Analysis of research into the role of trauma and stress in the etiology of multiple sclerosis

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Accelerated Cure Project, Inc.

Multiple sclerosis (MS) is a demyelinating disease of the central nervous system characterized by inflammatory and chronic lesions, local permeability of the blood-brain barrier, and atrophy of the gray and white matter. The etiology of MS is not well understood, but evidence points to the involvement of both genetic and environmental factors. MS also appears to be a heterogeneous disease, with multiple sets of risk factors; therefore two people with MS may have somewhat different genetic risk factors and have experienced different environmental exposures but still both receive a diagnosis of MS.

Trauma, both physical and psychological, is an important contributor to human pathology and must be considered as a possible risk factor for MS. This Cure Map document (Phase 2 of the Trauma track) summarizes the evidence for and against the involvement of physical and psychological trauma in the development of MS. This document follows the categorical framework set forth in the Phase 1 Trauma document, "A framework for describing physical and psychological trauma as a cause of disease." As in that document, physical and psychological trauma are treated separately here, although it should be kept in mind that physical trauma is often accompanied by psychological effects and thus the two forms of trauma are often experienced together.

Preparation of this document involved performing literature searches for studies having to do with MS and trauma (using relevant words from the Phase 1 Trauma document as search terms), checking reference lists for additional documents, and analyzing the studies found. Many of the studies we located examined the relationship between trauma and characteristics of established MS such as relapses. While these studies examined events taking place after MS onset, rather than before onset, we included them anyway since any evidence of an impact of trauma on disease events would indirectly support a role for trauma in MS etiology as well.

Supporting material for this document can be found in "MS Trauma Studies," a database summarizing the studies included in this analysis. All Cure Map documents can be downloaded from the Accelerated Cure Project web site at www.acceleratedcure.org/curemap/docs.php.

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I. Physical Trauma

The following sections discuss key characteristics of physical trauma and its effects with respect to MS:

- Mechanism of injury
- Activity and intent
- Location at time of injury
- Severity
- Location and extent of damage
- Epidemiology of trauma

(For more information about these categories, please refer to our Phase 1 Trauma document: "A framework for describing physical and psychological trauma and stress as a cause of disease.")

Mechanism of injury

The mechanism by which injury can be inflicted on a person include transfer of energy and physical interference with normal bodily functions. Of these, transfer of energy has been more extensively studied with respect to MS.

TRANSFER OF ENERGY

Kinetic energy

Our classification scheme divides trauma involving kinetic energy into three categories: penetrating trauma, blunt trauma, and mechanical stress.

Penetrating trauma (e.g., gunshots, stabbing, cutting, animal bites):
In considering penetrating trauma as a possible trigger of MS, one injury type that should be evaluated in particular is penetrating trauma that results in a breach of the blood-brain barrier (BBB). Numerous studies have associated gadolinium-enhancing regions on MRI with newly forming lesions, suggesting that openings in the BBB may result in harm to myelin and neural tissue by allowing entrance to certain cells or molecules.

However, there is currently no evidence suggesting that penetrating trauma to the head or spinal cord is a frequent trigger of MS. None of the retrospective or cohort studies performed to assess the frequency of prior injuries in people with MS have identified an association between any type of penetrating trauma and MS onset or exacerbations[1-3]. The types of penetrating trauma these studies have analyzed include surgery, stitches, lumbar puncture, spinal anesthesia, dental procedures, and abrasions and lacerations. Another study found that only one member of a cohort of 942 lumbar disk surgery patients developed MS during an average follow-up period of 11 years post-surgery[4]. Although it can be argued that most of the penetrating injuries reported in these studies would have occurred outside the central nervous system (CNS) and thus might be unlikely to provoke

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inflammation in the CNS, these results do indicate that penetrating trauma does not commonly lead to MS.

Nevertheless, because MS is believed to be an etiologically heterogeneous disease, it may still be possible that an episode of penetrating trauma has played a role in triggering disease in a subset of people with MS. Some evidence concerning the potential for penetrating trauma to trigger lesion development comes from studies of neurosurgical treatment of MS. A study performed in 1966 of needle thalamotomy (destruction of part of the thalamus) in people with MS showed the formation of new lesions adjacent to the needle's path[5]. Several recent studies have described the use of thalamotomy or deep brain stimulation/chronic thalamic stimulation in MS, but while they often report adverse effects, unfortunately most of these do not investigate new lesion formation via MRI or other means[6-9]. One group of researchers did conduct MRI imaging in a small number of MS patients following the placement of electrodes for chronic thalamic stimulation. They found no new lesion development in proximity to the electrodes after a follow-up period of "several weeks"[10] or an unspecified period of time[11]. Altogether, this evidence indicates that penetrating trauma to the head/spine may promote the formation of new lesions in people with existing MS but does not necessarily lead to new lesion development. Therefore it is possible that penetrating trauma could likewise trigger the onset of MS in a person predisposed to develop this disease. However, as noted above, this is not likely to be a common route to developing MS.

