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A pilot study of the prevalence of psychiatric disorders in PLS and ALS

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Abstract

The prevalence of psychiatric disorders in primary lateral sclerosis (PLS) is currently unknown. In the present study, we compared the prevalence of psychiatric illness in patients with PLS and amyotrophic lateral sclerosis (ALS). We hypothesized that if the psychosocial stress of motor neuron disease predisposes patients to depressive disorders, patients with ALS (with a poorer prognosis and more disability than patients with PLS) should have a higher prevalence of depressive disorders than patients with PLS. We administered the gold standard of psychiatric assessment, the SCID, to 19 PLS and 13 ALS patients. We found a prevalence of current depressive disorders in PLS patients that was, by a nonsignificant trend, lower than that of ALS patients. The prevalence of current depressive disorders in the ALS patients was higher than previously reported and similar to that observed in non-neurological medical disorders. Other psychiatric disorders were rare. In conclusion, depressive disorders were the most commonly observed psychiatric disorders in both PLS and ALS. By a non-significant trend, the PLS patients had a lower current prevalence of depressive disorders than the ALS patients. These data are consistent with the hypothesis that the psychosocial stress of MND is a risk factor for depression.

Keywords

PLS; ALS; psychiatric disorder; depression; major depressive disorder

Introduction

Amyotrophic lateral sclerosis (ALS) and primary lateral sclerosis (PLS) are motor neuron diseases (MNDs) with distinct clinical phenotypes. While ALS is the most common motor

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neuron disease, affecting both the upper motor neurons in the cerebral cortex and lower motor neurons in the spinal cord and brainstem (1), PLS is a rarer condition, primarily affecting upper motor neurons (2–6). Although ALS was first recognized as a motor neuron disorder, more recent studies have shown pathological changes beyond the motor areas of the brain, including in the dorsolateral prefrontal cortex (7,8), a brain area associated with an increased incidence of Major Depressive Disorder in patients with brain injury (9). In the current study, we compare the prevalence of psychiatric disorders in ALS and PLS using the gold standard of psychiatric diagnosis – the Structured Clinical Interview for DSM-IV [Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition] Diagnosis – Patient Edition (SCID) (10).

Consistent with involvement of frontal cortex, a proportion of patients with ALS develop cognitive impairment associated with frontal lobe dysfunction. Approximately 50% of patients with ALS show some frontal cognitive impairment (11–13) and up to 15% meet full criteria for frontotemporal dementia (12). The degree of extramotor frontal cortical involvement in PLS remains unclear (14–16).

To date there are no published studies of psychiatric symptomatology in PLS patients. The literature on the prevalence of depressive disorders in ALS suffers from significant heterogeneity in assessment tools (Table I). Rates of depression in this population, based on published studies, range considerably from near 0% to 75%. In the 13% of ALS patients involved in these studies who have had a diagnostic interview, the prevalence of major depression has a narrower range, from 0 to 11%, lower than that reported in medically ill patients (31–33). However, some researchers have hypothesized that this apparent ‘protective’ effect of ALS on depression may reflect the anosodiaphoria often associated with frontal lobe dysfunction (34). In the current study, dementia and pseudobulbar affect were evaluated to exclude these potential confounds to a correct psychiatric diagnosis.

Having a serious medical illness is a risk factor for the development of depressive disorders (33). However, the prognoses of ALS and PLS are significantly different. The median survival time in ALS from the onset of symptoms about is 3–5 years, while in PLS the survival time is often several decades (1–6). Thus, one could hypothesize that if the psychosocial stress of motor neuron disease predisposes patients to depressive disorders, patients with ALS should have a higher prevalence of depressive disorders than patients with PLS. If, however, the prevalence of depressive disorders between the patients with ALS and PLS is similar, it suggests that they share a biological predisposition, whether it stems from upper motor neuron (UMN) impairment or from extramotor frontal impairment.

