

# Bipolar disorder preceding the onset of multiple sclerosis

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## ABSTRACT

Multiple sclerosis (MS) is the most common inflammatory demyelinating brain disease. The occurrence of psychiatric disorders, especially for major depression, in the course of MS is high. Reports concerning bipolar disorder (BD) remain rather scarce although early descriptions were found in the old neurological literature. The purpose of this article is to provide a critical review of the epidemiology, comorbidity, and treatment findings regarding BD preceding the onset of MS.

**Key words:** Bipolar disorder, comorbidity, multiple sclerosis, onset

## INTRODUCTION

Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system associated with inflammatory demyelination. In the United States, the prevalence of MS is 0.1%. MS affects more women than men, with an estimated female-to-male ratio of about 2:1. The median and mean ages of MS onset are 23.5 and 30 years of age, respectively. The peak age of onset is about 5 years earlier for women, but the onset of MS can rarely occur as late as the 7th decade.

Although the etiology of MS is unknown, the most widely accepted theory is that MS begins as an inflammatory autoimmune disorder mediated by autoreactive lymphocytes. Later, the disease is dominated by microglial activation and chronic neurodegeneration. Inflammation, demyelination, and axon degeneration are the major pathologic mechanisms that cause the clinical manifestations.

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Bipolar disorder (BD) is a major psychiatric illness with an estimated lifetime prevalence of 2.1% among United States adults. In regard to gender, BD type I occurs with equal frequency in both men and women, but BD type II is more common in women, accounting for up to 30-40% of previously diagnosed unipolar depression.<sup>[1]</sup> The age of onset of BD is most commonly around 20 years of age (peaking at ages 15-25 years). BD men appear to have 4-5 years earlier onset than BD women. First onset mania is very rare among elderly people.

The pathophysiology of BD is heterogeneous. Recent scientific findings consider BD as a suite of related neurodevelopmental conditions with interconnected functional abnormalities, early onset, and worsening over time. In addition to accelerating loss of volume in brain regions known to be essential for mood regulation and cognitive function, consistent findings have emerged at a cellular level, providing evidence that BD is reliably associated with dysregulation of glial-neuronal interactions, especially microglia which appear to be overactive. Furthermore, inflammation in the periphery of the body is increased in both depressive and manic phases of the illness, with at least

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some return to normality in the euthymic state. These findings are consistent with changes in the HPA axis, which are known to drive inflammatory activation.<sup>[2]</sup>

The occurrence of psychiatric disorders in MS was systematically described as early as in 1872 by Charcot.<sup>[3]</sup> Mental changes in MS included pathological laughing and weeping (pseudobulbar affect), euphoria, mania, depression, anxiety, psychosis, and maladaptive personality changes.

The main body of the literature focuses on the comorbid depression found in MS, whereas reports concerning BD remains rather scarce although early descriptions of manic episodes in MS were found in the old neurological literature.<sup>[4-6]</sup>

This disproportion reflects the fact that depression is the most frequent among psychiatric disorders in MS, with a lifetime prevalence of 25-50%, a figure two to five times higher than that found in the general population, depending on the country studied.<sup>[7]</sup>

The purpose of this article is to provide a critical review of the epidemiology, comorbidity, and treatment findings regarding BD preceding the onset of MS.