Blunt trauma:
Animal studies have shown that percussive injury to the head may be followed by induction of inflammatory protein release and increased permeability of the blood-brain barrier, suggesting that blunt trauma may play a role in the etiology of MS. However, as with penetrating trauma, blunt trauma has not been shown to play a major role in the development or course of MS. For example, one prospective study found no effect of closed head trauma on exacerbations[3]. Likewise, a study of medical records reported that blunt trauma from falls, impact with heavy objects, and motor vehicle accidents appeared to have no influence on exacerbation rate or disability progression in MS[4]. Several other studies that have examined the role of trauma in MS may have included blunt trauma but these did not specify the nature of the traumatic events (see "Unspecified trauma" below).

Mechanical stress:
Mechanical wear and strain is another injury mechanism that can induce or contribute to tissue damage. Various forms of mechanical stress have been postulated to contribute to MS pathology. For instance, Chaudhuri and Behan (2001) describe 39 cases of MS encountered in their practice that developed or were exacerbated following automobile or other accidents that resulted in hyperextension of the cervical spinal cord (whiplash)[12]. They also cite animal studies showing that these types of accidents can cause disruption of the blood-brain barrier. Compression of the spinal cord has also been proposed to contribute to demyelination. For example, a post-mortem examination of two people with both MS and cervical spondylitis revealed more extensive demyelination in cervical segments where the spinal cord was compressed through spondylosis[13]. Others have speculated about an association between MS and ankylosing spondylitis, but no definitive study has yet been performed[14]. Another spinal cord examination of 18 people with MS showed twice as many lesions in the cervical cord compared with lower levels, and a high frequency of fan-shaped lesions in lateral columns[15]. The author of this paper suggested that mechanical stresses on denticulate ligaments cause vascular leakages leading to lesions.

Unfortunately, controlled studies that assess the role played by mechanical stress in MS are lacking. Only one prospective study appears to have specifically inquired about mechanical stress injuries; this

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study reported that sprains appeared to have no effect on exacerbation rate in a clinical cohort[3].

Unspecified physical trauma:
Several studies that examined the role of physical trauma in MS did not specify the basis of the injury, but presumably for most of these some form of kinetic energy transfer was involved:

- A higher frequency of trauma within 12 weeks of MS onset was found in an MS cohort compared with a reference cohort; the types of trauma were not specified but included dental extraction[16]
- A retrospective case-control study found no significant differences between MS cases and controls for accidents producing unconsciousness[1]
- A retrospective case-control study found no significant differences between MS cases and controls for head injury, neck and back injury, major or minor physical trauma, or fracture; in addition, prospective analysis of the cases found no influence on exacerbation for any type of injury except electrical injury[2]
- A prospective study of an MS clinical cohort found no effect on exacerbation rate for fractures[3]
- A medical record linkage study reported that the risk of MS was not significantly increased in a head injury hospitalization cohort compared with a reference cohort hospitalized for other reasons[17]

Thermal energy

Although overheating can lead to a worsening of neurological symptoms in MS (Uhthoff's phenomenon), with potentially fatal consequences[18, 19], this worsening is only a pseudoexacerbation and does not involve the formation of new lesions or the development of other new pathologies. No evidence has been produced to date linking heat stress to the development, exacerbation, or progression of MS. In fact, the very low prevalence of MS at tropical latitudes compared with colder climates argues against heat stress as a factor that increases the risk of MS.

Thermal tissue burns have not been extensively studied, but one prospective MS cohort study did not detect an effect on exacerbation rate for burns[3].

As for hypothermia, while altered thermoregulation caused by damage to brain structures such as the hypothalamus can cause core hypothermia in people with MS[20], no evidence has been produced showing that hypothermia or its more serious consequences such as frostbite increases the risk of MS.

Chemical energy

Trauma resulting from exposure to chemicals is covered under the Toxics track of the Cure Map.

Electrical energy

Electrical shock as a trigger of MS onset or exacerbations has not been extensively studied. One prospective MS cohort study[2] and a follow-up to that study[3] found an association between electrical injuries and risk of subsequent relapse. Another study which assessed mortality in construction workers found an increased prevalence of MS among electrical power installers[21]. However, studies of Danish and Swedish utility workers exposed to electromagnetic fields found no significantly increased frequency of MS for these occupations[22-24].

If electrical shock is capable of causing or exacerbating MS, it might be expected that

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electroconvulsive therapy (ECT), which is used in certain situations to treat psychiatric symptoms of MS, would have adverse effects in people with MS. A few case reports have been published to describe the outcome of this treatment in MS, two of which reported no adverse effects or changes in MRI lesions in single patients[25, 26] and one of which described neurological deterioration in one patient but not in two others[27]. No controlled clinical trials have been performed to more rigorously assess the effects of ECT on MS.

Radiation

Research concerning radiation as a potential risk factor for MS has focused on the effects of ionization rather than localized traumatic damage. For more information on this research, please refer to the Toxics track of the Cure Map.

Acoustic waves/ultrasound

Hearing can be impaired in people with MS, for instance as a result of lesions in auditory pathways, but there is no evidence to date that acoustic trauma plays a role in the etiology of MS. Similarly, ultrasound has not been proposed as a potential trigger of MS.