Material and methods

Patients

Subjects were seen as part of an ongoing research study to better characterize MND in the electromyography section of the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH) in Bethesda, Maryland. Patients were referred by outside neurologists or self-referred. An informant (a spouse, family member, or friend) accompanied the subject in most cases or was contacted on the telephone. During

their visit, the patients received a complete neurological evaluation by a neurologist (MKF) including an EMG, if not performed in a previous visit. All subjects gave written informed consent for the protocol. All aspects of the study and the consent procedure were approved by the NINDS IRB. Demographic and clinical data on the patients are presented in Table II. In Table II, the number of patients on antidepressant medications is listed. All of these patients were on an SSRI, one was also on bupropion and one was also on modafinil.

PLS patients—Patients with PLS met the diagnostic criteria for pure PLS (6). See Table II for characteristics of these patients including a measure of symptom severity (the ALS Functional Rating Scale-Revised).

ALS patients—Patients with ALS fulfilled the revised El Escorial criteria (35) for probable or definite ALS. See Table II for characteristics of these patients. More patients with PLS than ALS were studied because the NINDS program from which the patients were recruited (the electromyography section) specializes in PLS and so more PLS patients were available to recruit.

Measures

A SCID (10) was performed on all patients by a psychiatrist trained to administer the SCID (EDH). In addition, the patients and informants received a clinical interview designed to screen for dementia in the patient from a clinician who specializes in the evaluation of patients with dementia (EDH). The informant interview was also used to assess for psychiatric and neurologic symptoms not reported or minimized by the patient. The interview with the patient and the interview with the informant were performed separately. The Folstein Mini-Mental State Exam (MMSE) (36), a brief test of general cognition, was performed on each patient. As has been noted (37), the MMSE is likely not sensitive to detect frontal lobe dysfunction. Therefore, the Frontal Assessment Battery (FAB) (38), a bedside test of frontal lobe dysfunction, was also performed. One item of the FAB, lexical fluency, was omitted to avoid repetition with a lexical fluency measure obtained in a different part of the evaluation. All of the patients received the SCID. Three patients did not receive the MMSE, and two did not receive the FAB.

Results

Psychiatric assessment

The results of the psychiatric evaluation are presented on Table II. Psychiatric diagnoses are listed if the patient met full criteria for an Axis I disorder. Diagnoses are reported as ‘lifetime’ (i.e. did they meet criteria at some point in their life) and ‘current’ (i.e. did the patient meet criteria at the time of evaluation). For example, if a patient suffered from Major Depressive Disorder (MDD) at the time of evaluation, he or she would be reported as both lifetime and current MDD. Note that a single patient could have more than one Axis I diagnosis. The ‘current other depressive disorder category’ included current minor depression, dysthymia, and adjustment disorder with depressed mood.

Depressive disorders were the most commonly observed psychiatric disorders in our patients (Table II). Similar numbers of patients with PLS and ALS had diagnoses of lifetime MDD.

However, a smaller proportion of patients with PLS than patients with ALS suffered from current depressive disorders (3 of 19 versus 6 of 13; $\chi^2 = 3.52$, $df = 1$, two-tailed $p = 0.06$). A large number of patients had lifetime MDD (7 of 19 for PLS and 7 of 13 for ALS). In a proportion of these patients (5 of 7 for the PLS and 3 of 7 for ALS), MDD preceded their MND.

