Affective Disorders in Patients with Multiple Sclerosis
Pathophysiology and Approaches to Management

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Abstract
Affective disorders are commonly seen in the multiple sclerosis (MS) population. Symptoms of MS overlap heavily with symptoms of major depression; however, the diagnosis of major depression is sought using the same clinical criteria as in the general population. Treatment with pharmacological intervention appears to have a high rate of success, although controlled studies are lacking. Both tricyclic antidepressants and selective serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitors are commonly used in MS clinics and are generally well tolerated for treatment of major depression. Data concerning the efficacy of pharmacological intervention are limited yet compelling, and we consider antidepressants an indispensable component of our drug armamentarium. Treatment of mania and bipolar disorder in the MS population is more problematic, primarily due to a paucity of literature on the subject. We have found both lithium and valproic acid (sodium valproate) to be effective and well tolerated in these patients. Pharmacological treatment of more nonspecific types of mood instability in affected patients with MS appears to be reasonably effective as well, and in this situation we have successfully used both antidepressants and mood stabilisers.
Multiple sclerosis (MS) is an inflammatory disorder affecting the CNS and is believed to be triggered by an unknown aetiological agent, perhaps viral, in a genetically susceptible host. The challenge to physicians is to intervene in these dysimmune processes to prevent disease progression and, equally importantly, to give symptomatic relief to patients experiencing the protean manifestations of multifocal CNS injury. From the earliest descriptions of MS to the present, psychiatric manifestations of the disease have been considered paramount. Anti-depressants are among the most frequently used pharmacological treatments recommended for patients with MS.

MS occurs in 0.1% of the population of the US and is similarly common in Europe, with a female to male predominance at about 2 to 1. The prevalence of MS is somewhat less in other geographic areas, but this is essentially a worldwide disease.

Patients with disabling multifocal or diffuse CNS diseases, including MS, have a high rate of depression. Disabling illnesses other than MS, which do not affect the CNS, are associated with a lower incidence of depression. Lifetime incidence studies examining depression in MS clinic populations indicate approximately 50% of patients will develop depression. In a sample of 250 patients in our clinic, 17% received pharmacotherapy for the diagnosis of major depression over a follow-up period of 4 years. Recurrence of major depression after discontinuation of pharmacotherapy is reported to occur in 52% of patients within 2 years after discontinuation.

1. Pathophysiology

MS plaques commonly occur in frontal, temporal and hypothalamic white matter and hence may disrupt important limbic connections and cause depression. In some patients with MS, acutely evolving depression may result from this interruption of limbic connections. More slowly evolving affective disorders may result from a neurochemical imbalance related to multiple chronic lesions. Multiple studies have documented a preponderance of lesions involving the limbic system in patients with MS who also have affective disorders, as would be expected. Honer et al. found increased numbers of temporal lobe lesions in depressed patients with MS as compared with nondepressed patients with MS. Using a broader survey of psychological symptoms in patients with MS, Reischies et al. found a positive correlation with these symptoms and frontal lobe involvement. Similarly, we have found ‘hypofrontality’ on single photon emission computerised tomography imaging in a group of depressed patients with MS (unpublished observations). Although total lesion load has not been correlated with development of depression in MS, total lesion load (as opposed to temporal and frontal lesion load) has been correlated with cognitive dysfunction. Cognitive dysfunction in MS has in turn been associated with development of depression.

Although much evidence exists to support theories of various mechanisms of dysimmunity in MS, the precise mechanisms of acute inflammation and chronic CNS injury in this disease remain to be elucidated. Efforts to link evidence of dysimmunity in depression with dysimmunity in MS can thus be criticised as highly speculative. On a purely clinical basis, psychological stress and acute depressive states do not seem to induce MS relapses, yet depression may certainly be a symptom of relapse.

New knowledge of the relationship between depression and MS may arise from the recent observations that cytokine therapy with the β-interferons may induce depression in some patients. The extensive use of β-interferons in present practice, however, argues against a strong relationship between depression and this therapy. Similarly, although corticosteroid therapy may induce acute affective disorders, the majority of these disorders occur in other settings.

2. Diagnosis

The diagnosis of affective disorders in the MS population is usually made by neurologists or primary care physicians through the process of a psychiatrically oriented interview, either formal or in-