

# Depression and Immunity: Inflammation and Depressive Symptoms in Multiple Sclerosis

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An increasing body of evidence suggests that patients who have major depressive disorder show alterations in immunologic markers including increases in proinflammatory cytokine activity and inflammation. Animal models of a depression-like syndrome called “sickness behavior” have shown clearly that cytokines are implicated in the development of these symptoms. Inflammation of the central nervous system (CNS) is a pathologic hallmark of multiple sclerosis (MS). Patients affected by this disease also show a high incidence of depression. Accumulating evidence for cytokine-mediated sickness behavior from animal studies suggests that some aspects of depression and fatigue in MS may be linked to inflammatory markers. This article reviews the current knowledge in the field and illustrates how the sickness behavior model may be applied to investigate depressive symptoms in inflammatory neurologic diseases such as MS.

## Major depression and medical comorbidity

Neuropsychiatric disorders, especially major depressive disorder, are now one of the leading causes of disability [1]. Major depressive disorder, with

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a lifetime incidence of more than 10% [2,3], is a potent risk factor for disease morbidity, with depressed persons showing a mortality rate twice that found in nondepressed persons [4–7]. Altered functioning of the immune system is a mechanism that might contribute to medical morbidity of major depression including risk of infectious disease [8] as well as inflammatory disorders [9]. Depressed persons show reductions of cellular and innate immune responses that are associated with susceptibility to infectious disease [10,11], whereas other studies have found that depression is linked to immune activation in patients who have inflammatory disorders such as rheumatoid arthritis [9] or cardiovascular disease [12,13] or who are undergoing cytokine therapy [14].

#### *Association of depression with enumerative and functional immune measures*

Increases in the total number of white blood cells and in the numbers and percentages of neutrophils and lymphocytes were among the first immunologic changes identified in depressed persons [15]. Further evaluation of lymphocyte subpopulations found that depression is related negatively to the number and percentage of lymphocytes (B cells, T cells, T-helper [Th] cells, and T-suppressor/cytotoxic cells) as well the natural killer (NK) cell phenotype, although such differences have not been replicated consistently [16].

To evaluate the function of the immune system in depressed patients, most studies have relied on results from assays of nonspecific mitogen-induced lymphocyte proliferation, mitogen-stimulated cytokine production, and NK cytotoxicity. More than a dozen studies have been conducted on lymphocyte proliferation in depression, and there is a reliable association between major depression and lower proliferative responses to the three nonspecific mitogens, phytohaemagglutinin, concanavalin-A, and pokeweed [16]. In addition, a number of independent laboratories have confirmed reduced NK activity in major depression [16].

#### *Cytokines and depression*

Animal models that use chronic mild stress to induce depression-like syndromes report alterations in immune parameters including increased interleukin (IL)-1 production [17]. Studies of stimulated cytokine production in humans have not yielded consistent findings, however. For example, in whole-blood assays, Kronfol and colleagues [18] found increased lipopolysaccharide-stimulated production of IL-1 and IL-6 but no change in the expression of tumor necrosis factor (TNF)- $\alpha$ . Other studies have suggested a shift in the relative balance of Th1 versus Th2 cytokine production with increases in the capacity of lymphocytes to produce interferon (IFN) in depression [19], but no difference in the stimulated production of IL-2 has been found [19,20]. These negative findings cannot be ascribed to differences in depressed samples, because reduced NK activity has been found in depressed patients whose IL-2 production was normal [20].

Recent attention has focused on evaluating different patterns of cytokine activation in subtypes of depression. Whereas one study found no differences in the capacity of lymphocytes to produce IL-2 in melancholic and non-melancholic depression [21], another study suggested that peripheral blood mononuclear cells of non-melancholic depressed patients showed a greater stimulated capacity to produce IL-1  $\beta$  and IL-1 receptor antagonist as compared with responses from controls and melancholic depressed patients [22], although earlier work by this group of investigators did not identify such increases in IL-1 production [23]. Nevertheless, further observations suggest that the melancholic, but not non-melancholic, depressed patients showed evidence of activation of the hypothalamic-pituitary-adrenal (HPA) axis, which is thought to inhibit immune activation and the expression of inflammatory markers and might account for the reported differences in the melancholic and non-melancholic groups [22].

