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A temporal framework for understanding the effects of stressful life events on inflammation in patients with multiple sclerosis ☆

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Abstract

A growing literature reports that stressful life events are associated with exacerbation and the subsequent development of brain lesions in patients with multiple sclerosis (MS). The evolution an MS exacerbation occurs over a period of many months and involves many different biological processes that change over time. Likewise, the experience of stress also occurs over time, with an onset, a shift from acute to chronic in some cases, and resolution. Each of these phases is associated with unique biological features. Thus, the impact of stress on MS exacerbation may depend on the temporal trajectories of stress and MS exacerbation, and when the intersection between these two trajectories occurs. This paper presents a temporal model, along with three different temporal relationships and associated mechanisms by which stress may impact MS exacerbation. These include the onset of a stressor, which may be mediated by mast cell activation, the point that a stressor begins to become chronic, which may be mediated by glucocorticoid resistance in immune cells, and the resolution of the stressor, which may be mediated by a drop in cortisol. These three hypotheses are not necessarily mutually exclusive. Data on psychosocial mediators and moderators are also briefly reviewed and future research directions are discussed.

Keywords: Multiple sclerosis; Stress; Psychoneuroimmunology; Behavioral medicine

1. Introduction

Multiple Sclerosis (MS) is a chronic, often disabling disease of the central nervous system (CNS) affecting up to 350,000 people in the United States (Anderson et al., 1992; Jacobson et al., 1997; Noonan et al., 2002). As with many autoimmune diseases, it affects women at roughly twice the rate of men, and the prevalence appears to be increasing (Cooper and Stroehla, 2003; Jacobson et al., 1997). Common symptoms include, but are not limited to, loss of function or feeling in limbs, loss of bowel or bladder control, sexual dysfunction, debilitating fatigue, blindness due to optic neuritis, loss of balance, pain, cognitive dysfunction, and emotional changes (Mohr and Cox, 2001).

Many patients with MS believe that stress can worsen their symptoms. A growing literature is addressing this question. However, we will argue that this literature has largely ignored the temporal relationships between stressful life events and MS disease activity. The purpose of this paper is to review the empirical literature on the effects of stress on MS and to place this literature in the context of the temporal relationships, using three hypothesized potential mechanisms. To accomplish this, we will provide a brief description of MS pathology and pathogenesis, review the evidence on the association between stress and MS exacerbation and present the temporal model with

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three hypotheses for potential mechanisms. We will also briefly explore the potential role of psychosocial mediators and moderators, and discuss future directions.

2. Brief review of MS pathology and pathogenesis

There are two distinct clinical disease markers in MS, exacerbation and progression. Exacerbation is defined as a sudden onset or increase in a symptom within 24 h, which resolves fully or partially over the course of weeks or months. Progression refers to a steady worsening in the absence of exacerbations. The course of MS is variable (Lublin and Reingold, 1996). Approximately 80% of patients begin with a relapsing-remitting (RR) course that is characterized by periodic exacerbations but no progression between exacerbations (Noseworthy et al., 2000). With a decade after diagnosis over 40% of patients with RRMS convert to secondary progressive MS (SPMS), which is characterized by the onset of progression between exacerbations and a decrease in the frequency of exacerbations. Approximately 10–15% of patients have a primary progressive course characterized by a steady progression of symptoms in the absence of exacerbations, and appears to have a different pathogenesis (Thompson et al., 2000). This paper will focus primarily on the effects of stress on relapsing forms of MS as there is almost no literature on stress in primary progressive MS.

MS is a disease in which the immune system attacks the myelin sheath surrounding the axons of neurons in the CNS. The precise etiology of the disease remains largely unknown. Given the clinical, genetic, neuroimaging, and pathological heterogeneity, the pathogenesis of MS is likely multifactorial, involving genetic susceptibility, environmental factors such as exposure to an antigen, developmental factors, autoimmunity, and neurodegenerative processes (Noseworthy et al., 2000). The pathogenesis of an MS exacerbation likely begins long before the emergence of clinical signs. Advanced neuroimaging studies indicate that changes in the ratio of bound to unbound water are evident weeks or even months before conventional neuroimaging evidence of inflammation, including gadolinium enhanced magnetic resonance imaging (Gd+ MRI), or clinical exacerbation (Filippi et al., 1998; Goodkin et al., 1998).

