Asthma and multiple sclerosis: an inverse association in a case-control general practice population

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Received 28 May 2002

Summary

Background: Th1/Th2 imbalance is hypothesized to up-regulate some diseases and down-regulate others. Compared to controls, multiple sclerosis (MS) (Th1-mediated) has been linked to a reduced risk of allergy and asthma (Th2-mediated), based on patient questionnaire studies and a review of asthma medication.

Aim: To investigate whether MS is associated with a reduced risk of Th2-associated diseases and an increased risk of Th1-associated diseases.

Design: Retrospective matched case-control study.

Methods: Three hundred and twenty MS patients and controls matched for age, gender, location and smoking were selected from the Welsh General Practice Morbidity Database from 1995–99. Case and control records were assessed for Th1-mediated and Th2-mediated diseases.

Results: Overall, 346 MS patients were identified, giving a prevalence of 127 per 100 000. There was an inverse relationship between multiple sclerosis (MS) and asthma (OR 0.33; 95%CI 0.15–0.77). No statistically significant relationships emerged between other Th2-associated (eczema, dermatitis) or any Th1-associated (rheumatoid arthritis, thyroid disorders, inflammatory bowel disease [IBD], type 1 diabetes) diseases and MS, although no patient in either group had treated type 1 diabetes. A trend existed for IBD, with 5/320 of cases affected and no controls; OR = 9.5; 95%CI 1.30–79; p = 0.063.

Discussion: This inverse association between MS and asthma is compatible with a Th1/Th2 imbalance. Although the Th1/Th2 theory is probably an over-simplification in MS, a shift from Th1 cytokine dominance towards Th2 may provide drug-targeting routes for MS.

Introduction

The conjecture that an imbalance in the ratio of type 1 to type 2 helper T-cells (Th1/Th2 imbalance) may cause increased frequency of one disease and decreased frequency of another has some support.¹ ⁴ A reduced prevalence of asthma, thought to be a predominantly Th2-mediated disease, has been reported in a population with type 1 diabetes, which is associated with a predominance of Th1 cells.³ Multiple sclerosis (MS) is thought to upregulate Th1, and has been linked in patient questionnaire-based studies with a reduced risk of IgE-mediated allergy² and a trend to a reduced risk of asthma.³ We also previously reported an unexpected finding of fewer bronchodilator and inhaled corticosteroid prescriptions in an MS population compared to controls, in 1996 (p = 0.008 and p = 0.03, respectively).⁴ We investigated the hypothesis that MS may be associated with a reduced risk of
Th2-associated diseases and an increased risk of Th1-associated diseases, using the Welsh General Practice Morbidity Database (GPMD). The GPMD began in 1992, is currently funded by the National Assembly for Wales and is open to all computerized GP practices in Wales using a nationally recognized coding system. The objective of the GPMD is to obtain data routinely entered into general practice computer systems for at least 10% of the Welsh population, with an age-structure similar to that in the whole of Wales. While it was recognized that use of only computerized practices may produce a biased sample, obtaining a representative population was considered more important than having representative practices. Validation details are available elsewhere.

Methods

All patients' anonymized computerized GP records collated in the GPMD over 5 years (1995–1999) were accessed. Patients with a Read code for MS recorded at any time from 1993, and who were still registered at sometime between 1995–1999, formed the cases. From these cases, patients who were aged ≥16 years in 1995 and were registered with a GP for at least one year were selected. Controls (without a Read code for MS) were randomly selected from the GPMD, and were matched to each individual MS patient for age, gender, GP surgery and, where possible, smoking. Controls selected for a previous study of prescription usage in an MS population, which resulted in the unexpected finding of fewer asthma-related prescriptions in the MS population compared to controls, were excluded from this study. The aim was to eliminate the chance possibility that the previous control population had an abnormally high incidence of asthma.

Individual patients' records were examined for evidence of Th1 or Th2 disease. To minimize GP variation of disease diagnosis, ‘treated disease’ was used where possible. Hence asthma required a diagnosis and prescription of a medication for asthma: patients with COPD or intrinsic asthma (i.e. non-atopic) were excluded. ‘Eczema’ required a diagnosis of eczema or dermatitis and prescription of at least one topical corticosteroid or emollient: solar or chemically-induced eczemas were excluded. Allergic rhinitis was not investigated, due to the propensity to self-diagnose and treat without a GP consultation. Inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) were recorded by diagnosis alone, and type 1 diabetes by diagnosis and prescription of insulin.

