Episodic Mood Changes Preceding an Exacerbation of Multiple Sclerosis

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ABSTRACT

Multiple sclerosis is a neurologic inflammatory disease that can manifest with psychiatric symptoms. Although depression is the most common psychiatric diagnosis in patients with multiple sclerosis, how depression develops is not fully understood. We present the case of an individual who displayed episodic mood changes preceding an exacerbation of multiple sclerosis symptoms. The clinical and research implications of this association are discussed.

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The neurologic inflammatory disease multiple sclerosis has long been understood to overlap with a number of psychiatric conditions, including depression, anxiety, and bipolar disorder. In 1926, Cottrell and Wilson[1] compiled a report of over 100 cases of psychopathology in individuals with multiple sclerosis, ranging from euphoria sclerotica to dysphoria. Literature[2–5] has indicated that there is an increased prevalence of psychiatric disorders in individuals diagnosed with multiple sclerosis compared to the general population.

Depression is the most common psychiatric diagnosis in patients with multiple sclerosis. A 2002 study[2] showed that the prevalence of major depressive disorder (MDD) was elevated in persons with multiple sclerosis relative to those without the disease and those reporting other conditions (adjusted odds ratio = 2.3, 95% CI, 1.6–3.3). In addition, this study[2] demonstrated that MDD prevalence in multiple sclerosis for those in the 18- to 45-year age range was high at 25.7% (95% CI, 15.6–35.7). Suicide is the cause of death in 15% of the multiple sclerosis population, with depression being the largest risk factor for completed suicide.[3] The connection between multiple sclerosis and depression has been postulated to arise from inflammation, which is believed to occur in both disease entities. There is growing evidence[4] that patients with MDD show alterations in immunologic markers including increases in proinflammatory cytokines, and, similarly, inflammation is pathological in the development of multiple sclerosis.

Although it is known that multiple sclerosis and depression may be linked, there is little information about the temporal relationship between episodes of multiple sclerosis and mood-related changes. Burns and colleagues[5] examined symptoms of anxiety and depression before and during confirmed exacerbations. It was found that depressive symptoms predicted subsequent confirmed exacerbations.[5] We present the case of a patient with relapsing-remitting multiple sclerosis in which severe psychiatric symptoms preceded the onset of a multiple sclerosis relapse.

CASE PRESENTATION

Neurologic History

Ms A is a 40-year-old right-handed woman diagnosed with relapsing-remitting multiple sclerosis 3 years before this presentation, although her first demyelinating event most likely occurred 10 years prior. She was started on glatiramer acetate, a disease-modifying medication, shortly after diagnosis but had been only intermittently compliant. Her last relapse requiring corticosteroids was at diagnosis, although she reported fluctuating symptoms. Her residual multiple sclerosis episodes had been characterized by a pattern of chronic pain, paresthesias in her arms and legs, dysarthria, word-finding difficulties, and some cognitive deficits. Her Expanded Disability Status Scale (EDSS)[6] score 6 months prior to her hospital admission was 4.5, indicating moderate physical disability. In addition to multiple sclerosis, Ms A also had been diagnosed with obstructive sleep apnea, polycystic ovarian syndrome, and rosacea.

Clinical Points

- Mood changes can precede exacerbations of multiple sclerosis symptoms and may delay diagnosis in some cases.
- Clinicians may be able to follow mood changes in order to better monitor the progression of multiple sclerosis; worsening mood symptoms may indicate that further imaging is necessary.
- An aggressive course of antidepressant medication may not be indicated in patients presenting with mood fluctuations in the context of multiple sclerosis exacerbations, as the mood symptoms may improve as the neurological symptoms improve.

Psychiatric History

Ms A has a history of recurrent depressive episodes as well as anxiety. She had been hospitalized 2 times during the previous 2 years. While she had never made a suicide attempt, she had a history of expressed suicidal ideation. She experienced her first episode of depression in early adulthood and shortly after began to gamble and abuse alcohol. Her symptoms had impacted her level of functioning to the point that she was unable to work or live independently. Her family history was significant for anxiety and problems with gambling in her mother and alcohol dependency in her brother.

Ms A was admitted to the hospital in the fall of 2013 after expressing a plan to overdose on medications. She was given the diagnosis of MDD on the basis of *DSM-5* criteria. At the time of admission, she was being treated with bupropion 150 mg, duloxetine 60 mg, topiramate 100 mg, and lorazepam 1 mg daily. Prior to this admission, she had been treated with adequate trials of citalopram, venlafaxine, and aripiprazole.