It is generally believed that inflammation and demyelination in MS are the result of autoreactive immune responses to myelin proteins. These are believed to be caused by molecular mimicry and a failure of self-tolerance. Researchers have found support for a number of infectious agents that may serve as a trigger, including the herpes viruses and Epstein–Barr virus (Sospedra and Martin, 2004). One theory, which has received considerable attention, is that the immune cascade is initiated through molecular mimicry, in which T-cells activated by the virus can also cross-react with auto-antigens such as myelin basic protein (MBP), myelin oligodendrocyte glycoprotein (MOG), and proteolipid protein (PLP) (Hohlfeld et al., 1995; Noseworthy et al., 2000). Activated Th1 cells secrete inflammatory cytokines that promote proliferation and adherence to the endothelium of the blood vessels through up-regulation of adhesion molecules. Recruitment of immune cells is facilitated by a variety of chemokines. Immune cell adhesion to the endothelium and transmigration cells across the blood–brain barrier (BBB) into the brain are facilitated by increases in matrix metalloproteinases, mast cells, and chemokines (Bar-Or et al., 2003; Sospedra and Martin, 2004). Antigen presenting cells within the CNS (astrocytes, microglia, and macrophages) further stimulate the T-cells by presenting myelin proteins, which are mistaken by the Th1 cells as the foreign antigen presented initially. This can result in an enhanced immune response whereby proinflammatory cytokines trigger a cascade of events resulting in proliferation of Th1 cells, and ultimately immune-mediated injury to myelin and oligodendrocytes (O'Connor et al., 2001). The proinflammatory cytokines that have been most commonly implicated in this process include interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukins (IL) 1β, 6, and 12. Damage to the myelin sheath may occur directly through cytokine-mediated injury, digestion of surface myelin by macrophages, antibody-dependent cytotoxicity, complement-mediated injury, and/or direct injury of oligodendrocytes by CD4+ and CD8+ T-cells (Bruck and Stadelmann, 2003). Some remyelination can occur via the local response by oligodendrocyte progenitor cells, however exposed axons may also be further injured and transected or severed by continuing inflammation (Bjartmar et al., 2003). We should note that many studies have also shown autoimmune reactions to MBP, MOG, and PLP in healthy control subjects, suggesting that autoreactivity alone is not sufficient to invoke the disease, and that failure to establish tolerance may play a critical role in MS (Sospedra and Martin, 2004).

While the process of inflammation and demyelination is the hallmark of the early, inflammatory period of the disease, it is increasingly recognized that other neurodegenerative processes become more prominent as the disease progresses (Confavreux et al., 2000; Trapp et al., 1998). While axonal transection in the earlier stages of the disease appears to be primarily due to inflammatory processes, degeneration of axons in later stages of the disease may be due to a lack of trophic support from myelin or myelin forming cells (Scherer, 1999). These two stages may correspond to the RR disease course seen earlier, in which there are exacerbations with quiescence between stages, and the SP course in which progression in the absence of exacerbation becomes increasingly prominent. To date the impact of stressful life events on progression or neurodegenerative processes remains largely unexamined. We will therefore focus this review on exacerbations and inflammatory processes.

3. Evidence of the relationship between stressful life events and ms exacerbation

Charcot, who first characterized MS in the 19th century, wrote that grief, vexation, and adverse changes in social circumstance were related to the onset of MS (Charcot, 1877). Since then numerous clinical studies have been conducted examining the relationship between stressful life events and MS exacerbation. A recent meta-analysis of 14 studies examining the effects of stressful life events on MS exacerbation found significantly increased risk of exacerbation associated with stressful life events ($d = .53$) (Mohr et al., 2004). While this is only a modest effect size, it is clinically relevant, given that the positive effect of the most commonly used disease modifying medications on exacerbation, interferon betas, is estimated at $d = .30$–$.36$ (Filippini et al., 2003).

