the authors). In addition, to estimate the proportion of ALS patients that would reach clinical criteria for FTD we included enquires about core behavioural changes, notably in social conduct (disinhibition), interpersonal relationships (lack of empathy) based on the Neary criteria and modifications proposed by Rascovsky et al. (3,19–21).

**Motor function**

The self-administered version of the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R), a disease-specific measure of global function and progression of disability in ALS, was used to assess motor function (22–24).

This is a 5-point scale from 0 (maximum disability) to 4 (normal motor function) and it contains four sub-scores: bulbar, fine motor, gross motor and respiratory function. The total score for normal function is 48.

**Behavioural changes**

Changes in behaviour were assessed using the revised version of the Cambridge Behavioural Inventory CBI-R (15,16), a 45-item carer based questionnaire, which assesses cognitive abilities, everyday function and neuropsychiatric symptoms in dementia. It has been shown to correlate highly with the Neuropsychiatric Inventory (NPI) (25). The CBI-R assesses the following domains: memory and orientation, everyday skills, self care, abnormal behaviour, mood, delusions and hallucinations, eating habits, sleep, stereotypical and motor behaviour and motivation (see Appendix 1, which is only available in the online version of the journal. Please find this material with the following direct link to the article: http://www.informahealthcare.com/10.3109.17482968.2010.520718. It rates frequency of symptoms (behavioural changes) since the onset of disease, on a scale of 0–4. Score 0 denotes no impairment; score 1, a few times per month; 2, a few times per week; 3, a daily occurrence; and score 4, constantly. The total score of each sub-scale was converted into percentage of impairment: 0–25% was classified as mild; 26–50% as moderate; 51–75% as severe; and more than 75% very severe. This grading scheme was based on the approach taken in a similar survey of neuropsychiatric symptomatology (26).

In a normal control sample asked to rate their spouse (n = 20), endorsements on the CBI-R are very sparse and virtually none exceeds mild levels in any domain.

**Depression anxiety and stress**

To measure changes in mood we used the Depression, Anxiety and Stress Scale (DASS), 21-item
version. The DASS is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety and stress (27). Patient self-report only was collected. Carers were allowed to help patients with writing difficulty to complete the DASS.

Statistical analysis

SPSS Statistics 17.0 was used for analysis of the results. To examine demographic and clinical features between groups, independent t-tests were used, and Mann-Whitney U-test where appropriate. Distribution of symptoms across groups was compared using Pearson’s χ² tests with Yates’ correction for continuity and Fisher’s exact test when pertinent. Logistic regression was used to analyse the impact of motor function, depression, anxiety and stress on behavioural changes.

Results

The baseline characteristics of the ALS patient group were representative for an ALS population (Table I). The mean age at onset of the patients was 58.2 ± 10.8 years, range 25–84 years. Gender distribution was 1.6 male/female, median duration of disease was three years (95% CI 0.5–15) and a positive family history was present in 6.5% of the patients. Distribution of patients by motor onset showed a predominance of limb (n = 72) over bulbar (n = 20) onset. Comparison of these sub-groups showed a significant difference in age of onset and disease duration (p <0.05).

Motor function

Comparison of ALSFRS-R total scores showed no significant difference between limb and bulbar onset (limb Md = 36, bulbar Md = 32.5; U = 612, z = −1.0, p = 0.3, r = 0.1). Not surprisingly, patients with bulbar onset had a lower median score on bulbar function (limb Md = 10, bulbar Md = 2; U = 155, z = −5.4, p = 0.000, r = 0.5). At the same time, the scores for fine motor function (limb Md = 8, bulbar Md = 11; U = 366, z = −3.8, p = 0.001, r = 0.3) and gross motor function (limb Md = 6, bulbar Md = 8.5; U = 492, z = −2.2, p = 0.001, r = 0.1) were lower in the limb-onset group. There was no significant difference between groups for the respiratory function sub-scores.

Table I. Demographic data of ALS patients.

