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THE RELATIONSHIP OF MS TO PHYSICAL TRAUMA AND PSYCHOLOGICAL STRESS

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

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Overview. The idea that physical trauma or psychological stress might be involved in either the causation or exacerbation of MS dates back to the time of Charcot and the earliest descriptions of the illness.[1] In 1897, for example, Mendel reported four cases of MS that began within a year of severe skull or spinal injury.[2] In 1901, Klausner found antecedent trauma in 24 of 126 (19.0%) new-onset cases of MS.[3] Similarly, in 1902, Hoffman reported a series of 100 new-onset MS patients, of whom 8 (8%) had experienced trauma within the previous year.[4] A 1922 report from a commission of the Association of Nervous and Mental Diseases concluded that "in a small percentage of cases the disease [MS] appears to be excited by trauma, but trauma cannot itself cause the disease."[5]

Despite such assertions, however, the debate about the relationship between MS and trauma continued. In 1933, Harris reported 16 of 234 cases (6.8%) that developed shortly after severe injury to the back or head,[6] and in 1934, Von Hoesslin found 58 of 516 cases (11.2%) that were precipitated by trauma occurring within the previous 2 months.[7] In 1950, Keschner, defining trauma only as severe cranial or spinal injury, found a possible relationship between trauma and the onset of MS in only 4 of 255 patients (1.7%).[8] He concluded, nonetheless, that "severe trauma to head or spinal column may aggravate the course of multiple sclerosis."[8] In 1952, McAlpine published the final results of the first controlled study of this relationship, reporting a history of trauma within the 3 months preceding the onset of MS in 36 of 250 patients (14.4%) compared with only 13 (5.2%) of 250 control subjects.[9] However, in 1954, Kurland and Westlund, in a population-based case-controlled study in Canada, reported no difference between 112 MS patients and 123 control subjects with respect to antecedent head injury.[10] In 1961, Ridley and Schapira[11] reported deterioration of MS symptoms following 8 of 57 operations (14.0%). Similarly, in 1964, Miller described in detail 7 cases of MS that developed less than a week (in many cases within hours) after traumatic injury.[12] In 1985, Kelly reported that each of 14 MS patients (100%) had experienced a severe exacerbation within 3 weeks following thalamotomy.[13]

Thus, despite the long history of this idea, the proposed causal link between these factors and MS has yet to be established or refuted conclusively (e.g., references 14 through 18). Much of this uncertainty and debate occurs because many reports that propose such a causal link are either uncontrolled series or reports using very small sample sizes (studies that today would be regarded as examples of Class III evidence). These reports are also complicated by the fact that memorable injuries (in the absence of known sequelae) are quite common. For example, the annual incidence of injuries of all types in the United States has been estimated to be 33.2 injuries/100 persons/year.[19] As a result, even well-designed retrospective case-controlled studies may be contaminated by substantial recall bias—a circumstance that underscores the need for prospectively acquired data. Nevertheless, any genuine causal link between either traumatic injury or psychological stress and the onset or exacerbation of MS would have very important implications for practicing physicians—not only for the recommendations they make to their patients, but also for the suitability of asserting such a link as evidence in the resolution of medicolegal matters (e.g., references 20 and 21). Recently, attempts have been made to address this question using modern

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epidemiologic methods (e.g., prospective cohort and retrospective case-control designs) that are more scientifically rigorous than many of the designs used previously. This analysis reviews these studies and the earlier controlled studies in an attempt to define the current state of knowledge in this area.

For this review, articles were searched for in Medline under keywords *multiple sclerosis and trauma* as well as under keywords *multiple sclerosis and stress*. Each member of the panel was also asked to identify relevant articles, chapters, or letters. We also reviewed reference lists for each article published after 1965 to identify articles not found by the computer search as well as articles published too early to have been included in the computer database. The reference lists of these additional articles were also reviewed for the same reason. For the purpose of this analysis, because no Class I studies were identified, only Class II studies (i.e., studies with a defined control population) were considered in detail. A summary of selected examples of the available Class III data is provided in the introduction above. A definition of the different classes of evidence is provided in the table.

