Multiple sclerosis after infectious mononucleosis: record linkage study

Michael J Goldacre, Clare J Wotton, Valerie Seagroatt, David Yeates

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Objective: To ascertain if infectious mononucleosis is a risk factor for the development of multiple sclerosis (MS); and, if it is, whether its effect is close to or remote in time from the onset of MS.

Design: Analysis of database of linked abstracts of records of hospital admission and death.

Setting: Health region in central southern England.

Main outcome measure: Ratio of rate of MS in a cohort of people admitted to hospital with infectious mononucleosis to the rate in a comparison cohort.

Results: Considering all time intervals from admission with infection to admission with MS, there was a non-significant increase of risk of MS in the infectious mononucleosis cohort (rate ratio 2.17, 95% confidence intervals 0.79 to 4.77). At the interval of 10 years or more, there was a significant increase in risk of MS (rate ratio 4.01, 1.48 to 8.93). The mean time from infectious mononucleosis to first admission with MS was 14 years.

Conclusion: This study adds support to the evidence that Epstein-Barr virus, the cause of infectious mononucleosis, is associated with MS. Its role is probably as an initiator of the disease process of MS, or as a contributor to its early development, rather than as an activator of latent, existing disease.

Multiple sclerosis (MS) is a disease of the central nervous system in which the myelin sheath of nerve fibres is destroyed. Its aetiology is largely unknown but an autoimmune process, after an infectious or non-infectious environmental exposure, is likely to be a contributing cause. Viral infection has long been suspected of playing a part in MS. There is increasing evidence that infection with the Epstein-Barr virus (EBV) is implicated. However, the timescale on which infection might act is still unclear. Seroepidemiological case-control studies have provided some of the most convincing evidence of a link between EBV and MS; but such studies usually cannot distinguish between recent infection or infection in the distant past. Infection could be an initiating aetiological factor, remote in time from the onset of MS; a later effect that influences the clinical manifestation of disease; or even a consequence of the onset of MS, perhaps resulting from increased susceptibility to infection.

In 2000, Ascherio and Munch undertook a systematic review of the case-control studies of EBV infection and MS. They identified eight studies in which EBV serology had been compared between people with MS and controls. They concluded that the consistency of association across the studies supported the likelihood that EBV plays a part in the aetiology of MS. In subsequent work, Ascherio et al and Levin et al undertook further case-control studies, nested within cohort studies that had been established for other purposes, in which serum had been stored before the onset of MS. They showed an association between EBV and MS in which EBV infection had occurred well before the onset of symptoms of MS. Marrie et al, in a case-control study, reported an increase in risk of MS in people who had evidence of EBV infection in the year before onset of MS. Lindberg et al linked data from a cohort of people with infectious mononucleosis—a common infectious disease in children, teenagers, and young adults that is caused by EBV—to a register of people with MS. Based on three cases of MS, they reported a significant increase of risk with a mean time interval of 12 years between infectious mononucleosis and MS.

We used a database of linked routine records of hospital care and of death to study the association between admission for infectious mononucleosis and subsequent MS. In particular, we wanted to discover if any association was at a long time interval from infection to MS.

METHODS

Population and data

The Oxford record linkage study (ORLS) 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 January 1 1963 to March 31 1999. The hospital data were collected routinely in the NHS as the Oxford Regional Health Authority’s hospital discharge statistics. The death data derive from death certificates. Data collected covered two health districts and their associated hospitals from 1963 (population 850 000), six districts from 1975 (population 1.9 million) and all districts and hospitals in the region from 1987 (population 2.5 million). The data for each person were linked together routinely as part of the region’s health information system. They are anonymised and archived. The infectious mononucleosis cohort was obtained by selecting records of people less than 60 years of age admitted for infectious mononucleosis. A reference cohort was constructed by similarly selecting records of people less than 60 years of age admitted for various medical and surgical conditions. This is our “reference” group of patients that has been used in other studies of inter-relations between diseases. We considered that cases of MS in the reference cohort would approximate to those in the general population of the region while allowing for migration from it (data on migration of individuals were not available). This makes the assumption, which we cannot test, that out-migration from the infectious mononucleosis and reference cohorts are similar. Anyone with a reference condition and infectious

Abbreviations: MS, multiple sclerosis; EBV, Epstein-Barr virus
mononucleosis was entered into the “infectious mononucleosis” cohort from the time of admission with infectious mononucleosis. We searched the database for any subsequent record of MS in the infectious mononucleosis cohort and the reference cohort.