In contrast to the inconsistent findings regarding association between depression and production of inflammatory cytokines, meta-analyses indicate that depression is associated with an increase in circulating levels of the proinflammatory cytokine IL-6 [16]. As compared with controls, elevated levels of IL-6 have been found in adults who have major depression [24–26], in depressed elderly populations [27] and in persons who have chronic medical disorders such as rheumatoid arthritis [9], cancer [28], and cardiovascular disease [29]. It is hypothesized that increases in circulating levels of proinflammatory cytokine are caused by activation of monocyte populations. Increases in circulating levels of other proinflammatory cytokines such as tumor TNF- $\alpha$  and IL-1 $\beta$  have been reported in depressed patients [30,31] including patients who have late-life depressive disorder [32]. The number of studies that have examined these additional cytokines is too few to make firm conclusions, however. One study also reported increased plasma levels of IL-12 in a large cohort of depressed patients [33].

### *Behavioral effects of proinflammatory cytokines*

Abundant evidence indicates that peripheral and central administration of cytokines is associated with the development of so-called “sickness behavior.” For example, in animal models, proinflammatory cytokine induction or administration yields a set of behavior changes characterized by decreased appetite, weight loss, sleep disturbances, retardation of motor activity, reduced interest in the physical and social environment, and loss of libido [34]. In healthy human volunteers, endotoxin-induced endogenous cytokine production is associated with the transient development of depressed mood, anxiety, and memory impairments [35].

The therapeutic administration of cytokines (eg, in antiviral or cancer therapy) provides another paradigm to study the effects of cytokines on behavioral and cognitive measures in humans. Several studies have reported that IFN- $\alpha$  administration in patients who have cancer or hepatitis C is

accompanied by behavioral side effects that are similar to the sickness behaviors observed in animals. A few studies have reported similar observations for IFN- $\beta$  (MS therapy), IL-1, IL-2, and TNF- $\alpha$  (cancer treatment). The most common side effects of these treatments are flulike symptoms such as fever, malaise, headache, and myalgia, which typically occur early (approximately 2 weeks) after the start of treatment but tend to attenuate as treatment continues. In contrast, neuropsychiatric symptoms, including anxiety, dysphoria, anhedonia, fatigue, anorexia, and cognitive and psychomotor slowing, generally occur after 1 to 3 months of therapy; these depressive symptoms persist unless treatment is terminated or supplemented by antidepressant medications [36]. Administration of IL-2 or IFN- $\alpha$  can activate the proinflammatory cytokine network and cause the subsequent elevation of IFN- $\gamma$ , IL-6, IL-8, and other cytokines. It therefore is conceivable that the comparatively late onset of neuropsychiatric symptoms reflects an epiphenomenon to the induction of endogenous cytokines.

#### *Brain signaling by cytokines*

Cytokines are relatively large, hydrophilic molecules that under physiologic conditions do not readily cross the blood–brain barrier. There are, however, several ways by which peripheral cytokines may enter the brain. For example, passive diffusion may allow entry of cytokines in certain brain regions (eg, the circumventricular regions) where the blood–brain barrier is less restricted or absent. Furthermore, active transport mechanisms have been identified for some cytokines such as IL-1 $\alpha$ , IL-1 $\beta$ , and TNF- $\alpha$  [37]. Other mechanisms by which peripheral cytokines may influence the brain include second-messenger induction through receptor binding on cerebral vascular endothelial cells and signaling through the vagus nerve [38].

Of particular relevance to this article, cytokines themselves have been found to promote degeneration of the blood–brain barrier in inflammatory conditions [39]. In MS a pronounced breakdown of the blood–brain barrier, entry of inflammatory cells into the CNS, and local production of cytokines within the brain are at the core of presumed pathogenesis. Thus in MS, the effect of cytokines on the brain, in addition to their contribution to neuronal and oligodendroglial damage, may be important for behavioral symptoms. This possibility is discussed in detail later.

