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Occasional Survey

CLINICAL VIRAL INFECTIONS AND MULTIPLE SCLEROSIS

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Summary

Over an 8 year period, 170 patients with multiple sclerosis (MS) and 134 healthy controls were assessed at monthly intervals in order to ascertain environmental factors which might be important in producing exacerbation or progression of the illness, and to compare the frequency of common viral infections in the two groups. During cumulative periods designated “at risk” (2 weeks before the onset of infection until 5 weeks afterwards) annual exacerbation rates were almost 3-fold greater than those during periods not at risk. Approximately 9% of infections were temporally related to exacerbations, whereas 27% of exacerbations were related to infections. Frequency of common infections was approximately 20-50% less in MS patients than controls; it was progressively less in those with greater disability. Even in minimally disabled patients with similar potential for infectious contacts, the infection rate was significantly less than in controls, suggesting that MS patients could have superior immune defences against common viruses.

INTRODUCTION

In 1976 we began a prospective study of patients with multiple sclerosis (MS) and healthy controls in order to ascertain factors which might trigger exacerbations. The effects of physical trauma, anaesthesia, influenza immunisation, and season have been published; we now report our findings on the frequency of clinical viral infections and the effects of such infections on annual exacerbation rates.

PATIENTS AND METHODS

Patients

Patients with MS, as defined by Schumacher Committee criteria, were invited to participate in the study. Over an 8 year period (Jan 1, 1976–Dec 31, 1983) 170 patients (67 males and 103 females) were followed for at least 1 year; average duration of observation was 5-3 years. Each patient was contacted monthly to complete a questionnaire about the occurrence of various events during the preceding 30 days, and was examined routinely every 3 months; additional examinations were done whenever exacerbations occurred. At the time of each neurological examination a disability status scale (DSS) rating was given. Between clinic visits there was frequent telephone contact with the clinic nurse (K. C.) to report new symptoms and to assure completion of the questionnaire on time. Mildly affected patients (DSS 0–2) were mostly employed outside the home in occupations similar to the controls (table I).

Controls

134 age-matched healthy adults (49 males and 85 females) were followed for a minimum of 1 year; mean period of observation was 4-6 years. 42 controls lived in the same household as a patient (38 spouses and 4 blood relatives). 17 additional controls were blood relatives of MS patients, but the remaining 113 were not related. Control subjects completed the same monthly questionnaire as the patients and telephone interviews were also used in this group to avoid a lapse of more than 30 days between reporting periods.

Exacerbation

An exacerbation was defined as a new neurological symptom, associated with an appropriate change in neurological examination, which lasted more than 48 h and was not associated with fever. The term implied a new lesion in the nervous system, or worsening of an existing lesion.

Viral Infections

Viral infections were identified by the symptoms commonly associated with them. Thus complaints such as coryza, sore throat, cough, and malaise, with or without fever, characterised most of the respiratory infections. Infections without fever or with fever <38°C were called “colds”; those with fever >38°C were designated as “flu”, with full recognition that many of the illnesses were not due to influenza viruses. When sore throat, malaise, cramps, and diarrhoea were prominent, the infection was called enteric. Herpetic eruptions (genital or oral) were usually characteristic but could not always be distinguished from aphthous ulcers. Viral cultures of patients, controls, and family were not done because this was beyond the scope of our exploratory study.

Periods at Risk and Not at Risk

The at risk (AR) period extended from 2 weeks before the onset of symptoms of infection until 5 weeks afterwards (a total of 7 weeks). All other periods in the study were not at risk (NAR). Annual exacerbation risks were calculated separately for each period. The AR period was defined at the beginning of the study. In a previous study we used an AR period of 1 week before onset of symptoms.

### Table I—Comparison of MS patients with minimal disability (DSS 0–2) with controls of similar age

|                | Patients (n=36) | Controls (n=105) |
|----------------|----------------|-----------------|
| Mean age (yr)  | 34.7 (±10.8 SD) | 34.4 (±9.9 SD)  |
| Mean household size | 2.9          | 3.0            |
| Employed outside home | 61%         | 68%            |
| Children under 18 yr at home | 53%        | 38%            |
| Children under 10 yr at home | 33%       | 20%            |
| Mo involved (%) | 10.5%         | 13.3%          |

*See table II.