### Statistical methods

We calculated standardised rates of subsequent MS in each cohort—the infectious mononucleosis and reference cohort—based on person years at risk. We took “date of entry” into each cohort as date of first admission for infectious mononucleosis or reference condition and “date of exit” as the date of subsequent admission for MS if it occurred, death, or 31 March, 1999, whichever was the earliest. We standardised by age (in five year age groups), sex, calendar year of first recorded admission (in single years), and district of residence. The combined infectious mononucleosis and reference cohorts were used as the standard population (that is, we used internal standardisation). We did the standardisation by calculating, within each age-sex-year-district stratum, the rate of MS per person years at risk in the standard population. We expressed these as an overall standardised rate, for each cohort, by adjusting the ratio of the summed observed numbers to the summed expected numbers in each stratum.

For each individual condition in the reference cohort as well as infectious mononucleosis, we calculated the ratio of the standardised rate in each cohort to the standard population. We then calculated the ratio of the standardised rate of occurrence in the infectious mononucleosis cohort relative to that in the reference cohort. The confidence interval for the rate ratio and $\chi^2$ statistics for its significance were calculated as described elsewhere. We did this to increase the precision of our estimates. We divided time intervals from infection to outcome into less than 1 year apart, 1–4, 5–9, and 10 years or more apart.

### RESULTS

There were 2767 patients in the infectious mononucleosis cohort. Their mean age at first admission was 18 years and the average length of follow up was 15.3 years. Table 1 shows the age distribution of the infectious mononucleosis patients at the time of first admission. Sixty per cent were under 20 years of age at the time of first recorded admission. There were 640 163 people in the reference cohort with a mean number of 53 347 in each five year age stratum (range 32 205 to 83 436 people in each stratum).

Overall, our results showed a non-significant association between infectious mononucleosis and subsequent MS (rate ratio 2.2; 95% confidence intervals 0.8 to 4.8 (table 2)). However, all six cases of infectious mononucleosis followed by MS occurred 10 or more years after admission for infectious mononucleosis and, at that time interval, this gave a ratio that was significantly high (rate ratio 4.0; 95% confidence intervals 1.5 to 8.9). We inspected the results for each individual condition in the reference cohort as well as for the cohort as a whole. We did this to ensure that no individual condition had an undue influence on the overall result.

It did not; and, in particular, the group of upper respiratory diseases showed no association with subsequent MS.

### Table 1

Age distribution of study population of people admitted to hospital with infectious mononucleosis: number and percentage of people in each age group at time of admission

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Infectious mononucleosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>0–4</td>
<td>129</td>
</tr>
<tr>
<td>5–9</td>
<td>219</td>
</tr>
<tr>
<td>10–14</td>
<td>320</td>
</tr>
<tr>
<td>15–19</td>
<td>1024</td>
</tr>
<tr>
<td>20–24</td>
<td>570</td>
</tr>
<tr>
<td>25–29</td>
<td>79</td>
</tr>
<tr>
<td>30–34</td>
<td>99</td>
</tr>
<tr>
<td>35–39</td>
<td>68</td>
</tr>
<tr>
<td>40–44</td>
<td>43</td>
</tr>
<tr>
<td>45–49</td>
<td>33</td>
</tr>
<tr>
<td>50–54</td>
<td>18</td>
</tr>
<tr>
<td>55–59</td>
<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>2767</td>
</tr>
</tbody>
</table>

### Table 2

Number of people in the infectious mononucleosis cohort with MS ("observed number"), expected number, ratio of rates in the infectious mononucleosis cohort to those in the reference cohort, and 95% confidence intervals for the rate ratio

<table>
<thead>
<tr>
<th>Virus infection</th>
<th>Observed number of MS in infectious mononucleosis cohort</th>
<th>Expected number of MS in infectious mononucleosis cohort</th>
<th>Adjusted rate ratio</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple sclerosis</td>
<td>6</td>
<td>2.8</td>
<td>2.17</td>
<td>0.79 to 4.77</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>10</td>
<td>0</td>
<td>0.1</td>
<td>0 to 25.4</td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>0</td>
<td>0.6</td>
<td>0.00</td>
<td>0 to 6.30</td>
</tr>
<tr>
<td>1–4 years</td>
<td>0</td>
<td>0.6</td>
<td>0.00</td>
<td>0 to 6.73</td>
</tr>
<tr>
<td>5–9 years</td>
<td>6</td>
<td>1.5</td>
<td>4.01</td>
<td>1.48 to 8.93</td>
</tr>
</tbody>
</table>

The mean age at admission for infectious mononucleosis of the six people who subsequently developed MS was 17 years (range 12 to 22). The mean time period from infectious mononucleosis to first recorded admission for MS was 14 years (range 11 to 18 years).