## EPIDEMIOLOGY OF BD IN MS

Few studies have investigated the prevalence of BD in patients with MS and vice versa. The first epidemiologic study of this kind, conducted on a large sample (more than 700,000 individuals) in Monroe County (NY),<sup>[8]</sup> found 10 patients had both MS and BD while epidemiologic data indicated that the expected number of cases would only be 5.4. Joffe *et al.*<sup>[9]</sup> conducted a systematic psychiatric evaluation on 100 consecutive MS patients attending a neurology clinic and found a 13% lifetime prevalence of BD. Fis *et al.*<sup>[10]</sup> examined the prevalence of BD among hospital service utilizers in Nova Scotia and compared these measures for the MS and non-MS population. The prevalence of BD in hospitalized MS patients was 1.97%, significantly higher than the 0.92% for the non-MS hospital utilizers. In a prospective study in 658 consecutive patients with MS attending an outpatient clinic, Edwards, and Constantinescu<sup>[11]</sup> found that MS population had significantly increased rates of BD compared to the general population (odds ratio = 22.02,  $P < 0.001$ ). Finally, Johansson *et al.*<sup>[12]</sup> studied comorbidity between MS and BD in a nationwide cohort. The risk of MS was compared in psychiatric patients and in matched unexposed individuals. The risk of MS was increased in patients with BD [hazard ratio (HR) = 1.8, 95% confidence interval (CI): 1.6-2.2,  $P < 0.0001$ ]

and major depression (HR = 1.9, 95% CI: 1.7-2.0,  $P < 0.0001$ ) while the risk of MS in schizophrenia was decreased (HR = 0.6, 95% CI: 0.4-0.9,  $P = 0.005$ ).

## BD PRECEDING MS' ONSET

We searched for original articles published in PubMed from inception to 2014 focusing on BD preceding the onset of MS. The search terms used were: (multiple sclerosis) AND (bipolar disorder). All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers. We selected 16 published articles of case reports where BD preceded the onset of MS [Table 1].

In 26 patients, 20 of which are female, the mean age of onset of BD and MS was 33.42 and 38.46 years, respectively. Nine patients had the onset of BD and MS at the same age. The onset of BD occurred before age 20 years in one patient while 13 patients experienced the onset between age 20 and 29 years, 3 patients between age 30 and 39 years, and 8 patients after age 40 years. The age of onset of MS has a different distribution among these patients: one patient had onset before age 20 years, 6 patients had onset between age 20 and 29 years, 6 patients had onset between age 30 and 39 years and 13 patients had onset after age 40 years.

Twenty-five of these patients were with BD type I (6 with a single manic episode, 6 with recurrent mania, 12 with episodes of both polarity, 1 with rapid cycling) while one had BD type II with rapid cycling. Thirteen patients (4 single manic episode, 3 recurrent mania, and 6 BD type I) had psychotic symptoms in at least one mood episode. Ten patients presented with relapsing/remitting course of MS, 9 with a progressive course, 4 cases presented with pure psychiatric symptomatology, 3 with other course of MS.

Only 3 cases had a positive family history for MS (cases 1, 12, and 22) whereas 6 patients had a psychiatric family history (cases 12-14-22-26 BD, 16 unknown, 19 unipolar).

Regarding the pharmacological treatment for mood episodes, patients received lithium, antipsychotics, antiepileptics, and antidepressants alone or in various combinations. In terms of treatment response according to psychiatric diagnosis, 60% of those with single mania, 66% of those with recurrent mania, 55.5% of those with BD type I presented full or partial response whereas those with rapid cycling had poorer responses to drugs. No cases of mania were induced by treatments.