PHYSICAL INTERFERENCE WITH VITAL BODILY FUNCTIONS

The potential effect on MS of trauma that involves physical interference with bodily functions (e.g., asphyxiation or restriction of blood flow) has not been studied.

Activity and intent

Certain activities are associated with a higher risk of particular types of physical trauma, and therefore any association between these activities and the development of MS may support a role for trauma in the disease.

SPORTS/LEISURE ACTIVITIES

Although participation in sports and similar activities has been investigated as a risk factor in other diseases such as ALS, we found no studies examining potential links between sports or recreational activities and subsequent development of MS.

OCCUPATION

Several studies have examined the question of whether certain occupations are associated with an increased risk of MS. These studies are summarized in tabular form in Appendix A. As can be seen, a wide range of occupations have been linked with MS, including commerce and administration, electrical power installation, healthcare, and paper manufacturing. However, no consistent theme appears to emerge regarding a significant association with a particular occupation. Furthermore, these studies generally do not explore the likelihood of physical trauma experienced in the workplace

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as a factor predisposing to MS. (One exception concerns the utility industry studies mentioned above which specifically analyzed exposure to electromagnetic fields[22-24].)

EDUCATION

Several studies have explored a possible association between number of years of education and risk of MS, with some finding a positive association[28-30] and others finding a negative association or no association[31, 32]. However, physical trauma experienced while attending school was not a focus of these studies.

TRANSPORTATION/TRAVELING

As mentioned above in the section on kinetic energy, although no controlled study has demonstrated an increased risk of MS following motor vehicle accidents, individual cases have been reported in which MS either developed or became worse after such incidents[12]. No other types of transportation-related accidents appear to have been discussed in the medical literature with respect to risk of MS.

WARFARE, TERRORISM, AND ACTS OF VIOLENCE

No studies have yet examined the question of whether the risk of MS is increased in individuals who are the victims of physical trauma as a result of warfare, terrorism, or violent acts. A number of studies have investigated MS epidemiology in populations of armed forces veterans, but not have explored whether physical trauma experienced in the line of duty is associated with MS risk.

Location at time of injury

Just as some activities are associated with risks of certain types of trauma, so too can specific locations (homes, institutions, schools, wilderness, etc.) present an elevated risk of injury of various types. However, no evidence exists to suggest that people with MS, prior to onset, spent more time than their peers in any type of location that is associated with a particular type of injury.

Severity

If one assumes that certain types of trauma can contribute to the risk of developing MS, then it can be hypothesized that the more severe the traumatic injury experienced by a person, the greater his or her subsequent risk of MS will be. However, very few studies have attempted to test this hypothesis. One study of medical records of patients hospitalized for head injury, using length of hospital stay as a proxy for injury severity, did not find an increased risk of MS in those whose hospital stays were longer[17]. Another study of a cohort of people suffering hyperextension-hyperflexion neck trauma found no correlation between injury severity as measured by an arbitrary 15-point scale and subsequent changes in MS severity[12].

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Location and extent of damage

Because the primary site of damage in MS is the central nervous system, most studies that have explored a link between trauma and the onset of MS and that have inquired about a particular site of injury have focused on injury to the head, neck, and/or back. Some investigators have published case reports describing MS that developed or worsened following injury to the neck[12]. A few case-control or cohort studies have also focused on head, neck, or back injuries. For example, Siva, et al. (1993) investigated subsequent MS onset in patients hospitalized for head injury or lumbar disk surgery, and found no evidence for increased risk of MS in these cohorts[4]. A similar, larger study of head injury patients was performed using UK medical records and provided similar results[17]. A few studies that included a wider range of traumatic injuries in their investigations, such as Bamford, et al. (1981)[2], also identified central nervous system injuries specifically. In general, case-control or cohort studies focusing specifically on head, back, and neck injury do not report an association between these injuries and onset or exacerbation of MS. However, one case-control study reported an association between risk of MS and head trauma occurring before age 16[33].

It should be noted that trauma to a localized area, such as an ankle sprain, can result in a systemic inflammatory response[34]. Therefore non-CNS injuries may also potentially play some type of role in MS, and indeed several of the cohort or case-control studies that we found examined non-CNS injuries such as skeletal fractures, sprains, childbirth, dental procedures, etc. However, although there are exceptions[16], most of these studies conclude that trauma in general does not increase the risk of MS[1, 2] or risk of relapse/worsening of MS[3, 4].

Epidemiology of trauma

The chance that a particular person will experience some type of significant physical injury is influenced by several personal characteristics, such as age and gender. The following paragraphs explore the extent to which risk factors for experiencing trauma are consistent with characteristics of people with MS.

AGE

Although it can occur earlier or later, the onset of MS symptoms typically occurs in a person's third or fourth decade of life. Therefore it is reasonable to ask whether there are forms of trauma that are more common in this age range. However, this question is complicated by the fact that because demyelinating disease activity is often subclinical, the age at which MS actually began in any given person cannot yet be known. In fact, it has been shown that ten or more years can elapse between the development of disease pathology and the onset of symptomatic disease[35]. Therefore, if trauma is capable of triggering the development of MS lesions, it is possible that a triggering event could have taken place in childhood or adolescence even in a person with adult onset MS.