<table>
<thead>
<tr>
<th></th>
<th>Total n = 92</th>
<th>Limb n = 72</th>
<th>Bulbar n = 20</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F</td>
<td>56/36</td>
<td>47/25</td>
<td>9/11</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age (mean, SD) years</td>
<td>62.3 ± 10.7</td>
<td>61.2 ± 11</td>
<td>66 ± 8.4</td>
<td>n.s</td>
</tr>
<tr>
<td>Age at onset (mean, SD) years</td>
<td>58.2 ± 10.8</td>
<td>56.3 ± 11</td>
<td>64 ± 8.2</td>
<td>0.005</td>
</tr>
<tr>
<td>Disease duration (Median, 95% CI)</td>
<td>3 (0.5–15)</td>
<td>4 (1–17.4)</td>
<td>2 (0.5–7.9)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Behavioural changes

As would be predicted, a high proportion of ALS patients had moderate-severe problems in everyday skills, self care and sleep according to carer reports, related principally to their physical disability (Figure 1A). Problems with memory and orientation were reported by carers in more than 60% of the patients, of whom 24% had moderate-severe difficulties (Figure 1B). Similarly, changes in abnormal behaviour, stereotypical and motor behaviour were found in more than 50%, with around 20% in the moderate-severe category. Reduced motivation was a prominent feature affecting more than 80% of the cases, with 41% having moderate-severe apathy: only 14% of the patients lacked problems in motivation (Figure 1C). The absence of abnormal beliefs (delusions and hallucinations) was striking, being present in only 5% of the patients. In contrast, moderate-severe problems in mood were reported in 33% of the patients and were lacking in 11% (Figure 1D). Lability and irritability were the most commonly noted symptom.

To examine the possible differences in CBI-R carer report for motor onset, we compared the severity of symptoms between limb (n = 64) and bulbar (n = 17) sub-groups. There was no significant association between motor onset and severity of symptoms on CBI-R.

Although approximately 20% of ALS patients presented moderate-severe changes in behaviour including abnormal behaviour or stereotypical behaviour, in many instances only one or two of these features were present so these patients did not reach the criteria for FTD. Based on the clinical questionnaire and the CBI-R, we estimated that 10 of 92 ALS patients (11%) met clinical criteria for behavioural FTD, with at least three of five core current diagnostic criteria (3). Six of these 10 ALS patients have been evaluated in the FRONTIER group by an experienced behavioural neurologist (JRH), with further interview of carer, neuropsychological assessment and imaging that confirmed the diagnosis of FTD in all instances.

Levels of depression

As shown in Figure 2, more than 70% of the ALS patients did not reach the threshold for depression on the DASS. Moderate to very severe depression was present in 21%. The percentage of ALS patients...
with anxiety and stress was lower: 18.5% of the patients reached moderate to extremely severe anxiety, and 14.1% the same levels of stress. There was a 60% overlap between those with moderate to very severe depression and anxiety.

Of those ALS patients presenting with depression of any level, 60% were receiving antidepressant treatment (as monotherapy). One patient was receiving benzodiazepines.

**Impact of mood disturbance and motor function on behaviour**

Logistic regression was performed to assess the likely contribution of mood disturbance to behavioural changes (CBI-R sub-scales: eating habits, abnormal behaviour, stereotypical and motor behaviour and motivation as dependent variables), when the latter were categorized as present or absent. The three independent variables in the model were the depression, anxiety and stress DASS21 sub-scales. None of these factors made a significant contribution to the presence, or not, of abnormal behaviour and eating habits, stereotypical and motor behaviours and lack of motivation.

In the same way, none of the motor factors analysed by logistic regression (ALSFRS-R sub-scales: bulbar, fine motor, gross motor and respiratory function) made a significant contribution to presence of behavioural features.

**Comparison of CBI-R between ALS and bvFTD**

Figure 3 shows the proportion of ALS and bvFTD patients with moderate or severe endorsement on the CBI-R. It can be seen that bvFTD patients had more...
How common are behavioural changes in ALS?

The Cambridge Behavioural Inventory-Revised (CBI-R) for ALS and bvFTD.

Figure 3. Comparison of the behavioural profile according to The Cambridge Behavioural Inventory-Revised (CBI-R) for ALS and bvFTD.

problems in everyday skills and sleep than ALS. Conversely, and probably due to the motor involvement, self care was more affected in ALS patients, but these differences were not statistically significant ($\rho > 0.05$). A higher percentage of bvFTD patients presented memory and orientation problems ($\chi^2 = 33.6, \rho = 0.000, phi = 0.56$).