While the studies examined in the meta-analysis were statistically homogenous (Mohr et al., 2004), closer inspection suggests that not all stressful life events have the same effects. Thirteen of the studies showed similar increased risk of exacerbation associated with stressful life events. All 13 of these studies examined the usual types of stressful life events encountered in the United States and Europe, where the studies were conducted. However, one study showed a decrease in risk of exacerbation during and after the stressful life event (Nisipeanu and Korczyn, 1993). This study found that MS patients being followed in a longitudinal study in Tel Aviv, Israel, were significantly less likely to have exacerbations during the several weeks they were under daily and nightly missile attack during the first Gulf War, and for two months thereafter, compared to other time points in the study. While it is possible that this isolated finding is due to chance alone, it may also be the result of the distinct type of traumatic stressors (e.g., sudden and life threatening). Such traumatic stressors may have very different effects on MS exacerbation compared to the more common types of stressors experienced by patients in most western countries which tend not to be life threatening but are often more chronic (e.g. family conflicts, stress in the work place, etc.) but not life threatening.

The findings of the meta-analysis have been confirmed using a more objective neuroimaging marker of MS BBB disruption associated with inflammation, Gd+ MRI. Gadolinium is a contrast agent injected into the blood stream during the MRI scan, which crosses the BBB at sites of focal MS inflammation, thereby providing images of active inflammation. Gd+ MRI is 5–10 times more sensitive than neurologist determinations of clinical exacerbation in evaluating active MS inflammation (Grossman, 1996). In a longitudinal study of MS patients receiving monthly Gd+ MRI, we have shown that stressful life events, particularly those involving family- and work-related stress, are associated with the subsequent development of Gd+ brain lesions (Mohr et al., 2000).

4. Hypothesized mechanisms

4.1. Effect of stressful life events and inflammatory stress on the HPA axis

It has been known for many decades that life events that are perceived as stressful can result in activation of the hypothalamic–pituitary–adrenal (HPA) axis. A recent meta-analysis of 208 laboratory studies of acute stressors found that the elements of the stressor critical to eliciting an HPA response are that it is uncontrollable and involves a social-evaluative threat (e.g., being judged negatively by others) (Dickerson and Kemeny, 2004). Such stressors result in hypothalamic production of corticotropin releasing hormone (CRH) and arginine-vasopressin (AVP). CRH stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH). The effect of CRH as an ACTH secretogue is enhanced by AVP. ACTH stimulates the adrenal cortex to produce cortisol, which is the final effector of the HPA axis, exerting an inhibitory effect on hypothalamic production of CRH. Thus, the HPA axis is self-regulating, in part through the inhibitory effect of cortisol. However, when stress becomes chronic, these feedback mechanisms become dysregulated. This dysregulation frequently results in increased levels of cortisol production (Chrousos, 1995), although under some circumstances of sustained stress, hypocortisolemia can occur (Heim et al., 2000). This dysregulation can occur through alterations in the number and/or function of glucocorticoid receptors in the hypothalamus, and through a shift from CRH drive to AVP drive (Tilders and Schmidt, 1998), which is less sensitive to glucocorticoid feedback.

Inflammation can also activate the HPA axis (Chrousos, 1995). The pro-inflammatory cytokines IL-6, IL-1, and TNF-α have been shown to stimulate CRH and AVP secretion in the hypothalamus (Akira et al., 1990; Bernardini et al., 1990; Tsigos and Chrousos, 2002), while other proinflammatory cytokines such as IFN-γ may participate indirectly by stimulating the production of cytokines that act on the HPA axis (Chrousos, 1995). This activation of the HPA axis leads to increased cortisol release. Due to the ubiquity of glucocorticoid receptors in cells and tissue involved in the immune response, virtually all components of the immune response can be modulated by cortisol, including leukocyte trafficking and function, production of cytokines and other mediators of inflammation, and inhibition of the effects of immune mediators on target tissues (Chrousos, 1995; Elenkov and Chrousos, 2002; Jessop et al., 2001) (indeed, glucocorticoids are the principal treatment for exacerbation in MS Kopke et al., 2004). This

system allows an organism to adjust to changes in levels of inflammation by increasing or decreasing the output of anti-inflammatory glucocorticoids, as needed.