A few studies have tried to define the temporal relationship between trauma and subsequent

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development of MS. Some investigators have reported MS onset occurring within three months of an accident or other form of trauma[12, 16], which suggests that trauma that is more common in young adults may be a risk factor (since onset is most common among this group). However, another study reports that head trauma below the age of 16 increases the risk of MS[33]. Yet another study, one that detected no significant contribution to MS risk for head trauma overall, similarly found no association for any particular time interval between head trauma and MS onset in people with MS[17].

Overall, no conclusions can be drawn at this time about a particular age range in which a person is more susceptible to any effects from trauma on the risk of MS. However, because head trauma is often singled out for analysis in MS research, it is interesting to note that the prevalence of traumatic brain injury requiring medical care is highest in infancy/childhood, declining with age until age 75. (As shown in Figure 1, the age ranges at greatest risk are 0-4 and 15-19.)

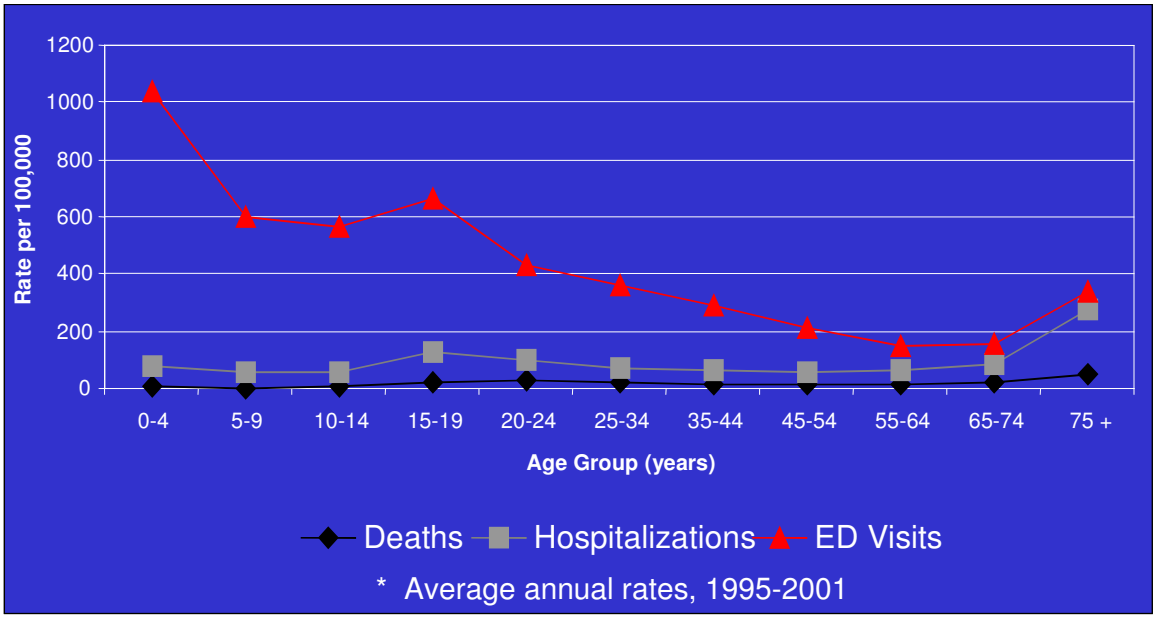

Figure 1: Traumatic brain injuries in the US by age group

(Langlois JA, Rutland-Brown W, Thomas KE. Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations, and Deaths. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2006.)

GENDER

Prevalence studies of MS in various geographic regions typically report an approximately 2:1 ratio for females compared with males (and there is evidence that this ratio is increasing in certain locales[36]). However, males are generally at higher risk of injury than females. Statistics from the US Centers for Disease Control and Prevention show that males are more likely than females to suffer injuries of any type for all age groups until age 55, after which women are at higher risk of injury. Traumatic brain injury is also more common in males than females in all age groups younger than 55 years old. The higher prevalence of traumatic injury in males compared with females argues against trauma being a predominant trigger of MS.

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PREGNANCY

Pregnancy can increase the risk of traumatic injury, and traumatic injury can increase the risk of complications during pregnancy. In addition, childbirth itself can result in injury to the mother or the infant. However, investigations of pregnancy and MS have reported that pregnancy either decreases or has no effect on a woman's risk of developing MS[37-40]. The specific contribution of childbirth complications to the risk of MS has not been well studied.

ALCOHOL AND DRUGS

Alcohol and drug abuse has not been extensively examined as a risk factor for MS. Two case control studies performed in Montreal[41] and Belgrade[42] did find evidence for association between MS risk and alcohol and/or drug abuse; however, it is unknown whether injury related to substance abuse prior to onset is elevated in people with MS.

OCCUPATION

As discussed above in the "Activity and Intent" section, no clear evidence has been produced that occupation-related injury is a significant contributor to MS risk.

PHYSICAL FITNESS AND HEALTH

Although both obesity and participation in physical exercise can increase the risk of injury, no studies have focused on whether people with MS were more or less physically fit and/or active than their peers prior to onset.