Table *Definitions of classification of evidence: quality of evidence ratings for therapeutic modalities*

Class	Definition
I	Evidence provided by one or more well-designed, randomized, controlled clinical trials
II	Evidence provided by one or more well-designed clinical studies such as case control and cohort studies
III	Evidence provided by expert opinion, nonrandomized historical controls, or reports of one or more

Before the scientific evidence is considered, however, it is important to address a few questions that are relevant to a consistent evaluation of the studies involved. The first question regards the biological plausibility of the proposed causal relationship between the trauma and the onset of MS or an attack. Clearly, in the absence of such biological plausibility, any epidemiologic evidence of an association, in order to be convincing, would need to be overwhelming. One possibility, which has been proposed frequently in the literature, relates to the idea that a breakdown of the blood-brain barrier (BBB) is an early and seminal event in the development of an MS lesion.[22-25] Physical trauma (even minor trauma) might injure the brain or spinal cord so as to disrupt the BBB and allow immune-competent cells from the periphery to gain access to the CNS and thereby gain exposure to CNS antigens. Indeed, such disruptions of the BBB are well known to occur following trauma, especially severe trauma. There is also ample evidence from MRI and elsewhere that the BBB is disrupted during the acute phase of an MS attack (e.g., references 26 through 28). In this circumstance, it is certainly plausible that the peripheral immune system might become activated against certain CNS myelin antigens such as myelin basic protein, proteolipid protein, myeline oligodendrocyte glycoprotein, or myelin-associated glycoprotein and thereby initiate an MS attack. In fact, there is substantial evidence, in other contexts, that trauma can result in demyelinating lesions in the CNS (e.g., reference 29). Whether the demyelination in this circumstance is the result of an immune-mediated attack similar to that seen in MS, however, is less clear.

As a consequence of considerations such as those, it seems reasonable to conclude that a causal relationship between trauma and either the onset or the exacerbation of MS is biologically plausible. Nevertheless, when a possible causal relationship between trauma and the onset of MS is considered, the mechanism of pathogenesis outlined above also raises certain other questions if trauma were to account for a substantial percentage of MS cases. For example, although head trauma often produces shear injury to the white matter, it also often results in injury to the cerebral cortex. As a result, it is unclear why the pathologic changes in MS would be largely (but not exclusively) confined to the white matter. Similarly, the marked female preponderance of MS would be unexpected if trauma were a major etiologic factor, because men (at all ages) are more prone to traumatic injury than women.[19] These considerations, however, have no bearing on the possible relationship between trauma and MS exacerbation.

It is becoming increasingly clear that activated T-lymphocytes can traffic normally from the bloodstream into the intact CNS (e.g., reference 30) without requiring breakdown of the BBB. Moreover, in experimental allergic encephalomyelitis, the animal model of MS, the inflammatory lesions in heterotopic brain transplants occur selectively in the core of the transplant, where the BBB is intact rather than at the edges of the transplant, where the BBB is absent.[31] Also, evidence is accumulating that changes within the normal-appearing white matter precede and predict the occurrence of gadolinium enhancement (a measure of BBB breakdown) on MRI.[32] Observations such as these raise the possibility that the breakdown of the BBB is not the initial event in the development of an MS lesion.

Interestingly, Rodriguez et al.[33] have reported that the earliest pathologic evidence of injury in an MS lesion is to the cell processes that are most distant from the oligodendrocyte soma (i.e., the inner lamellae of the myelin sheath). This is unlike the findings in experimental allergic encephalomyelitis, where the outer lamellae of the

myelin sheath are the first structures to be involved pathologically,[34] and where it is known that peripheral lymphocytes directed against CNS myelin antigens are responsible for the myelin destruction. If confirmed, the observations of Rodriguez et al. suggest that the initial injury is to the cell body of the oligodendrocyte rather than to the myelin sheath itself, raising the possibility that the immune response to myelin antigens is a secondary effect of the oligodendrocyte injury.[33,35] Even so, however, this does not preclude the possibility that a BBB disruption might lead to this injury.

The second question relates to the kinds of evidence that might be acceptable as a demonstration of a causal relationship between trauma or psychological stress and MS. A least two acceptable approaches for establishing such a link are recognized. One (a cohort study) is to demonstrate, prospectively, that the incidence of MS onset or attacks is higher in persons or patients following traumatic injury or stress than in similar persons who have not experienced such antecedent events. Another, less direct, method (a case-control study) is to demonstrate that prior traumatic injury or stress is more common in patients than in matched control subjects. Each of these methods, however, has its own associated difficulties (e.g., reference 36), and each raises other important questions. For example, following a traumatic injury, it is not clear how long the onset of MS or the MS attack can be delayed from the trauma before it is no longer reasonable to link the two events. Certainly, in a BBB breakdown, the disruption would be expected to be time limited, peaking early and having a sharp falloff with time. Thus, Poser[17] has suggested that 3 months is an appropriate time frame because this is the typical duration of gadolinium enhancement of acute MS lesions on MRI.[26-28] Others have argued for an even shorter time (e.g., references 12 and 23). As noted above, however, many authors have used periods of up to a year (e.g., references 2 through 4), whereas still others have chosen periods of 3 to 6 months.[9,37-39] Regardless, it is clear that some upper limit needs to be established. Because most authors seem to agree that after a year any association is unreasonable, (e.g., references 2 through 9, 12, 13, 17, 23, and 37 through 39), a year or so seems to be a reasonable upper limit.