Cognition

In Table II, the MMSE is reported as points lost because several of the patients could not perform some of the MMSE items due to motor difficulties and so these items were omitted from scoring. On the basis of clinical interview with the patients and informants, none of the patients met criteria for dementia (10), or had symptoms of gross frontal lobe dysfunction (personality changes, inappropriate behaviors, aphasia, emotional withdrawal, apathy, hyperphagia, etc.) (39). One PLS patient was given a diagnosis of mild cognitive impairment (MCI), but this was an amnesic/dysexecutive type. Overall, the PLS patients lost significantly fewer points on the MMSE than the ALS patients (PLS mean = 0.9, SD = 0.9 points; ALS mean = 2.6, SD = 1.9 points; Mann-Whitney $U = 47.0$, $p < 0.05$). At the age and education level of our patients, the published norms for the MMSE are a mean of one point lost and a standard deviation of 1.5 points (40). Thus, the PLS patients are at the norm of the MMSE, while the ALS patients are one standard deviation below the norm. The PLS patients did not score significantly different than the ALS patients on the FAB (PLS mean = 13.9, SD = 1.1; ALS mean = 13.0, SD = 2.4; Mann-Whitney $U = 82.5$, $p = 0.45$). The norms of the FAB (omitting the lexical fluency item) for normal controls are a mean of 14.3 and a standard deviation of 0.8 (38). Thus the PLS patients performed similarly to the healthy subjects on the FAB, and the ALS patients were greater than one standard deviation below the healthy subjects. The FAB item on which the ALS patients, as a group, lost the most points was item no. 5 on the FAB: Go–No–Go (inhibitory control). Although the ALS patients performed below the mean of the normal controls on the FAB, their performance was much better than that observed with FTD patients (mean on the FAB with all items included of 7.7) (38).

Discussion

The prevalence of current depressive disorders observed in the PLS patients was less, in a non-significant trend, than that of ALS. The point prevalence of current MDD in ALS (3 of 13 or 23%) was higher than that reported by previous studies that used a clinical interview (Table I). Also, the prevalence of all current depressive disorders was higher in ALS (6 of 13 or 46%) than reported in most previous studies (Table I). The prevalence of depressive disorders we found in our ALS patients is comparable to that for other medical disorders (31–33), including Alzheimer's disease (41).

One could hypothesize that if the psychosocial stress of disability and a fatal illness predispose patients to depression, ALS should have a greater prevalence of depression than PLS, whereas if they share a neurobiological predisposition (UMN or extramotor frontal dysfunction), they should have similar prevalences of depression. The finding that our ALS patients had a prevalence of depressive disorders similar to non-neurologic medical

disorders suggests that, in our small sample, ALS does not appear to be protective against depression, nor to put patients at risk for depression, compared to comparable disorders. The PLS patients generally have a better prognosis and less rapid progression to disability than the ALS patients and they had a lower prevalence of current depressive disorders. These findings are compatible with a model of psychosocial stress, a potentially fatal illness, and disability predisposing patients to depressive disorders rather than a model of a direct biological cause of depression in PLS or ALS. A less likely, but alternative, explanation is that greater apathy in the ALS patients could ‘temper’ the effects of a reactive depression.

An interesting finding is that the prevalence of depressive disorders preceding MND is unexpectedly high in both groups (8 of 31, overall). This is considerably higher than the prevalence of depressive disorders in the general population (42). The reason for this is unclear. It could represent a selection bias; for unknown reasons MND patients with previous histories of depression could be more likely to pursue participation in this research project at NIH. Alternatively, depressive symptoms could reflect an MND prodrome in some patients that occurs prior to overt motor symptoms. A depressive prodrome has been identified for other neurodegenerative disorders including Alzheimer's disease and Huntington's disease (43,44).

The prevalence of frontotemporal dementia in our patients is lower than has been reported for ALS (11,12). A possible explanation is that patients with frontotemporal dementia in addition to MND were less able or willing to come to NIH and participate in this type of research. On the MMSE the ALS patients lost significantly more points than the PLS patients, although the mean number of points lost on the MMSE by the ALS patients was low.

In summary, using the gold standard of psychiatric assessment in a small sample of patients, we found a point prevalence of all active depressive disorders that was, by a non-significant trend, lower for PLS than ALS patients and higher in ALS patients than previously reported. The PLS patients had a similar prevalence of lifetime MDD to the ALS patients. Both groups had a high prevalence of MDD that preceded their MND. By clinical assessment none of the patients was demented. These findings suggest that the association between depressive disorders and MND may be attributable to patients having a fatal illness and disability rather than a direct effect of the illness on mood. These findings should be expanded and explored in larger groups of MND patients.

