The Prevalence of Bipolar Disorders and Association With Quality of Life in a Cohort of Patients With Multiple Sclerosis

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Clinical observations of mood instability in multiple sclerosis (MS) have led to the hypothesis that bipolar disorder (BD) may be more prevalent in persons with MS than in the general population. This cross-sectional study assesses the prevalence of BD among patients with MS using standardized psychiatric diagnostic interviews and evaluates quality of life. This study demonstrates a higher prevalence of BD in patients with MS compared with the general population. It also reveals the negative impact of BD on quality of life, raises the concern that BD can occur before the onset of neurological symptoms in MS, and suggests that, in some cases, BD may delay diagnosis of MS.

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Multiple sclerosis (MS) is a chronic autoimmune inflammatory demyelinating disorder of the central nervous system and the second most common cause of severe disability and decreased quality of life in young adults.[1] Neuropsychiatric symptoms are well recognized, as MS can present with primarily psychiatric or neuropsychiatric features.[2,3] Patients with MS are more likely to suffer from depression[4] and other mood disorders[5,6] compared with the general population.[7] It is also known that there is an increased risk of psychiatric disorders even before a definite diagnosis of MS is made, with a high odds ratio of 1.4.[8] Mood disorders are also associated with lower treatment compliance, poor outcomes and functional status, and overall decreased quality of life among MS patients.[9] Although symptoms of major depressive disorder (MDD) can occur before the onset of neurological symptoms of MS,[10,11] few studies have focused on the relationship between bipolar disorder (BD) and MS.

Approximately 3.4% of the general population suffers from BD,[7] the disability-adjusted years for which are greater than that for all forms of cancer or other major neurological diseases, including epilepsy and Alzheimer's disease. This is likely due to the earlier onset and chronic disease course.[7] When misdiagnosed as unipolar depression, BD may contribute to worse quality of life and affect treatment adherence in persons with MS.[12] The initial presentation of BD may include a depressive phase or a manic phase with or without psychotic symptoms. All of these presentations have been temporally associated with MS[13–17] and pharmacological treatments of MS,[18,19] making expeditious and confident diagnosis difficult. It remains unclear whether and/or to what degree BD may, in some cases, be a prodromal feature of MS.

The objectives of this study were to assess the prevalence of BD among patients with MS using standardized psychiatric diagnostic interviews and evaluate quality of life among MS patients with BD. We also investigated whether BD occurred prior to the onset of MS neurological symptoms, as well as the influence of BD on MS diagnosis.

METHODS

Standard Protocol Approvals, Registration, and Patient Consents

This was a cross-sectional study. Participants were identified from an MS clinic at a single tertiary referral center. Written informed consent was obtained from all patients participating in the study. The study was approved by the University of Massachusetts Medical School Institutional Review Board. Inclusion criteria included a diagnosis of MS based on the 2010 revised McDonald criteria[20] and between 18 and 90 years of age. To avoid confounding by concurrent other neurological and/or psychiatric conditions, the study samples were restricted to BD in MS. The specific exclusion criteria were any concurrent, major neurological diagnosis (e.g., stroke, myasthenia gravis), current or history of a

primary psychotic disorder (e.g., schizophrenia), active substance abuse within the past 3 months, and recent or remote uncontrolled endocrine disorder. The diagnosis of BD was established via the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Edition (SCID-I/NP).[21]

Data Collection

A total of 152 consecutive samples of patients with a diagnosis of MS were enrolled in the study between January 2014 and May 2015. MS patients were screened for BD using the standardized Mood Disorder Questionnaire (MDQ).[22]

The MDQ is a self-report questionnaire screening for a lifetime history of bipolar spectrum disorder symptoms, derived from the DSM-IV criteria. It is well known to have good internal consistency on detecting lifetime manic symptoms,[23] and its validity in detecting recent episode (defined as less than 2 years) is reportedly excellent (sensitivity of 0.83, specificity of 0.82 with the standard cut-off point of equal or greater than 7).[23] MDQ also has been well utilized in the MS population, and MDQ positivity for BD is known to be much higher in MS.[6] Subjects must score at least 7 criteria questions, with symptoms occurring during the concurrent period, and with the disturbance causing at least "moderate" to "severe" impairment in functioning.[24] The cut-off score used was greater than equal to 7. The patients scoring positive on the MDQ underwent the SCID-I/NP[21] for definitive diagnosis of BD by psychiatry trained physicians. Medical records were reviewed in standardized fashion by physicians and trained abstractors.