Additionally, it is uncertain what kinds of trauma should be included in the analysis. Although many authors have included minor traumatic events (e.g., dental procedures, minor abrasions, bruises) as examples of "trauma" in their analyses, it is not clear that the biological plausibility outlined above applies to any of these circumstances. Thus, in 1993, Poser argued that "trauma never actually causes MS and…in order for trauma to be considered in aggravating or accelerating the course of the disease, there must be evidence of injury to the head, neck or back above the lumbosacral region, i.e., above the conus."[22] Other authors might disagree (e.g., references 9 and 12). Nevertheless, in attempting to establish a causal link between trauma and MS, it seems prudent (as Poser suggests) to concentrate on injuries to the head and spine, where altered CNS function can be demonstrated or inferred. Moreover, under any circumstance, it is preferable to consider each class of traumatic injury separately because any relationship between MS and trauma will probably be different for different antecedent events.

A third question relates to how best to evaluate the many (and often bitter) criticisms that have been leveled at either individuals or individual studies on this topic (e.g., references 14 through 18, 25, 40, and 41). Clearly, there is considerable room for disagreement, but at the very least, in order for a criticism to be valid, the concerns raised must affect the trial results in a plausible manner. For example, criticizing a study with negative results because the authors failed to make adjustments for multiple statistical comparisons is inappropriate because any such adjustment will only make the findings less (not more) significant. Similarly, a study that includes only severe trauma or long-lasting exacerbations cannot be invalidated solely on this basis, because this choice would not be expected to bias the findings in favor of one group or another; this choice may, however, limit the power of the study to detect a difference between groups or may limit the inferences that can be drawn from the results. For example, studying only cases of severe trauma would limit conclusions (in a strict sense) to only the occurrence of MS following severe injury. Nevertheless, it is a reasonable presumption (based on the biological plausibility outlined above) that any association between trauma and MS should be most apparent for more serious traumatic injury or for more serious MS attacks because these circumstances would be expected to produce or be associated with the greatest breakdown in the BBB.

Studies reporting negative results can also be criticized reasonably for lacking the statistical power to reliably detect an effect of trauma on MS. However, even if a particular study is underpowered, its results may still be used to exclude certain specific alternative hypotheses to the null. For example, if an experimenter decides to test the hypothesis that a particular coin is biased (55%) in favor of heads and tosses the coin only 10 times, the study is grossly underpowered. If, however, the coin lands tails on all 10 tosses, the original hypothesis is exceedingly unlikely ($p = 0.0003$) and should be rejected. Indeed, *any* hypothesized bias in favor of heads should be rejected on the basis of this experimental outcome ($p < 0.001$). It is often said that negative studies cannot exclude an association between variables. Nevertheless, although this is true, it is also true that a negative study limits the magnitude of any possible association. Thus, the 95% CI around any experimental observation can be used to

establish an upper and lower bound for the plausible (i.e., $p \geq 0.05$) difference between groups that can be posited, given the experimental data.

Last, in the literature regarding the relationship between trauma and MS, some discussion has been devoted to the issue of the reliability and appropriate role of anecdotal evidence in the science of medicine. Some authors dismiss such evidence as being of only limited worth (e.g., references 10 and 42). Others emphasize that such evidence from detailed case studies has frequently provided important medical insights (e.g., references 9 and 25). Both viewpoints are partially correct. Anecdotal evidence can often point to the appropriate direction of future scientific inquiry. The conclusions of such inquiry, however, must be buttressed by more rigorous scientific evidence. Physicians should not base their beliefs entirely on anecdotal (i.e., Class III) evidence.

