Screening for cognitive and behavioural impairment in amyotrophic lateral sclerosis: Frequency of abnormality and effect on survival

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Screening for Cognitive and Behavioral Impairment in Amyotrophic Lateral Sclerosis: frequency of abnormality and effect on survival

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Abstract:

Objective: To screen for cognitive and behavioral impairment in people with amyotrophic lateral sclerosis (ALS) and controls with neuromuscular disease and to correlate these with clinical features.

Methods: 108 people with ALS and 60 controls with other neuromuscular diseases were recruited and assessed with the Addenbrooke’s cognitive examination-III (ACE-III), the Frontal assessment battery (FAB), and the executive function component of the Edinburgh cognitive and behavioral ALS screen (ECAS). The Amyotrophic lateral sclerosis-Frontotemporal dementia questionnaire (ALS-FTD-Q) and the Motor Neuron Disease Behavioral instrument (MiND-B) were administered to the caregivers of people with ALS. The prevalence of abnormalities was determined and correlated with clinical features and survival. In 37 people with ALS, serial studies were performed.

Results: The frequencies of cognitive impairment based on the ACE-III and FAB were 30.0% and 14.0%, in ALS and 11.7% and 3.3% in controls, respectively. Age and years of education influence the results of the ACE-III and ECAS executive function. In ALS, the frequencies of behavioral impairment based on ALS-FTD-Q and MiND-B were 32.1% and 39.4 %, respectively. There is significant correlation of ALS-FTD-Q and MiND-B with the ALSFRS-R score. ALS participants with cognitive impairment measured with ACE-III had significantly shorter survival time than those without. ALS participants with behavioral impairment measured with ALS-FTD-Q had worse prognosis than those without. No significant difference was found between the first two serial cognitive tests based on ACE-III and FAB by using generalized estimating equation.
**Conclusion:** There is a greater frequency of cognitive impairment in people with ALS than in patients with other neuromuscular diseases. The cognitive and behavioral tests are potential biomarkers of the prognosis of ALS. The results of cognitive tests are stable over 6 months and possibly longer.

**Keywords:** Amyotrophic lateral sclerosis, cognitive impairment, behavioral impairment, survival, longitudinal study
Introduction

Amyotrophic lateral sclerosis is defined by progressive loss of upper and lower motor neurones [1]. Some people with ALS also have frontotemporal dementia (FTD) while others have lesser degrees of cognitive impairment [2]. Some of the overlap between ALS and FTD is associated with the presence of a C9orf72 gene mutation [3, 4]. Different approaches have been used to study the frequency of cognitive impairment. Full neuropsychological testing is time-consuming. Therefore a variety of simple tools have been used to screen for cognitive impairment in ALS. These include Addenbrooke’s cognitive examination–III (ACE-III), an updated version of the ACE-R [5-8], the Frontal assessment battery (FAB) [9-11], the Edinburgh cognitive and behavioral ALS screen (ECAS), which includes tests of social cognition, [12-16] and the ALS cognitive behavioral screen (ALS CBS) [17]. Table 1 shows the elements tested in the different tools. Other scales have been developed to detect behavioral dysfunction in ALS [18, 19]. These include the Amyotrophic lateral sclerosis-Frontotemporal dementia questionnaire (ALS-FTD-Q) and the Motor Neurone Disease Behavioural instrument (MiND-B), which are administered to carers.

With such screening tools, the incidence of the cognitive impairment in ALS ranges from 30 to 75% [20-23] and the rate of behavioral impairment ranges from 14% to 40% [12, 23-25] (Table 2).
Table 1 Summary of domains tested by screening tools used in ALS

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>ACE-III</th>
<th>FAB</th>
<th>ECAS</th>
<th>ALS CBS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Memory</td>
<td>Yes*</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Verbal fluency</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Language or conceptualization</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Visuospatial</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Prehension behaviour</td>
<td>No</td>
<td>Yes*</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Executive function</td>
<td>No</td>
<td>Yes*</td>
<td>Yes*</td>
<td>Yes</td>
</tr>
<tr>
<td>Social cognition (as part of executive function)</td>
<td>No</td>
<td>No</td>
<td>Yes*</td>
<td>No</td>
</tr>
</tbody>
</table>