A growing literature has challenged early assumptions that autoimmune disease was associated with HPA hyporeactivity in response to stress and inflammation (Harbuz, 2002). Much of the research on HPA reactivity in MS has used stimulation through injection of human CRH and/or ACTH. MS patients generally show significantly greater hyperreactivity rather than hyporeactivity, compared to healthy controls (Fassbender et al., 1998; Grasser et al., 1996; Schumann et al., 2002; Then Bergh et al., 1999), although some studies have reported a subgroup that appears to show hyporesponsiveness (Grasser et al., 1996; Schumann et al., 2002; Wei and Lightman, 1997). There is some suggestion that hyporesponsiveness may be due to greater lesion load in the hypothalamus and that more intact hypothalami of MS patients show a chronically activated CRH system (Huitinga et al., 2004). While these studies, in themselves, do not specifically address whether or not stress response is altered in MS, they do suggest that the HPA axis, which is involved in the mediation of stressful life events, is altered in MS, generally towards hyperreactivity.

One would expect, under normal circumstances, that stressful life events should reduce the risk of MS exacerbation, due to elevated levels of cortisol production. Indeed, in rodent models of MS, including experimental allergic encephalomyelitis (EAE) and Theiler's virus infection, stress in the form of electric shock or restraint suppresses clinical and histopathological changes as well as lymphocyte numbers and activity (Bukilica et al., 1991; Campbell et al., 2001; Kuroda et al., 1994; Sieve et al., 2004; Whitacre et al., 1998). In light of these rodent models and what one might logically expect given the regulatory role of cortisol, the finding that in humans stress is often associated with increased risk of inflammation and exacerbation is somewhat paradoxical.

4.2. The temporal model

A number of reviews of the literature have proposed biological models by which stressful life events might increase risk of MS inflammation and/or exacerbation (Marchetti et al., 2001; Martinelli, 2000; Mohr and Cox, 2001; Morale et al., 2001; Rabin, 2002). None of these reviews, including our own work, have clearly articulated the importance of the temporal relationships between the stressful life event and the disease process. This is critical, since both the course of the exacerbation and the course of the stressor occur over varying lengths of time, with different pathogenic processes at different stages. Fig. 1 displays a model of the relationship between a stressor and the disease event. Both the disease event (in this case exacerbation) and stress (particularly chronic stress) occur over time, having an onset, a period during which they are present more or less continuously, and a resolution. This model facilitates consideration of the relationship between the pathogenic features of stress and exacerbation at each stage of development.

Stressors occur over a period of time. The biological mediators of stressors vary, depending on the point in the evolution of the stressor one examines. The onset of a stressor, particularly if the onset is sudden, salient, and intense, is often accompanied by sympathetic activation, increases in epinephrine and norepinephrine, and activation of the HPA axis. As the stressor becomes chronic, the HPA axis can become dysregulated, often resulting in higher levels, and sometimes lower levels, of circulating cortisol (Sapolsky et al., 2000). Resolution or adaptation to the stressor under normal circumstances results in re-regulation of the HPA axis and return of circulating levels of cortisol to baseline. Thus, the biological mediation of stressors changes with evolution of the stressor. As such, the impact of stress response on disease processes is likely to depend on the point in the evolution of the stress response one examines.

MS exacerbation also has a long trajectory, as displayed in Fig. 1. For many years it was assumed that BBB breakdown was a very early event in the development of an MS brain lesion and clinical exacerbation. However, newer neuroimaging techniques such as magnetic transfer ratio (MTR) imaging have shown that changes in the ratio of bound to unbound water begin to occur in white matter tissue several months before the emergence traditional neuroimaging markers of inflammation such as Gd+ MRI lesions (Filippi et al., 1998; Goodkin et al., 1998). While the specific nature or processes involved in these changes are not well understood,

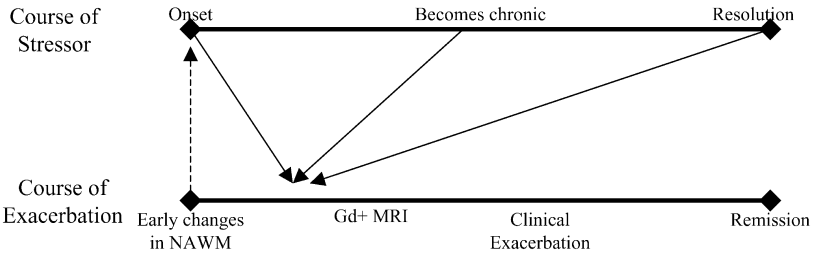

Fig. 1. Temporal model of stress and exacerbation Gd+ MRI, gadolinium enhancing MRI; NAWM, normal appearing white matter.