All patients were evaluated with Multiple Sclerosis Quality of Life−54 (MSQOL-54) instrument that has physical and mental components. The MSQOL-54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument.[25,26] This instrument generates 12 subscales that include physical function, role limitations-physical and emotional, pain, emotional wellbeing, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. Along with 12 subscales, two summary scores are generated: the physical health composite and the mental health composite summary. There are two additional single-item measures as well: sexual function and change in health. Composite scores are determined as a weighted sum of selected subscales scores.[25] Values for both physical and mental composite scores range from 0 to 100, with 100 reflecting a good quality of life. The subsequent data analysis included stratifying the total MSQOL-54 physical and mental composite scores by the presence of BD and reviewing the subgroup scores to identify the specific function that may significantly attribute to the total scores. A total of 121 subgroup analyses were completed, which included 10 patients with MS meeting the SCID criteria for definite diagnosis of BD and 111 patients with MS who did not have BD.

The relevant past psychiatric history was obtained from participants diagnosed with BD during the SCID. Medical records of all screened participants were reviewed to extract details regarding psychopharmacological treatment and family history of psychiatric disorders, as well as details of MS history and use of disease-modifying agents. Medical records were also reviewed to identify concurrently prescribed psychopharmacologic agents regardless of their putative indication, including the use of mood stabilizers, anxiolytics, antidepressants, stimulants, and antipsychotics. It is important to note that our study design did not focus on comorbid psychiatric conditions associated with MS (such as substance disorders, anxiety, depression, attention deficit hyperactivity disorder, or thought disorders), as the goal of the study was to exclusively focus on BD in MS.

To address whether mood symptoms of BD presented prior to MS-symptom onset, a post-SCID telephone survey, as well as a chart review by physician, was also conducted addressing the dates of onset of BD symptoms, formal diagnosis of BD, onset of MS neurological symptoms, and formal diagnosis of MS by physicians via the revised McDonald diagnostic criteria for MS.[20]

Statistical Analysis

Normal distribution of data was assessed using the Shapiro-Wilk test. The Mann-Whitney U test and Fisher's exact test were used to compare continuous and categorical variables, respectively. A two-sided p value <0.05 was considered significant. All statistical analyses were performed using IBM SPSS Statistics, version 20.0.0 (IBM, Armonk, N.Y.).

RESULTS

The baseline characteristics of the studied patient population as stratified by the presence of BD are shown in Table 1. The mean age of study participants was 49 years (median age: 51 years). The median age of participants screening positive versus negative for BD did not differ (43 years versus 52 years, p=0.09). The number of females among the MS patients without BD was 105/142 (73.9%), while 9/10 (90%) had BD (p=0.453). The majority of studied participants had a diagnosis of relapsing remitting MS.

Among the 16 participants who screened positive on the MDQ (10%), 10 participants (6.5%) scored positive for BD via SCID ($p<0.001$).

Bipolar disorder type 1 was more prevalent than type 2 in the study group (60% versus 30%, $p<0.001$). Only 50% of the participants with BD were receiving any psychopharmacological treatment (p=0.001). Interestingly, for patients with BD, 50% (5/10) were receiving either a selective serotonin reuptake inhibitor or an anxiolytic, which is not standard of care for BD.

The medical record review revealed that 66/142 (46.45%) of MS patients without the diagnosis of BD were receiving antidepressants or anxiolytics for coexisting depression/anxiety

disorders, and 7% of MS patients without BD were on multiple therapies for complex psychiatric comorbidities.

There were no statistically significant differences in the age, sex, race, MS subtype, and MS disease-modifying therapies among MS patients with and without BD. There was no statistically significant association with MS disease duration and diagnosis of BD. There was a significant association between family history of BD and the presence of BD in subjects ($p<0.001$).