ALS CBS: ALS cognitive behavioural screen  
ECAS: Edinburgh cognitive and behavioral ALS screen  
ACE-R: Addenbrooke’s cognitive examination revised  
FAB: Frontal assessment battery  
*Test used in the present study
Table 2 Summary of the recent papers in cognitive and behavioral impairment

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Country/year</th>
<th>No of patients</th>
<th>Percentage of cognitive impairment</th>
<th>Percentage of behavioral impairment</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS CBS</td>
<td>USA/2016</td>
<td>274</td>
<td>54%</td>
<td>14%</td>
<td>Murphy et al.[23]</td>
</tr>
<tr>
<td>ECAS</td>
<td>China/2016</td>
<td>84</td>
<td>36%</td>
<td>27%</td>
<td>Ye et al.[13]</td>
</tr>
<tr>
<td>ECAS</td>
<td>Italy/2016</td>
<td>107</td>
<td>37%</td>
<td>54%</td>
<td>Poletti et al.[16]</td>
</tr>
<tr>
<td>ALS CBS</td>
<td>USA/2015</td>
<td>86</td>
<td>62%</td>
<td>37%</td>
<td>Bock et al.[26]</td>
</tr>
<tr>
<td>FAB</td>
<td>Greece/2015</td>
<td>34</td>
<td>50%</td>
<td>N/A</td>
<td>Nidos et al.[27]</td>
</tr>
<tr>
<td>ALS CBS</td>
<td>Spain/2015</td>
<td>50</td>
<td>46%</td>
<td>18%</td>
<td>Turon-sans et al.[28]</td>
</tr>
<tr>
<td>ACE-R</td>
<td>China/2014</td>
<td>145</td>
<td>30%</td>
<td>N/A</td>
<td>Wei et al.[22]</td>
</tr>
<tr>
<td>FAB</td>
<td>Canada/2014</td>
<td>44</td>
<td>21%</td>
<td>N/A</td>
<td>Osborne et al.[29]</td>
</tr>
<tr>
<td>MoCA</td>
<td>Canada/2014</td>
<td>39</td>
<td>53%</td>
<td>N/A</td>
<td>Osborne et al.[29]</td>
</tr>
<tr>
<td>FAB and FBI</td>
<td>China/2014</td>
<td>126</td>
<td>32%</td>
<td>46%</td>
<td>Wei et al.[30]</td>
</tr>
<tr>
<td>ECAS</td>
<td>Germany/2014</td>
<td>136</td>
<td>22%</td>
<td>30%</td>
<td>Lule et al.[14]</td>
</tr>
<tr>
<td>FAB</td>
<td>USA/2009</td>
<td>16</td>
<td>50%</td>
<td>N/A</td>
<td>Oskarsson et al.[31]</td>
</tr>
</tbody>
</table>

ALS CBS: ALS cognitive behavioral screen
ECAS: Edinburgh cognitive and behavioral ALS screen
ACE-R: Addenbrooke’s cognitive examination revised
FAB: Frontal assessment battery
FBI: Frontal behavior inventory
MoCA: Montreal cognitive assessment
Current evidence suggest that some people with ALS have cognitive and behavioral impairment, and others do not. The cause of this is unclear. As already mentioned, carriage of a repeat expansion in C9orf72 is a cause of cognitive impairment in ALS, but there could be other factors. There have been attempts to determine whether clinical features are correlated with the presence of cognitive and behavioral testing. Some studies have found cognitive impairment to be more common in people with bulbar onset than limb onset of ALS [32]. However, other studies suggest that site of onset has no influence on the presence of cognitive impairment [33-35]. Therefore further information is required.

There have also been studies of whether the presence of cognitive or behavioral impairment affects prognosis, as might be the case if the presence of cognitive impairment indicates more severe or widespread disease. Some studies have suggested that the presence of cognitive impairment [36] or behavioral abnormality is associated with worse prognosis [37]. However, other studies suggest that cognitive impairment has no influence on survival [35]. Therefore further information is required.

Another possibility is that cognitive impairment, and other extramotor features of ALS, might develop in all people with ALS over time, as disease spreads more widely [38]. If this were the case, cognitive impairment would correlate with disease severity, but there is little information about this. There is conflicting information about whether there is later development of cognitive impairment in patients who are cognitively normal at onset of ALS [39-42]. Further information is required about this issue as well.