GEOGRAPHY AND RACE

Many studies have evaluated MS prevalence rates across ethnicities and geographic regions. In general, MS appears to be most common in Caucasians who live at higher latitudes, although people of other races and locations can also develop the disease. However, no injury patterns associated with race or geography have been documented as relevant to MS.

Conclusions

While trauma has not received as much attention as a potential contributor to MS as other factors, such as genetics and immunology, it has at times been the subject of lively debate. This is perhaps because the question of whether physical trauma can trigger the onset of MS is of interest not only from a scientific standpoint, but also from a medicolegal standpoint, with several lawsuits having been brought by people claiming that their MS was precipitated by an injury[43, 44].

Over the past several decades, various types of evidence have been presented regarding the possible effect of physical trauma on MS. These include animal studies, medical records analysis, prospective studies on trauma and relapse rate, post-mortem pathology studies, etc. Evidence that physical

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trauma can open the blood-brain barrier, exposing the central nervous system to peripheral immune factors, and that trauma can trigger an immune cascade of inflammatory cytokines, shows that it is biologically plausible for trauma (certain types of trauma, at least) to increase the risk of MS. Post mortem studies also suggest that lesions may preferentially form at sites of mechanical stress. However, evidence from clinical studies looking for associations between MS and trauma have not yet produced compelling evidence that trauma is a significant risk factor. Similarly, epidemiological evidence such as gender prevalence data does not support a strong role for trauma as an MS risk factor.

This does not mean that physical trauma plays *no* role in the development of MS. It may be that injury can increase the risk of MS but only to a small degree and/or only in a small percentage of people who have other risk factors for the disease. Several criticisms have been leveled against some of the studies mentioned in this document (e.g., lack of statistical power), and design differences among studies (different definitions of injury, multiple definitions of "at-risk" time periods for relapse following injury, etc.) have prevented satisfactory synthesis of results. Therefore further study on this topic is needed. Perhaps additional large-scale studies (e.g., medical records studies[17]) that investigate specific types of injury such as whiplash that have been hypothesized to trigger MS would help resolve the question of trauma's involvement in MS.

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II. Psychological Trauma and Stress

The following sections discuss these key characteristics of psychological trauma and stress with respect to their possible roles as risk factors for the onset of MS:

- Nature of psychological stressor
- Risk factors for exposure to psychological trauma/stress
- Response to trauma/stressor
- Personal factors that influence response to stressor

Nature of psychological stressor

The characteristics of a stressful event or series of events can influence its resulting psychological effect on a person. These characteristics include whether the event directly or indirectly affects the person, whether the event actually takes place or is threatened, how severe the event is, and whether the event happens once or repeatedly or as a series of events.

Only a few studies have tried to assess the history of stressful events in people with MS prior to onset. These have focused on characteristics of stressors such as number of stressors and severity; other factors such as direct/indirect effect on the individual and threatened vs. actual occurrence have not been examined.

Other studies have looked for correlations between stressful events and measures of disease activity such as relapses, progression, and MRI lesion development. It is unclear whether these studies have any bearing on whether stress is a risk factor or trigger of MS, but their findings may provide at least indirect evidence to help answer this question. As with trauma/MS onset studies, these investigations tend to focus on number and severity of stressors as factors that may affect disease activity.

Following is a brief review of the studies concerning the effects of stress on MS onset, relapses, disease progression, and MRI activity.

STRESS AND ONSET

Most investigations of emotional trauma as a risk factor for MS have relied on retrospective case-control analyses where cases and controls were asked about their history of stressful events[45-49]. Some of these studies (e.g., Warren, et al.[48] and Grant, et al.[49]) did report greater number or greater severity of stressors experienced by MS cases prior to onset, but because they were retrospective, the possibility of recall bias should be kept in mind. One recent study took a more objective approach by cross-linking a national MS registry with a database listing bereaved parents who had lost a child to death[50]. This study did find an increased risk of MS for these parents, particularly those for whom the death was unexpected. Since this is the only investigation on this topic that made use of hypothesis-independent data sets, additional studies of this type are warranted.

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STRESS AND RELAPSES

Several prospective studies have reported an increased risk of exacerbations in the weeks or months following stressful life events[51-54], although not all have found an association[4, 55]. Findings are mixed on the importance of stressor severity; studies have variously reported that more severe stressors are more likely to cause relapses[51], that severity of stressors does not affect relapse risk[52, 54], and even that very severe stress may reduce the risk of relapse[56] (although this was a small study of short duration). Other aspects of stress such as duration have been examined by particular studies. For instance, one study found that acute (<6 months duration) but not chronic (>6 months) stressors were associated with relapses[54].

A recent meta-analysis of studies on this topic concludes that, overall, stressful life events do appear to modestly increase the risk of exacerbations[57]. However, it has been pointed out that subclinical disease activity preceding a relapse may cause changes in cognition or behavior which increase the risk of stressful events occurring prior to clinical symptoms. Therefore the association between stress and relapses may work in both directions. Additionally, as stated above, demonstration of an association between stressors and relapses does not necessarily indicate that stress increases the risk of MS *onset*.