Statistical analysis used SPSS. Odds ratios (OR) are quoted, with 95% CIs.

Results

In all, 346 MS patients were identified from 28 GP practices, with a total mean yearly list size of 256 709 patients. The prevalence of MS was 127 per 100 000. Included in the analysis were 320 MS patients who were aged ≥16 years in 1995, with at least one year of data. Patient demographics are presented in Table 1.

Of the disease associations investigated, only the prevalence of asthma was significantly different (Table 2), with MS patients being less likely to have treated asthma compared to controls, with an OR of 0.33 (95%CI 0.15–0.77). There was a trend for MS patients to be less likely to have eczema compared to controls (18/320 vs. 27/320), but this failed to reach statistical significance (OR 0.67; 95%CI 0.37–1.20). There were no statistically significant relationships between Th1 diseases and MS. However, a trend existed for inflammatory bowel disease (IBD), with 5/320 of cases affected and no controls; OR ≥; 95%CI 1.30–∞; p = 0.063. Re-analysis of the data excluding patients prescribed a cytotoxic immunosuppressant still gave a significant difference for asthma (7/315 cases vs. 20/315 controls; OR 0.35; 95%CI 0.15–0.81; p = 0.021). Exclusion of both cytotoxic immunosuppressant and corticosteroids resulted in a similar trend, which failed to reach statistical significance (5/246 cases vs. 10/246 controls; OR 0.50; 95%CI 0.18–1.4; p = 0.30).

### Table 1: Demographic data for multiple sclerosis (MS) patients and controls

<table>
<thead>
<tr>
<th></th>
<th>MS patients</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>320</td>
<td>320</td>
</tr>
<tr>
<td>Females (%)</td>
<td>211 (65.9%)</td>
<td>211 (65.9%)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>46.7 (range 17–84)</td>
<td>46.7 (range 17–84)</td>
</tr>
<tr>
<td>Mean no. of years in study (SD)</td>
<td>4.7 (0.76); range 1–5</td>
<td>4.7 (0.79); range 1–5</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoked</td>
<td>112 (35.0%)</td>
<td>125 (39.1%)</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>85 (26.6%)</td>
<td>89 (27.8%)</td>
</tr>
<tr>
<td>Not recorded</td>
<td>123 (38.4%)</td>
<td>106 (33.1%)</td>
</tr>
</tbody>
</table>

754

H.L. Tremlett et al.
**Discussion**

The reduced prevalence of asthma (OR 0.33; 95% CI 0.15–0.77) in this MS population is compatible with a Th1/Th2 imbalance. However, the lack of statistically significant associations (positive or negative) with MS and other Th1/Th2-mediated diseases indicates this explanation is probably an oversimplification. The controversial concept that MS is based purely on an up-regulation of Th1 lymphocytes and associated cytokines, and down-regulation of Th2, has been regarded as incomplete by others.7–9 There are examples of Th2 cells mediating unexpected effects, such as inducing experimental autoimmune encephalomyelitis in transgenic mice.9 Other reasons for the inverse association with asthma found here could include reduced mobility and employment rates associated with MS, which might reduce occupational and exercise-induced asthma. However, these types of asthma only account for a minority of cases, with other factors such as house dust mites and pets providing greater stimuli.10 Smoking is associated with airways hyper-responsiveness, so may worsen asthma symptoms, although is unlikely to actually cause asthma.11 Smoking lifestyle was matched where possible, although in approximately one-third of both cases and controls, the GP had not recorded this variable. There was however no published evidence to suggest that MS patients have a reduced propensity to smoke compared to the general population, thus smoking is unlikely to be a confounding factor. The reduced prevalence of asthma in the MS group did not appear related to the use of cytotoxic immunosuppressants or corticosteroids, both used to control MS, although prescription of these drugs prior to 1995 was not assessed. The actions of cytotoxic immunosuppressants in particular could conceivably have long-lasting effects, but this is unlikely to have a major impact on the analysis given their limited use in this population, with <2% of our MS patients prescribed a cytotoxic immunosuppressant. It is acknowledged that 215/320 MS patients in this study had also been included in a previous analysis of prescription use in an MS population, which lead to the unexpected finding of fewer asthma-related prescriptions in the MS population compared to controls.4 We feel this is justified by: the use of a fresh control population; an additional 105 MS patients not previously examined; a new study design spanning 5 years instead of one year; and a distinct study question.