The first aim of the present study is to measure cognitive and behavioral impairment in the ALS patients by using 5 different clinic based questionnaires (ACE-
III, FAB, the executive component of the ECAS, ALS-FTD-Q, MiND-B), and to compare with controls with other neuromuscular disease, with the hypothesis that cognitive and behavioral impairment is greater than in neuromuscular disease. The rationale for this study is that people with neurological disorders would be more suitable controls than healthy people, because people with neuromuscular disease attending the same department would have similar background and experience many of the same difficulties as people with ALS attending our clinic.

The second aim is to determine whether the presence of cognitive and behavioral impairment is related to the clinical features of the patient, to test the hypothesis, based on previous reports, that bulbar onset of ALS is correlated with cognitive impairment, and that age and education would influence cognition in ALS, as is the case in healthy people [43] and that cognitive impairment is related to disease severity as would be the case if cognitive impairment occurs with more severe and widespread disease. The rationale for this was to provide further information about this unresolved issue. The third aim is to evaluate the effects of cognitive and behavioral impairment on survival, with the hypothesis that the presence of cognitive impairment indicates more severe and widespread disease, and would be expected to worsen prognosis.

The final aim is to determine if there is deterioration in cognition over time. The reasoning behind this study was to investigate whether patients who are cognitively normal at onset develop dysfunction over time, or whether ALS can be divided into people with cognitive issues and people without cognitive issues.

Methodology

1.1 Subjects:
People with probable or definite ALS [1] were recruited from the multidisciplinary MND clinic at Royal Brisbane and Women’s Hospital (RBWH). The
caregivers of the patients were also asked to complete questionnaires about the behaviour of the person with ALS. There was no systematic genetic screening; however, 5 people with ALS are known to have causative mutations (3 with C9orf72 repeat expansions, one with transactive response DNA binding protein (TARDBP) mutation and one with superoxide dismutase 1(SOD1) mutation). Of 81 people with ALS for whom there was information about the family history of ALS, 10 had familial ALS. Information about a family history of dementia was available from 54 people with ALS, of whom 10 had a positive family history.

The controls were people with neuromuscular diseases with no evidence of disease of the central nervous system. Informed written consent was obtained from all participants and caregivers. This research project was approved by the RBWH ethics committee (HREC/15/QRBW/68).

1.2 Clinical details:
The age, gender, the date of onset of symptoms and the site of onset of symptoms were recorded. The revised ALS Functional Rating Scale (ALS-FRS-R) [44] was recorded at each visit. When applicable, the date of death was recorded and the length of survival from onset of disease to death or censoring was calculated.

1.3 Cognitive and behavioral tests
All participants were tested with the ACE-III, which has a maximum possible score of 100. A score of less than 88 was defined as possible cognitive impairment [45]. The FAB, with a maximum possible score of 18, was also administered to all participants. A score of less than 12 was regarded as high possibility of cognitive impairment [10].

The executive function section of the ECAS (which includes reverse digit span, alternation, sentence completion and social cognition) was added to the testing panel
later in the study. It was administered to 41 people with ALS and 30 controls. The cutoff value for cognitive impairment is 33 of 48 [12]. Some people with ALS were unable to complete the tests due to physical disability. This was the case for 19 people for the ACE-III and for 3 for the FAB. To deal with this, we calculated the percentage of correct responses of the items that were tested, and then estimated the final score as this percentage of the total possible. This approach is an approximation, but has been used by others in this field [46].

Carers were tested with ALS-FTD-Q and MiND-B to detect behavioral abnormalities. The MiND-B evaluates disinhibition, apathy and stereotypical behaviour. The cutoff values for ALS-FTD-Q and MiND-B were 29 and 34, respectively [18, 19]. The relationship between the carer and the person with ALS was also recorded.

To evaluate any changes over time, serial cognitive tests, at intervals of 6 months or more, were obtained from 37 patients.

