Depression in amyotrophic lateral sclerosis

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Abstract
Depression is an under-recognized comorbidity associated with amyotrophic lateral sclerosis (ALS). The goals of this study were to prospectively estimate the prevalence of depression and other ALS related symptoms and to study the impact of depression on enrollment in research studies. One hundred and twenty-seven people with ALS completed the ALS Depression Inventory (ADI-12) and answered questions about ALS related symptoms and research study enrollment preferences. Demographics, ALS symptoms, medications, functional status, and research enrollment were compared between depressed and non-depressed patients. Results showed that the prevalence of mild and severe depression was 29% and 6%, respectively. More than one-third of our ALS patients were receiving anti-depressants to treat depression, sialorrhea, and pseudobulbar affect. Depression prevalence was not correlated with disease duration or progression. Except for anxiety, none of the ALS related symptoms predicted depression. The presence of depression did not have an effect on the decision to enroll in research studies. In conclusion, major depression is less common in our ALS cohort than in the general population. The diagnosis of depression can be masked by some ALS related symptoms and it has no impact on enrollment in ALS clinical trials.

Keywords
ALS; depression; management; symptomatic; enrollment

Introduction
The prevalence of depression in the ALS population is reported at 4 – 56% depending on the assessment measure (1 – 6). The presence of depression has a negative effect on quality of life in ALS (7 – 9) and psychological stress is associated with a greater risk of mortality in ALS patients (10). The impact of depression on enrollment is unknown and it is unclear whether patients with depression have been reluctant to enroll in previous studies of depression in ALS, thus underestimating the true prevalence of depression in this condition.

Enrollment is a key factor that determines the feasibility and conduct of clinical trials. It is estimated that ALS clinical trials enroll less than 25% of the total ALS population (11). Patient stress and depression were significant factors that affected enrollment in the Cardiac Arrhythmia Suppression Trial (CAST) (12). The impact of depression on ALS patients' decision to enroll in clinical trials is unknown.

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The purpose of this study was to estimate the prevalence of ALS related symptoms including depression and anti-depressants use in a large cohort of people with ALS and to explore the relationship between depression and enrollment in ALS research studies.

Materials and methods

Study design and population

This cross-sectional study was approved by the Massachusetts General Hospital (MGH) Institutional Review Board (IRB). Eligible participants were patients with a clinical diagnosis of ALS defined as suspected, possible, laboratory-supported probable, probable, or definite ALS (13). All eligible patients seen at the MGH ALS multidisciplinary clinic between March 2009 and March 2010 were asked to participate. Patients who were new to our clinic and came only for one second-opinion visit were excluded.

Study procedures

While in clinic, all eligible patients were asked to complete the ALS Depression Inventory (ADI-12) (2) and to answer questions about ALS related symptoms, depression history, and research enrollment preferences. Patients who declined to participate were not asked again at subsequent clinic visits.

ALS Depression Inventory (ADI-12)—This is a self-reported questionnaire developed specifically to screen for depression in ALS (2). It describes mood, anhedonia and energy, and does not refer to motor related symptoms seen in ALS. It requires participants to estimate how much they agree with 12 statements with respect to their mood in the last two weeks. Scores range from ‘12’ (best possible) to ‘48’ (worst possible) with scores between 23 and 29 indicating mild depression and those above 30 indicating severe depression (2). The ADI-12 was validated against the structured clinical interview for DSM-IV (SCID), as the gold standard for diagnosis of depression (14).

ALS related symptoms—Participants were asked to answer ‘yes’ or ‘no’ to the presence of the following ALS symptoms with respect to the last two weeks: cramps, stiffness, shortness of breath, swallowing difficulty, insomnia, loss of appetite, increased saliva, uncontrolled laughing or crying, fasciculations, anxiety, fatigue, and pain.