OTHER STRESS/MS STUDIES

Schwartz, et al. (1999) followed a group of people with MS for up to six years to study the effect of stress on MS progression[58]. The authors reported a bidirectional relationship between stress and MS, namely that having a higher number of stressful events results in a higher risk of progression, which in turn increases the likelihood of stressor occurrence.

Another prospective study analyzed whether stress was associated with the development of gadolinium-enhancing lesions, indicators of new disease activity that, unlike relapses, can be objectively measured. This study concluded that moderately stressful life events, but not major negative events, were associated with the appearance of new lesions four to eight weeks later[55].

Risk factors for psychological trauma/stress

An alternative, albeit more indirect, approach to exploring whether trauma plays a role in triggering MS is to evaluate whether people with MS, on average, had a higher than normal risk before onset of experiencing psychological trauma or stress. Risk factors for exposure to psychological trauma include socioeconomic status, age, gender, and other factors.

SOCIOECONOMIC STATUS

People in lower socioeconomic brackets are more likely to be exposed to assaultive violence and also appear to be at higher risk for chronic stress than those who are better off socially and financially. While no concerted investigation focusing specifically on socioeconomic associations with MS has been undertaken, several case-control studies conducted in different parts of the world have analyzed income, occupation, and years of education as part of a set of factors that may correlate with MS risk.

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Although some of these studies found no association between MS risk and socioeconomic factors[31, 47], several have reported a higher prevalence of MS among people with more years of education or greater affluence[28, 30, 59, 60], arguing against a significant role of chronic stress or violent trauma in MS onset.

AGE

As discussed above in Physical Trauma, it is impossible to tell when MS disease activity begins in any given person, since clinical symptoms may not be felt for several years. MS incidence peaks in the third and fourth decade of life, so it is possible that psychological trauma occurring in early adulthood, adolescence, or even childhood can play a role. Emotional trauma and stress can occur in anyone at any age, but it is worth noting that adolescents and young adults are more likely than other age groups to experience assaultive violence.

GENDER

MS affects approximately twice as many women than men, although recent research indicates that this ratio may be increasing over time[36]. Males are more likely than females to have personally experienced assaultive trauma (through gunshots, stabbings, and other personal assaults, involvement in military combat, etc.). However, women are more likely than men to have been sexually assaulted. Nonassaultive stressors (e.g., the sudden death of a loved one) appear to be distributed more equally between males and females.

OTHER CHARACTERISTICS

Other factors that may increase the chance of a person being exposed to psychologically traumatic events include having a background of psychiatric conditions (e.g., depression), having a personal or family history of substance abuse, and having a history of childhood conduct problems. Drug/alcohol abuse has been associated with MS risk in a small number of studies[41, 42], but otherwise these risk factors have not been extensively evaluated.

Response to trauma/stressor

PSYCHOLOGICAL RESPONSES TO TRAUMA

If psychological stress or trauma can increase the risk of developing MS later, then other persistent effects of stress/trauma might conceivably also be more frequently detected in people with MS compared with controls.

Lasting psychological response to traumatic experiences can take the form of several disorders, such as:

- Acute stress disorder (ASD)
- Post traumatic stress disorder (PTSD)
- Depression
- Panic disorder
- Borderline personality disorder (BPD)

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- Substance abuse
- Dissociative identity disorder (DID)

Some of these disorders, such as depression and substance abuse, have been shown to be increased in people with MS[61, 62] and may simply be a consequence of MS (through the disease's effects on the central nervous system, a psychological reaction to having the disease, or a side-effect of medication). However, the existence of depression or related disorders prior to onset of MS has also been documented in a few studies. One study found a higher percentage of people with MS compared with chronic lower back pain sufferers reporting a depressive episode prior to onset (52% vs. 17%)[63]. Similar findings were presented by Whitlock and Siskind (1980) who compared MS subjects with subjects with other neurological diseases[64]. Several case reports have described people diagnosed with mental disorders who are later diagnosed with MS (e.g., Hutchinson, et al. (1993)[65]). Finally, Keschner (1950) reports finding 13 out of 255 people with MS who had a history of psychological problems from between a month to 15 years prior to onset of MS (the specific disorders were not named)[66].

While the existence of psychiatric conditions prior to MS onset is congruent with a role for psychiatric stress or trauma in triggering MS, these conditions may also have simply been the initial symptoms of MS in these subjects, but not recognized as such until subsequent symptoms developed.

PHYSIOLOGICAL EFFECTS OF PSYCHOLOGICAL TRAUMA/STRESS

In a similar vein, if significant psychological stress or trauma can increase the risk of MS, then the associated physiological after-effects of these experiences might be more commonly found in people with MS than in controls. Persistent physiological effects of psychological events can include changes to neuroendocrine functions and anatomical structures involved in stress reactions.