1.4 Statistical analysis

Statistical analysis was performed with SPSS 20 software. To compare groups, ANOVA was used, if the variables were normally distributed. Otherwise, the data were compared with the Mann-Whitney U test for two independent groups. To compare the proportions of groups, the $\chi^2$ test was used. To determine whether cognitive and behavioral function were influenced by clinical features, multiple logistic regression was used to evaluate the effects of age, gender, disease duration at the time of testing, years of education, site of onset and relationship of the carer to the person with ALS. To determine whether there was an association between disease severity measured by ALSFRS-R and scores of cognitive and behavioral testing, we used the Spearman rank test. To assess the effects of cognition and behavior on survival, Kaplan-Meier curve
and log rank test were utilized to compare survival between patients with normal and those with abnormal results. A Cox proportional regression model was used to report the hazard ratio and 95% confidence interval for each cofactor affecting prognosis. A generalized estimating equation model was used to test the longitudinal data. The model based estimator was chosen in the covariance matrix. Unstructured working correlation matrix was selected. P<0.05 was considered as significant.

Results

1.1 Clinical features

Clinical features of patients and controls, and numbers of participants for each test, are given in Table 3. The diagnoses of the people with neuromuscular disease are given in Error! Reference source not found..

Table 3 Clinical features of the patients and controls

<table>
<thead>
<tr>
<th></th>
<th>ALS</th>
<th>Other neuromuscular disease</th>
<th>P value#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>108</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Males: females</td>
<td>68/40</td>
<td>35/25</td>
<td>0.5550</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>63.8±10.6</td>
<td>62.3±12.1</td>
<td>0.4025</td>
</tr>
<tr>
<td>Years of school education( median, range)</td>
<td>11 (5,30)</td>
<td>10 (7,19)</td>
<td>0.1160</td>
</tr>
<tr>
<td>No tested with ALSFRS-R</td>
<td>88</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>No tested with ACE-III</td>
<td>108</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>No needing adjustment of ACE-III*</td>
<td>19</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>No tested with FAB</td>
<td>108</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>No needing adjusting of FAB*</td>
<td>3</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>No with executive section of ECAS</td>
<td>41</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>
No tested with ALS-FTD-Q
84 N/A

No tested with MiND-B
66 N/A

*In these patients, some test items were omitted and the score was adjusted

Table 4 Diagnoses of controls

<table>
<thead>
<tr>
<th>Disease category</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral nerve disorder</strong></td>
<td></td>
</tr>
<tr>
<td>Idiopathic neuropathy</td>
<td>15</td>
</tr>
<tr>
<td>Carpel tunnel syndrome</td>
<td>2</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>2</td>
</tr>
<tr>
<td>Guillain–Barré syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Pelvic neurofibroma</td>
<td>1</td>
</tr>
<tr>
<td>Charcot-Marie-Tooth disease</td>
<td>5</td>
</tr>
<tr>
<td>Anterior interosseous syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Anti Myelin-associated glycoprotein (MAG) neuropathy</td>
<td>1</td>
</tr>
<tr>
<td>Brachial plexus injury</td>
<td>1</td>
</tr>
<tr>
<td>Cramp fasciculation syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Chronic inflammatory demyelinating polyneuropathy</td>
<td>3</td>
</tr>
<tr>
<td>Schwannoma posterior tibial nerve</td>
<td>1</td>
</tr>
<tr>
<td>Small fibre neuropathy</td>
<td>2</td>
</tr>
<tr>
<td>Trigeminal neuropathy</td>
<td>1</td>
</tr>
<tr>
<td>Multifocal motor neuropathy</td>
<td>2</td>
</tr>
<tr>
<td><strong>Muscle disease</strong></td>
<td></td>
</tr>
<tr>
<td>Mitochondrial myopathy</td>
<td>2</td>
</tr>
</tbody>
</table>
Pompe disease 1
Inclusion body myositis 3
Facioscapulohumeral muscular dystrophy 5
Myopathy 1
Idiopathic hyperCKemia 1
**Anterior horn cell non-ALS**
Spinal muscular atrophy type 2 1
**Myasthenia gravis** 7
Total 60

1.2 What is the prevalence of cognitive and behavioral impairment?

The frequency distributions of ACE-III and FAB scores in disease controls and ALS patients are shown in Figure 1. The cognitive test scores are summarized in Table 5. There are significant differences in total ACE-III, ACE-III attention and language scores and FAB total score between the groups. There were no significant differences in the other components of the ACE-III or in the executive section of the ECAS. The percentages of each group with cognitive impairment are shown in Table 6. Between people with ALS and controls there is a significant difference in the percentage with abnormal results of ACE-III and FAB. However, no significant differences were found between the two groups in the scores of ECAS executive function and social cognition.