#### *Effects of cytokines on neuroendocrine function and neurotransmitters*

Several biologic mechanisms have been proposed to explain the association between depression and inflammation. The effects of cytokines on neurotransmitters in the CNS, most notably serotonin and norepinephrine, are explained by a prevailing biologic hypothesis of depression, which states that serotonin deficiency plays a crucial role in the pathogenesis of this disorder. This hypothesis is based largely on the observation that pharmacologic enhancers of serotonergic neurotransmission (eg, selective serotonin

re-uptake inhibitors) are effective antidepressants. Evidence suggests that some cytokines may be involved in serotonergic depletion in the CNS. For example, IFN- $\alpha$  has been shown to interfere with serotonin metabolism and reduce serotonergic availability [40]. Similarly, cytokines may affect the noradrenergic system, which also is thought to play an important role in depression. Pronounced and sustained hypersecretion of brain norepinephrine has been reported in patients who have major depression [41]. A number of studies have shown that IL-1 administration can activate the central noradrenergic system in animals markedly [40], thus providing another potential pathway related to cytokine-induced depression.

Another important mechanism involves the activation of the neuroendocrine system by cytokines. Patients who are depressed show elevated levels of corticotropin-releasing hormone (CRH) [42], and this key peptide is involved in integrating neural neuroendocrine as well as immune responses to stress. Release of this peptide in the brain alters a variety of immune processes, including aspects of innate immunity, cellular immunity, and *in vivo* measures of antibody production [43,44]. Peripheral immune measures also change after lesioning of the brain (eg, hypothalamus) or in response to the stimulation of certain brain regions that ultimately impact CRH systems. The brain controls immune cells in lymphoid tissue in the same way it controls other visceral organs, namely by coordinating autonomic and neuroendocrine pathways. When these pathways are blocked by specific factors that bind to sympathetic or hormone receptors, the effects of CRH on immune function are blocked also [45,46].

### **Clinical application: depression in multiple sclerosis**

Immune infiltration and inflammation of the central nervous system are pathologic hallmarks of MS [47], and cytokines are secreted in the brain by invading cells as well as by resident microglia and astrocytes [48]. Depression is one of the most common symptoms in MS: numerous clinical studies have reported that patients who have MS have a lifetime risk of major depression of 25% to 50% [49]. A recent large-scale community-based study [50] showed that 40% of patients who had MS had clinical depressive symptoms. Based on the sickness behavior literature reviewed previously, it is possible that inflammatory markers may be linked causally to the high prevalence of depression in patients who have MS. Depressive disorders within neuromedical illnesses such as MS present special challenges for detection and treatment. In particular, the understanding of the pathogenesis of depressive symptoms in MS is crucial for the development of novel treatment strategies.

Although the presence of depression in MS does not seem to be related to the severity of neurologic impairment [51] and also can occur in early stages of the disease [52], it has a strong impact on the patient's functional status. Patients who have MS and comorbid depression perform more poorly on

tests of cognitive function [53,54]. It also has been shown that depression adversely affects quality of life in patients who have MS [55], contributes to disruptions of social support [56], and interferes with work attendance [57]. Because depression is linked to poorer treatment compliance [58], it potentially can affect long-term health outcomes. Finally, it is reported that depression is the most powerful determinant of suicidal intent in patients who have MS [59].

Despite evidence that depression is a major complication of MS with implications for the health status of these patients, this condition remains underdiagnosed and undertreated [59]. It is therefore important to understand better the pathogenesis of depression and its potential interactions with MS disease processes to develop novel treatment options.

### *Pathogenetic models of depression in multiple sclerosis*

To date, little is known about the pathogenetic factors that account for the development of depressive symptoms in MS. Several models have been proposed to explain the strong association of depression and MS. A recent consensus statement issued by experts assembled by the National Multiple Sclerosis Society [60] stated that the pathogenesis is most likely multifactorial, including psychologic, social, neurobiologic, immunologic, and genetic factors. Some of the pathogenetic models proposed are reviewed briefly here.