it is clear that vulnerability begins in the tissue long before active inflammation begins. Once there is BBB breakdown and active inflammation at that site, attempts at regulation of the inflammation occur, including the production of Th2 cytokines such as IL-10. If regulation is not sufficiently successful within a brief period of time, clinical signs of exacerbation occur. Even in the absence of treatment with glucocorticoids, active inflammation at the site of the lesion will subside over a period of weeks or months, but may leave some residual, permanent symptoms if sufficient irreparable demyelination or axonal damage resulted from the inflammation. Thus, our current understanding is that the pathogenesis, development, and resolution of MS exacerbation can span many months. The impact of stressful life events on MS exacerbation is likely to depend when the stressor occurs in the evolution of an MS exacerbation.

Thus, as depicted in Fig. 1, there are numerous potential points the evolution of a stressor that can interact with numerous points in the evolution of an MS exacerbation. For example, the onset of the stressor could potentially be associated with the early changes in normal appearing brain tissue, the beginnings of inflammation, the failure of regulatory efforts and subsequent exacerbation, or the remission of exacerbation. The same could potentially be true at other stages of stress, including as stress becomes chronic, or as it resolves. Each of these potential effects could have unique biological features and pathways.

Finally, it must be emphasized that the effects of a stressor at any point in time could potentially be either stimulatory or permissive. That is, the stress could have a direct effect that is either necessary or sufficient to initiate a pathogenic process. Alternatively, particularly in light of the regulatory effects of cortisol on inflammation, stress could have permissive effects that are neither necessary nor sufficient to initiate pathogenic processes, but which nevertheless may enhance ongoing inflammatory processes or inhibit regulatory pressures.

The existing data in MS suggest that the onset of stressful life events occurs several weeks to two months before the occurrence of clinical signs of exacerbation or neuroimaging markers of inflammation (Ackerman et al., 2002; Buljevac et al., 2003; Mohr et al., 2000; Sibley, 1997). We note that other potential timeframes between stress onset and onset of specific MS disease markers, particularly shorter time frames such as hours or days, remain unexplored and cannot necessarily be ruled out at this time. Because the extant literature identifies the stressful life event as occurring in advance of these markers of disease activity, any point along the evolution of the stressor could potentially affect the MS disease process including stress onset, change from acute to chronic, and the resolution of the stressor (see Fig. 1). We will review the evidence for each of these temporal hypotheses and present a hypothesized model. These hypotheses are not mutually exclusive.

4.3. Stress resolution hypothesis

This hypothesis suggests that it is the resolution of the stress rather than the onset of stress that facilitates the development of active inflammation during this prodromal period. While chronic stress is commonly marked by increased levels of cortisol (McEwen, 1998), trials of stress management programs have reported that cortisol decreases as a result successful stress management intervention (Antoni et al., 2000). MS patients with relapsing disease also often show evidence of low levels of ongoing inflammation not noticeable by the patient or by usual neuroimaging but detectible by triple-dose Gd+ MRI (Silver et al., 1997; Tortorella et al., 1999). Thus, as cortisol rises following the onset of a stressful situation, the person with MS would receive some increased control over inflammation. However, as the stressor resolves, the concomitant reduction in cortisol would represent a decrease in control over inflammatory processes, and could leave the individual at an increased risk for exacerbation. Patients' belief that the cause of exacerbation is a stressful life event would be an attributional error. That is, patients may be less likely to attribute an exacerbation to a positive event, such as the resolution of a stressor, and more likely to attribute it to the onset of the stressor, even if this occurred some weeks earlier.