Of the patients with known causative genes, one with C9orf72 repeat expansion had normal cognitive function, and the other patients (2 with C9orf72 repeat expansions, one with TARDBP mutation and one with SOD1 mutation) had cognitive impairment, defined as abnormal result on ACE-III testing.
Table 5  Results of cognitive tests

<table>
<thead>
<tr>
<th>Test</th>
<th>ALS median range</th>
<th>Controls median range</th>
<th>P value#</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-III total score</td>
<td>92 (60-100)</td>
<td>94 (79-100)</td>
<td>P=0.023*</td>
</tr>
<tr>
<td>Attention score (mean SD)</td>
<td>16.4±1.9</td>
<td>17.2±1.0</td>
<td>P=0.003**</td>
</tr>
<tr>
<td>Memory score (mean SD)</td>
<td>23.1±2.9</td>
<td>23.6±2.0</td>
<td>P=0.552</td>
</tr>
<tr>
<td>Fluency score (mean SD)</td>
<td>10.9±3.0</td>
<td>11.6±2.2</td>
<td>P=0.343</td>
</tr>
<tr>
<td>Language score (mean SD)</td>
<td>24.5±2.1</td>
<td>25.2±1.0</td>
<td>P=0.024*</td>
</tr>
<tr>
<td>Visuospatial score (mean SD)</td>
<td>15.3±1.1</td>
<td>15.5±0.9</td>
<td>P=0.305</td>
</tr>
<tr>
<td>FAB total score</td>
<td>16(6-18)</td>
<td>17(12-18)</td>
<td>P=0.004**</td>
</tr>
<tr>
<td>ECAS executive score (SD)</td>
<td>40(17-45)</td>
<td>40(26-47)</td>
<td>P=0.487</td>
</tr>
<tr>
<td>Social cognition subsection</td>
<td>12(0-12)</td>
<td>12(0-12)</td>
<td>P=0.192</td>
</tr>
</tbody>
</table>

*: P<0.05  **: P<0.01  # Mann-Whitney U test was used.

Table 6  Percentage of people with cognitive impairment

<table>
<thead>
<tr>
<th>Test</th>
<th>Cut off value for abnormality</th>
<th>ALS percent abnormal</th>
<th>Controls percent abnormal</th>
<th>P value#</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-III</td>
<td>≤88</td>
<td>30.0%</td>
<td>11.7%</td>
<td>P=0.013*</td>
</tr>
<tr>
<td>FAB</td>
<td>≤12</td>
<td>14.0%</td>
<td>3.3%</td>
<td>P=0.033*</td>
</tr>
<tr>
<td>ECAS executive</td>
<td>≤33</td>
<td>22.0%</td>
<td>16.7%</td>
<td>P=0.802</td>
</tr>
</tbody>
</table>

*: P<0.05, # χ2 test was used

The behavioral test scores are shown in Table 7. The frequencies of behavioral impairment measured by ALS-FTD-Q and MiND-B are 32.1% and 39.4% respectively. The rates of disinhibition, apathy and stereotypical behaviour are 9.1%, 21.2% and 7.6%, respectively.

Table 7  Results of behavioral testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Cut off value for abnormality</th>
<th>ALS median range</th>
<th>Percentage with abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS-FTD-Q score</td>
<td>≥22</td>
<td>15(0-57)</td>
<td>32.1%</td>
</tr>
<tr>
<td>MiND-B total score</td>
<td>&lt;34</td>
<td>34(14-36)</td>
<td>39.4%</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>&lt;13</td>
<td>16(8-16)</td>
<td>9.1%</td>
</tr>
<tr>
<td>Apathy</td>
<td>&lt;9</td>
<td>11(4-12)</td>
<td>21.2%</td>
</tr>
<tr>
<td>Stereotypical behaviour</td>
<td>&lt;5</td>
<td>8(2-8)</td>
<td>7.6%</td>
</tr>
</tbody>
</table>
Correlation between cognitive and behavioral impairment and other clinical features

Multiple logistic regression analysis was used to investigate whether age, gender, years of education, disease duration at the time of testing and site of onset influenced the results of the ACE-III, FAB and ECAS cognitive tests. The detailed results are given in Supplementary 1 file. For ACE-III, age and years of education influence the results. One year increase in age can increase hazard odds of cognitive impairment on ACE-III testing by 5.3%, while one year increase in the years of school education can reduce hazard odds of cognitive impairment by 27%. There was no effect of site of onset, disease duration and gender on the results of ACE-III testing.