The presence of BD was associated with significantly reduced MSQOL-54 physical and mental composites ($p=0.003$ and $p<0.001$, respectively). Tables 2 and 3 show the MSQOL-54 subgroup scores (PCS-54 and MCS-54) as stratified by the presence of BD. For PCS-54, poor health perception ($p=0.011$), energy fatigue ($p=0.036$), physical role limitations ($p=0.007$), social function ($p<0.001$), and physical health distress ($p=0.003$) subscales were noted to drive the differences in the PCS-54 between persons with and without BD. The differences in the MCS-54 scores between persons with and without bipolar disorders are all statistically significant, as each subscale showed p values <0.05.

TABLE 1. Baseline Characteristics (unadjusted) of the Studied Patient Population as Stratified by Presence of Bipolar Disorder[a]

Characteristic	Bipolar Negative (N=142)	Bipolar Positive (N=10)	p
Age (years); median (IQR)	52.0 (15.0)	43.0 (26.0)	0.093
Sex; N (%)			0.453
Female	105 (73.9%)	9 (90.0%)	
Male	37 (26.1%)	1 (10.0%)	
MSQOL physical composite; median (IQR)	53.3 (35.3)	32.1 (14.5)	0.003
MSQOL mental composite; median (IQR)	66.3 (37.6)	29.9 (12.4)	<0.001
Race/ethnicity; N (%)			0.505
Caucasian	133 (93.7%)	9 (90.0%)	
Hispanic	7 (4.9%)	1 (10.0%)	
African American	2 (1.4%)	0 (0.0%)	
MS subtype; N (%)			0.519
Relapsing-remitting	114 (80.3%)	10 (100.0%)	
Primary progressive	4 (2.8%)	0 (0.0%)	
Secondary progressive	24 (16.9%)	0 (0.0%)	
SCID; N (%)			<0.001
Positive for bipolar disorder	0 (0.0%)	10 (100.0%)	
Negative for bipolar disorder	6 (4.2%)	0 (0.0%)	
Bipolar diagnosis subtype; N (%)			<0.001
No bipolar disorder	142 (100.0%)	0 (0.0%)	
Bipolar disorder type 1	0 (0.0%)	6 (60.0%)	
Bipolar disorder type 2	0 (0.0%)	3 (30.0%)	
Bipolar disorder not otherwise specified	0 (0.0%)	1 (10.0%)	
Family history of bipolar disorder; N (%)			<0.001
None	102 (71.8%)	1 (10.0%)	
Positive	29 (20.4%)	7 (70.0%)	
Undetermined	11 (7.7%)	2 (20.0%)	
MS DMTs; N (%)			0.097
No DMT	30 (21.1%)	4 (40.0%)	
Single DMT	108 (76.1%)	5 (50.0%)	
Dual DMT*	4 (2.8%)	1 (10.0%)	
Psychiatric medications; N (%)			0.001
None	63 (44.4%)	0 (0.0%)	
Mood stabilizer or antipsychotic	3 (2.1%)	0 (0.0%)	
Multiple therapies**	10 (7.0%)	5 (50.0%)	
Other(s) (SSRIs/anxiolytics)	66 (46.45%)	5 (50.0%)	
Disease duration (years); median (IQR)	1.0 (3.0)	1.0 (3.0)	0.834

[a] DMT=disease-modifying therapy; IQR=interquartile range; MS=multiple sclerosis; MSQOL=Multiple Sclerosis Quality of Life; SCID=Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Edition; SSRI=selective serotonin reuptake inhibitors.

*Combination of two disease modifying MS therapies in secondary progressive MS after a failure of monotherapy. (e.g., copaxone and mycophenolate in two patients, copaxone and rituximab in one patient, copaxone and interferon beta 1a in one patient, and interferon beta 1a and methotrexate in one patient)."

**Combination of psychopharmacological therapies, including antipsychotics, anxiolytics, mood stabilizers, antidepressants, and stimulants used for coexisting psychiatric disorders.