### *Psychosocial factors*

A simple explanation for the occurrence of depression in MS is that it is primarily reactive in nature, that is, a response to facing a chronic illness characterized by an uncertain prognosis and with no therapeutic cure available. There is no direct correlation between disease severity and depression in MS [51]. Whether or not depression develops in response to the illness, psychosocial factors such as coping strategies or social support may play a role. For example, coping and social support seem to mediate the relationship between disease and depression in MS [61,62], although depression is not simply a failure of patients to cope with the psychosocial challenges [60]. Interventions designed to provide social support (eg, peer groups) have failed to show an effect on mood [63]. Furthermore, psychosocial factors alone cannot account for the higher frequency of depression seen in MS than in other chronic progressive diseases [64]. It therefore has been proposed that depression may be related to disease-specific processes such as CNS damage or changes in immune parameters, as hypothesized previously in this article.

### *Damage to the central nervous system*

Another plausible explanation for the higher incidence of depression in MS may involve disease-specific and damage to particular locations in the CNS. Pujol and colleagues [65] reported a specific association of lesions in

the left suprainular white matter and depressive symptoms, accounting for a significant 17% of the depression variance. More recently, black holes as detected on T1-weighted images (which are thought to reflect severe tissue damage) in superior frontal and superior parietal regions have been found to predict depression [66]. Feinstein and colleagues [67] found greater volume of left medial inferior prefrontal lesions detected on T2-weighted images. One other study has shown more frontal atrophy in patients who have MS and depression than in nondepressed patients who have MS [68]. Although these studies suggest that the location and severity of MS lesions may be associated with certain depressive features in MS, no clear anatomic pattern has been established so far.

*Experimental autoimmune encephalomyelitis is associated with depression-like behavioral symptoms*

A limited number of studies have investigated sickness behavior in experimental autoimmune encephalomyelitis (EAE), the animal model of MS. Behavioral signs including anorexia, weight loss, and reduced social exploration characterize EAE [69], and these behavioral alterations occur after immunization but before the onset of neurologic signs of disease. Hence it is thought that these symptoms reflect motivational defects rather than impairments in motor function. For example, EAE is accompanied by decreased sucrose consumption (but no change in water consumption), which can be interpreted as a sign of anhedonia. Furthermore, in accordance with a cytokine-mediated pathogenesis of these symptoms, a later study showed that the onset of sickness behavior coincided with inflammatory cell infiltration of the brain as well as mRNA expression of IL-1, TNF- $\alpha$ , and prostaglandin E2 in brain tissue [70]. Anti-inflammatory treatment ameliorated the behavioral effects [71].

*Aspects of depression and fatigue in multiple sclerosis resemble sickness behavior seen in animal models*

One intriguing aspect of depression in MS is its relation to fatigue. Fatigue is a common symptom in depression and in MS. Mohr and colleagues [72] noted “a relationship between fatigue and depression has long been suspected in MS,” but “why and how this relationship might exist has remained generally unarticulated.” Although earlier studies have not found evidence for an association of depression and fatigue in MS [73,74], later reports usually have confirmed a moderate correlation [75–79]. The relationship seems to differ in the different dimensions of fatigue (the association was stronger with mental fatigue than with physical fatigue [76]), thus suggesting that different mechanisms may contribute to fatigue in MS. A cytokine-mediated pathogenesis of depression and mental fatigue (but not physical fatigue) could explain these differential associations.

*Clinical evidence for the role of inflammation in multiple sclerosis sickness behavior*

Depression is a suspected side effect of MS treatment with IFN $\beta$ -1a. It has been suggested that IFN treatment in MS may induce depression or worsen existing depressive symptomatology. Although several studies have investigated this hypotheses using datasets from phase III clinical trials, it seems that anecdotal evidence of increased depression during IFN treatment is explained better by prior history of depression [80].