For ECAS executive function, one year increase in education can decrease 26% of ratio of cognitive impairment. The other clinical factors did not affect the test result.

For FAB, the site of onset affected the results. Compared with lower limb onset, people with bulbar onset of ALS had 61% less hazard odds ratio of cognitive impairment. There is no significant correlation between other variables and cognitive impairment as measured by FAB.

The effects of the clinical variables in ALS-FTD-Q and MiND-B are also presented in Supplementary 1 file. Age, gender disease duration and the relationship of the carer to the person with ALS have no significant effect on behavioral impairment.

The results of ACE-III and FAB in patients with and without positive family history of ALS and dementia are summarized in Supplementary 1 file. The presence of a positive family history of ALS or dementia had no significant effect on the cognitive impairment based on ACE-III and FAB results.
We assessed the correlation between disease severity measured by ALSFRS-R and cognitive function measured by ACE-III, FAB and ECAS by using Spearman correlation tests (Supplementary 2 file). There was no significant correlation. This indicates that cognition does not worsen as the disease becomes more severe.

We also tested the relationship between disease severity and behavioral testing. The Spearman correlation tests between ALS-FTD-Q or MiND-B and ALSFRS-R score are shown in Figure 2. There is a significant negative relationship between ALS-FTD-Q and ALSFRS-R score. There is a significant positive association between MiND-B and ALSFRS-R score. This indicates that behavioral impairment becomes worse as disease becomes more advanced.

1.4 Correlation with the survival time in cognitive and behavioral tests

We then investigated the effect on survival of cognitive and behavioral impairment measured by ACE-III, FAB, ALS-FTD-Q and MiND-B. The results for ACE-III, FAB and ALS-FTD-Q are shown in Figure 3. We first plotted Kaplan Meier survival curves. The survival curve of MiND-B is presented in Supplementary 3 file. There is a significant effect on survival of cognitive and behavioral impairment measured by ACE-III and ALS-FTD-Q. For cognitive impairment measured by FAB, there was an apparent effect, but this was not statistically significant. For behavioral impairment measured by MiND-B, there was no apparent effect on survival.

We then performed Cox regression analysis of the effects of cognitive and behavioral testing and other clinical features on survival. The Cox regression models of ACE-III, FAB, ALS-FTD-Q and MiND-B which included age, gender and site of onset are shown in Supplementary 3 file.

Patients with cognitive impairment defined by performance on ACE-III had significant shorter survival than the patients without cognitive impairment (P=0.0276),
with no additional effect of age or gender. There was no significant effect on survival time based on FAB (P=0.1746). The site of onset affected the survival time of patients with bulbar onset leading to a significant increase in comparison with the patients with lower limb onset after adjusting the age, gender and cognitive impairment (P=0.045).

Patients with behavioral impairment based on ALS-FTD-Q had significantly shorter survival than the patients without (P=0.0054). There are no significant differences between survival time of patients with and without behavioral impairment assessed with MiND-B (P=0.5685). The Cox regression model of MiND-B illustrates that other variables including gender, age, disinhibition, apathy and stereotypical behaviour do not impact the survival time of the patients.

1.5 The longitudinal study of cognition

We performed a longitudinal study of 37 people with ALS. This was to determine whether cognitive impairment develops over time in people who are cognitively normal on first testing. The longitudinal curves for 37 patients with different sites of onset based on ACE-III and FAB are presented in Figure 4 and Figure 5 respectively. The five domains of ACE-III serial tests results are shown in Supplementary 4 file. Some patients show a decline with serial testing, but most do not. There were fewer tests for the third and fourth time points due to death or advanced progression of the patients.