### Table II—Frequency of common viral infections in MS patients with various disability ratings and controls of same age

| Patients Mean* DSS (range) No | Mean age (yr) | Infections | Mo involved (%) | Mo involved (%) |
|-------------------------------|---------------|------------|----------------|----------------|
| 0–2                          | 36            | 34.7       | 236            | 10.5           |
| 2–4                          | 32            | 37.8       | 143            | 6.3            |
| 4–6                          | 48            | 48.2       | 214            | 6.7            |
| 6–8                          | 44            | 47.7       | 163            | 5.5            |
| 8–10                         | 10            | 47.1       | 23             | 3.1            |

| Controls Mean Age (yr) | Infections | Mo involved (%) | Mo involved (%) | χ² | p |
|-----------------------|------------|----------------|----------------|----|---|
| 0–2                   | 105        | 34.4           | 744            | 5574 | 13.3 | 9.45 | <0.005 |
| 2–4                   | 107        | 37.8           | 739            | 5862 | 12.6 | 21.53 | <0.001 |
| 4–6                   | 51         | 48.4           | 296            | 2896 | 10.2 | 22.56 | <0.001 |
| 6–8                   | 61         | 47.6           | 359            | 3436 | 10.4 | 47.53 | <0.001 |
| 8–10                  | 73         | 47.3           | 426            | 4312 | 9.9  | 31.76 | <0.001 |

*Mean DSS = average of entry and exit DSS scores.
accentuation of exacerbation rates occurred in patients of all controls during 4'6 years. Only 4 cases of herpetic eruption occurred in 170 MS were evident for all categories of viral infection, they were years. Moreover, although the differences in infection rates levels of disability, except that the numbers of exacerbations also in those with moderate and low rates (table v). The same apparent not only in patients with frequent exacerbations but greater than those in NAR periods (table iv). This effect was...

RESULTS

Frequency of Total Viral Infections in MS Patients and Controls

Viral-like infections were significantly less frequent in patients than in controls; the difference was most pronounced in patients with severe disability. Table ii shows that there was a linear drop in the frequency of such infections with advancing disability. Although much of this difference might be attributed to the patients' sheltered lives, giving rise to fewer infectious contacts, this may be only a partial explanation. The frequency of viral infections was also significantly lower in patients with trivial disability (DSS 0-2) whose daily activities were comparable to controls. Table i shows that patients with mild MS resembled controls with respect to important determinants of infection frequency such as age, household size, employment outside the home, and contacts with children under the age of 10 years. Moreover, although the differences in infection rates were evident for all categories of viral infection, they were not pronounced for herpetic simplex-like infections (table iii), in which clinical symptoms in adults are-usually due to re-emergence of latent virus rather than person-to-person contact. Only 4 cases of herpetic eruption occurred in 170 MS controls during 4.5 years, whereas 25 cases occurred in 134 controls during 4.6 years.

Viral-like Infections, Exacerbation Rates, and Progression of MS

Exacerbation rates in AR periods were almost 3-fold greater than those in NAR periods (table iv). This effect was apparent not only in patients with frequent exacerbations but also in those with moderate and low rates (table v). The same accentuation of exacerbation rates occurred in patients of all levels of disability, except that the numbers of exacerbations...
10--41%. The present results are similar to those of Sibley and Foley who did a prospective study of 34 patients over a period of 3 years and found that 33 of 69 exacerbations (48%) were temporally associated with a common infection—ie, the infection occurred within a period from 3 weeks before to 1 week after the exacerbation. Concurrent controls were not used in that study but it was noted that the infection rate was lower than that in a large study of infections in healthy families in the same area; 10 at the time, under-reporting of infections not associated with MS exacerbations was suspected, but in light of the present results this conclusion was probably incorrect. In the previous study, patients were aware that the relation of infection to MS was the subject of the investigation; in the present study, infection was only one of many factors being investigated, and care was taken to avoid any patient preconception.