More than 70% of the bvFTD patients had moderate-severe problems across all behavioural features: in contrast, around 20% of the ALS cases had problems on other behavioural domains except lack of motivation, which was present to a moderate to severe degree in 40%. The proportion of patients presenting behavioural problems was significantly higher in the bvFTD group than ALS in the following domains: eating habits ($\chi^2 = 39.2, \rho = 0.000, phi = 0.62$), abnormal behaviour ($\chi^2 = 34.5, \rho = 0.000, phi = 0.57$), stereotypical and motor behaviours ($\chi^2 = 26.3, \rho = 0.000, phi = 0.50$), motivation ($\chi^2 = 14.3, \rho = 0.001, phi = 0.37$), abnormal beliefs ($\chi^2 = 6.1, \rho = 0.001, phi = 0.24$), and mood ($\chi^2 = 11.7, \rho = 0.001, phi = 0.33$).

Discussion

The present study has identified a high rate of behavioural changes in ALS patients, as reported by carers, especially apathy. Positive symptoms, notably abnormal behaviour, stereotypical and motor behaviours and changes in eating habits were also reported in at least half of the ALS group, being rated as severe in around 25% of cases. Although mild degrees of mood disturbance were common, significant depression was unusual and, more importantly, appeared not to contribute to the presence of apathy or other behavioural changes. The pattern of motor features and stage of disease were not a major determinant in the presentation of behavioural changes and while the profile of behavioural changes was similar to that seen in bvFTD, the rate of core symptoms was considerably lower, in keeping with the fact that only 11% reached the criteria for bvFTD.

We turn now to the major symptom, lack of motivation or apathy. This finding confirms previous studies that have also surveyed carers of ALS patients, reporting 30–50% of apathy (11–13). Apathy is a complex construct which comprises a lack of motivation and quantitative reduction of voluntary behaviours (28) and thus a number of possible causes including dementia and depression (29). An obvious question in ALS is the contribution of depression to the apathy reported by carers. In our study less than 25% of ALS patients reported a significant degree of depression, yet 40% were apathetic. Moreover, further logistic regression showed that depression was not related to presence of apathy or other behavioural symptoms. In addition, neither anxiety nor stress were major factors implicated in the presence of behavioural changes. This finding supports a previous study that showed no correlation between apathy and depression, disease duration, or ALS-FRS-R scores (12).

The higher rate of mood related features on the CBI-R compared to the self-rated DASS is of some interest. It is likely that carers are rating irritability, restlessness and emotional lability as mood symptoms whereas the DASS 21 is a more precise reflection of depression.

The medial prefrontal cortex and basal ganglia have been consistently implicated in motivation and processes with lesions in these areas producing apathy (28). In ALS, apathy has been shown to correlate with deficits in verbal fluency (8,11), which in turn was associated with impaired activation in anterior cingulate gyrus and middle and inferior frontal gyrus in a functional MRI study (30). In support of this, a neuropathological study reported that apathy was associated with tissue loss in the right ventromedial superior frontal gyrus (31). In summary, there is strong evidence to connect apathy with frontal pathology in ALS.

In addition to apathy, carers also reported moderate-severe stereotypical and motor behaviours in around 20% and abnormal eating habits in at least 11% of the ALS patients, symptoms that are characteristic of FTD. This finding agrees with the estimated frequency of 11% of the ALS patients who met current criteria for bvFTD. It is likely that a higher proportion of ALS patients would eventually fulfill criteria if they were included in a longitudinal study. Patients with ALS present, by definition, with motor features, and the behavioural changes emerge later in the course of the disease. Future studies should focus on the temporal profile and emergence of neuropsychiatric features as the disease progresses. In line with this assertion, formal comparison with bvFTD showed that although the profile of behavioural changes was similar to that seen in bvFTD,
the rate of all core symptoms was significantly less in ALS than in bvFTD. This is not easily explained by under-reporting by ALS carers since the rate of impairment in everyday skills and sleep disturbances was higher in ALS.

In summary, a substantial proportion of ALS patients manifested behavioural changes of the type seen in FTD, with 11% fulfilling criteria of frontotemporal dementia. Apathy was the most prominent feature in ALS patients and is likely to influence management issues considerably; patients may manifest reluctance to initiate not only physical activity but also mental activity and speech, as well as lack of empathy (32,33). The impact of these neuropsychiatric symptoms on carers requires further investigation.

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References


Supplementary material available online
Appendix 1: Cambridge Behavioural Inventory Revised (CBI-R)