DISCUSSION
It is probable that several factors interact to cause MS. In susceptible people, an initiating event is followed by a response that leads to the destruction of myelin. Susceptibility may include not only genetic predisposition but also dietary and nutritional factors. The response to infectious mononucleosis, which is probably one of the causes of multiple sclerosis, may be implicated.

The timescale on which infection might act is unclear: infection could be an initiating factor for MS, remote in time before it, or a later factor that precipitates manifestation of disease.

We also found a significant increase in MS 10 years and more after infectious mononucleosis: the mean period from infectious mononucleosis to first recorded admission with MS was 14 years.

Infectious mononucleosis probably contributes to the initiation of MS.

Policy implication
Infection with Epstein-Barr virus, the cause of infectious mononucleosis, is probably one of the causes of multiple sclerosis.

Variables to make the infectious mononucleosis and reference cohorts equivalent in these respects. There is no routine collection of clinical data on outpatients in England and therefore no data exist on the percentage of people with infectious mononucleosis who are treated as outpatients and inpatients. There are also no routinely available clinical data on the private sector for hospital care. Private expenditure figures on healthcare are available for the United Kingdom as a whole. They show that private expenditure, as a percentage of all healthcare expenditure, has increased from 3.5% in 1973 (the earliest available data) to 8.5% in 1998. Thus, the use of private hospital care is small and, furthermore, it is predominantly used for elective surgery rather than acute medical care. We doubt that many people acutely ill enough to require hospital care for infectious mononucleosis would have been admitted to private rather than NHS hospitals in the period covered by the study. We also think that most patients with MS would have been admitted for NHS care on at least one occasion. Although there has probably been a tendency towards ambulatory rather than hospital care for MS patients recently, the decision on whether or not to admit MS patients is unlikely to have been influenced by whether they had had an admission for infectious mononucleosis many years previously.

There are two published studies that used similar designs to ours. The study by Lindberg et al used a cohort of records of infectious mononucleosis linked to records of MS. They reported a significant association between infectious mononucleosis and MS, based on three cases of MS in the cohort, with a long time interval between the two conditions. Our study, too, is based on small numbers of people with both infectious mononucleosis and MS. However, studies of similar design could be performed using other longstanding linked databases—for example, in the Scandinavian countries, Scotland and Western Australia—to increase numbers on which to base firm conclusions.

In conclusion, we found a significant association between infectious mononucleosis and MS 10 years and more apart. The mean interval from infectious mononucleosis to MS was 14 years. This compares with the interval of 12 years reported by Lindberg et al. Our findings add epidemiological evidence to the likelihood that EBV is a cause of MS in some people. They also add to the evidence that the effect of EBV infection is remote in time. This being so, it suggests that EBV infection is probably an initiator of MS rather than an activator of clinical manifestations of latent disease.

ACKNOWLEDGEMENTS
The database was funded by the former Oxford Regional Health Authority and, over many years, it was built by Leicester Gill and Glenys Bettley. The Research and Development Directorate at the Department of Health funds the Unit of Health Care Epidemiology to undertake research using the database. We thank Sir Donald Worton, Seagroatt, et al.
Acheson for helpful discussions. Sir Donald founded the Oxford record linkage study and directed it from 1963–68.

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Conflicts of interest: none declared.

REFERENCES

APHORISM OF THE MONTH

“If you always do what you always did, you always get what you always got.”
(Anon)

One of the defining characteristics of human beings is held to be their capacity to learn from experience, yet how often is the response to delivery failure to increase the exhortation just to do better or work smarter, rather than think of another way of tackling the issue? Even the current fashion for scenario planning tends to reinforce this. It is customary to have three scenarios:

- business as usual
- smart working with performance management
- doing things differently

The problem is that, like circus animals trained to jump through hoops, health planners and managers don’t know what they don’t know, and may have a limited repertoire of response to complex problems. The only way to break new ground in to lateral problem solving is by creating environments that embrace diverse analysis, ideas, and experiences.

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