For statistical analysis, we used generalized estimating equations for the first two tests of ACE-III and FAB (Supplementary 4 file). The GEE analysis for ACE-III found that there was no significant difference between the first two consecutive tests (P=0.080). However, patients with bulbar onset of ALS have 3.25 higher ACE-III scores than the patients with lower limb onset over the time course (P=0.033).
The GEE analysis for FAB found no significant difference between the first two serial tests (P=1.00). For FAB, the site of onset did not affect the results of FAB performance over time (P=0.190).

Discussion

This study assessed cognition and behaviour in people with ALS by using simple clinic based testing. As comparison we used people with neuromuscular disease. In our cohort, the prevalence of cognitive impairment was approximately 30% and 14% based on ACE-III and FAB, respectively. This is similar to the rates of cognitive impairment found in previous studies [13, 16] (Table 2). The prevalence of behavioral impairment in our cohort is also just over 30% and approximately 40% based on ALS-FTD-Q and MiND-B. This is slightly less than that found by others [16, 30] (Table 2).

Previous studies compared people with ALS with normal healthy controls [12, 24] or had no controls. Our controls came from the same population as the people with ALS. None of the controls had evidence of disease of central nervous system, although two had mitochondrial myopathy, which could indicate a multi-system disorder. Both the average scores and the frequency of cognitive impairment were significantly different between the groups. In the ACE-III subdomains, significant differences were found in attention and language. Our study did not find fluency difference between the two groups, in contrast to previous studies that compared ALS patients with healthy controls [47, 48]. We note that the tasks and scoring of fluency vary among the different tools, reducing the ability to compare results.

We used multiple logistic regression analysis to investigate factors that influence the development of cognitive or behavioural impairment in ALS. We found that age and years of education affect the cognition measured by ACE-III. This is unsurprising
as age and years of education are known to affect cognitive performance in the healthy population [43] and to reduce the risk of dementia [49]. Age and lower levels of education have been observed in several previous ALS studies as risk factors for cognitive impairment [13, 21, 50], although others found no significant effect of these factors [35, 51, 52]. Using age corrected or education level corrected scoring guide would be desirable in future studies of cognition in ALS.

Previously, some studies have found that people with bulbar onset of ALS are more likely to have cognitive impairment than those with spinal onset [39, 53, 54], but others do not [33, 35, 55]. In our study, the site of onset had no effect of the presence of cognitive impairment as determined by the ACE-III, but site of onset influenced cognitive impairment based on FAB logistic regression results. In our cohort, the bulbar onset patients had decreased ratio of cognitive impairment and longer survival in the Cox regression model. This needs to be studied further.

In our cohort, the patients with cognitive or behavioral impairment based on ACE-III and ALS-FTD-Q had worse prognosis than the ones without. This is consistent with some previous studies [56, 57] but contrary to other studies [35, 58]. In our study, stereotypical behaviour, apathy, and disinhibition do not predict the survival of ALS patients, which is consistent with one previous study using the same scale [59]. However another study found that the apathy measured with the revised version of the Cambridge behavioral inventory (CBI-R) is good indicator of survival [60]. Classifying the patients into different level of cognitive and behavioral impairment could be better than using cutoff value in predicting the prognosis. A possible explanation for the worse prognosis of patients with cognitive impairment is that they have a disease that is more widespread and extensive than those with only motor symptoms. Another possibility is that those with cognitive impairment have different
causative genes than those without. The most prominent gene that causes ALS with cognitive impairment is C9orf72 [3, 4], but there are others such as TARDBP and fused in sarcoma (FUS) [61, 62].

In our longitudinal study, only a limited number of people had more than two tests. Because of variability in attendance at the clinic, the interval between two consecutive time points ranges from 6 months to 33 months. Therefore we used a generalized estimating equation (GEE) to investigate whether there is difference between first two serial tests. The GEE statistical model is very robust to abnormal distributions, missing data and heterogeneity in timing of measurement. No significant difference was found between the first two visits in both ACE-III and FAB, which suggests that the cognitive test performance is relatively stable, and these patients who are cognitively normal at first testing will remain so over time. However, more people with ALS are needed at later time points to clarify this.