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Table I

Previous studies on the prevalence of depressive disorders in patients with ALS.

| Study | n | Assessment tool | Clinical criteria | Prevalence of depression |
|----------------------------|----------|---|--------------------------|---------------------------------|
| Houpt et al., 1977 (17) | 40 | Structured clinical interview | no | 35% |
| Schiffer et al., 1984 (18) | 84 | Chart review | no | Less than 5% |
| Newrick et al., 1984 (19) | 45 | Unstructured clinical interview | no | 7% |
| Bocker et al., 1990 (20) | 16 | Self-report | no | 75% |
| Hogg et al., 1994 (21) | 52 | Rating scale | no | 44% |
| Tedman et al., 1997 (22) | 40 | Rating scale | no | 30% |
| Moore et al., 1998 (23) | 18 | Rating scale | no | 23% |
| Ganzini et al., 1998 (24) | 100 | Structured clinical interview | yes | MDD = 11% |
| Rabkin et al., 2000 (25) | 56 | Structured clinical interview (SCID) | yes | MDD = 2% |
| Miller et al., 2000 (26) | 1707 | Self-report | no | 31.3% |
| Bungener et al., 2005 (27) | 27 | Semi-structured clinical interview | yes | MDD = 0% |
| Rabkin et al., 2005 (28) | 80 | Clinical interview (Patient Health Questionnaire) | yes | MDD = 9% |
| Wicks et al., 2007 (29) | 190 | Two self-report measures | no | 56%; 13% |
| Hammer et al., 2008 (30) | 39 | Structured clinical interview (SCID) | yes | MD = 10% |

Table II

Characteristics and psychiatric diagnoses of the ALS and PLS patients.

| | ALS | PLS |
|--|-------------------|-------------------|
| <i>n</i> | 13 | 19 |
| Age | 57.6 (12.5) years | 57.7 (6.7) years |
| Education | 14.4 (2.7) years | 15.6 (2.6) years |
| Handedness | 12 Right, 1 Left | 16 Right, 3 Left |
| Onset region | All limb | 17 limb, 2 bulbar |
| ALSFRS-R | 35.1 (7.5) | 38.3 (4.7) |
| Pseudobulbar affect | 2 | 11 |
| Time since symptom onset | 2.6 (1.4) years | 11.5 (5.9) years |
| Interval to diagnosis | 1.7 (1.4) years | – |
| MMSE | 2.6 (1.9) | 0.9 (0.9) |
| FAB | 13.0 (2.4) | 13.9 (1.1) |
| Taking antidepressant medication | 3 | 7 |
| Current MDD | 3 | 1 |
| Lifetime MDD | 7 | 7 |
| Current MDD in partial remission | 1 | 1 |
| Current substance-induced mood disorder | 0 | 0 |
| Lifetime substance-induced mood disorder | 0 | 1 |
| Current other depressive disorder | 2 | 1 |
| MDD prior to MND | 3 | 5 |
| Current EtOH abuse | 1 | 0 |
| Lifetime EtOH abuse | 3 | 2 |
| Current phobia | 2 | 0 |
| Lifetime phobia | 2 | 0 |
| Current panic disorder | 0 | 0 |
| Lifetime panic disorder | 0 | 2 |
| Current PTSD | 0 | 0 |
| Lifetime PTSD | 0 | 2 |
| Current MCI | 0 | 1 |
| Lifetime MCI | 0 | 1 |

Values are presented as means with the standard deviation in parentheses. ALSFRS-R = ALS Functional Rating Scale-Revised; MDD = major depressive disorder; MMSE = Folstein Mini-Mental State Exam; FAB = Frontal Assessment Battery; PTSD = post-traumatic stress disorder; MCI = mild cognitive impairment. We did not record time interval to diagnosis for the PLS patients