Physical trauma and MS. *Discussion of the studies.* The first controlled study of the effects of trauma on MS was reported by McAlpine and Compston in 1952[9] following a preliminary report by McAlpine in 1946.[43] The study involved interviewing 250 MS patients in addition to 250 control patients who were selected randomly from the admissions to the Middlesex hospital, and who were matched with MS patients with respect to sex and age at the time of the interview. Those authors reported that 36 patients (14.4%) had a history of trauma within the 3 months preceding the onset of their MS, compared with only 13 (5.2%) of the control subjects ($\chi^2 = 11.3$; $df = 1$; $0.001 < p < 0.01$).

In order to interpret such a result and compare it to other studies, however, it is best if the magnitude of the reported effect (the effect size) is expressed in units that are independent of sample size. One way of doing this in a 4-cell case is to use the odds ratio (OR), together with its 95% CI, as discussed by Hibberd.[36] This statistic also provides directional information depending on whether the observed OR is above or below 1.0. Similarly, the effect size for a chi-square analysis can be expressed using the **w** statistic, as discussed by Cohen,[44] a statistic than can also be extended naturally (for the 2-cell goodness-of-fit case) to provide both directional and effect size information. In this circumstance, **w** ranges from –1.0 to +1.0 depending on the direction and magnitude of the effect. On this scale, **w** = 0.1 or **w** = -0.1 represents a small positive or negative effect size, **w** = 0.3 or **w** = -0.3 represents a medium effect size, and **w** = 0.5 or **w** = -0.5 represents a large effect size.[44] A 95% CI around **w** can be calculated from the critical value ($p = 0.05$) of the chi-square distribution above and below the experimental observation. This latter method can be applied to any chi-square analyses of 2 cells,[44] thereby making the difference clinical studies of trauma and MS (which often use 2-cell designs) easy to compare. When either method is used, however, the results of McAlpine and Compston[9] are highly significant; OR = 3.07 (CI = 1.58 to 5.94); **w** (2-cell) = 0.47 (CI = 0.22 to 0.71).

There are, however, important concerns about this study. First, there were notable differences in the time between interview and disease onset in the two groups (patients being interviewed about more remote events). Because this study was self-reported and retrospective, this time difference may have resulted in substantial recall bias, as discussed earlier. Second, there are also concerns about the comparability of the control and MS groups for factors other than age or sex. Because of these difficulties, the authors themselves concluded that "although statistically significant differences occur between the two groups, it is not always possible to accept their validity with confidence."[9] Third, and more importantly, there are concerns about the details of the trauma involved. Few details are provided in the article. It is clear that peripheral trauma, head trauma, and dental procedures were included in the definition of trauma but that operative trauma was not.[9,43,45] However, the breakdown of the numbers of patients in each of the different categories of trauma is not known, nor is the nature and extent of the injuries documented or defined. These authors also examined the effect of trauma on MS exacerbations within the 3 months following injury in patients already having a diagnosis of MS. This analysis failed to demonstrate any significant effect of trauma on the occurrence of MS attacks, although, again, many of the details of this analysis are missing.

In summary, although this study has a retrospective case-controlled design, it provides only weak Class II evidence in favor of an association between trauma and the onset of MS, the weakness being largely due to the lack of details about the actual data and descriptions of the data analysis. It also provides weak Class II evidence against a relationship between trauma and MS exacerbation, although, again, the lack of details prevents firm conclusions from being drawn.

In 1954, Kurland and Westlund[10] investigated 112 patients with MS and 123 control subjects who were carefully selected from the same community as the MS patients. These authors reported no significant association between "head injuries causing unconsciousness" and the onset of MS (time frame not specified). Again, this case-controlled study would best be classified as weak Class II evidence against an association between moderately severe head trauma and MS, the major weaknesses, as with the study of McAlpine and Compston,[9] being the lack of details about the actual findings and data analysis.

In 1968, Alter and Speer[46] reported a study of 36 patients with MS, each of whom was paired with two control subjects matched for sex and age. Patients and control subjects were interviewed with regard to the various events (including surgery and accidents resulting in unconsciousness) that had occurred an unspecified time before the onset of illness (the "assigned onset" for control subjects was made comparable to the onset in the patients with whom they were paired). Neither surgery (**w** = -0.03; CI = -0.26 to 0.20) nor head trauma (**w** = 0.11; CI = -0.24 to 0.45) was significantly associated with MS onset. Thus, this case-controlled study provides some Class II evidence against an association between either surgery or moderately severe head trauma and MS onset, although the small number of patients studied, and the resultant wide CIs, weaken the strength of the negative evidence.