Temporal relationship of onset of BD symptoms and development of neurological symptoms of MS after post-SCID telephone survey are summarized in Table 4. Among the 10 BD patients that were interviewed via telephone, eight patients reported onset of mood symptoms prior to the onset of neurological symptoms of MS, and one patient reported concurrent mood and neurological symptoms. Three participants believed the presence of mood symptoms delayed their diagnosis of MS (Table 4). Interestingly, physician interpretation of chart documentation showed that eight participants with BD had complained to their treating physician that the presence of their mood disorder might have delayed their MS diagnosis. The remaining chart review on two participants did not document any delay in diagnosis of MS by the presence of mood disorder.

DISCUSSION

Our study shows a BD prevalence of 6.5% among MS patients, which is higher than what is reported in the general population (3.4%).[27] This is consistent with another report of a higher prevalence of BD in MS in Swedish[5] and Canadian[28] cohorts. Specifically, the known prevalence of

TABLE 2. Multiple Sclerosis Quality of Life-54 Physical Subscale Characteristics as Stratified by the Presence of Bipolar Disorder[a]

Subscale Characteristic	Bipolar Negative (N=111)	Bipolar Positive (N=10)	p
Physical function	8.5 (10.2%)	7.7 (3.1%)	0.409
Health perception	8.5 (6.8%)	4.3 (4.0%)	0.011
Energy fatigue	5.3 (3.6%)	2.6 (5.0%)	0.036
Role limitations physical	3.0 (12.0%)	0 (0.0%)	0.007
Pain	6.8 (6.2%)	5.1 (5.3%)	0.189
Sexual function	5.3 (4.3%)	3.0 (5.7%)	0.144
Social function	9.0 (4.0%)	4.5 (3.5%)	<0.001
Physical health distress	6.6 (5.0%)	3.0 (2.9%)	0.003

[a] Data are N (%).

BD in MS includes 0%−16.2%,[29] and a recent large population-based Canadian cohort study showed a higher BD prevalence of 4.7% compared with 2.3% in the general population.[28] That study also showed that comorbid psychiatric conditions, such as BD, MDD, anxiety, and schizophrenia, are more common in MS.[28] Similar to the prior work, our study also showed a significant association between family history of BD and BD diagnosis among MS patients.[27]

It has been previously shown that there is a strong association between depression and bipolar disorder type 2, as well as a poorer quality of life in MS.[12] Our study is unique in that after screening BD via MDQ, the diagnosis of BD was confirmed via gold standard diagnostication utilizing SCID administered by physicians with psychiatric training. Furthermore, the study used a more extensive assessment of quality of life by the MSQOL-54 that combines both generic and MS-specific items into a single instrument. Not only does our study show the strong association between BD and poorer quality of life in MS, but also that both physical and mental quality of life are negatively affected.

The study further analyzed the effects of subscale MSQOL-54 components in BD, and it has shown that health perception, energy fatigue, physical role limitations, social function, and physical health distress are negatively affected by the presence of BD ($p<0.05$). Although the subscale scores in physical function, pain, and sexual function were lower in patients with BD, it was not statistically significant. It is speculated that they can be affected by other disease mechanisms and multiple neuroanatomical pathway involvements in MS.

This suggests that multidisciplinary coordination and effective treatment of BD may potentially improve the overall quality of life in MS patients. Only 50% (N=5) of our subjects who had a diagnosis of BD were receiving any psychopharmacological treatments ($p<0.001$). This is an important observation because lack of psychopharmacological treatments can worsen psychiatric symptoms and adversely affect outcome,[30–33] including leading to suicidality,[34,35] lost productivity,[36] and even additional MS exacerbations.[37] This is particularly relevant to quality of life evaluations in MS, as comorbid psychiatric conditions are seemingly more prevalent, underdiagnosed, and undertreated in persons of low socioeconomic status.[9]

The strong association between family history of BD and BD in MS are known.[38,39] It remains uncertain whether psychiatric features of MS are part of the underlying neurobiology of the disease, comorbidities of chronic illness, or adverse reactions of treatment.[30]