While there is currently no specific evidence for or against this hypothesis in humans, the EAE literature does offer some support. While most EAE studies find that stress suppresses disease activity, these studies routinely sacrifice the animals following the stress induction protocol, typically after 1–14 days. In an innovative study, Whitacre kept the animals alive after the stress induction and found that 10 days after the termination of the stress protocol the clinical signs of EAE returned and in many cases were worse than among the unstressed control animals (Whitacre et al., 1998). While it must be acknowledged that there are problems generalizing animal models to human disease, these findings nevertheless support the hypothesis that the resolution of a stressor can have a permissive effect on inflammatory processes, and suggest that this should be further examined among MS patients.

4.4. Development of chronic stress: glucocorticoid resistance

The glucocorticoid resistance hypothesis suggests that exposure to chronic stress reduces the number and/or function of glucocorticoid receptors on immune cells, thereby making them less responsive to regulatory control by cortisol. Glucocorticoid resistance has been reported on several occasions in mice exposed to social stressors (Avitsur et al., 2001, 2002; Stark et al., 2001, 2002). There is some support for the notion that immune cells of patients with MS are less sensitive to the regula-

tory effects of glucocorticoids than the cells of healthy individuals (DeRijk et al., 2004; Stefferl et al., 2001). Furthermore, this glucocorticoid resistance is seen primarily among RRMS patients in the earlier, more inflammatory phase of the illness as opposed to SPMS patients who are shifting to a more progressive, neurodegenerative phase of the disease. Glucocorticoid resistance can occur in other autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematoisis and has been attributed to the chronic treatment with glucocorticoids (Chikanza et al., 1992; Sher et al., 1994; Tanaka et al., 1992). However, chronic treatment with glucocorticoids is rare in MS and acute glucocorticoid treatment has not been associated with glucocorticoid resistance in MS (DeRijk et al., 2004).

We propose that glucocorticoid resistance in MS has two related etiologies, independent of the use of glucocorticoid treatments. Patients who experience chronic stressors are also likely to experience increased levels of cortisol (McEwen, 1998). While these levels are far lower than those used for pharmacological purposes, they nevertheless have been shown to produce glucocorticoid resistance in humans (Miller et al., 2002). Second, chronic, low-grade inflammation seen in relapsing forms of MS (Silver et al., 1997; Tortorella et al., 1999) may be responsible for the mild hypercortisolemia seen in these patients (Then Bergh et al., 1999; Wei and Lightman, 1997). Thus, patients may produce chronic, if small elevations in cortisol in an attempt to regulate inflammation and maintain self-tolerance. The dual effects of stressful life events and inflammation on the immune system may result in a down-regulation of glucocorticoid receptor number and function, thereby reducing the impact of HPA regulation of inflammation.

Under conditions of down-regulated glucocorticoid receptors, if there is a small increase in auto-reactive inflammation, immune cells would be less responsive to the regulatory effects of cortisol. The auto-reactive immune cascade would be able to continue uncontrolled until a full-blown exacerbation had occurred. Thus, chronic stress, while not causing exacerbation, may leave patients less able to maintain self-tolerance when autoreactive MS immune processes are initiated.

4.5. Stress onset: the mast cell hypothesis

In our experience, many patients complain that the effects of stress on MS symptoms can occur within hours. We are not aware of any good empirical work validating or examining these reports. Laboratory stressors such as the Trier Social Stress Test (TSST) have been shown to produce significant elevations in pro-inflammatory cytokines in some studies (Ackerman et al., 1996, 1998), although not in others (Heesen et al., 2002, 2005). (We note that Ackerman reported in a personal communication that the cognitive tasks are not as effective as public speaking in eliciting and neuroendocrine stress response among MS patients, possibly because MS patients do not expect themselves to perform as well on cognitive tasks; the two studies that did not elicit a stress response only used cognitive tasks.) However, even when the TSST produced increases in pro-inflammatory cytokines, these elevations were similar to those seen in healthy controls. Similarly, acute stressors such as injury have not been associated with exacerbation (Goodin et al., 1999). However, it is possible that there are subtle permissive effects and increased risk under specific circumstances. For example, low levels of glucocorticoids, consistent with endogenous cortisol response to moderate stress, may have numerous effects that can promote inflammation, including increased T-cell proliferation (Wiegers et al., 1993, 1995). Indeed, these permissive effects may be particularly enhanced within the central nervous system (Dinkel et al., 2003). However, the mechanism that has been most thoroughly investigated with respect to potential MS pathways involves the acute activation of mast cells (Theoharides, 2002; Zappulla et al., 2002).

