Does trauma trigger multiple sclerosis? 1: A controversy

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The potential role of trauma in the development of multiple sclerosis is important but controversial. Patients commonly ask about this and it has important medicolegal ramifications. In addressing such issues this article will consider both physical and psychological trauma, examine pathogenic mechanisms, and discuss the evidence for and against a relationship.

Multiple sclerosis (MS) is the commonest neurological disorder affecting young adults, and all hospital physicians and GPs are likely to have experience of caring for these patients.

The question of whether trauma triggers onset or exacerbations in MS is frequently asked by MS patients of their medical advisors. It is important both from the scientific standpoint and also in terms of counselling patients. It remains a controversial issue and has been the subject of a number of medicolegal cases, as discussed in a companion article (Weatherby et al, 2003).

It is a natural tendency to blame any illness on antecedent events. In a condition of uncertain aetiology this is particularly tempting, and the underlying causes of MS currently remain unclear. Patients may be genetically susceptible, as a number of genome screens attest. However, even the highest estimates put the genetic contribution at no more than 40%. The environment therefore plays a significant role. Although viral agents are acknowledged as important triggers to disease exacerbation and onset, most experienced neurologists are likely to have seen cases where an attack has occurred in close temporal relationship to an episode of trauma. Historically many papers have reported a striking relation to trauma (Klausner, 1901; Harris, 1933; McAlpine and Compston, 1952). In spite of numerous studies subsequently performed, the literature remains controversial.

The object of this review is to consider the biological theory and evidence for and against an association between physical or psychological trauma and MS.

PHYSICAL TRAUMA

Evidence for a relationship with MS

For any putative association to be viable it must make biological sense. The arguments behind the biological plausibility of an association are therefore first discussed.

It is believed that one of the first events to occur in the pathology of MS is dysregulation of the immune system, which allows T cells specific for myelin basic protein to be activated in the periphery. Although the healthy blood–brain barrier is impermeable to large molecules there is evidence that activated T cells are able to cross the blood–brain barrier and enter the CNS. Within the CNS they attack the myelin basic protein and so cause damage and demyelination.

If trauma causes a breakdown in the blood–brain barrier, patients constitutionally susceptible to MS ('potential demyelinators') may be vulnerable to trauma either triggering disease onset or exacerbations.

Is there evidence that blood–brain barrier breakdown can occur as a result of physical trauma? Broadly speaking the evidence can be divided into that from animal experiments, observations in humans and magnetic resonance imaging (MRI) studies (Poser, 1987, 1994a, 2000a).

Animal studies: Evidence suggesting blood–brain barrier breakdown has been found in animals suffering mechanical brain injury too slight to produce other neuropathological changes (Povlishock et al, 1978). This has been taken to suggest that physical trauma may cause new lesions that would not have otherwise occurred but for trauma. The finding that spontaneous concussive CNS injury causes diffuse microscopic lesions of blood vessels that would escape notice on superficial examination

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of the brain (Hardman, 1979) may suggest that minor trauma can be relevant. Significant increases in blood–brain barrier permeability in animal brains subject to whiplash injury have been reported (Domer et al, 1979) and may be clinically important because whiplash injury is a frequent occurrence in road traffic accidents.

Human observations: Needle thalamotomy in MS patients has been found to result in the formation of new plaques adjacent to the needle tract at several levels (Gonsette et al, 1966). This suggests that direct trauma may provoke further MS plaques and, by extrapolation, may precipitate exacerbation. A cohort of 39 cases have been described in which MS onset or MS exacerbations bore a temporal relationship to hyperextension-hyperflexion neck injury (Chaudhuri and Behan, 2001).

MRI studies: Close anatomical correspondence between MS plaques and compression of spinal cord by spondylosis, discs or whiplash injuries to neck have been noted (Poser, 1998).

What would be a reasonable timescale for physical trauma to be linked to MS? Invoking the blood–brain barrier mechanism, the potential 'window of opportunity' for physical trauma to provoke MS symptoms would be the time period that the blood–brain barrier was permeable to autoreactive T cells. Signal enhancement (following gadolinium contrast) is an indicator of blood–brain barrier breakdown. The duration of enhancement of a new lesion generally lasts from 2 weeks to 3 months, but for most lesions it is between 2 and 6 weeks (Miller et al, 1988; Barkhof et al, 1992; Thompson et al, 1992). It would therefore appear that if an exacerbation were to be caused by physical trauma it would be likely to occur within 3 months.

