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Depression and immunity: Inflammation and depressive symptoms in multiple sclerosis

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Abstract

An increasing body of evidence suggests that patients with major depressive disorder show alterations in immunological markers including increases in proinflammatory cytokine activity and inflammation. Animal models of a depression-like syndrome called sickness behavior have clearly shown that cytokines are implicated in the development of these symptoms. Inflammation of the CNS is a pathological hallmark of multiple sclerosis (MS). Patients affected by this disease also show a high incidence of depression. In light of accumulating evidence for cytokine-mediated sickness behavior from animal studies, it is possible that some aspects of depression and fatigue in multiple sclerosis may be linked to inflammatory markers. Here, we review the current knowledge in the field and illustrate how the sickness behavior model may be applied to investigate depressive symptoms in inflammatory neurological diseases such as multiple sclerosis.

1. Major depression and medical co-morbidity

Neuropsychiatric disorders, especially major depressive disorder, are now one of the leading causes of disability [1]. Major depressive disorder, which exceeds a lifetime incidence of 10% [2, 3], is a potent risk factor for disease morbidity with depressed persons showing a mortality rate twice that found in non-depressed persons [4–7]. Altered functioning of the immune system is implicated as 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 infectious disease susceptibility [10, 11], whereas other studies have found that depression is linked to immune activation in patients with inflammatory disorders such as rheumatoid arthritis [9] or cardiovascular disease [12, 13], or who are undergoing cytokine therapy [14].

1.1. 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 immunological changes identified in depressed persons [15]. Further evaluation of lymphocyte subpopulations found that depression is negatively related to the number and percentage of lymphocytes (B cells, T

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cells, T helper cells and T suppressor/cytotoxic cells) as well the NK cell phenotype, although such differences have not been consistently replicated [16].

For the evaluation of the function of the immune system in depressed patients, a majority of studies have relied on results from assays of non-specific mitogen-induced lymphocyte proliferation, mitogen-stimulated cytokine production, and NK cytotoxicity. More than a dozen studies have now been conducted on lymphocyte proliferation in depression and there is a reliable association between major depression and lower proliferative responses to the three non-specific mitogens including phytohaemaglutinin (PHA), concanavalin-A (Con A), and pokeweed (PWM) [16]. In addition, a number of independent laboratories have confirmed the finding of reduced NK activity in major depression [16].

1.2 Cytokines and depression

Aanimal models that use chronic mild stress to induce depression-like syndromes report alterations in immune parameters including increased IL-1 production [17]. However, studies of stimulated cytokine production in humans have not yielded consistent findings. For example, in whole blood assays, Kronfol *et al.* [18] found increased lipopolysaccharide-stimulated production of IL-1 and IL-6, but no change in the expression of tumour necrosis factor α. Other studies have suggested a shift in the relative balance of T helper 1 vs. T helper 2 cytokine production with increases in the capacity of lymphocytes to produce interferon in depression [19], yet 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, as depressed patients who show no difference in IL-2 production evidence declines of NK activity [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 between 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 interleukin-1 β and interleukin-1 receptor antagonist as compared to responses from controls and melancholic depressed patients [22]. However, 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 HPA axis which is thought to inhibit immune activation and the expression of inflammatory markers, which might account for the reported differences in these two groups of diagnostic depression [22].

In contrast to the inconsistent findings regarding association between depression and production of inflammatory cytokines, meta-analyses indicate that depression is associated with increase in circulating levels of the pro-inflammatory cytokine, interleukin-6 (IL-6) [16]. Importantly, as compared to controls, elevated levels of IL-6 have been found in adults with major depression [24–26], as well in depressed elderly populations [27] and in those with 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 due to activation of monocyte populations, and increases in circulating levels of other proinflammatory cytokines such as tumor necrosis factor-α (TNF) and interleukin-1β (IL-1) have been reported in depressed patients [30, 31] including late-life depressive disorder [32]. However, the numbers of studies that have examined these additional cytokines is too few to make firm conclusions. One study also reported increases of plasma levels of IL-12 in a large cohort of depressed patients [33].