Mast cells have been referred to as an immune gate to the brain (Theoharides, 2002). Increasing evidence suggests that this gate may be opened by environmental stressors (see Theoharides, 2002; Zappulla et al., 2002 for reviews). Mast cells are multifunctional effector cells of the innate immune system and are distributed broadly throughout human tissue, including vascular endothelium in the brain (Zappulla et al., 2002). For over a century it has been known that mast cells are found in MS demyelinated plaques, particularly around the venules and capillaries (Kruger, 2001; Kruger et al., 1990). Mast cells may participate in MS exacerbation by facilitating vascular permeability. Mast cells are known to be critical in the initial retardation of leukocytes rolling along the endothelium and the subsequent firm adhesion and extravasation (Kubes and Granger, 1996; Kubes and Ward, 2000). Extravasation is facilitated by mast cell-produced tryptase, as well as adhesion molecules (Kanbe et al., 1999; Theoharides, 2002; Zappulla et al., 2002). All of these vasodilators have been implicated in BBB permeability in MS (Piccio et al., 2002; Spuler et al., 1996; Tuomisto et al., 1983; Waubant et al., 1999).

Mast cell activity is also triggered by stress. Restraint stress has been shown to increase BBB permeability in rats through mast cell activation (Esposito et al., 2001) and subordination stress has been shown to increase numbers of mast cells across a number of brain regions (Cirulli et al., 1998). A principal mediator of stress-related mast cell activation is CRH (Theoharides et al., 1998). Hypothalamic CRH is a primary hormonal response to stressful life events. However, CRH is also present at sites of inflammation. Stress-related BBB breakdown via mast cell activation has repeatedly been shown to be facilitated by immune CRH (Esposito et al., 2001; Singh et al., 1999; Theoharides et al., 1998). Recent studies further indicate

that increases in hypothalamic CRH consistent with stress responses can increase immune CRH and induce mast cell degranulation, thereby increasing BBB permeability (Esposito et al., 2002). This would suggest that stress onset might have a permissive effect on MS exacerbation by facilitating BBB breakdown.

5. Psychosocial factors

5.1. Psychosocial mediators

Numerous models of the effects of stressors on immune function suggest or imply that the psychological component responsible for inflammation would be emotional arousal or distress. In a longitudinal study examining the effects of treatment for depression on immune function in MS patients, we showed that reductions in depression were associated with declines in T-cell production of IFN-γ (Mohr et al., 2001). Importantly, the reductions in IFN-γ production were seen not only for a non-specific antigen, but also for myelin oligodendrocyte glycoprotein, suggesting that treatment for depression can have an effect on highly specific factors in the pathogenesis of MS inflammation and exacerbation. We also examined the effects of change in each of the affective, cognitive, and vegetative symptoms (Louks et al., 1989). While there was a trend towards an association between improvement in affective symptoms and decreased IFN-γ production ($r = .41$, $p = .11$), there was a strong relationship between improved cognitive symptoms (e.g., self-accusation, guilt, and sense of failure) and reductions in IFN-γ production ($r = .61$, $p = .02$) Mohr et al., 1999. There was no significant effect for change in vegetative symptoms ($p = .25$). While we cannot exclude the role of affective distress, these findings suggest that cognitions may play an important role mediating IFN-γ production in MS.

5.2. Psychosocial moderators

The association between stress and MS exacerbation appears to be significant and clinically meaningful, but it is not a strong relationship. Some patients appear able to experience considerable stress without any exacerbation. Other patients appear vulnerable to the effects of stressful life events at some points and more resilient at other points. This suggests that moderators play an important role. While genetic and disease-related moderators are likely important, these have not been investigated in the context of stress in MS. However, a few psychosocial moderators have received some attention, including coping and social support.