In 1991, Sibley et al.[38] reported the final results of their prospective cohort study, which had been published earlier in preliminary form by Bamford et al.[37] This study involved 170 patients with clinically definite MS who were monitored prospectively at monthly intervals for a mean of 5.2 years. Also monitored, in a similar manner, were 134 control subjects without neurologic disease who were matched to patients with respect to sex and age distribution. These workers reported that the frequency of trauma was two to three times higher in patients than in control subjects (no statistical confirmation given), which they seem to attribute to the greater propensity of patients with MS for sustaining trauma as a result of their neurologic disability. The control group was otherwise not used in the analysis of their data. For their principal analysis, the authors defined, within the MS cohort, periods of time when the patients were "at-risk" for an exacerbation because of having sustained a traumatic injury within the previous 3 months, and also periods of time when they were "not-at-risk" because they had been free of trauma during the previous 3 months. The statistical analysis consisted of using a 2-cell goodness-of-fit chi-square test (e.g., reference 44) comparing the actual number of exacerbations observed during the at-risk and not-at-risk periods with the expected number of such exacerbations based on the null hypothesis that the number of exacerbations would reflect the same attack rate within each time-period (i.e., the overall attack rate for both time periods combined). These authors reported no significant difference between the actual and the expected number of exacerbations, either for trauma as a whole or for any specific category of traumatic injury, with the possible exception of electrical injury. The effect of electrical injury, however, was of only marginal significance ($p < 0.02$), was based on a very few patients, and was unadjusted for multiple comparisons. This observation, therefore, is of uncertain validity. Although not specifically indicated in the manuscript, it is, nonetheless, possible to calculate the effect sizes and CIs for different categories of trauma from the data given in table 2 of their article and thereby provide a measure of how large an effect (of trauma on MS) might have been missed by this study. Thus, for trauma as a whole, **w** = 0.06 (CI = -0.07 to 0.19), for closed head injuries with and without loss of consciousness, **w** = 0.02 (CI = -0.20 to 0.24), and for major surgical procedures, **w** = -0.11 (CI = -0.34 to 0.12).

In summary, these data provide strong Class II evidence that effectively excludes anything more than a modest effect (**w** < 0.24) of trauma within the previous 3 months on exacerbations of MS. In fact, the actual observations are considerably more supportive of no association than they are of an effect of this magnitude.

In 1993, Siva et al.[39] reported their experience with the Mayo Clinic defined population of Olmsted County, MN. They studied an incidence cohort of 225 new-onset MS cases occurring between 1905 and 1991 as well as a prevalence cohort of 164 MS patients residing in the county for the year preceding December 1, 1991. They studied MS exacerbations that occurred within a 1-year time period, divided into the 6 months before ("not-at-risk") and the 6 months after ("at-risk") traumatic injury. Their definition of trauma included head trauma severe enough to produce skull fracture, loss of consciousness, focal neurologic deficits, or posttraumatic amnesia, as well as peripheral and spinal trauma severe enough to result in fractures. These authors also studied a cohort of 819 patients (age 10 to 50 years) who had sustained head trauma (as defined above) to assess the likelihood of MS developing within the 10 years following such an injury. They found only 39 patients with trauma in the prevalence cohort, none of whom had experienced head trauma during the average of 19 years when these patients were monitored. Only 36 of the 39 such trauma patients are shown in their figure and, of these, only 13 had experienced exacerbations during the 1-year study period.[39] Of those, the authors found only 4 patients who had an exacerbation during the at-risk period who did not also have an exacerbation in the not-at-risk period. This was not significantly different compared with the 6 patients who had an exacerbation in the not-at-risk period but not in the at-risk period (**w** = -0.2; CI = -0.81 to 0.41). They also reported that in only 2 of the 819 patients who experienced head trauma (as defined above) did the trauma antedate the onset of MS; in both instances, the trauma was remote (3 and 21 years before MS onset).