**Table 1: List of patients, identified in case reports, where BD preceded the onset of MS**

Case number	Gender	BD onset	BD type	Treatment; response	MS onset	MS presentation and course	Neuroimaging findings	Reference
1	Male	58	Manic episode	Li; full resolution	58	Progressive spastic and ataxic quadriparesis	NR	[13]
2	Female	27	Manic episode	NS	28	R/R cervical cord	MRI: lesions in centrum semiovale, periventricular regions; cerebral and cerebellar atrophy	[14]
3	Female	15	Manic episode	APs; full resolution	15	R/R neuropsychiatric symptoms	MRI: diffuse white matter signal intensity along ventricles extending to the centrum semiovale bilaterally	[15]
4	Female	48	Manic episode	Li + APs; significant improvement	48	Progressive lethargy, restlessness, difficulty concentrating, urinary incontinence, periodic disorientation	MRI: lesions in periventricular and subcortical areas, corpus callosum, right cerebral peduncle, right brainstem	[16]
5	Female	54	Manic episode	AE + AP; poor response	54	Progressive neuropsychiatric symptoms and cognitive impairment	MRI: diffuse and multifocal lesions in cerebral hemispheres	[17]
6	Female	50	Manic episode	AP; poor response	50	Progressive neuropsychiatric symptoms and cognitive impairment	MRI: multiple punctate and patchy periventricular lesions, including Dawson's finger	[17]
7	Male	20	Recurrent mania	Li + APs; full resolution at 1st episode; poor response subsequently	29	Progressive unilateral vision loss, diplopia, paresthesia, ataxia and gait difficulties	CT: diffuse concentric patchy areas	[18]
8	Female	50	Recurrent mania	APs; partial response	56	Progressive ataxic hemiparesis and cognitive deficits	MRI: lesions in centrum semiovale, periventricular regions, thalamus; marked frontal and parietal atrophy	[14]
9	Female	39	Recurrent mania	NS	41	R/R brainstem and thoracic cord	NR	[14]
10	Female	21	Recurrent mania	NS	37	Progressive hemiparesis and ataxia	MRI: lesions in centrum semiovale, periventricular regions	[14]
11	Female	42	Recurrent mania	Li + APs; full resolution	49	Arms paraesthesias, ataxic gait	MRI: multiple hypersignal lesions in periventricular area, cerebellum, corpus callosum, one large and active lesion on right frontal lobe with peripheral oedema; remarkable brain atrophy	[19]
12	Female	27	Recurrent mania	NS	43	Left lower extremity weakness and unstable gait	MRI: lesions in the periventricular and subcortical areas, bilateral centrum semiovale, right pontine and right cerebellar cortex	[20]
13	Female	26	BD-I RC	Li + Aps + AEs; poor response	29	Progressive ataxia, left hemiparesis, intractable nausea vomiting, bowel bladder incontinence, bilateral Babinski	CT: several enhancing lesions in left parietal area, several periventricular areas of low attenuation	[21]
14	Female	46	BD-II RC	Li + ADs; poor response	49	Progressive ataxic gait	CT: normal	[21]
15	Male	23	BD-I	AP; full resolution	27	Progressive ataxic gait, blurry vision, vertical, lateral and intermittent rotary gaze nystagmus	CT: normal	[22]
16	Female	49	BD-I	Li + APs; poor response	49	R/R sensory alterations left leg	NR	[22]
17	Female	25	BD-I	APs + Li; full resolution at first episode; poor response subsequently	30	R/R brainstem and cervical cord	NR	[14]

Contd...

Table 1: Contd...

Case number	Gender	BD onset	BD type	Treatment; response	MS onset	MS presentation and course	Neuroimaging findings	Reference
18	Male	21	BD-I	Li + APs; poor response	31	Progressive spastic and ataxic quadriparesis	MRI: lesions in centrum semiovale, periventricular regions, subcortical areas, thalamus, temporal lobes; cerebral atrophy	[14]
19	Female	22	BD-I	NS	27	R/R brainstem and cervical cord	MRI: three lesions in the periventricular area of right hemisphere, one lesion in the left cerebellar hemisphere	[14]
20	Female	33	BD-I	Li + ADs; good response	33	R/R brainstem, lower paraparesis, ataxic gait	MRI: periventricular and temporal horn lesions, one lesion in the right fronto-basal region, bilateral lesions in the splenium of corpus callosum, corona radiata, centra semiovalia, few subcortical lesions; moderate atrophy in supratentorial compartment and trunk of corpus callosum	[23]
21	Female	48	BD-I	NS	48	R/R neuropsychiatric symptoms (+ atonic bladder developed at age 81)	Neuropathology: small, atrophic brain; moderate ventriculomegaly; numerous lesions in periventricular location, right superior frontal convolution, cingulate gyrus, centrum semiovale, corpus callosum, left cerebellar folia	[24]
22	Male	20	BD-I	NS	40	Mild pyramidal signs on the left side	MRI: lesions in the periventricular and subcortical areas, bilateral centrum semiovale, corpus callosum	[20]
23	Female	26	BD-I	AP; full resolution	26	R/R brainstem	MRI: one lesion located parasagittally within the left parietal lobe	[25]
24	Female	39	BD-I	APs + AD; full resolution	40	R/R motor deficit left side, gait impairment, urinary incontinence	MRI: lesions in periventricular area and cervical cord	[26]
25	Male	20	BD-I	Li; poor response	31	R/R paresthesia and weakness left side, urinary incontinence	MRI: lesions in periventricular area, corpus callosum, cervical spine at C2 and C3	[27]
26	Female	20	BD-I	Li; good response	32	R/R quadripyramidal syndrome with right kinetic cerebellar syndrome	MRI: multiple lesions in periventricular and semioval areas, cervical spine at C6	[27]