Some recent studies have investigated the inflammation hypothesis of depression in MS by correlating endogenous inflammatory markers and depressive symptoms. The first study published by Fassbender and colleagues [81] showed that during relapse MS patients who had higher depression scores had significantly increased white blood cell counts in the cerebrospinal fluid. Depression scores also were higher in patients who had MRI evidence for CNS inflammation as indicated by gadolinium-enhancing lesions on T1-weighted MRI. Depression scores in this study also correlated with activation of the HPA axis. In another study assessing MS patients during relapse, Kahl and colleagues [82] reported that mRNA levels of TNF- $\alpha$  and IFN- $\gamma$  obtained from whole-blood samples were increased, and both cytokines significantly correlated with scores on the Beck Depression Inventory (BDI). Th2-type cytokines such as IL-10 and IL-4 were not correlated with BDI scores. During remission in a subgroup of patients (with follow-up at 3 and 6 months and 1 year), only TNF levels showed a significant correlation with BDI scores. In line with these findings, Mohr and colleagues [83] also showed a positive correlation of depression and in vitro IFN- $\gamma$  production. In this small study, amelioration of depression after psychotherapy or antidepressant medication treatment was paralleled by decreases in the capacity to produce IFN- $\gamma$ . In another study, treatment of MS depression with lofepramine, a derivative of the antidepressant medication imipramine, was associated with decreases of gadolinium-enhancing lesion load on T1-weighted scans [84].

A few studies have investigated the association of inflammatory markers and fatigue in MS. An early study could not find correlations of fatigue and urinary neopterin, C-reactive protein, and soluble intercellular adhesion molecule 1 in a sample of 38 patients who had MS [85]. More recently, however, cytokines typically associated with sickness behavior have been found to be associated with MS fatigue. For example, Flachenecker and colleagues [86] showed a positive correlation with TNF- $\alpha$  mRNA levels. Heesen and colleagues [87] reported correlations of TNF- $\alpha$  and IFN- $\gamma$  in vitro production and fatigue severity. TNF- $\alpha$  levels also were associated with self-report measures of daytime sleepiness.

In summary, these findings are in accordance with the cytokine hypothesis of MS depression and fatigue. It is not known, however, whether depression is secondary, primary, or coincidental with inflammation in this

population, even though treatment with antidepressant medication has been shown to decrease inflammatory markers in MS.

## Summary

There is strong evidence that depression involves alterations in multiple aspects of immunity that may contribute to the development or exacerbation of a number of medical disorders and also may play a role in the pathophysiology of depressive symptoms. Accordingly, aggressive management of depressive disorders in medically ill populations or individuals at risk for disease may improve disease outcome or prevent disease development. On the other hand, in light of data suggesting that immune processes may interact with the pathophysiologic pathways known to contribute to depression, novel approaches to the treatment of depression may target relevant aspects of the immune response. Taken together, the data provide compelling evidence that a psychoimmunologic frame of reference may have profound implications regarding the consequences and treatment of depression.

In addition, this approach may be used to investigate the possibility that peripheral and central production of cytokines may account for neuropsychiatric symptoms in inflammatory diseases. This article summarizes evidence for a cytokine-mediated pathogenesis of depression and fatigue in MS. The effects of central inflammatory processes may account for some of the behavioral symptoms seen in patients who have MS that cannot be explained by psychosocial factors or CNS damage. This immune-mediated hypothesis is supported by indirect evidence from experimental and clinical studies of the effect of cytokines on behavior, which have found that both peripheral and central cytokines may cause depressive symptoms. Emerging clinical data from patients who have MS support an association of central inflammation (as measured by MRI) and inflammatory markers with depressive symptoms and fatigue.

Based on the literature reviewed in this article, subtypes of MS fatigue and depression may exist that are caused by different pathogenetic mechanisms, including inflammation and CNS damage as well as psychosocial factors or predisposition. The existence of these subtypes could have important clinical implications. For example, an inflammatory depression may require different therapeutic approaches than a reactive depression in MS. Future research should aim to characterize these subtypes better with the goal of optimizing treatment.

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