The apparent triggering of MS attacks by infections is probably not a nonspecific effect of any infection. By the same methods of analysis, for example, we have found no relation between bacterial infections (mostly of the urinary tract) and worsening of MS. Moreover, although the annual exacerbation rate almost trebled during AR periods, only 8-6% of infections were associated with worsening of MS. Such a low rate of triggering might be explained, in part, by the fact that many new lesions find no clinical expression. However, specific triggering only by a certain virus or class of viruses might be another reason.

If viral triggering is important to formation of MS lesions, why are only 27% of MS exacerbations associated with evidence of infection? One possible explanation is the known frequency of inapparent infection—eg, as many as 80% of primary entero viral infections are symptomless. Recurrent infections by the same virus are often associated with partial immunity and inapparent infection; reinfections with rhinoviruses, parainfluenza and respiratory syncytial viruses, and other important organisms in respiratory illness, are usually symptomless. 14

Since seasonal studies in Arizona, 5 Cleveland, 7 Canada, 15 and Newcastle upon Tyne 16 have shown spring and summer peaks in exacerbation rates; this clustering may be attributable to certain viruses with a similar seasonal incidence. Coronaviruses show this pattern, 17 but, because there was a 4--5 week latency between infection and exacerbation in some of our cases, other viruses with slightly earlier seasonal peaks must also be considered. Isolation and identification of viruses during clinical infections in MS patients and family members should clarify the precise role of these infections in the pathogenesis of MS, and establish which agents may be most important.

While MS patients have fewer common infections than either family members or controls, it is difficult to know whether sheltering, immunity, or both, are responsible. The fact that a difference from controls can be shown even in MS patients with insignificant disability and the same number of contacts—especially with school children—suggests that immune defences may play a role. It is possible that they have more inapparent infections, perhaps as the result of more efficient natural defences against these common viruses. The finding of a much more rapid progression rate in mildly affected MS patients with infrequent symptoms of clinical infection suggests that overactive immune mechanisms determine not only a greater frequency of inapparent infection, but also swifter progress of disease.

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TABLE VI—MEAN MS EXACERBATION RATE IN AR AND NAR PERIODS BY MEAN DISABILITY

| Mean DSS DSS rating | Patients | Mean age (entry) | Infections/yr | Exacerbations/AR | Exacerbations/NAR | Wk AR | Exacerbation rate/yr AR | Exacerbation rate/yr NAR |
|---------------------|---------|------------------|--------------|----------------|----------------|------|-----------------|------------------|
| 0--2                | 36      | 34-7             | 1-28         | 28             | 47             | 1652 | 0-88*          | 0-31             |
| 2--4                | 32      | 37-8             | 1-00         | 19             | 51             | 1001 | 0-99*         | 0-41             |
| 4--6                | 48      | 48-2             | 0-81         | 14             | 47             | 1498 | 0-49*         | 0-20             |
| 6--8                | 44      | 47-7             | 0-66         | 6              | 31             | 1141 | 0-27          | 0-14             |
| 8--10               | 10      | 47-1             | 0-38         | 0              | 3              | 161  | 0-00          | 0-06             |

*SE of difference in means = 0-08. p=0-0027.
†SE of difference in means = 0-00. p=0-001.

TABLE VII—FREQUENCY OF CLINICAL VIRAL INFECTION, AND PROGRESSION OF MS DISABILITY IN 170 PATIENTS OVER 5--3 YR

| Entry DSS rating | Infections | Mean age | Mean infections/yr | Mean progression of DSS/yr | Exacerbation rate/yr AR | Exacerbation rate/yr NAR |
|------------------|------------|----------|--------------------|---------------------------|-------------------------|--------------------------|
| 0--4             | <1/yr      | 37       | 43                 | 0-53                      | 0-43*                   | 0-42                     |
|                  | 46         | 33       | 1-68               | 0-19*                     | 0-12                    | 0-37                     |
| 5--9             | <1/yr      | 64       | 50                 | 0-41                      | 0-13                    | 0-16                     |
|                  | >1/yr      | 23       | 44                 | 1-55                      | 0-15                    | 0-22                     |

*SE of difference in means = 0-08. p=0-0027.
†SE of difference in means = 0-16. p<0-001.