BD: bipolar disorder; MS: multiple sclerosis; Li: lithium; NR: not reported; NS: not specified; R/R: relapsing remitting; MRI: magnetic resonance imaging; AP: antipsychotic; AE: antiepileptics; AD: antidepressant

We did not find any correlation between BD type and MS course type nor between the pattern of white matter lesions and BD type, although lesions were commonly detected in the periventricular and subcortical white matter, the centrum semiovale bilaterally, frontal, parietal and temporal lobes.

## CONCLUSION

The survey of the literature found few epidemiological studies and several case reports of BD clearly preceding MS onset. Based on these data, only limited conclusions can be drawn. In the sample analyzed, the mean ages

of onset of both BD and MS were higher than those reported in the literature. Furthermore, the mean difference between BD onset and MS is 5 years although 9 patients (34.6%) had the onset of BD and MS at the same age. The higher age of onset of MS may indicate that only the form with a later age of onset increases the risk or the co-occurrence/comorbidity with BD.

A high percentage of BD presented with manic episodes (single/recurrent), a finding that may indicated differences between BD occurring in MS patients and those in the general population. Similarly, the higher rate of psychotic features and the low rate of positive

family history may also indicate differences between BD in MS and in the general population.

The available data are insufficient to formulate any hypothesis regarding the etiopathological independence of the two conditions or explain the high rates of co-occurrence and differences in clinical features. In addition, the lack of systematic treatment response data does not permit any comparison between BDs with and without MS. As evidence emerges regarding the inflammatory correlates of both, BD and MS, the value of anti-inflammatory treatments in preventing, delay or ameliorating the course of BD requires further investigations. The limited data on case reports of BD preceding MS yielded several interesting observational findings that might provide information for future research and clinical characterization.

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#### Conflicts of interest

There are no conflicts of interest.

