PAPER

Risk of multiple sclerosis after head injury: record linkage study

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Background: The possibility that head injury may influence the development of multiple sclerosis (MS) has been studied inconclusively in the past.
Objective: To determine whether head injury is associated with an increased risk of MS.
Method: Analysis of database of linked hospital and death records, comparing the occurrence of MS in a cohort of people admitted to hospital with head injury and a reference cohort.
Results: The rate ratio for MS after head injury, compared with the reference cohort, was 1.1 (95% confidence interval, 0.88 to 1.36). There was no significant increase in the risk of MS at either short or long time periods after head injury. Using length of hospital stay as a proxy for severity of injury, there was no significant increase in the rate ratio for MS after head injuries with hospital stays of less than two days (rate ratio = 1.1 (0.71 to 1.57)), two or more days (rate ratio = 1.0 (0.68 to 1.45)), or seven or more days (rate ratio = 1.3 (0.64 to 2.34)).
Conclusions: The method used, record linkage, ensures that patients' recollection of injury, or any tendency to attribute MS to injury, cannot have influenced the results. Injuries to the head were not associated with either the aetiological initiation or the clinical precipitation of onset of multiple sclerosis.

The aetiology of multiple sclerosis (MS) is largely unknown, but autoimmune processes initiated by infectious or non-infectious environmental exposures in genetically predisposed individuals are contributing causes. The environmental factors that lead to MS may not necessarily be the same in different people. The question of whether trauma can sometimes play a causal role in the aetiology of MS has been debated since the earliest descriptions of the illness.[1] It has also been the subject of several medicolegal cases in the last 10 years.[2 3]

If trauma plays a role, it might do so by initiating the aetiological processes that lead to MS or by precipitating the clinical onset of latent disease. One mechanism hypothesised as a causal pathway between injury and MS is through a breakdown of the blood–brain barrier.[4–6] If this occurs, it is most likely to happen after head injury. Most publications on injury and MS have been case reports and interview based case–control studies. Case reports, although useful for formulating hypotheses, cannot demonstrate whether trauma preceding MS is more than a chance finding because the observations are uncontrolled. Case–control studies have generated contradictory results.[7–9] They are generally dependent on the patients' memory and are prone to recall bias. Recall bias and patients' attribution of injury as a possible cause of their MS are impossible in prospective cohort studies, with recruitment of subjects at the time of injury, and in studies of injury and MS that are based on the linkage of data from records that have been compiled independently of one another. However, such designs have been uncommon. Accordingly, we have undertaken a large record linkage study of MS in people after head injury. Our aim was to determine whether there are distinctive patterns of head injury in people before the onset of MS and, if so, to address the question of whether the injury might be a cause of MS or a precipitating factor for it.

METHODS

Population and data

We used data from the Oxford record linkage study (ORLS) which includes brief statistical abstracts of records of all hospital admissions (including day cases) in NHS hospitals, and all deaths, regardless of where they occurred, in defined populations within the former Oxford NHS region from 1 January 1963 to 31 March 1999. The hospital data were collected routinely in the NHS as the Region's hospital discharge statistics. The death data derive from death certificates. Data collection covered part of one health district and its associated hospitals from 1963 (population 350 000), two districts from 1966 (population 850 000), six districts from 1974 (population 1.9 million), and all eight districts of the region and their associated hospitals from 1983 (population 2.5 million). The data for each individual were linked together routinely, on an ongoing basis, as part of the region's health information system. The current programme of analysis of the data has been approved by the English NHS Central Office for Research Ethics Committees (reference number 04/Q2006/176).

A cohort was compiled comprising data on all people admitted with head injury (*International Classification of Diseases* codes 850–54 in the ninth revision, and equivalent codes in the seventh, eighth, and 10th revisions). A reference cohort, to compare with the head injury cohort, was constructed by similarly selecting records of individuals admitted for a wide range of medical and surgical conditions. This is our ''reference cohort'' of patients that has been used in other studies of interrelations between diseases,[10 11] except that we excluded all people with injuries from the reference cohort. We considered that the incidence of MS in the reference cohort would approximate that in the general population of the region, while allowing for migration from it (data on migration of individuals were not available). We excluded all people with MS recorded before or at the same admission as that for injury or for the reference cohort conditions; and we excluded those aged 85 years and over at the time of head injury or reference condition. We then searched the database for any subsequent record of MS in the head injury cohort and the reference cohort.

Abbreviations: MS, multiple sclerosis; ORLS, Oxford record linkage study

Table 1 Age distribution of study population of people admitted to hospital with head injury: number and percentage of people in each age group at time of admission

Age group (years)	Head injury	
	No	%
0–4	15620	14.1
5–9	14508	13.1
10–14	12927	11.7
15–19	17064	15.4
20–24	11782	10.6
25–34	11653	10.5
35–44	7281	6.5
45–54	5786	5.2
55–64	5020	4.5
65 +	9352	8.4
Total	**110 993**	**100**

Statistical methods

In comparing the rate of MS in the injury and reference cohorts, we took ''date of entry'' into each cohort as the date of first admission for injury or reference condition, and the ''date of exit'' for each individual patient as the date of subsequent admission for MS, or death, or 31 March 1999, whichever was the earliest. In comparing the injury and reference cohorts, we first calculated rates of subsequent MS, standardised by age (in five year age groups), sex, calendar year of first recorded admission, and district of residence, taking the combined injury and reference cohorts as the standard population. This standardisation was undertaken to ensure that the populations under comparison were equivalent in these respects. We then calculated the ratio of the standardised rate of occurrence of MS in the head injury cohort relative to that in the reference cohort. The confidence interval for the rate ratio and statistics for its significance were calculated as described by Breslow and Day.[11]

People in each five year age group who were admitted for a head injury were compared with as many people with the reference conditions as there were in the ORLS dataset in each group, in order to maximise statistical power. We divided time intervals from admission for an injury to admission for MS into less than 6 months, 6 to 11 months, 12 to 23 months, 24 to 35 months, 36 to 47 months, 48 to 59 months, 5 to 9 years, and 10 years and over. We wanted a measure of severity of head injury but no direct measure is recorded in the hospital statistical record. In the absence of such a measure, we reasoned that the length of time spent in hospital for the injury would generally be a good proxy for its severity. Accordingly, as well as studying the cohorts overall, we also divided the head injury cohort into those people who stayed two days or longer, and those who stayed seven days or longer, in hospital.