Enrollment preferences—Enrollment preferences were defined as the percentage of eligible subjects that are willing to participate in a certain study. Participants were asked to answer ‘yes’ or ‘no’ to the following questions: “Are you currently participating in any ALS research study?”, “Are you interested in participating in a non-therapeutic ALS research study focused on understanding ALS?”, and “Are you interested in participating in a research study using a new experimental medication?”. Actual enrollment in any ALS research study was recorded at the same visit. There was at least one ALS clinical trial actively recruiting at our center throughout the duration of this study.

The revised ALS functional rating scale (ALSFRS-R) and forced vital capacity (FVC) were obtained on the same visit day. Demographics, and a current medication list and their indications were obtained from clinic charts.

Statistical analysis

The standard cut-offs for ADI-12 scores of 23 to 29, and greater than or equal to 30, were used to determine the presence of mild depression and severe depression, respectively. Means and standard deviations for normally distributed continuous variables were compared between depressed and non-depressed subjects using linear regression models that account
for potential confounders such as age, gender, disease duration, time from symptom onset to ALS diagnosis, site of ALS onset, and riluzole use. The Bonferroni method was used to correct for multiple testing. Time variables, such as disease duration and time from symptom onset to ALS diagnosis, were compared between depressed and non-depressed subjects using Cox regression models. The $\chi^2$ test was used to compare categorical variables.

Results

Prevalence of depression in ALS

Of 131 eligible patients with ALS, 127 (97%) completed the questionnaire and are described in Table I. Nine participants had pure upper motor neuron disease (7%), one had pure lower motor neuron disease (0.7%), and 117 participants had both upper and lower motor neuron signs (92%). The mean ADI-12 score was 20.3 ($\pm$ 5.7). Using the standard cut-offs, 29% of the participants had mild depression and 6% had severe depression.

Demographics, disease duration, and functional status

Age, ALS family history, riluzole use, site of disease onset, time from symptom onset to ALS diagnosis, and disease duration were not significant predictors of mild or severe depression. Men were more likely to be depressed compared to women ($p = 0.01$). Functional status measured by ALSFRS-R ($p = 0.7$) and respiratory status measured by FVC ($p = 0.3$) were not different between depressed and non-depressed participants.

ALS related symptoms

The prevalence of 11 different ALS symptoms in depressed and non-depressed participants is shown in Figure 1. Dyspnea ($p = 0.03$), insomnia ($p = 0.02$), anxiety ($p = 0.0006$), pain ($p = 0.004$), and fatigue ($p = 0.004$) were more likely to be present in participants with mild or severe depression. All $p$-values are adjusted for age, gender, disease duration, time from symptom onset to ALS diagnosis, site of onset, and riluzole use. Only anxiety ($p = 0.005$) was an independent predictor of depression when other significant ALS related symptoms were added to the regression model.

Anti-depressants use

Thirty-eight percent of participants who completed the questionnaire were treated with anti-depressants. Half of those participants (19%) were using anti-depressants specifically to treat depression, and the other half were using anti-depressants to treat sialorrhea, pseudobulbar affect, or insomnia. Serotonin-specific reuptake inhibitors (SSRIs) were the most commonly prescribed medications for depression (Figure 2).

Enrollment in research studies

ADI-12 measurements and enrollment data were obtained from 97% of eligible patients. Of those 97%, the majority of participants (83%) were interested in enrolling in ALS research studies. More than half of the participants were interested in enrolling in a clinical trial testing new treatments for ALS. Thirty-nine percent of participants were interested in enrolling in non-interventional studies. The actual enrollment rate in any ALS research study was 32%. Gender, age, disease duration, ALSFRS-R, FVC, and depression had no impact on enrollment preferences or actual enrollment rate.
Discussion

The prevalence of mild and severe depression in patients with ALS was 29% and 6%, respectively. The prevalence of a major depressive disorder in the general population is about 10% (15), which is higher than in our ALS cohort. One possible explanation for lower rates of severe depression in ALS is that more than one-third of ALS patients are receiving anti-depressants to treat salivary, pseudobulbar affect, and insomnia. Referral bias of more motivated and less depressed patients to multidisciplinary clinics is another possible explanation for the relatively lower rate of depression in our sample.