There was a reduced prevalence of eczema in this MS population, which did not reach statistical significance (OR 0.67; 95% CI 0.37–1.20). Analysis of peripheral blood lymphocytes have shown that the majority of atopic dermatitis cases are Th2-mediated.12 This could not be confirmed in this population, which, with the low rate of GPs recording whether the dermatitis was atopic in origin or not, may explain the lack of statistical significance.

The predicted increase of Th1-associated co-morbidity in this MS population was not found. However, there was an increased prevalence of IBD, as reported by others.13 Whether this is related to a Th1/Th2 imbalance or perhaps a shared risk factor (genetic or environmental) needs to be investigated, although, similar to atopic dermatitis, it appears unlikely that all cases of IBD are wholly dominated by one type of Th cells, as was once thought.14 Other studies have found an increased prevalence of diabetes mellitus in an MS population compared to controls.15,16 We specifically investigated type 1 diabetes, assuming this to be Th1-mediated, but no patient in the control or MS group was prescribed insulin. This is probably a reflection of the sample size: using age-standardized rates in England and Wales,17 only 1.4 control patients in this population would have been expected to have insulin-treated diabetes.

### Table 2

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>MS patients affected (%)</th>
<th>Controls affected (%)</th>
<th>p*</th>
<th>OR</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Th2-associated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>7 (2.2%)</td>
<td>25 (7.8%)</td>
<td>0.014</td>
<td>0.33</td>
<td>0.15–0.77</td>
</tr>
<tr>
<td>Eczema</td>
<td>18 (5.6%)</td>
<td>27 (8.4%)</td>
<td>0.2</td>
<td>0.67</td>
<td>0.37–1.20</td>
</tr>
<tr>
<td><strong>Th1-associated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD</td>
<td>5 (1.6%)</td>
<td>0</td>
<td>0.063</td>
<td>$\infty$</td>
<td>(1.30–$\infty$)</td>
</tr>
<tr>
<td>RA</td>
<td>5 (1.6%)</td>
<td>4 (1.3%)</td>
<td>1.0</td>
<td>1.25</td>
<td>0.36–4.30</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>0</td>
<td>0</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

*p*McNemar test.
Further studies are required to confirm or refute the inverse association between MS and asthma found here, ideally in an asthma population. It would also be interesting to evaluate whether those MS patients with asthma have a cytokine profile shifted more towards Th2 than those without. Th2 cells maybe responsible for re-myelination of neuronal axons in MS by stimulating repair-enhancing antibody-producing B-cells.\(^{18}\) The possibility therefore exists that asthmatic MS patients may have less severe MS than non-asthmatics. A shift away from Th1 cytokine dominance towards Th2 is thought to explain the beneficial mode of action of glatiramer acetate,\(^{19}\) indicating an exploitable drug-targeting route for MS. However, deliberate deviation towards the Th2 phenotype in MS may come at a price—as was found when one-third of secondary-progressive MS patients treated with Campath-1H developed Graves’ disease.\(^{20}\)

Limitations of the study were minimized by the matching of controls, but included: reliance on the GP for the diagnosis of disease and entering this and prescription data onto the computer; the use of only computerized GP surgeries could have created a biased sample. No adjustment was made for the use of multiple statistical comparisons.

**Acknowledgements**

Thanks to Dr Robert Newcombe for his statistical advice, to Dr Alan Jones for his helpful comments on the study design and Professor Paul Morgan, Medical Biochemistry, University of Wales College of Medicine for reviewing the paper. The study was funded by the Welsh School of Pharmacy. Dr Helen Tremlett is now a research fellow funded by the MS Society of Canada.

**References**

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