Depression before and after diagnosis of multiple sclerosis

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Depression was examined in 45 patients evaluated within 2 months of diagnosis of MS. At the time of testing, 40% of the MS sample met the diagnostic criteria for major depression, 22% had adjustment disorder with depressed mood and 37% showed no evidence of mood disorder. Personal and family history of depression in patients with MS was also examined and compared with a sample of patients with chronic low back pain (CLBP) who were matched for age, gender, marital and employment status and current level of depression. Fifty-two percent of patients with MS reported experiencing a depressive episode before the onset of MS compared with 17% of patients with CLBP (P<0.001). Sixteen patients with MS (33%) reported family history (parent or sibling) of treatment for depression compared with seven (13%) of patients with CLBP (P<0.05). MS patients with a history of depression reported more initial symptoms than MS patients without a history of depression. Clinical and theoretical implications of the findings are discussed.

Keywords: depression; diagnosis; chronic pain

Introduction

To date, several investigations have addressed the relation between emotional distress and MS.1–4 The prevalence of depressive illness in patients with MS exceeds that of the general population, and may even exceed the prevalence of depression in other chronic illnesses.1,4 Point prevalence rates of depression in samples of MS patients have ranged from 15% to 36%, and lifetime prevalence rates as high as 54% have been reported.5,8,9

There are also indications that depression may occur before the development of symptoms of MS.5,7–12 As early as 1868, Charcot11 commented on the role of emotional factors as initiators of MS:

... the circumstances most commonly assigned as causes of this disease, by patients, appertain to the moral order – long continued grief or vexation...

Despite anecdotal reports, the association between depression and the onset of MS remains unclear. Many early studies predated the development of standardized assessment procedures, and it is unclear whether methods used could reliably distinguish between clinically significant depression and non-pathological adjustment reactions.7,10–12 Even when standardized assessment procedures have been used, patients have been required to report on periods of emotional distress that may have occurred more than 10 years before testing.5,9

In the present study, the relation between MS and past history of depression was addressed by comparing newly diagnosed MS patients with a sample of patients with chronic low back pain (CLBP) who were matched for current level of depression. Patients with CLBP were chosen as controls since this condition is also associated with disabling physical symptoms, high rate of unemployment and a high rate of depressive illness.10,15 Two important differences between the two groups include the risk for major neurological impairment, which is greater for MS patients, and pain, which is more frequent and severe in CLBP patients. If patients with MS are more likely to have a past history of depression than CLBP patients who are matched for current depression, the data would strongly suggest an association between the pathophysiology of MS and depression, and not simply a reaction to diagnosis.

The present research had three primary objectives:

1. To examine the prevalence of depressive illness in newly diagnosed MS patients.

2. To compare personal and familial history of depression in patients with MS and a sample of patients with CLBP matched for current level of depression.

3. To examine differences in physical symptoms between MS patients with and without a history of depression.

Methods

Sample

The sample consisted of 46 (36 women, ten men) consecutive new referrals to the MS Clinic at the Ottawa General Hospital. All patients had a diagnosis of clinically probable or definite MS according to the criteria of Posner et al.10 Diagnoses were made by one of four neurologists, and illness severity was assessed by the Expanded Disability Status Scale (EDSS).17

Patients were included in the study only if they had not previously been given a diagnosis of MS. One patient was diagnosed with bipolar disorder, and was not considered in statistical analyses.

Forty-five patients with CLBP were drawn from the medical records of the Pain Clinic at The Rehabilitation Centre in Ottawa to serve as controls. For each MS patient, a CLBP patient was selected of the same gender, age (±2 years), level of education (±2 years), employment status and diagnosis of depression. The population of CLBP patients from which controls were drawn is described in greater detail in a separate paper.18

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Procedure
All new patients referred to the MS Clinic were contacted by the clinic coordinator within 6–8 weeks of their diagnosis, and were asked to participate in the research. Patients were then contacted by the project assistant and scheduled for a clinical interview with one of three clinical psychologists. The Diagnostic Interview Schedule, Affective Syndromes (DIS)\(^{18}\) was used to assess depressive illness, and diagnoses of depressive illness were made according to DSM-III-R criteria.\(^{20}\) Fatigue was considered a symptom of depression only if it was present every day, throughout most of the day, regardless of the level of activity or fluctuations with temperature changes. For both the MS and CLBP samples, the structured interview inquired about past history of depression including the patients' retrospective reports of symptoms sufficient to meet the diagnostic criteria for major depression, personal history of treatment for depression and history of treatment of depression in family members.