This study, at least for some of its analyses, lacks statistical power. For example, if the incidence rate of MS onset in Olmsted County (as estimated by others) is 5.17 cases/100,000 population/year, one would only expect 0.42 cases of MS developing in this 8,190 person-years of follow-up represented by this study.[15,16] Even if this estimated rate is an underestimate of the true incidence rate, as argued by the authors,[18] it is unlikely that the

expected number of new cases of MS could ever be adequate to allow study of the relationship between trauma and MS with such a small sample, particularly when only MS occurring within a year of the trauma is considered. Indeed, it may be, as discussed by Hibberd,[36] that it is simply not feasible to study differences in the occurrence of MS following some antecedent event because the low incidence rate of MS requires such a large number of subjects to be monitored prospectively. The power of their analysis assessing the relationship between trauma and MS exacerbations is similarly limited. Indeed, as discussed above, the authors observed only 10 patients discordant for exacerbations in the at-risk and not-at-risk periods, and in whom this relationship could be assessed. As a result, the CI for this experimental observation (see above) is extremely wide. Moreover, there are also a few uncertainties about the analysis as reported. For example, it is unclear from the figure whether patients who are listed as having exacerbations within either the at-risk or the not-at-risk period had only one exacerbation, or whether they had more than one exacerbation; if more than one, it is unclear whether the exacerbation rates were compared and were the same. Also, it would be of interest to know the total number of exacerbations and the exacerbation rate in the entire prevalence cohort during the period of observation and to compare this rate in patients with and without trauma.

Despite these uncertainties and the occasional lack of statistical power, however, the population-based methods of case ascertainment, retrieval, and diagnostic coding used by the Mayo Clinic are rigorous, and the population of study is well defined.[18] As a result, and independently of the above considerations, certain results of this study have important implications with regard to any proposed general relationship between serious head trauma and either the onset of MS or its exacerbation. None of the 225 patients with new-onset MS in Olmsted County between 1905 and 1991 had serious head trauma in the year preceding the onset of their illness. This observation alone limits the upper bound (95% confidence limit for λ; Poisson distribution) for any proposed occurrence of antecedent head trauma in MS to no more than 1.3%. Similarly, none of the 164 patients identified as having MS and residing in Olmsted County on December 1, 1991, had even a single episode of head trauma within the 6 months preceding an exacerbation during the average of 19 years when these patients were monitored. Thus, even though the total number of exacerbations in this prevalence cohort is not known, it seems almost certain that the actual number of exacerbations would be at least several hundred, given the 3,116 person-years of follow-up represented by this prevalence cohort. If so, the lack of even one episode of head trauma within the 6 months preceding an exacerbation would limit the possible number of MS exacerbations associated with antecedent head trauma to only a fraction of a percent of the total number of exacerbations (95% confidence limit for λ; Poisson distribution). Thus, although the statistical power for some of the analyses used by this study is low, this is largely caused by the fact that serious head trauma is simply not a factor in the MS of this patient population. Certainly, the findings of this study argue strongly against anything even approaching the prevalence of MS related to head trauma that is suggested by some of the Class III data reviewed earlier.

In summary, despite some limitations to this study, the results provide strong Class II evidence that restricts any posited association between serious head trauma and the onset of MS to no more than 1.3%. The association between serious head trauma and MS exacerbation is similarly limited to no more than a fraction of a percent of cases by these results.

In 1996, Gusev et al.[47] performed a case-control study of 155 patients with MS compared with 155 control subjects matched to the patients on the basis of sex, age, and national origin. As part of this study, the authors examined the occurrence of antecedent head trauma (severe enough to cause loss of consciousness) in the two groups. The report lacks some of the relevant details such as the timing of the head trauma relative to disease onset or even the range of ages at onset in the patients. Nonetheless, the authors found that head trauma was not significantly associated with a higher risk of MS with an OR of 1.13 (CI = 0.62 to 2.03). When only head trauma occurring after age 15 (i.e., the head trauma most likely to have occurred within a year of disease onset) was considered, however, the authors actually found more such episodes in the control subjects than in the patients (OR = 0.59; CI = 0.22 to 1.58). Thus, although somewhat incomplete, this study still provides reasonably good Class II evidence against an association between moderately severe head trauma and MS onset.

Psychological stress and MS. *Discussion of the studies.* The possible role of psychological stress in either the cause or the exacerbation of MS is more difficult to evaluate than the role of physical trauma. Part of the difficulty has been caused by a lack of any clear biological plausibility for the proposed relationship. Nevertheless, there has recently been a growing interest in the interactions that occur between stress and the immune system, in the influence of the immune system on the distribution of T-cell subsets, in the association of a disordered hypothalamic-pituitary-adrenal axis and MS, and in the possible influence of stress-induced heat-shock proteins on the pathogenesis of the disease (e.g., references 48 through 52). As a result, it now seems that details of a plausible biological model may well evolve. Another factor that has hampered research in this area has been the lack of any