In terms of anatomical changes, atrophy of the gray and white matter is an established feature of MS. While damage to structures reported as vulnerable in traumatic disorders (such as the hippocampus in PTSD) has been documented in MS, damage in MS does not target a small number of structures but rather is widespread and may even follow certain evolutionary patterns according to disease course[67]. No evidence has been produced showing that atrophy or abnormalities in structures such as the hippocampus are pre-existing features of MS caused by emotional trauma. Other changes such as increases in the number and activity of corticotropin-releasing hormone neurons have also been reported in MS brain tissue[68, 69], but again, no evidence ties these phenomena to previous psychological events. Enlargement of the adrenal glands, which has been described in depressed people and suicide victims, was also found in a postmortem study of ten MS subjects (none of whom had a history of depression)[70]. This enlargement may be an effect of MS; there is no evidence that enlarged adrenal glands are present prior to development of MS.

Alterations in hypothalamic-pituitary-adrenal (HPA) axis function as determined by neuroendocrine tests have also been documented in MS. Several studies have reported HPA axis abnormalities such as increased cortisol levels and failure of HPA feedback suppression in people with MS, and positive associations have been found between HPA dysfunction and various disability measures[71-76]. Decreased sensitivity to glucocorticoids, also described in people suffering from depression, has been detected in MS subjects[77]. A few experiments have induced acute psychological or cognitive stress in MS subjects and controls with the aim of comparing the resulting immunologic and neuroendocrine responses[78-81]. While some of these studies have reported differences in responses (e.g., a lower increase in IFN-gamma production in people with MS suffering from fatigue), no overall pattern has

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yet emerged.

Taken together, these studies indicate that various HPA abnormalities are associated with MS. While some of these alterations are consistent with features of trauma-related psychological syndromes, it is also possible that these changes, when seen in people with MS, are a result of disease activity or neuronal damage to structures involved in HPA axis control[82]. Without specific evidence linking these alterations to past events, it cannot be concluded that persistent HPA dysfunction in people with MS is due to stress or emotional trauma experienced prior to MS onset.

Personal factors that influence response to stressor

The nature and strength of the reaction to a psychologically traumatic event is influenced by various characteristics of the person experiencing that event. Therefore it is worthwhile examining whether any of these characteristics are different in people with MS compared with the population at large.

GENDER

Women are at approximately twice the risk of developing MS as men, and are also at increased risk for a number of psychological disorders such as depression and panic disorder. It is believed that biological differences between the genders account for these disparities in risk, although not enough is known about how gender influences MS and mental health disorders to determine whether the gender disparity in MS has anything to do with the psychological response to stressful events or situations.

INTELLIGENCE

Intelligence levels may play a role in influencing a person's response to an emotional shock. For example, higher intelligence is thought to protect against development of PTSD. However, there is no consistent evidence that intelligence is either positively or negatively associated with MS. As noted above, a few studies have found differences in years of education between MS subjects and controls, but education level is not simply a function of intelligence.

PRIOR TRAUMATIZATION

No evidence exists that people with MS were more or less likely than the general population to have had a history of adversity or abuse that would affect their responses to later stress.

SOCIAL SUPPORT STRUCTURE

There are no indications that people with MS have in the past had inadequate social support for coping with traumatic incidents. However, one study has investigated social support as a factor that may influence the risk of relapses[83]. This study found no association between the size or perceived quality of a person's social support structure and subsequent relapses, although the activity of seeking social support for stressors related to MS did predict a higher relapse rate. The authors conjecture that early symptoms of impending relapses may trigger a need for additional support and therefore form the basis of this association.

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OTHER PERSONALITY CHARACTERISTICS (E.G., COPING)

There is no information on the coping styles employed by people with MS prior to the onset of their disease. However, there is evidence that coping style can moderate the effects of stress on subsequent development of lesions[84].

GENETICS

Although genetic factors appear to influence the development of conditions such as PTSD or depression, there is no evidence that these particular factors are also involved in the etiology of MS.

IMMEDIATE RESPONSES TO TRAUMA AND TREATMENT RECEIVED

There is no information about any peritraumatic responses or form of treatment received following past psychologically stressful events in people who went on to develop MS. Therefore these factors cannot be connected with an altered risk of MS.

Conclusions

The available evidence shows that emotional stress may influence the risk of MS, but more work is needed to support the association. Case-control studies of emotional trauma or stress and MS onset are very few and most are affected by the possibility of recall bias. The Danish study showing that bereaved parents are at higher risk of MS than the general population[50] was noteworthy for its lack of such bias (although other confounders may have been present). However, it is only one study and will need to be replicated. Similarly, investigations into stress and MS events, which tend to show an association and therefore indirectly support the hypothesis that stress can trigger MS, are often based on the subjective measurement of exacerbations. The only study showing an association between stress and objectively-measured MRI lesions will need to be replicated to permit greater confidence in this connection.

It should be noted that the effect sizes presented by the studies finding an association between trauma/stress and MS are often modest. Therefore, if trauma or stress does increase the risk of MS, it likely can only lead to MS if other factors are present. Additionally, due to the assumed heterogeneity of the disease, there may exist people who are at risk of MS but not susceptible to stress as an MS trigger. The limited magnitude of stress's potential contribution to MS onset is supported by the lack of any demographic evidence showing that the MS population is also a high-risk population for exposure to trauma or particular responses to trauma.