Disease duration and physical impairment were not predictors of depression in our cohort, suggesting that depression is not related to advanced ALS or to approaching end of life. The male gender predominance of depression in our ALS cohort (p 0.01) contrasts the female predominance of depression in the general population.

Research enrollment in orphan diseases such as ALS is key for efficient testing of new treatments. In our study, 97% of eligible patients completed the ADI-12 and answered the enrollment questions. This high enrollment rate in this study was intentional and expected from the study design asking patients to complete one page of questions while in the waiting room, a process that is routinely performed in many clinics. We found that even though 83% of patients with ALS were open to enrolling in research studies, less than one-third did actually go on to enroll, which is close to previously estimated ALS clinical trials enrollment of 25% (11). Cancer trials have similar enrollment rates that are highly variable between different trials: 5% in lung cancer trials and 45% in lymphoma trials (16,17). Enrollment in ALS trials does not appear to be affected by trial factors, such as eligibility criteria or the use of placebo (11). We were able to show that patient factors such as age, gender, disease duration, functional status, and depression had no effect on ALS patients’ decisions to enroll in clinical trials.

Finally, ALS related symptoms may mask the diagnosis of depression due to the overlap in symptoms. The prevalence of ALS related symptoms was identified in this study and, except for anxiety which is a known symptom of depression, none of these ALS related symptoms appeared to contribute to depression.

Acknowledgments

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References


Figure 1.
Comparison of ALS symptoms in participants with and without depression. *P < 0.05 after adjusting for potential confounders. Fascics: fasciculations; PBA: pseudobulbar affect.
Figure 2.
Anti-depressant categories used in ALS. A) Percentages of anti-depressants prescribed for any indication. B) Percentages of anti-depressants prescribed specifically to treat depression. TCA: tricyclic antidepressants; SSRI: selective serotonin reuptake inhibitors; SRI: serotonin reuptake inhibitors; SNRI: serotonin-norepinephrine reuptake inhibitors; DRI: dopamine reuptake inhibitors.
### Table I

Patient characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Total n = 127</th>
<th>Depressed n = 45 (35%)</th>
<th>Non-depressed n = 82 (65%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ADI-12 Score (points)</td>
<td>20.3 (±5.7)</td>
<td>26.7 (±3.7)</td>
<td>16.8 (±2.7)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>61 (±12)</td>
<td>59 (±12)</td>
<td>62 (±12)</td>
<td>0.3</td>
</tr>
<tr>
<td>Mean time from symptom onset to diagnosis (weeks)</td>
<td>80 (±104)</td>
<td>84 (±100)</td>
<td>77 (±106)</td>
<td>0.8</td>
</tr>
<tr>
<td>Mean time since diagnosis (weeks)</td>
<td>78 (±110)</td>
<td>79 (±114)</td>
<td>77 (±109)</td>
<td>0.9</td>
</tr>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>58%</td>
<td>45%</td>
<td>55%</td>
<td>0.01*</td>
</tr>
<tr>
<td>female</td>
<td>42%</td>
<td>23%</td>
<td>77%</td>
<td></td>
</tr>
<tr>
<td>Family history (%)</td>
<td>9%</td>
<td>9%</td>
<td>9%</td>
<td>0.9</td>
</tr>
<tr>
<td>Bulbar onset (%)</td>
<td>24%</td>
<td>21%</td>
<td>26%</td>
<td>0.5</td>
</tr>
<tr>
<td>ALSFRS-R (score)</td>
<td>33 (±8)</td>
<td>33 (±7)</td>
<td>32 (±9)</td>
<td>0.7</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>79% (±25)</td>
<td>75 (±21)</td>
<td>81 (±27)</td>
<td>0.3</td>
</tr>
<tr>
<td>Riluzole use (%)</td>
<td>67%</td>
<td>64%</td>
<td>68%</td>
<td>0.7</td>
</tr>
<tr>
<td>Anti-depressant use (%)</td>
<td>38%</td>
<td>49%</td>
<td>32%</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Standard deviations provided in parentheses.