Multiple sclerosis and depression

Anthony Feinstein

Abstract
Clinically significant depression can affect up to 50% of patients with multiple sclerosis over the course of their lifetime. It is associated with an increased morbidity and mortality and is regarded by patients as one of the main determinants of their quality of life. This review summarizes current perspectives relating to diagnosis, the utility of self report screening questionnaires, warning signs of suicidal intent and the biological and psychosocial variables implicated in mood change. In particular, the association between depression and structural brain abnormalities, including those derived from diffusion tensor imaging, is highlighted. Depression is treatable, as the results from randomized controlled trials of antidepressant medication, cognitive behavior therapy and mindfulness therapy, reveal. These positive findings are offset by data showing that depression in a neurological setting is often overlooked and under treated.

Keywords
depression, diagnosis, pathogenesis, mortality, brain imaging, treatment

Introduction
The importance of adequately managing depression in a disorder like MS cannot be overstated. Not only is depression frequently part of the clinical presentation of MS, it is one of the main determinants of quality of life, may further compromise cognitive function, can lead to suicidal intent and suicide itself, often impairs relationships and reduces compliance with disease modifying treatments. These powerful negatives are, however, offset by an important positive. Depression is often treatable. Therein lies the challenge, for data show convincingly that depression is often overlooked in a busy neurological clinic and if detected, more often than not, inadequately treated. If this is to change, clinicians from all disciplines involved in the care of MS patients need to become more familiar with the facts emerging from a small yet burgeoning literature.

Prevalence
Depression as a symptom is virtually ubiquitous in the lives of any patient with a disabling disease. A distinction must therefore be made between a symptom and the syndrome of major depression, as defined by classification systems such as the DSM-IV or ICD-10. The syndrome refers to a collection of signs and symptoms at the heart of which is low mood and an inability to enjoy life as before. This change in emotion must be accompanied by a number of vegetative features (altered sleep, appetite, etc.) and distorted beliefs (feelings of guilt, worthlessness, life is not worth living and so on). The lifetime prevalence for this syndromal diagnosis in MS approaches 50%, a replicated figure derived from tertiary care neurological clinics. This is three times the rate reported in the general population. Community derived MS data tell a similar story.

Symptom specificity
A challenge faced by the clinician is that of determining whether certain symptoms relate to depression or to MS. The most widely cited example is fatigue. Other potential confounders are insomnia, altered appetite and impaired memory and concentration. Failure to make these distinctions can lead to diagnostic false positives. To minimize this possibility greater weight can be assigned to the presence of depressive beliefs, an approach adopted by self report rating scales for detecting depression in the
presence of a physical illness. Examples of these are the Hospital Anxiety and Depression Scale and the Beck Fast Screen for depression in medically ill patients, both of which have been validated for patients with multiple sclerosis.\textsuperscript{12,13} Useful as they are for screening purposes and clinical trials, self-report questionnaires cannot generate a diagnosis of major depression. For that a clinical interview is required.

**Suicide**

Data suggest that over a quarter of MS patients contemplate suicide.\textsuperscript{3} Risk factors are the presence of major depression, the severity of the depression, social isolation and alcohol abuse. While only a minority of suicidal patients will act on their intent, the frequency of completed suicide in individuals with MS exceeds chance. Epidemiologic findings from Canada suggest the rate is seven times that in the general population\textsuperscript{14} whereas Scandinavian data report a more modest twofold increase.\textsuperscript{15} Young males within the first five years of diagnosis were found to be most at risk.

**The association between depression and indices of MS disease**

There is no clear association between the presence of depression and disease related variables. The relationship with physical disability is equivocal with some studies, but not others, reporting a link.\textsuperscript{16,17} The same situation pertains to disease course and duration.\textsuperscript{18,19} The reasons for these mixed findings can be traced to the diversity of the disease itself. For example, patients with the same duration of MS may have markedly different relapse rates and disease course. Furthermore, the degree of physical disability may be determined by a combination of cerebral and spinal involvement, each having a potentially different effect on mood. While it is therefore intuitive to attribute depression to progressive physical deterioration, the important determinant of mood may be less closely related to the EDSS than how an individual adjusts to adversity and the kinds of coping strategies utilized.

**Etiology**

Imaging data have established a clear link between depression and structural brain changes. The strength of the brain–behavior association, however, is weaker than that reported for other neuropsychiatric sequelae of MS such as cognitive dysfunction\textsuperscript{20} and pseudobulbar affect,\textsuperscript{21} reflecting the more complex etiology of depression. As such, psychosocial factors assume an added importance, as the suicidal intent data have already shown. Any discussion of etiology should therefore view biological and psychological theories as complementary rather than exclusionary or competing.

**Brain imaging**

It is no coincidence that the first consistently robust associations between depression and MRI indices of disease owed much to technological advances in image acquisition and analysis, including improved MRI field strength, computerized lesion volume estimation, more anatomically precise lesion localization and a shift away from focusing exclusively on T2 weighted lesions. Making use of some of these advances, Pujol et al.\textsuperscript{22} showed that MS patients with moderately severe depression who were neither demented nor on steroid treatment had greater lesion involvement of the dominant arcuate fasciculus. While not considered part of the limbic system, this region is well connected to the lateral aspect of the temporal lobes and, by extension, the amygdala.