Hospital Course

While in the hospital undergoing psychiatric treatment, Ms A reported 2 flare-ups of her multiple sclerosis symptoms. The first flare-up occurred just after psychiatric admission. She described waking up feeling confused and drowsy and was having word-finding difficulties. She was seen in consultation by the hospital's neurology service, and the glatiramer acetate subcutaneous injections were restarted. It was the neurology team's impression that Ms A had experienced a worsening of her multiple sclerosis symptoms but that her depression was playing a large role in the clinical picture. Neuropsychological testing revealed impairment of processing speed but no significant changes to visual and verbal memory, difficulties with executive functioning, and bilateral impairment of motor coordination and manual speed. The profile reflected a combination of the effects of depression and symptoms related to multiple sclerosis.

After 2 days of persistent drowsiness, Ms A began to report that she was feeling alert. Over the next few weeks, a progressive improvement in her mood was also noted. The second flare-up occurred 3 weeks into her hospitalization when Ms A suddenly appeared depressed. She was reporting no specific changes in her personal life and denied recent stressors. She endorsed feeling depressed and suicidal on a daily basis. In spite of doubling the bupropion dose to 300 mg and regular attendance at group therapy sessions, the depression continued to worsen. On day 13 of her admission, 7 days after the initial episode resolved, she again began to describe new neurologic changes. This flare-up was defined by a tingling sensation bilaterally in both legs as well as burning pain. Ms A, who already had some struggles with mobility, was confined to her hospital bed. Laboratory investigations including complete blood count and thyroid functioning showed normal results. The neurology team was once again informed, and a magnetic resonance image (MRI) with no gadolinium was ordered, which demonstrated an increase in the size of a previously seen T2 hyperintense lesion in the white matter of the left occipital lobe. The neurologic symptoms persisted for approximately 1 week before subsiding.

Outpatient Treatment

In 2015, approximately 1½ years after her discharge from the hospital, Ms A presented with a third flare-up of multiple sclerosis symptoms. At an outpatient appointment with her psychiatrist, she described shifting to a period of mood lability but endorsed no suicidal ideation. She had been adherent to the prescribed maintenance treatment of bupropion 300 mg daily. Within days of her mood shift, Ms A began to once again complain of worsening physical symptoms. She reported left-sided weakness and fatigue in her arms bilaterally. She felt that her overall coordination was declining. At this point, an MRI of her head was repeated, which demonstrated a new hyperintense lesion consistent with a new multiple sclerosis lesion as well as the growth of an existing multiple sclerosis T2 hyperintense lesion. Approximately 3 weeks later at another appointment with her outpatient psychiatrist, Ms A reported resolution of her mood symptoms as well as her neurologic symptoms, with no adjustment to her medications or treatment plan.

DISCUSSION

While the relationship between multiple sclerosis and depression has been well studied, little is understood with respect to how the 2 clinical entities are temporally linked. In our case, each flare-up of neurologic symptoms appeared to be preceded by a shift in mood, with worsening symptoms of depression just prior to the onset of neurologic changes. As neurologic symptoms improved, mood symptoms also improved in each case. The pattern exhibited was reoccurring, despite keeping Ms A on a maintenance dose of medication. The literature to date has not explored the role of maintenance antidepressant therapy in MDD.

A 2011 study[7] suggested that MDD may occur as a prodrome to multiple sclerosis and may actually delay the diagnosis in some cases. The authors of the study[7] reported that 14% of subjects noted depressive symptoms as a prodrome to multiple sclerosis, with a mean onset

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of 6 months of depressive symptoms before the onset of neurologic symptoms.

The onset of depressive symptoms at later points during the progression of multiple sclerosis has also been reported. Noy et al[8] postulated that as the illness course develops, coping mechanisms may be compromised and reactive mood symptoms may ensue. They suggested that this may be especially true of relapsing-remitting multiple sclerosis, wherein there is chronic uncertainty of the timing of neurologic symptoms.[8]

Depression can be primary or secondary in origin to the development of multiple sclerosis. Postulated mechanisms for the development of mood symptoms in the setting of multiple sclerosis include autoimmune factors, lesional factors, psychosocial stress, and iatrogenic causes. The focus of research has been the link of inflammatory markers in the pathogenesis of multiple sclerosis and depression. Gold and Irwin[4] looked at the relationship between depression and immunity in patients with chronic-progressive multiple sclerosis and found that depressed patients had a significantly higher number of $T4^+$ helper cells in peripheral blood. With a paucity of studies being conducted in this area, it is difficult to ascertain how the possible autoimmune basis of depression relates to the progression of the disease.

It will be important to investigate how a prodromal mood shift may relate to an exacerbation of neurologic symptoms. With evidence of this pattern in future studies, clinicians may be able to follow mood changes in order to better monitor the illness progression of multiple sclerosis. Worsening mood symptoms may indicate that further imaging should be done in order to investigate the possibility that brain or spinal cord lesions have changed or that de novo lesions are present. Treatment implications may follow as well; an aggressive course of antidepressant medication may not be indicated in individuals presenting with mood fluctuations in the context of multiple sclerosis exacerbations. Further research will be required to look at the role of immunomodulating drugs in the treatment of multiple sclerosis–related mood symptoms.

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