Delays in MS diagnosis and greater disability at time of diagnosis are associated with psychiatric and medical comorbidity among MS patients.[7] Low mood among MS patients has also been associated with structural and functional brain abnormalities, suggesting that depression in MS may arise directly from the demyelination process and be of a different etiology than depression in non-MS patients.[40,41] For example, a diffusion tensor imaging study demonstrated reduced fractional anisotropy—a measure of white-matter pathology—in frontal and temporal lobes of depressed patients with MS compared with nondepressed patients with MS.[42] In addition, a recent whole-brain structural connectivity analysis demonstrated altered patterns of white-matter connectivity, specifically the right hippocampus and right amygdala, which differentiated MS patients with depression from nondepressed patients.[43]

A potential etiological relationship between MS and BD also has been suggested,[5] and neuroinflammation may contribute to the pathogenesis of mood disorders as indicated by positron emission tomography[44] and postmortem identification of inflammatory biomarkers.[45] It has also been suggested that there is a possible genetic association between MS and BD.[38,46,47] It has been hypothesized that MS-related inflammation relates to the mood symptoms of BD. Alternatively, mood symptoms could be exacerbated by MS treatments (e.g., interferon beta and steroids). In our study, there was no significant difference between the MS treatment agents and presence of BD diagnosis.

A number of participants reported mood symptoms preceding neurological features of

TABLE 3. Multiple Sclerosis Quality of Life-54 Mental Subscale Characteristics as Stratified by the Presence of Bipolar Disorder[a]

Subscale Characteristics	Bipolar Negative (N=111)	Bipolar Positive (N=10)	p
Mental health distress	8.4 (7.0%)	3.9 (4.2%)	0.005
Overall quality of life	11.4 (5.6%)	7.4 (5.3%)	0.012
Emotional well-being	19.7 (9.3%)	12.2 (9.0%)	0.002
Emotional role limitations	16 (16.0%)	0 (3.6%)	<0.001
Cognitive function	9.0 (6.0%)	4.9 (7.3%)	0.002

[a] Data are N (%).

TABLE 4. Characteristics of Bipolar Disorder (BD) Onset and Diagnosis in Relation to the Onset and Diagnosis of Multiple Sclerosis (MS)[a]

Subject Number (BD+, MS+)	Age at BD Symptom Onset (Years)	Age at BD Diagnosis (Years)	Age at MS Symptom Onset (Years)	Age at MS Diagnosis (Years)	Reported Delay in MS Diagnosis due to BD Symptoms Based on Phone Interview	Reported Delay in MS Diagnosis due to BD Symptoms Based on Interpretations of Physician Chart Review
1	16 or 17	19 or 20	18	18	No	Yes
2	Teens	39	20s	51	Yes	Yes
3	18	34	18	29	No	No
4	Teens	20	48	51	No	Yes
5	Late 20s or age 30	31 or 32	35	35	No	Yes
6	30s	38	48	48	No	Yes
7	Teens	Previously undiagnosed by psychiatrist (tested positive on SCID)	24	28	No	No
8	19 or 20	27	29	35	Yes	Yes
9	23	23	23	23	No	Yes
10	Teens	27	28	32	Yes	Yes

[a] BD=Bipolar disorder; MS=multiple sclerosis; BD+=bipolar disorder confirmed via the Structured Clinical Interview for DSM-IV-TR Axis I Disorders; MS+=confirmed multiple sclerosis via the MacDonald criteria.

MS. This is a notable observation and warrants further investigation. "Diagnostic overshadowing" is a form of bias in which somatic symptoms or complaints may be misattributed to pre-existing neuropsychiatric pathology and presumably led to delays in accurate diagnosis. It has been previously reported in children with neurological conditions, such as intellectual disability[48] and autism spectrum conditions,[49] and in psychiatric patients presenting to emergency departments.[50,51] To date, and to our knowledge, there have been no well-powered longitudinal epidemiological studies clarifying the role of diagnostic overshadowing or demonstrating symptoms of BD consistently predating MS.