Previous studies showed conflicting results. One study found that in bulbar onset patients, cognitive impairment was progressive over time [39], another found that 37% of patients developed cognitive deficit over a six month follow-up period [40], and another found that cognitive impairment was greater at the later stages of disease, when only 14% of patients had normal cognition [41], thus providing evidence that cognition is progressively affected in ALS. The previous serial studies of cognition are summarised in Table 8. If there were a progressive deterioration of cognition over time, this could be due to the spread of pathology from motor regions to other regions, through prion-like spread, as has recently been proposed [63]. However, the finding that some patients have cognitive impairment at presentation while others remain cognitively normal throughout disease would be more consistent with ALS being a heterogeneous disease [38, 64].
One weakness of this paper is that we have only limited genotyping. Another weakness is that we used simple screening tools that may not have detected subtle deficits. However, the tools that we have used are available for use in ALS clinics and provide evidence that some patients with ALS have cognitive impairment, which is a poor prognostic marker, that patients who are cognitively normal at onset show little evidence of deterioration over 6 months and possibly longer, and that age and education are risk factors for cognitive impairment in ALS.
Table 8 Summary of longitudinal studies of cognition in ALS

<table>
<thead>
<tr>
<th>Study</th>
<th>Number</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.J. Strong et al. [34]</td>
<td>8</td>
<td>Cognitive impairment in the patients with bulbar onset but with limb-onset appeared to progress over the time course.</td>
</tr>
<tr>
<td>K.M. Robinson et al. [65]</td>
<td>19</td>
<td>7 of 19 patients had a decline of cognition over time.</td>
</tr>
<tr>
<td>F.Trojs et al. [41]</td>
<td>74</td>
<td>Cognitive impairment was more serious in the advanced stage of ALS.</td>
</tr>
<tr>
<td>S.Abrams et al. [66]</td>
<td>20</td>
<td>No evidence of deterioration of cognition over time.</td>
</tr>
<tr>
<td>E.Kasper et al. [42]</td>
<td>93</td>
<td>No significant decline in executive function over time.</td>
</tr>
<tr>
<td>M.Kilani et al. [67]</td>
<td>18</td>
<td>No decline in cognitive function over 12 months</td>
</tr>
<tr>
<td>M.Elamin et al. [68]</td>
<td>98 for the second visit 48 for the third visit</td>
<td>Cognitive function declined faster in patients who were cognitively impaired at the first visit.</td>
</tr>
<tr>
<td>H.Schreiber et al. [69]</td>
<td>52</td>
<td>Cognitive deficits did not substantially decline on follow-up.</td>
</tr>
</tbody>
</table>

The list and the captions of Figures

1. Figure 1: Frequency distribution of ACE-III and FAB score in ALS and controls. A: Frequency distribution of ACE-III in ALS patients B: Frequency distribution of FAB in ALS patients. C: Frequency distribution of ACE-III in disease control D: Frequency distribution of FAB in disease control.
2. Figure 2: Correlation of behavioural testing with disease severity. A: ALS-FTD-Q correlation with ALSFRS-R. B: MiND-B correlation with ALSFRS-R. Significant negative correlation was found between ALS-FTD-Q score and ALSFRS-R score (P=0.0068). Significant positive correlation was found between MiND-B score and ALSFRS-R score (P=0.02). The solid red line and red curve line are the simple linear regression and its 95% confidence interval, respectively.

3. Figure 3: Survival curve of ACE-III, FAB and ALS-FTD-Q. A: Kaplan Meier survival curve of ACE-III B: Kaplan Meier survival curve of FAB C: Kaplan Meier survival curve of ALS-FTD-Q.

4. Figure 4: ACE-III longitudinal results in three different site of onset. The longitudinal curves were plotted in every patient according to different site of onset.

5. Figure 5: FAB longitudinal results in three different site of onset. The longitudinal curves were plotted in every patient according to different site of onset.
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Reference


R. Rusina, P. Ridzon, P. Kulist'ak, O. Keller, A. Bartos, M. Buncova, L. Fialova, F. Koukolik, R. Matej, Relationship between ALS and the degree of cognitive impairment,


Fig. 1
Fig. 2
Fig. 3
Fig. 4
Fig. 5
Highlights

- Comparison of cognitive and behavioral impairment between ALS patients and patients with neuromuscular disease.
- Multiple cognitive and behavioral tests were used in this study.
- Longitudinal study was done in the cognitive tests of ALS patients.