Evidence against a relationship with MS

Historically most of the studies suggesting a temporal association with trauma were anecdotal and retrospective. They may have been subject to recall bias. Blood–brain barrier breakdown occurs frequently in MS, which raises the possibility that reported associations could occur by chance.

It seems likely that the blood–brain barrier breakdown hypothesis is too simplistic. Perivenular inflammation may be an important part of early disease pathogenesis as well as blood–brain barrier breakdown, and there is evidence accumulating that changes in the normal appearing white matter precede development of gadolinium enhancement (Filippi et al, 1998). Regarding animal evidence, it is not certain whether any type of trauma that can disrupt the blood–brain barrier has the potential to cause new lesions in MS and whether trauma-triggered demyelination is the same as demyelination in MS. Direct trauma to the exposed brain may not be a good model for the genesis of MS. In addition, the animal model for MS, experimental allergic encephalomyelitis (EAE), is not a perfect MS mimic.

From an observational point of view, there is no evidence that MS is more common in sportsmen or women, which would suggest that a major role for trauma in onset or exacerbation is unlikely.

In view of such uncertainties, a number of epidemiological studies have been performed to search for an association between trauma and MS. In general these studies have hypothesized that the strongest relationship would be with more severe trauma (greater damage to blood–brain barrier).

Epidemiological studies: An 8-year study was performed to prospectively record all episodes of physical trauma and to measure the effect on exacerbation rate and progression of MS (Sibley et al, 1991). One hundred and seventy MS patients and a group of matched controls were followed. The number of exacerbations in the 3- and 6-month periods after an episode of trauma (termed an 'at risk' period; AR) were compared with the number of exacerbations at other times (when 'not at risk'; NAR).

The incidence of trauma was found to be approximately three times higher in MS patients than controls. No significant relationship was found between trauma and MS deterioration in the AR period. In a subgroup with more frequent exacerbations a higher proportion of relapses were observed in the NAR period, and a statistically significant negative correlation between traumatic episodes and exacerbations was reported. When a subanalysis of trauma type was performed electric shocks were significantly associated with exacerbation during a 3-month but not 6-month AR period, and no other trauma types were found to have significant associations.

In 1993 Siva and colleagues reported another epidemiological study. This aimed to assess the effect of trauma on patients with MS, and also to assess the risk of developing MS after trauma. The AR period was chosen as 6 months after trauma. No significant difference in the number of exacerbations in the 6 months preceding and the 6 months following the episodes of trauma was found. No significant effect on disability progression was observed. To examine

the risk of developing MS after trauma, a cohort of 819 patients with head injury and 942 patients undergoing lumbar disc surgery was examined. In the head injury cohort two patients later developed MS (one 21 years later and one 3 years later). In the lumbar disc cohort one patient developed MS (3 years later). The study concluded that peripheral fractures and trauma are not associated with MS exacerbations or MS-related disability, and that head injury and lumbar disc surgery are not associated with the onset of MS.

A subcommittee of the American Academy of Neurology reviewed the evidence linking trauma and MS (Goodin et al, 1999). Only class II evidence was considered (case-control or cohort studies), there being no class I evidence. Essentially the conclusions were 'that there was strong evidence limiting any posited association between serious head trauma and onset of MS to no more than 1.3%' and that the 'association between serious head trauma and MS exacerbation is similarly limited to no more than a fraction of a per cent of cases'.

The drawbacks to the epidemiological studies: It is often said that negative studies cannot exclude an association between variables. Furthermore it must be pointed out that the epidemiological studies have been criticized for being underpowered, for examining 'inappropriate or irrelevant trauma' (e.g. lumbar disc surgery) and including trauma that is 'too mild' (e.g. abrasions and lacerations). As the American Academy of Neurology review was based to a large extent on the epidemiological studies described above, it has been subject to similar criticisms (Chaudhuri and Behan, 2000; Lehrer, 2000; Poser, 2000b).