consistent or agreed-upon measure of stress. This is not to suggest that different types of stress cannot be measured in valid and reliable manners. Rather, as discussed in connection with the possible relationship between MS and physical trauma, it seems likely that any relationship between psychological stress and MS will be different for different types and degrees of life stress, and this complicates interpretation of the existing data. This is of particular concern in an area such as stress, where the possible variations are so numerous. For example, stress can be acute and self-limited, it can be chronic and long-lasting, or it can be somewhere in between. Its severity can range from a minor disruption of a person's life to a life-threatening or psychologically traumatic life event. Neither is it clear that the stress produced in all these different circumstances will result in the same pathophysiologic mechanisms. Moreover, there is almost certainly considerable variability in the actual impact of similar life events (e.g., divorce, loss of employment, or the death of a loved one) on different individuals. As a result of such complexities, more precision and consistency about what is measured are necessary.

There are also concerns about the use of retrospective interviews, a technique typically used by studies in this area. These interviews, in which subjects are asked to remember and report on life events that preceded the onset or exacerbation of MS, are quite prone to recall bias. Thus, there is an urgent need to obtain tightly defined prospective data in this area if an association between these life events and MS is to be established. Possibly in part because of such difficulties, the experience in the different controlled trials has been mixed. Thus, early controlled trials tended not to find a significant relationship between MS and stress (e.g., references 54 through 56), whereas some of the more recent trials, possibly because of more rigorous definitions of stress, have reported a positive association (e.g., references 57 through 60).

For example, in 1982, Warren et al.[57] studied 100 MS patients and 100 control subjects with various other neurologic or rheumatologic diseases. The two groups were matched with regard to age, sex, race, and MS risk zone of residence. The authors conducted interviews of both patients and control subjects about various life events that might or might not have occurred during the 2 years before disease onset. Using part of the Holmes and Rahe scale for stressful life events, these authors found that 79% of the MS patients and only 54% of the control subjects ($p < 0.001$) reported more unwanted stress than usual in the 2-year study period. They also found that patients had experienced three times the total number of stressful life events (180) than had control subjects (59) during the 2-year period.

In 1986, Rabins et al.[56] reported on 20 MS patients with exacerbation who had previously filled out a life-event questionnaire, the Holmes-Rahe schedule of recent events (SRE), both within the month before the exacerbation and previously. They found only 3 of the 20 patients with an SRE score in the month preceding exacerbation that was 1 SD above their prior mean score and only 2 of 20 with an SRE score 1 SD below their prior mean score. With so few observations, however, this study lacks the statistical power to enable any firm conclusions to be drawn.

In 1988, Franklin et al.[58] prospectively studied the relationship between exacerbations of MS and stressful life events (SREs) determined from the Psychiatric Epidemiology Research Interview. Fifty-five patients completed the study, in which these interviews were administered at consecutive 4-month intervals until an exacerbation occurred. Twenty-five patients experienced exacerbation during an average of 20 months of follow-up. These 25 patients did not have significantly more SREs in the 6 months preceding an exacerbation (20.2 events) than did the 30 control subjects (17.2 events) during a comparable period of time. Exposure to "extreme events," by contrast, was marginally higher in the patients than in the control subjects ($p < 0.05$). Thus, this study, despite its prospective nature, provides only marginal evidence in favor of an association between extreme stress and MS attacks.

In 1989, Grant et al.[59] reported the results of a study of 39 MS patients and 40 nonpatient volunteers matched on the basis of age, sex, marital status, and socioeconomic positions. Patients and control subjects were evaluated on the life events and disability scale. These authors found that in the 6 months preceding the onset of MS, 62% of the patients and only 15% of control subjects had experienced "severely threatening events" as defined by the life events and disability scale ($p < 0.001$).

In 1991, Warren et al.[60] interviewed 95 pairs of MS patients who were either in exacerbation or in remission, using the general health questionnaire to measure emotional stress (a score of ≥5 on this scale defined emotional stress). These authors found that in the 3 months preceding an exacerbation, 56.8% of the patients had experienced such intense emotionally stressful events, compared with only 28.4% of the patients who were in remission at the time of the interview ($p < 0.001$)

In 1993, Nisipeanu and Korczyn[61] reported on their experience in Israel during the Persian Gulf War of January and February 1991. Among 32 MS patients entered into a therapeutic trial on the basis of having had at least 1 attack per year between 1989 and 1990, they found 3 who experienced exacerbation either in the 2 months of the war or in the 2 months following. This attack rate was reported to be significantly lower ($p < 0.01$) than the prewar (and also pretherapeutic trial) attack rate. However, the very brief time of observation, the small number of subjects

studied, and most notably the well-documented tendency for MS attack rates to drop spontaneously following entry into a therapeutic trial (e.g., references 62 through 64) raise important concerns about the validity of these findings.