Other related efforts that must be undertaken in order to fully understand the stress/MS connection include understanding the biological connection between stress and MS. Several hypotheses have been put forth, many having to do with interactions between the stress response system and the immune system. For instance, certain types of acute stress may stimulate the immune system; other types of stress may result in immune suppression which may be followed by a “rebound.” Chronic stress may result in glucocorticoid resistance in immune cells, thereby weakening the ability of the HPA axis to downregulate inflammation[85]. Another hypothesis is that the release of stress hormones

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leads to a mast cell-mediated increase in blood-brain barrier permeability[86], allowing entry of inflammatory cells into the brain. The effects of MS can in turn alter the body's response to stress, for instance through causing neurodegeneration in relevant regions such as the hypothalamus.

Other questions remaining to be answered include why it is that depression and other psychological symptoms are frequently noted in people with MS, and what causes the HPA axis alterations that are often detected in people with MS. Resolution of all of these questions will help in determining the role of stress and trauma in MS and potentially lead to ways of preventing and curing this disease.

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Appendix A

Occupation/Industry	Study	Risk of MS	Region
Agriculture	Souberbielle BE, 1990[67]	=*	Paris, France
	Landtblom AM, 1993[12]	=	Sweden
	Casetta I, 1994[68]	-	Ferrara, Italy
	Lauer K, 1985[69]	=	Southern Hesse, Germany
Chemical	Lauer K, 1985	+ (female only)	Southern Hesse, Germany
	Lauer K, 1989	+	Denmark (insignificant in Norway, Switzerland, and Sweden)
	Lauer K, 1990	+	France
Commerce	Casetta I, 1994	=	Ferrara, Italy
Commerce and administration	Lauer K, 1985	+ (female only)	Southern Hesse, Germany
Construction	Lauer K, 1985	= (male only)	Southern Hesse, Germany
Domestic work and restaurant trade	Lauer K, 1985	- (female only)	Southern Hesse, Germany
Driving	Lauer K, 1985	=	Southern Hesse, Germany
Education	Lauer K, 1985	=	Southern Hesse, Germany
	Souberbielle BE, 1990	=	Paris, France
Electrical work	Lauer K, 1985	+ (male only)	Southern Hesse, Germany
	Robinson C, 1995	+	United States
	Johansen C, 1999	=	Denmark
	Johansen C, 2004	=	Denmark
Engineering industry	Hakansson N , 2003	=	Sweden
Food	Lauer K, 1989[70]	=	Norway, Switzerland, Denmark, Sweden
	Lauer K, 1990[71]	=	France
Hairdressers	Souberbielle BE, 1990	+	Paris, France
Health work	Lauer K, 1985	+ (female only)	Southern Hesse, Germany
	Souberbielle BE, 1990	=	Paris, France
	Casetta I, 1994	=	Ferrara, Italy
	Kurtzke J, 1997	=	United States
Industry	Casetta I, 1994	=	Ferrara, Italy
Laborers	Kurtze J, 1997	-	United States
Leather/shoe working	Amaducci L, 1982	+	Florence, Italy
	Lauer K, 1989	+	Switzerland, Norway (insignificant in Denmark, Sweden)
Metal work	Landtblom AM, 1993	=	Sweden
	Lauer K, 1985	+ (male only)	Southern Hesse, Germany
	Lauer K, 1989	+	Switzerland (insignificant in Denmark, Norway, Sweden)
	Lauer K, 1990	+	France
Mining	Lauer K, 1989	=	Denmark, Norway, Sweden, Switzerland
Nurse anaesthetists	Flodin U, 2003[72]	+	Sweden
	Stenager E, 2003[73]	=	Denmark
Paper manufacturing	Lauer K, 1989	+	Norway, Switzerland, Denmark (insignificant in Sweden)
	Lauer K, 1990	=	France
Professional occupation	Kurtzke J, 1997	+	United States
Printing and publishing	Lauer K, 1989	+	Switzerland, Denmark (insignificant in Norway, Sweden)
	Lauer K, 1990	=	France
Public administration	Casetta I, 1994	+	Ferrara, Italy
Quarrying	Lauer K, 1989	=	Denmark, Norway, Sweden, Switzerland
Radiology	Landtblom AM, 1993	+	Sweden
Skilled work	Casetta I, 1994	=	Ferrara, Italy
Teaching	Walsh, 2001	+	United States

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Occupation/Industry	Study	Risk of MS	Region
Textile and clothing	Lauer K, 1989	+	Denmark (insignificant in Switzerland, Norway, Sweden)
	Souberbielle BE, 1990	=	Paris, France
	Lauer K, 1990	+	France
Textile and leather manufacturing	Lauer K, 1985	=	Southern Hesse, Germany
Trade occupation	Kurtzke J, 1997	+	United States
Unemployed	Souberbielle BE, 1990	=	Paris, France
	Casetta I, 1994	=	Ferrara, Italy
	Kurtzke J, 1997	-	United States
Utility workers	Johansen CM, 1999[74]	=	Denmark
	Johansen C, 2004	=	Denmark
Welding	Landtblom AM, 1993	=	Sweden
Wood processing	Lauer K, 1989	+	Norway, Switzerland (insignificant in Denmark and Sweden)
	Lauer K, 1990	=	France

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