PSYCHOLOGICAL TRAUMA

The effect of psychological trauma is more difficult to evaluate than physical trauma. There is less clear-cut biological plausibility, although interactions between the immune system and stress (e.g. via hypothalamic–pituitary–adrenal axis) are increasingly recognized and may provide an effector mechanism. There is no agreed 'measure' of psychological trauma and the impact of significant life events varies between individuals.

Evidence for a relationship with MS

A number of studies have found a relationship between reported psychological stress and onset or exacerbation of MS.

In 1982 Warren et al studied 100 MS patients and 100 control subjects and considered psychological stress in the 2 years preceding MS onset. They found that 79% of MS subjects, compared with 54% of controls, had experienced more unwanted stress than usual in the preceding 2 years before disease onset. Considering the 6-month period before disease onset, 62% of patients reported 'severely threatening' events, compared to 15% of controls (Grant et al, 1989). Considering the 3-month period before an MS exacerbation, a study of 95 pairs of MS patients (Warren et al, 1991) found that 57% of MS patients had experienced intense emotionally stressful events, compared with only 28% of patients 'in remission'.

Evidence against a relationship with MS

Retrospective studies of psychological trauma may be subject to recall bias. A prospective study in 1988 (Franklin et al, 1988) examined the relationship between MS exacerbations and stressful life events in 55 patients interviewed every 4 months until an exacerbation occurred. No significant difference in life events was noted between MS patients with exacerbations and controls, although exposure to 'extreme events' was slightly higher in patients than controls. An observational study examined the effect of the stress of potential missile attack on MS in 32 MS patients studied during the Persian Gulf war of 1991 and found that the number of relapses during the war and the following 2 months was significantly less than before the war (Nisipeanu and Korczyn, 1993).

An American Academy of Neurology report (Goodin et al, 1999) concluded that:

> **'on the basis of several class II studies, the relationship between antecedent stress and either MS onset or MS exacerbation is considered possible…[although]…the prospective data are insufficient to establish any such relationship with reasonable certainty.'**

As physical and psychological trauma have essentially been studied separately, it has not been possible to consider the effect of psychological trauma induced by physical trauma.

CONCLUSIONS

In spite of data from epidemiological studies and a report from the American Academy of Neurology, the question of whether a patient's MS would have developed or was aggravated by trauma remains the subject of sometimes intense consideration. The level of evidence required by courts may differ from that needed from a scientific standpoint. Arguably medicolegal issues

(discussed in the companion article; Weatherby et al, 2003) could be of more immediate relevance to a patient, and may be a major driving force behind the vigour of the debate. HM

Conflict of interest: none.

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Weatherby MJC, Weatherby SJM, Hawkins CP (2003) Does trauma trigger multiple sclerosis? 2: A medicolegal view. *Hosp Med* (in press)

KEY POINTS

- The question as to whether trauma triggers onset or exacerbations in multiple sclerosis (MS) is clinically and medicolegally important.
- An increase in physical trauma or psychological stress is frequently reported before onset or disease exacerbation in MS.
- The biological basis for an association between MS and physical trauma is that physical trauma causes a breakdown in the blood–brain barrier, and autoreactive T cells enter the CNS causing the cascade of events leading to demyelination and axonal loss. Interactions between emotional stress and the immune system may provide a biological basis for an association between psychological trauma and MS.
- The duration of blood–brain barrier breakdown generally lasts from 2 weeks to 3 months, but in most cases it is between 2 and 6 weeks. If an exacerbation were to be caused by physical trauma it would therefore be most likely to occur within 3 months.
- The evidence supporting an association between MS and physical trauma is largely based on animal and laboratory studies and supported by clinical observations, and case-control and cohort studies.
- Larger epidemiological studies have not found a significant link between physical trauma and MS.
- A report from the American Academy of Neurology has concluded that there is no evidence of a significant association between MS onset or exacerbation and physical trauma, while an association with psychological trauma was considered possible.
- The epidemiological studies and thus the American Academy of Neurology report have been criticized for considering the 'wrong' sorts of trauma and for being underpowered.
- Medicolegal factors may, in part, be responsible for the continuing debate.