Bakshi et al.\textsuperscript{23} were the first to demonstrate an association between depression and the presence of hypointense or T1 lesions, while the severity of depression was also correlated with measures of frontal lobe and third and lateral ventricular atrophy. The failure to find a link between depression and hyperintense lesions suggested to the authors that severe and persistent mood change was more likely a consequence of chronic and destructive brain changes. Notwithstanding the study’s limitations in the method of lesion detection, the result was important for it widened the scope of imaging inquiry. This approach was followed by a subsequent study that used detailed, computer based volume quantification of T1 and T2 weighted lesions and atrophy, both regional and generalized.\textsuperscript{24} Structured clinical interviews were used to divide the sample into those with and without a diagnosis of major depression. Adding to the validity of the findings, the two groups were matched demographically, cognitively and in terms of psychosocial stressors. The results revealed that the depressed subjects were significantly more likely to have a higher lesion volume, both hyper- and hypointense, in the left medial inferior frontal region and less gray matter volume and increased CSF volume in left anterior temporal regions. Of note was that imaging indices accounted for 42\% of the variance when it came to explaining the presence of major depression. The importance of temporal lobe pathology in mood regulation is underscored by two further MS studies reporting an association between depression and a reduction in hippocampal volume.\textsuperscript{25,26}

Complementing the lesion and atrophy data is a diffusion tensor imaging (DTI) study that focused on normal appearing white (NAWM) and gray (NAGM) matter.\textsuperscript{27} Reduced fractional anisotropy in NAWM and
elevated mean diffusivity in NAGM, once more localized to the temporal lobes, differentiated depressed from euthymic MS patients. Significantly, the DTI changes independently predicted the presence of depression.

To date, brain imaging of depressed MS subjects has essentially explored structural correlates, apart from an early PET study in which temporal lobe perfusion abnormalities were noted. The absence of fMRI studies is particularly striking given the prominent and informative role played by this imaging modality in the general psychiatry-depression literature. fMRI has nevertheless offered new insights in our understanding of why MS patients may be particularly vulnerable to developing depression. Comparing MS patients who were neither depressed nor anxious with a group of healthy controls, Passamonti et al. demonstrated differences in cerebral activation when it came to processing emotional versus neutral stimuli. In particular the MS group showed increased activity within the ventrolateral prefrontal cortex (vlPFC) and a lack of connectivity between the amygdala and the vlPFC and medial PFC regions. Given the importance of these regions in modulating mood and affect, the findings provide evidence of an ongoing compensatory cerebral process at work in the MS brain attempting to maintain an euthymic state. By extension, the result also highlights an inherent vulnerability within some MS patients to the development of a mood disorder. With the brain having to work that much harder to maintain normal mood, less functional reserve remains to deal with stressful life events that are often the precipitant of a depressive disorder.

**Psychosocial factors**

While there is a sizeable literature devoted to exploring psychosocial influences on mood, a major limiting factor in interpreting these studies has been the cross-sectional nature of their data. This point needs emphasis, for relying on depressed subjects to subjectively assess putative, causative social factors is inherently biased. With this in mind, what the studies reveal is that uncertainty, inadequate coping strategies, helplessness, loss of recreational opportunities, poor quality relationships, high levels of stress and fatigue are all implicated in depression.

Considerable attention has been devoted to exploring one of these variables, namely coping styles, where evidence suggests that emotion focused rather than problem focused strategies leave the patient at increased risk for depression. Of note is that cognitively impaired MS patients are more likely to adopt a maladaptive approach characterized by high levels of avoidance when dealing with problems generated by their disability. This too leaves them vulnerable to depression. When the relative contributions of all psychosocial and disease related variables are weighed, four independent predictors of depression have been identified, namely emotion based coping, uncertainty, the loss of hope and the degree of physical disability. These collectively account for 40% of the depression variance. A recent study comparing MS patients with and without major depression reported that evening cortisol concentrations did not decline in the former. Elevated serum cortisol concentrations in depressed MS patients have also been associated with reduced hippocampal volumes. Additional support for a dysfunctional HPA axis comes from a study showing that raised cortisol levels in depressed MS subjects were not suppressed with the administration of the exogenous steroid dexamethasone and moreover were linked to the presence of gadolinium enhanced brain lesions.

**Treatment**

It is noteworthy that despite the prominence of depression in the lives of MS patients there are few well constructed psychopharmacologic studies. Anecdotal case studies abound attesting to the effectiveness of selective serotonin reuptake inhibitors (SSRIs), but the
Finally, any discussion of treatment for depression must make mention of electroconvulsive therapy (ECT), reserved as it should be for patients who have not responded to medication and CBT, or for those who are so acutely suicidal time is of the essence in alleviating the low mood. Limited evidence suggests the treatment is safe and effective. The presence of contrast enhanced lesions may, however, be a risk factor for disease exacerbation. It is therefore recommended that a gadolinium enhanced MRI be completed before the benefits and risks of treatment are considered.

Faced with a choice of effective treatments, how should a clinician proceed? A consensus opinion expressed by members of a task force struck by the National MS Society in the USA recommends that treatment modalities be combined in an integrated biopsychosocial model. While this may seem intuitive, validation of this approach is still awaited. Real-world considerations will also dictate that in a busy neurological clinic treatment algorithms for depression are likely to be adjusted according to the availability of resources and access to them. These potential challenges should not, however, deflect attention away from detection and the provision of best available treatments. The morbidity and mortality associated with depression demands no less.

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References