The Beck Depression Inventory (BDI)\(^{21}\) was used as an index of severity of depression. The BDI has been standardized on psychiatric and non-psychiatric samples, and has been recommended for the measurement of depressive symptoms in medical patients.\(^{2,21}\) Patients with MS were also asked to report the nature and number of their first neurological symptoms. Initial symptoms were classified into the following categories: muscle weakness and fatigue; numbness and tingling; vision and speech problems; muscle spasms; dizziness or vertigo; bowel and bladder problems; and cognitive and emotional difficulties. Patients with MS also completed measures of coping and marital functioning; the data on these measures will be the subject of a future report.

Results
Comparison of samples
Demographic information on the two patient samples is presented in Table 1. The mean age of the MS sample was 34.4 years and of the CLBP sample was 35.5 years. In each sample, 28 (60%) patients were married and 23 (50%) were employed. Both patient samples had a duration of illness, defined as the time since the diagnosis, of less than 2 months. However, the patient samples differed with respect to the time since the onset of first symptoms. MS patients reported that their first symptoms began on average 2.9 years before diagnosis, while CLBP patients reported that their pain symptoms began 4.6 years before diagnosis.

Prevalence of depression
In the MS sample, 40% (18/46) of patients met the DSM-III-R criteria for major depression. Twenty-two per cent (10/46) met the criteria for adjustment disorder with depressed mood, one patient was diagnosed with bipolar disorder and 37% (17/46) did not satisfy the criteria for any affective disorder. Four of the 18 patients with major depression satisfied the criteria for melancholic type (e.g. depression with early morning awakening and diurnal mood variation). The DSM-III-R diagnosis of major depression with melancholia is similar to what has previously been referred to as endogenous depression. While the diagnosis of major depression (without melancholia) may be compared with reactive depression, within the DSM-III-R classification no assumption is made about the precipitants of depression. In other words, a symptom profile reflecting prominent vegetative symptomatology is the distinguishing feature of major depression with or without melancholia, not the presumed organic or psychological basis of the depression. There were no cases of dysthymia. There was no significant association between sex and diagnosis of depression (\(\chi^2=0.68, P<0.70\)).

Twelve of the 18 patients with a diagnosis of major depression reported that the onset of their current depressive episode followed shortly after the diagnosis of MS, two patients reported that the onset of their current episode was less than 2 years before diagnosis and four patients reported that they had been experiencing chronic depression for several years before the onset of initial symptoms of MS. The patient with bipolar disorder reported that the onset of manic depressive illness occurred a few weeks before the diagnosis of MS and reported attempting suicide following the diagnosis of MS. No other patient reported attempting suicide.

History of depression
Data relevant to personal and family history of depression are presented in Table 2. In these analyses, MS patients were compared with the sample of CLBP patients, matched for current depressive symptomatology. Eighteen patients with CLBP were selected with a current diagnosis of major depression. However, there were no cases of adjustment disorder in the pool from which the CLBP sample was drawn. In order to

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic characteristics of patients with MS and CLBP</th>
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<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>34.4 (7.1)</td>
</tr>
<tr>
<td>Male/female</td>
<td>10/35</td>
</tr>
<tr>
<td>Married (%)</td>
<td>64</td>
</tr>
<tr>
<td>Employed (%)</td>
<td>53</td>
</tr>
<tr>
<td>Time since symptom onset (mean years)</td>
<td>2.9 (3.9)</td>
</tr>
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</table>

Values in parentheses are standard deviations

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<tr>
<th>Table 2</th>
<th>History of depression in patients with multiple sclerosis compared with patients with chronic low back pain</th>
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<tr>
<td>Multiple sclerosis</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>Self-reported history of depression</td>
<td>51</td>
</tr>
<tr>
<td>Previously treated for depression</td>
<td>23</td>
</tr>
<tr>
<td>Family history of depression</td>
<td>36</td>
</tr>
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Group comparisons were made using the chi-square test: *\(P<0.001\), **\(P<0.05\)
provide matched controls for MS patients with adjustment disorder, ten CLBP patients who did not have a diagnosis of depressive illness were selected with BDI scores within two points of MS patients with adjustment disorder.

Overall, 51% of patients with MS reported experiencing a depressive episode before diagnosis of MS compared with 17% of patients with CLBP ($\chi^2=11.0, P<0.001$). Ten patients with MS (22%) reported receiving treatment for depression before the diagnosis of MS compared with three (7%) patients with CLBP ($\chi^2=4.4, P<0.05$). Sixteen patients with MS (35%) reported a family history (parent or sibling) of treatment for affective illness compared with seven (15%) of patients with CLBP ($\chi^2=4.7, P<0.05$).