## REFERENCES

1. Angst J, Cui L, Swendsen J, Rothen S, Cravchik A, Kessler RC, Merikangas KR. Major depressive disorder with subthreshold bipolarity in the National Comorbidity Survey Replication. *Am J Psychiatry* 2010;167:1194-201.
2. Maletic V, Raison C. Integrated neurobiology of bipolar disorder. *Front Psychiatry* 2014;5:98.
3. Charcot JM. Leçons Sur les Maladies du Système Nerveux. Paris: Delahaye; 1872. (In French)
4. Redlich E, von Economo C. Demonstration mikroskopischer Präparate eines Falles von multipler Sklerose mit psychose. *Jahrb f Psychiat* 1909;30:315-8. (In German)
5. Euziere J. Les troubles psychiques dans la sclérose en plaques. *Arch Gén Méd* 1909;3:746-56. (In French)
6. Brown S, Davis TK. The mental symptoms of multiple sclerosis. *Arch Neurol Psychiatry* 1922;7:629-34.
7. Feinstein A, Magalhaes S, Richard JF, Audet B, Moore C. The link between multiple sclerosis and depression. *Nat Rev Neurol* 2014;10:507-17.
8. Schiffer RB, Wineman NM, Weitkamp LR. Association between bipolar affective disorder and multiple sclerosis. *Am J Psychiatry* 1986;143:94-5.
9. Joffe RT, Lippert GP, Gray TA, Sawa G, Horvath Z. Mood disorder and multiple sclerosis. *Arch Neurol* 1987;44:376-8.
10. Fis KJ, Morehouse SA, Brown MG, Skedgel C, Murray TJ. Hospital-based psychiatric service utilization and morbidity in multiple sclerosis. *Can J Neurol Sci* 1998;25:230-5.
11. Edwards LJ, Constantinescu CS. A prospective study of conditions associated with multiple sclerosis in a cohort of 658 consecutive outpatients attending a multiple sclerosis clinic. *Mult Scler* 2004;10:575-81.
12. Johansson V, Lundholm C, Hillert J, Masterman T, Lichtenstein P, Landen M, Hultman CM. Multiple sclerosis and psychiatric disorders: comorbidity and sibling risk in a nationwide Swedish cohort. *Mult Scler* 2014;20:1881-91.
13. Solomon JG. Multiple sclerosis masquerading as lithium toxicity. *J Nerv Ment Dis* 1978;166:663-5.
14. Hutchinson M, Stack J, Buckley P. Bipolar affective disorder prior to the onset of multiple sclerosis. *Acta Neurol Scand* 1993;88:388-93.
15. Heila H, Turpeinen P, Erkinjuntti T. Case study: mania associated with multiple sclerosis. *J Am Acad Child Adolesc Psychiatry* 1995;34:1591-5.
16. Young CR, Weiss EL, Bowers MB Jr, Mazure CM. The differential diagnosis of multiple sclerosis and bipolar disorder. *J Clin Psychiatry* 1997;58:123.
17. Asghar-Ali AA, Taber KH, Hurley RA, Hayman LA. Pure neuropsychiatric presentation of multiple sclerosis. *Am J Psychiatry* 2004;161:226-31.
18. Peselow ED, Fieve RR, Deutsch SI, Kaufman M. Coexistent manic symptoms and multiple sclerosis. *Psychosomatics* 1981;22:824-5.
19. Modrego PJ, Ferrandez J. Familial multiple sclerosis with repetitive relapses of manic psychosis in two patients (mother and daughter). *Behav Neurol* 2000;12:175-9.
20. Kosmidis MH, Bozikas VP, Giannouli V, Karavatos A, Fokas K. Familial comorbidity of bipolar disorder and multiple sclerosis: genetic susceptibility, coexistence or causal relationship? *Behav Neurol* 2012;25:341-9.
21. Kellner CH, Davenport Y, Post RM, Ross RJ. Rapidly cycling bipolar disorder and multiple sclerosis. *Am J Psychiatry* 1984;141:112-3.
22. Garfield DA. Multiple sclerosis and affective disorder: 2 case reports of mania with psychosis. *Psychother Psychosom* 1985;44:25-33.
23. Salmaggi A, Eoli M, La Mantia L, Erbetta A. Parallel fluctuations of psychiatric and neurological symptoms in a patient with multiple sclerosis and bipolar affective disorder. *Ital J Neurol Sci* 1995;16:551-3.
24. Casanova MF, Kruesi M, Mannheim G. Multiple sclerosis and bipolar disorder: a case report with autopsy findings. *J Neuropsychiatry Clin Neurosci* 1996;8:206-8.
25. Akkaya C, Kocagoz SZ, Turan OF, Taskapilioglu O, Kirli S. Onset of multiple sclerosis following post-partum depressive and manic episodes. *Psychiatry Clin Neurosci* 2007;61:698-9.
26. Cerqueira AC, Nardi AE, Souza-Lima F, Godoy-Barreiros JM. Bipolar disorder and multiple sclerosis: comorbidity and risk factors. *Rev Bras Psiquiatr* 2010;32:454-6.
27. Sidhom Y, Ben Djebara M, Hizem Y, Abdelkefi I, Kacem I, Gargouri A, Gouider R. Bipolar disorder and multiple sclerosis: a case series. *Behav Neurol* 2014;2014:536503.