1.3. Behavioral effects of proinflammatory cytokines

Abundant evidence supports the notion 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 and/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 (e.g. 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-α administration in patients with 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-β (multiple sclerosis therapy), IL-1, IL-2, and TNF-α (cancer treatment). The most common side effects of these treatments are flu-like symptoms such as fever, malaise, headache and myalgia, which typically occur early (approx. 2 weeks) after the start of treatment but tend to attenuate once treatment is continued. In contrast, neuropsychiatric symptoms including anxiety, dysphoria, anhedonia, fatigue, anorexia, cognitive and psychomotor slowing generally occur after 1 to 3 months of therapy; these “depressive” symptoms persist unless treatment is terminated or supplemented by anti-depressant medications [36]. It is important to note that administration of IL-2 or IFN-α can activate the proinflammatory cytokine network and cause the subsequent elevation of IFN-γ, IL-6, IL-8 and others. It is therefore conceivable that the comparatively late onset of neuropsychiatric symptoms reflects an epiphenomenon to the induction of endogenous cytokines.

1.4. Brain signaling by cytokines

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

Of particular relevance to this review, cytokines themselves have been found to promote BBB degeneration in inflammatory conditions [39]. In the case of multiple sclerosis, a pronounced breakdown of the BBB, 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 oligodentroglial damage may be important for behavioral symptoms in MS. This will be discussed in detail in section 2.

1.5. Cytokine effects on neuroendocrine function and neurotransmitters

Several biological 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 (NE), is guided by a prevailing biological hypothesis of depression, which states that serotonin deficiency plays a crucial role in the pathogenesis of this disorder. This hypothesis is largely based on the observation that

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

Another important mechanism refers to the activation of the neuroendocrine system by cytokines. Depressed patients 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 following lesioning of the brain (e.g., hypothalamus) or in response to the stimulation of certain brain regions which ultimately impact CRH systems. The brain controls immune cells in lymphoid tissue in the same manner 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 is also blocked [45, 46].

2. Clinical application: Depression in multiple sclerosis

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

Whereas the presence of depression in MS does not appear to be related to severity of neurological impairment [51] and can also occur in very early stages of the disease [52], it has a strong impact on the patients' functional status: MS patients with co-morbid depression perform more poorly on tests of cognitive function [53, 54]. It has also been shown that depression adversely affects quality of life in MS patients [55], contributes to disruptions of social support [56], and also interferes with work attendance [57]. Since depression is also linked to poorer treatment compliance [58], it can potentially affect long-term health outcome. Finally, it is reported that depression is the most powerful determinant of suicidal intent in MS patients [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 better understand the pathogenesis of depression and its potential interactions with MS disease processes in order to develop novel treatment options.

2.1. Pathogenetic models of depression in MS

To date, little is known about the pathogenetic factors that account for the development of depressive symptoms in multiple sclerosis. 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 stated that the pathogenesis is most likely multifactorial including psychological, social, neurobiological as well as immunological and genetic factors. Here, we briefly review some of the pathogenetic models proposed.

Psychosocial factors—A simple explanation for the occurrence of depression in multiple sclerosis is that it is primarily reactive in nature, i.e. a response to facing a chronic illness characterized by the uncertainty of prognosis with no therapeutic cure available. However, 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 appear to mediate the relationship between disease and depression in MS [60, 61], although depression is not simply a failure of patients to cope with the psychosocial challenges [62]. Interventions designed to provide social support (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 compared to other chronic progressive diseases [64]. It has therefore been proposed that depression may be related to disease-specific processes such as CNS damage or changes in immune parameters as hypothesized above.

Damage to CNS—Another plausible explanation for the higher incidence of depression may thus be disease-specific nature and location of damage to the CNS. Pujol et al. [65] reported a specific association of lesions in the left suprainsular white matter with depressive symptoms, accounting for a significant 17% of the depression variance. More recently, T1 black holes (which are thought to reflect severe tissue damage) in superior frontal and superior parietal regions predict depression [66]. Feinstein et al. [67] found greater left medial inferior prefrontal cortex T2 lesion volume and left anterior temporal CSF volume associated with depression, which together accounted for 42% of the depression variance. One other study has shown more frontal atrophy in MS patients with depression compared to non-depressed MS patients [68]. While these studies suggest that MS lesion location and severity may be associated with certain depressive features in MS, no clear anatomical pattern could be established so far.