In the MS sample, 4 of the 16 patients with a family history of affective illness indicated that their relative had been treated for manic depression, and three others indicated that their relative had attempted suicide; none of the CLBP patients reported a family history of manic depression or family history of suicide attempts.

A personal history of prior depression was significantly more frequent in MS patients with a current diagnosis of major depression (72%) than in patients with no affective disorder (35%) ($\chi^2=4.8, P<0.05$), but not significantly more frequent than in patients with adjustment disorder (40%) ($\chi^2=2.6, P<0.10$). Patients with major depression were more likely to report a family history of depressions (33%) than patients with adjustment disorder with depressive mood (40%) ($\chi^2=0.9, NS$) or patients with no affective disorder (35%) ($\chi^2=0.8, NS$).

The temporal relation between the first episode of depression and initial symptoms of MS was examined in the subsample of patients who were either currently experiencing their first major depressive episode (n=5) or who reported a history of major depression (n=23). These data must be interpreted cautiously since they are based on patients’ ability to accurately remember initial symptoms and to accurately distinguish between symptoms of MS and depression. Fifteen of 28 patients (54%) with a current or previous episode of depression reported that symptoms of depression occurred within 1 year of the onset of MS symptoms. Few of these patients were able to recall the dates of symptom onset with sufficient precision to determine whether depression immediately preceded or followed the onset of MS symptoms. Nine (32%) patients indicated that symptoms of depression predated onset of MS symptoms by at least 1 year. Only four patients (14%) indicated that symptoms of depression occurred more than 1 year after the onset of MS symptoms.

**Depression and current and initial symptoms of MS**

EDSS scores were positively skewed with a range of 0–6 and a mean and median of 2.1 and 2.0 respectively. To account for the skewed distribution and the ordinal nature of the scale, EDSS scores were categorized as low (less than 2) or high (greater or equal to 2). Chi-square analysis revealed that the severity of neurological impairment as measured by the EDSS did not vary significantly as a function of current diagnosis of depression ($\chi^2=1.5, P<0.45$). A marginally significant association between the degree of neurological impairment and the presence or absence of personal history of depression was observed ($\chi^2=3.51, P<0.06$), suggesting that prior depression may predispose individuals to more severe illness. The severity of neurological impairment was not significantly associated with a family history of depression ($\chi^2=0.09, P<0.75$) or with sex ($\chi^2=0.39, P<0.53$).

The distribution of initial symptoms as a function of a history of depression is presented in Table 3. Patients with a history of depression reported experiencing significantly more initial symptoms of MS than patients who did not report a history of depression ($M=2.0$ vs $M=1.5$. Student’s $t$ [43]=2.57, $P<0.01$). Patients with a history of depression were more likely to experience muscle weakness and fatigue as initial symptoms than patients without a history of depression ($\chi^2=6.1, P<0.01$). No other significant differences emerged.

**Discussion**

In the present study, 40% of newly diagnosed MS patients met the diagnostic criteria for major depression and 22% met the criteria for adjustment disorder with depressed mood. Symptom severity and symptom duration are the primary distinguishing characteristics of major depression and adjustment disorder with depressed mood. Untreated, major depression may persist for as long as 1 year and contribute to significant functional impairment, while adjustment disorder is expected to resolve within 6 months. Previous research has revealed similarly high rates of major depression in the early stages of MS, even in the absence of severe neurological impairment. Adjustment disorder has not been reported in previous research, suggesting that the symptoms of adjustment disorder may resolve shortly following diagnosis of MS.

<table>
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<th>Table 3</th>
<th>Initial symptoms of MS as a function of history of depression</th>
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<tr>
<td><strong>History of depression</strong></td>
<td>Yes</td>
</tr>
<tr>
<td>Age (mean years)</td>
<td>34.6 (7.3)</td>
</tr>
<tr>
<td>Total number of initial symptoms (mean)</td>
<td>2.0 (0.6)</td>
</tr>
<tr>
<td>Time since symptom onset (mean years)</td>
<td>2.6 (3.1)</td>
</tr>
<tr>
<td>Frequency of patients reporting</td>
<td></td>
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<tr>
<td>Muscle weakness or fatigue</td>
<td>11/23</td>
</tr>
<tr>
<td>Numbness or tingling</td>
<td>9/23</td>
</tr>
<tr>
<td>Dizziness or vertigo</td>
<td>8/23</td>
</tr>
<tr>
<td>Vision or speech problems</td>
<td>10/23</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>3/23</td>
</tr>
<tr>
<td>Bowel or bladder problems</td>
<td>0/23</td>
</tr>
<tr>
<td>Pain</td>
<td>4/23</td>
</tr>
<tr>
<td>Emotional difficulties</td>
<td>1/23</td>
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</table>

Group differences in age, total number of symptoms and time since symptom onset were analysed using Student’s $t$. Values in parentheses are standard deviations. Frequencies of patients reporting different initial symptoms were analysed using the chi-square test.
The findings of the present research also show that MS patients are more likely than patients with CLBP to have experienced an episode of depression before diagnosis of MS. Although a relation between MS and a history of depression had been suggested by Charcot almost 130 years ago, previous research efforts have lacked the empirical rigor necessary to establish a firm link. The present study represents the first demonstration of a relationship between MS and a history of depression using a standardized assessment in a sample of newly diagnosed MS patients.