In 1997, Sibley[65] reported the final results of a prospective evaluation of life events preceding an exacerbation in 170 MS patients, determined as part of the monthly questionnaire discussed previously.[37,38] The results of this study had been reported earlier in preliminary form by Pratt.[54] Although the possibility of an association between MS exacerbation and antecedent stress is discounted in those articles, the actual analysis of the data[66] indicated a marginally significant ($p < 0.02$) association between job or marital stress with the subsequent occurrence of MS exacerbation (**w** = 0.22; CI = 0.01 to 0.43). As a result, and despite its prospective nature, this study does not provide conclusive evidence either for or against an association between antecedent stress and MS exacerbation.

In summary, there is Class II evidence both for and against an association between antecedent stress and the onset or exacerbation of MS. Moreover, the strength of the favorable evidence is tempered by the lack at present of a clear biological model, the lack of an agreed-upon definition of stress, the possible bias of retrospective interviews, the apparent inconsistency of the relationship, and, perhaps most importantly, by the lack of any conclusive prospective data. However, because radiographic attacks of MS occur frequently and can be easily documented by serial gadolinium-enhanced MRI scanning, and because stress is frequent even in control subjects as outlined above, it should now be possible to study the association between stress and exacerbations of MS prospectively and thereby convincingly test the proposed relationship.

Conclusions. *Physical trauma.* On the basis of strong and generally consistent Class II evidence, any posited association of trauma, especially head trauma, with more than a small effect on either MS onset or MS exacerbation is excluded. Moreover, the preponderance of the Class II evidence supports no association between physical trauma and either MS onset or MS exacerbation.

Psychological stress. On the basis of several Class II studies, the relationship between antecedent stress and either MS onset or MS exacerbation is considered possible. Nevertheless, as outlined above, the existing Class II studies on this relationship have important limitations, and at present, the prospective data are insufficient to establish any such relationship with reasonable medical certainty.

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Disclaimer

This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The American Academy of Neurology recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

Appendix 1

Panel of experts: Douglas S. Goodin, MD (chair and lead author), George C. Ebers, MD; Kenneth P. Johnson, MD; Moses Rodriguez, MD; William A. Sibley, MD; and Jerry S. Wolinsky, MD.

American Academy of Neurology Therapeutics and Technology Assessment Subcommittee members: John Ferguson, MD (chair); Elliot Mark Frohman, MD, PhD; Robert Goldman, MD; Douglas Goodin, MD (facilitator); Philip B. Gorelick, MD, MPH; Chung Hsu, MD, PhD; Andres Kanner, MD; Anne Marini, MD; E. Steven Roach, MD; and Edward Westbrook, MD.

Appendix 2

Definitions

Safe: A judgment of the acceptability of risk in a specified situation, e.g., for a given medical problem, by a provider with specified training, at a specified type of facility.

Effective: Producing a desired effect under conditions of actual use.

Established: Accepted as appropriate by the practicing medical community for the given indication in the specified patient population.

Possibly useful: Given current knowledge, this technology appears to be appropriate for the given indication in the specified patient population. If more experience and long-term follow-up are accumulated, this interim rating may change.

Investigational: Evidence insufficient to determine appropriateness, warrants further study. Use of this technology for given indication in the specified patient population should be confined largely to research protocols.

Doubtful: Given current knowledge, this technology appears to be inappropriate for the given indication in the specified patient population. If more experience and long-term follow-up are accumulated, this interim rating may change.

Unacceptable: Regarded by the practicing medical community as inappropriate for the given indication in the specified patient population.

Suggested strength of recommendations

Type A: Strong positive recommendations, based on Class I evidence, or overwhelming Class II evidence when circumstances preclude randomized clinical trials.

Type B: Positive recommendation, based on Class II evidence.

Type C: Positive recommendation, based on strong consensus of Class III evidence.

Type D: Negative recommendation, based on inconclusive or conflicting Class II evidence.

Type E: Negative recommendation, based on evidence of ineffectiveness or lack of efficacy, based on Class II or Class I evidence.

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