2.2. EAE 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 prior to the onset of neurological 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 brain inflammatory cell infiltration as well as brain tissue mRNA expression of IL-1β and TNF-α and prostaglandin E2 [70]. Interestingly, anti-inflammatory treatment ameliorated the behavioral effects [71].

2.3. Aspects of depression and fatigue in MS resemble sickness behavior seen in animal models

One intriguing aspect of depression in MS is its relation to fatigue. Fatigue is a common symptom both in depression as well as in MS. Mohr et al. 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” [72]. While earlier studies have not found evidence for an association of depression and fatigue in MS [73, 74], later reports have usually confirmed a moderate correlation [75–79]. Interestingly, the relationship appears to differ between different dimensions of fatigue, as it was stronger with mental fatigue than 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 provide an explanation for these differential associations.

2.4. Clinical evidence for the role of inflammation in MS `sickness behavior'

Depression is a suspected side effect of multiple sclerosis (MS) treatment with interferon β-1a. It has been suggested that interferon treatment in MS may either induce depression or worsen existing depressive symptomatology. However, although several studies have investigated this hypotheses using datasets from phase III clinical trials, it appears that anecdotal evidence of increased depression during interferon treatment is most likely better explained 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 et al. [81] showed that during relapse, MS patients with higher depression scores had significantly increased white blood cell counts in CSF. Depression scores were also higher in patients with MRI evidence for CNS inflammation as indicated by Gd-enhancing lesions on MRI. Interestingly, depression scores in this study also correlated with activation of the HPA axis. In another study assessing MS patients during relapse, Kahl et al. [82] reported that mRNA levels of TNF-α and IFN-γ obtained from whole blood samples were increased and both cytokines were significantly correlated with scores on the Beck Depression Inventory. Th2-type cytokines such as IL-10 and IL-4 were not correlated with BDI scores. During remission in a subgroup of patients (follow-up at 3–6 months and 1 year), only TNF levels showed a significant correlation with BDI scores. In line with these findings, Mohr et al. [83] also showed a positive correlation of depression and in vitro IFN-γ production. In this small study, amelioration of depression after psychotherapy or antidepressant medication treatment was paralleled by decreases in IFN-γ production capacity. In another study, treatment of MS depression with lofepramine, a derivative of the antidepressant medication imipramine, was associated with decreases in T1 lesion load [84].

A few studies have investigated the association of inflammatory markers and fatigue in MS. An early study [85] could not find correlations of fatigue and urinary neopterin, CRP, and sICAM-1 in a sample of 38 MS patients. However, more recently, cytokines typically associated with sickness behavior have been found to be associated with MS fatigue. For example, Flachenecker et al. [86] showed a positive correlation with TNF-α mRNA levels. Heesen et al. [87] reported correlations of TNF-α and IFN-γ in vitro production and fatigue severity. TNF-α levels were further associated with self-report measures of daytime sleepiness.

In summary, these findings are in accordance with the cytokine-hypothesis of MS depression and fatigue. However, it is not known whether depression occurs secondary,

primary or coincidental with inflammation in this population, even though antidepressant medication treatment has been shown to decrease inflammatory markers in MS.

3. Conclusion

There is strong evidence that depression involves alterations in multiple aspects of immunity that may not only contribute to the development or exacerbation of a number of medical disorders but 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 also be applied to investigate the possibility that peripheral and central production of cytokines may account for neuropsychiatric symptoms in inflammatory diseases. In this paper, we summarized evidence for a cytokine-mediated pathogenesis of depression as well as fatigue in MS. The effects of central inflammatory processes may account for some of the behavioral symptoms seen in MS patients, which cannot be explained by psychosocial factors or the CNS damage hypothesis. This immune mediated hypothesis is supported by indirect evidence from experimental and clinical studies on the effect of cytokines on behavior, in which peripheral as well as central cytokines may cause depressive symptoms. There are emerging clinical data from MS patients to provide support for an association of central inflammation (as measured by MRI) as well as inflammatory markers with depressive symptoms and fatigue.

Based on the literature reviewed above, 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. This 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 better characterize these subtypes, which has the potential to optimize treatments.

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