On the basis of findings showing that subpopulations of lymphocytes vary in number as a function of emotional distress in patients with MS, Foley et al. have suggested that emotional distress may serve as one of the triggers for the inflammatory or immunological changes that occur in MS. This perspective is consistent with the results of several investigations showing a negative association between depression and indices of immune function. The findings of the present study suggest that history of depression may be associated with a greater number of initial symptoms of MS and more severe neurological impairment. However, conclusions must be made cautiously given that statistical analysis of the relation between prior depression and EDSS scores was only marginally significant.

The prevalence of family history of depression was twice as high in patients with MS than in patients with CLBP who were matched for current level of depression. Minden et al. reported that 17 of their sample of 50 MS patients had a family history of depression or alcoholism. Consistent with our findings, family history of depression was unrelated to current diagnosis of depression. The possibility of a genetic link between MS and depression has been discussed by Schiffer et al., who reported a high prevalence of family history of affective illness in MS patients, primarily in patients with bipolar disorder. While only one patient in the present study was diagnosed with bipolar disorder, this may be due to the younger age of the sample. Since bipolar disorder does not always begin with a manic episode, a number of patients with major depression may later develop bipolar disorder.

Some caution in interpreting the results of the present study is necessary. Retrospective interviews were used to address personal and family history of depression. The validity of retrospective information on personal history of depression is dependent on the accuracy of patients’ memories. The validity of patient-reported family history of depression is limited by the accuracy of patients’ memories as well as the degree to which patients’ family members shared information about their affective illnesses. Patients with MS also differ from those with CLBP in the ambiguity of initial symptoms and the susceptibility to misdiagnosis. There is no simple solution to these problems. At this time, prospective analyses of the temporal relation between depression and MS are precluded by the absence of methods of identifying individuals at risk for MS.

Could depression be overdiagnosed in patients with MS? Somatic symptoms of depression, particularly fatigue, overlap with symptoms of MS. The DSM-III-R states that physical symptoms that are clearly due to a physical condition should not be considered symptoms of depression. In the present study, fatigue was considered to be a symptom of depression only if fatigue did not vary as a function of activity level or temperature. While this approach may provide some assurance that prevalence rates of depression in MS are not being inflated by symptom overlap, fatigue is not the only overlapping symptom. Other depressive symptoms such as psychomotor retardation, sleep disturbance (hypersomnia) and concentration difficulties may also be symptoms of MS, but it is more difficult to differentiate the emotional or organic origin of these symptoms. The question of diagnostic confounds in depression and physical illness has been addressed by several investigators and recommendations typically emphasize the need for caution. Given the clinical and theoretical implications of inaccurate diagnoses of depression, more research is urgently needed to develop means of clearly differentiating emotional and organic symptoms of MS.

In previous research, both neurological and psychological positions have been advanced to account for the relation between depression and MS. Debates over the relative tenability of neurological or psychological models persist even though neither model has been advanced with sufficient clarity or specificity to yield testable predictions about the mechanisms linking MS and depression. Emerging evidence suggests that the emotional status of MS patients probably represents the combined outcome of dynamic neurological and psychological processes involved in disease and adaption. For example, it is possible that a recursive process may be initiated in MS and depression where depression may contribute to disease activity, and physical deterioration may in turn contribute to depressive symptoms. The task of future research will be to specify how biological and psychological processes interact in determining the emotional and neurological status of patients with MS.

There are several clinical implications of the findings of the present study. The high prevalence of major depression observed in this study highlights the need to screen for major depression in newly diagnosed MS patients who may require treatment. The relation between personal history of depression and severity of illness leads to the hypothesis that early detection and treatment of depression may improve outcomes in individuals who begin to show symptoms of MS that may reduce illness severity. To date, there have been no controlled studies of the efficacy of different treatments of depression in patients with MS, and thus the effects of successful treatment of depression on disease course remains unknown. Anecdotal reports of improved MS symptomatology following treatment indicate that this may prove to be a promising line of enquiry.

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