In our cohort, three patients reported a delay in MS diagnosis due to their coexisting neuropsychiatric symptoms of BD during the structured telephone interview. A physician chart review documented that eight out of 10 patients with BD had reported previously delayed MS diagnosis, which was attributed to the presence of their comorbid psychiatric issues. The telephone interview may reflect a recall bias, and physician chart review may also involve bias of the physician interpreting the available chart data. It is possible that the discrepancy between the chart review and the telephone survey may be related to the inherent methodological differences in obtaining this information. Alternatively, this discrepancy may be contributed to cognitive impairment, which is relatively common among persons with comorbid MS with BD, as supported by the literature.[52] However, this possibility remains untested and unproven in this study, since we did not directly assess study participants for cognitive impairments.

Interestingly, a substantial subset of patients was prescribed antidepressants and anxiolytics. Their prescription suggests the possible presence of additional psychiatric comorbidities in the studied cohort, consistent with prior reports of such in similar cohorts of persons with MS.[4–7,12,28] However, our study was not designed to directly determine the presence of depression or anxiety disorders in our MS cohort, and the true prevalence of these conditions in this cohort therefore remains uncertain. Retrospectively evaluating the primary etiology in diagnostic delay is intrinsically difficult. To date, population based studies in Croatia,[53] Canada,[54] Denmark,[55] Spain,[56] and the United States[23,57] have documented referral and diagnostic delays in persons with MS, attributable to availability of subspecialty services, age, and nature of initial presentation. Marrie et al.,[57] in particular, have written at length about diagnostic delay in MS, citing a mean delay of 7.03 years, confirming association with age at onset and noting increased risk of delay with comorbid mental (and nonpsychiatric) confounders, which also seem to increase disability at presentation. This raises the concern that better and more thorough screening, detection, assessment, and treatment need to be done to improve patient care.

There are several limitations to this study, including the cross-sectional design, absence of a study-specific comparison cohort without MS, and relatively small size of the current study population. As the study population was drawn from a tertiary care center, it may not be representative of the general MS population, and ascertainment bias may have potentially overestimated the prevalence of BD compared with community-based samples. Moreover, given the design of the study, participant recall and misclassification bias may be present. As noted above, coexisting psychiatric diagnoses and cognitive status also were not studied, and the absence of data addressing these issues limits the scope of the findings to the comorbidity of MS and BD alone.

The SCID could not be completed for all 152 patients, and thus the sensitivity of the MDQ as a predictor of BD in this population of MS patients could not be assessed. However, despite the possible false negative rate of MDQ, our study

shows higher than expected prevalence of BD in patients with MS and also particularly demonstrated the negative impact of BD on quality of life in MS. As the Expanded Disability Status Scale and MS functional composite scores were not analyzed in this study, we cannot comment on the degree of baseline functional disability in our cohort. Including these measures, as well as measures of cognitive impairment, in future studies may further improve our understanding of neuropsychiatric association between MS and BD.

It is possible that this study underestimates the prevalence of BD in persons with MS, given the utilization of the MDQ as a screening measure. The MDQ only has moderate sensitivity for the detection of BD, with the known overall sensitivity and specificity for detecting BD being 0.58 and 0.67, respectively for persons already diagnosed with BD.[58] Furthermore, MDQ is known to have even lower sensitivity of 0.281 but high specificity of 0.972 in detecting BD in the general population.[24] If these prior reports are consistent in this population, BD may have an even higher prevalence in MS than previously recognized.

CONCLUSIONS

Understanding the comorbidity of BD in MS should raise awareness for better screening of patients and improvement in treatments. However, ongoing challenges in addressing bipolar disorders include the difficulty in establishing diagnoses, prescribing appropriate treatments, getting patient cooperation, and addressing high suicidality risk.[59] Understanding the high risk of BD in MS and the potential genetic and pathophysiological implications between MS and BD would raise awareness for better screening of patients and improvement in treatments.

This study showed a higher than expected prevalence of BD in patients with MS compared with the general population and has shown that BD adversely affected the quality of life in the studied cohort with MS. This raises the concern that BD may occur before the onset of neurological symptoms in MS and delay the diagnosis of MS in patients suffering from neurological and psychiatric symptoms. This suggests that there is a critical need to recognize and address psychiatric comorbidities such as BD early in the course of MS and initiate appropriate therapy to improve outcomes.

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