RESULTS

There were 110 993 individuals in the head injury cohort and 534 600 in the reference cohort. Table 1 summarises the age distribution of patients in the injury cohort: 72% were under 35 years, and 90% under 65 years, at the time of injury. The mean period of follow up was 16.7 years.

The rate ratio for MS after head injury, compared with the reference cohort, was 1.1 (95% confidence interval (CI), 0.88 to 1.36); exact p value 0.42; table 2. There was no significant increase in risk of MS at either short or long time intervals after head injury (table 2). There was no significant increase in the rate ratio for MS after head injuries with hospital stays of less than two day (rate ratio = 1.1 (95% CI, 0.71 to 1.57)), two or more days (rate ratio = 1.0 (0.68 to 1.45)), or with hospital stays of seven or more days (rate ratio = 1.3 (0.64 to 2.34)).

DISCUSSION

Despite the long history of the idea that neurological trauma might be involved in either the causation or exacerbation of MS, the proposed association has yet to be established or refuted conclusively. Much of this uncertainty arises because most reports that suggest a causal link are uncontrolled reports of small numbers of patients,[4 12] or case–control studies that are open to the criticisms of possible recall bias and being based on small numbers with low statistical power. In 1952, McAlpine and Compston published the first relatively large case–control study of trauma and MS.[6] In 250 MS patients and 250 controls, they found that 36 (14.4%) had a history of trauma in the three months before the onset of MS, compared with 13 (5.2%) controls (odds ratio 3.07 (95% CI, 1.58 to 5.94)). However, the publication lacks details about the types of trauma involved and the data analyses used. In 1968 Alter and Speer reported a study of 36 patients with MS, each of whom was paired with two control subjects matched for sex and age.[8] Patients and controls were interviewed about various events that had occurred during an unspecified period before MS onset. Head trauma was not significantly associated with MS onset, although the very small number of patients studied means that the statistical power of the study was very low. In 1993, Siva *et al* undertook a population based record linkage study of MS onset and exacerbation following head injury.[13] They found no association between head injury and MS onset. Of 819 head injury cases, none developed MS within six months; two patients later developed MS (one had the injury three years after and the other 21 years after head injury). This study, too, has been criticised for lack of statistical power.[14]

Table 2 Occurrence of multiple sclerosis with different time intervals after injury*

Time from injury to MS	Observed number of MS in injury cohort	Expected number of MS in injury cohort	Adjusted rate ratio	95% CI
<6 months	8	8.4	1.0	0.40 to 1.99
6–11 months	2	3.0	0.7	0.08 to 2.60
12–23 months	9	7.5	1.2	0.53 to 2.58
24–35 months	2	3.5	0.6	0.07 to 2.69
36–47 months	9	7.3	1.2	0.54 to 2.82
48–59 months	5	4.7	1.1	0.32 to 2.97
5–9 years	21	19.5	1.1	0.65 to 1.77
10+ years	49	44.4	1.1	0.82 to 1.47
Total	**105**	**97.9**	**1.1**	**0.88 to 1.35**

*Number of people in the head injury cohort with MS (''observed number''), expected number, ratio of rates in the injury cohort to that in the reference cohort, and 95% confidence intervals for the rate ratio.
CI, confidence interval; MS, multiple sclerosis.

A weakness of our study is that it only covers people who were admitted to hospital for their injury and for MS. It could be argued that any effects of trauma on MS may have been missed because they only occurred in the subset of patients who were not admitted with MS. We think that this is unlikely: we see no reason to suppose that previous head injury would influence whether patients who subsequently developed MS would be admitted to hospital. The strengths of our study are that it is large; records of head injury and MS were made independently and only subsequently brought together, and therefore recall bias and attribution bias are avoided; it was undertaken in a geographically defined but otherwise unselected population; and it included analysis of both short and long periods of follow up. We found no significant association between head injury and MS overall, or in patients with severe injury (as estimated by the proxy of length of hospital stay), or at any time interval between injury and MS. Our findings add weight to the evidence that head trauma does not contribute to the aetiology or precipitation of MS.

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APPENDIX

Conditions used in reference cohort, with Office of Population, Censuses and Surveys (OPCS) code edition 3 for operation and ICD9 codes for diagnoses (with equivalent codes used for other coding editions): appendicectomy (OPCS 441–444); tonsillectomy/adenoidectomy (OPCS 230–236); total hip replacement (OPCS 810–811); total knee replacement (OPCS 812); cataract (ICD9 366); squint (ICD9 378); otitis externa, otitis media (ICD9 380–382); haemorrhoids (ICD9 455); varicose veins (ICD9 454); upper respiratory tract infections (ICD9 460–466); deflected nasal spectum, nasal polyp (ICD9 470–471); impacted tooth and other disorders of teeth (ICD9 520–521); inguinal hernia (ICD9 550); ingrowing toenail, other diseases of nail (ICD9 703); sebaceous cyst (ICD9 706.2); internal derangement of knee (ICD9 717); bunion (ICD9 727.1).

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