The patient's ability to manage stressful life events also appears to affect the relationship between stressors, and exacerbation and inflammation. Cross-sectional work has shown that patients in exacerbation tend to report that they have more emotion-focused coping and lower social support, compared to patients who are not in exacerbation (Warren et al., 1991). We examined the effect of coping prospectively on the relationship between stressful life events and the development of Gd+ MRI. We did not find main effects for coping style on the incidence of new Gd+ MRI brain lesions. However, greater use of distraction to cope with stressors was predictive of a significantly weaker effect of stressors on the development of new brain lesions (Mohr et al., 2002). Similarly, there was a trend for instrumental coping in the same direction, while there was a trend for greater emotional preoccupation (a ruminative style) to be predictive of increased effects of stressors on the development new brain lesions. This suggests that coping may be an important moderator of the relationship between stressful life events and MS inflammation.

Social support has also been implicated as a factor in MS exacerbation (Warren et al., 1991). As noted above, several studies suggest that stressors that impact the risk of MS exacerbation are social in nature, including family and work stressors (Mohr et al., 2000; Sibley, 1997). Certainly, these kinds of stressors can be considered markers of erosion in the patient's social network. However, we have found more specific evidence that social support may have a buffering effect. The effect of depression on T-cell production of IFN-γ noted above was significantly moderated by social support. Specifically, the relationship between depression and IFN-γ production was particularly strong among patients with low levels of support, but was virtually non-existent among patients with high social support (Mohr and Genain, 2004).

Such moderators are potentially important as they could alter the risk of exacerbation following stressful life events in any of the three hypothesized mechanisms or temporal relationships. They are also critical, since adaptive coping may prevent the occurrence of some types of stressors, reduce the distress associated with stressors that cannot be avoided, and influence cognitions that, as noted above, may be related to MS inflammation (Gottlieb, 1997; Mohr et al., 1997). Psychosocial moderators are also potentially useful as they may be modifiable through psychosocial intervention.

6. Summary and future directions

The literature to date has found fairly consistent support of an association between stressful life events and MS exacerbation (Mohr et al., 2004). The evolution of both stress and MS exacerbation occur over time with changing biological mediators. Thus, the impact of stress on MS exacerbation likely depends on when the temporal trajectories of stress and MS exacerbation intersect. We presented support from humans and/or EAE models for three temporal relationships: the onset of a stressor

(the mast cell hypothesis), the point that a stressor begins to become chronic (glucocorticoid resistance), or the resolution of the stressor. These three hypotheses are not necessarily mutually exclusive. They are also not exhaustive. Stress could also have an effect on earlier stages of MS disease processes. For example, the death of a child has been associated with increased risk of developing MS many years later (Li et al., 2004). However, at this point there are not sufficient data to develop a viable biological model that would explain this finding.

To date, the best studies examining the effects of stress on MS exacerbation have been longitudinal. While longitudinal studies are stronger than cross sectional designs, they nevertheless leave open the possibility that a third factor may be responsible both for exacerbation and for reports of increased stress and distress. For example, given that changes in normal appearing white matter occur before both the onset of the stressors and the onset of Gd+ MRI or exacerbation, it is possible that distress or perceived stress is an early marker of such neurological changes rather than a permissive agent that increases risk. This hypothesis is represented by the dotted line in Fig. 1. This would be consistent with the growing literature on the behavioral effects of cytokines (Maier and Watkins, 1998).

The question of the relationship between stress and MS exacerbation can only be definitively answered via controlled experiments. Given these potential temporal relationships, laboratory stressors such as the TSST may illuminate immediate effects, but are not useful for exploring many of the potential temporal relationships described in this paper. However, using stress management programs it is possible to alter how people respond to stressors both in terms of psychological consequences as affect and cognitions, and biological consequences, including cortisol (Antoni et al., 2000; Gaab et al., 2003). Furthermore, stress management can prevent the occurrence of some types of stressors by teaching enhanced coping skills (O'Roark, 1995; Richardson et al., 1994; Timmerman et al., 1998). Thus, a controlled, randomized clinical trial of a stress management program would provide the strongest test of the hypothesis that stress causes MS exacerbation or inflammation and could serve as a platform to explore some of the hypotheses described in this paper. In addition, such a trial could lead to novel methods for the management of MS exacerbation. We have recently been funded and have initiated such a randomized controlled trial using quantitative post-contrast neuroimaging at high field 3T and objective blinded neurological assessment.

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