Use of Penicillin and Other Antibiotics and Risk of Multiple Sclerosis: A Population-based Case-Control Study


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A 2006 study from the United Kingdom found that penicillin use may decrease the risk of multiple sclerosis (MS). To confirm this finding, the authors conducted a nationwide case-control study in Denmark, using the Danish Multiple Sclerosis Registry to identify 3,259 patients with MS onset from 1996 to 2008, and selected 10 population controls per case \((n = 32,590)\), matched on sex and age. Through the National Prescription Database, prescriptions for antibiotics redeemed from 1995 to 2008 and before the date of first MS symptom/index date were identified. Conditional logistic regression analysis was used to compute odds ratios associating antibiotic use with MS occurrence. In total, 1,922 patients (59%) redeemed penicillin prescriptions before the index date and 2,292 (70%) redeemed any type of antibiotic prescription. Penicillin use was associated with an increased risk of MS (odds ratio \(= 1.21\), 95% confidence interval: 1.10, 1.27). Use of any type of antibiotic was similarly associated with an increased risk of MS (odds ratio \(= 1.41\), 95% confidence interval: 1.29, 1.53). The odds ratios for different types of antibiotics ranged between 1.08 and 1.83. Thus, this study found that penicillin use and use of other antibiotics were similarly associated with increased risk of MS, suggesting that the underlying infections may be causally associated with MS.

Abbreviations: ATC, Anatomical Therapeutic Chemical; MS, multiple sclerosis.

Multiple sclerosis (MS), an inflammatory demyelinating disease of the central nervous system, has a complex etiology thought to be influenced by both genes and the environment (1, 2), yet few environmental causes have been determined (3). Based on the assumption that Chlamydia pneumoniae could be involved in the etiology of MS, and therefore that antibiotics active against these bacteria could be associated with a lower risk of MS, Alonso et al. (4) conducted a case-control study nested within the United Kingdom’s General Practice Research Database. In that study, which included 163 MS cases, use of antibiotics active against C. pneumoniae was not associated with a decreased risk of MS. However, the authors unexpectedly found an inverse association between use of penicillin and the risk of developing MS. The decreased risk of MS was confined to only those persons who had used penicillin for a long duration (>2 weeks) during the 3 years before the index date, as compared with no use; the odds ratio was 0.5 (95% confidence interval: 0.3, 0.9) (4). Since this finding was not based on any prior hypothesis, Alonso et al. encouraged replication in other populations (4). Therefore, we used Danish medical databases to examine the risk of MS associated with use of penicillin in a nationwide case-control study.

MATERIALS AND METHODS

The source population for this case-control study was all inhabitants of Denmark (approximately 5.3 million) observed between January 1, 1995, and December 31, 2008. All Danish residents are provided with tax-supported medical care. A unique 10-digit civil registration number is assigned to all residents by the Central Office of Civil Registration, and this number allows unambiguous linkage between all of Denmark’s population-based registries (5).
MS cases

We identified patients with MS, including information on year of first MS symptom, through the Danish Multiple Sclerosis Registry (6). This registry was established in 1956 and includes data on patients with MS diagnosed after 1921. The registry receives information from all departments of neurology, MS rehabilitation centers, practicing neurologists, and pathologists in Denmark, as well as the National Patient Registry. The completeness of the Multiple Sclerosis Registry is estimated to be approximately 90% (6). All patient records in the registry have been classified according to current standardized diagnostic criteria (currently those of Poser et al. (7) and the revised McDonald criteria (8)). The year of first symptom was determined by the Multiple Sclerosis Registry neurologist on the basis of all available information, including the patient’s medical file. In the current study, we assigned January 1 of the year of first symptom as the date of clinical onset of MS. We included all confirmed MS cases with a reported disease onset between 1996 and 2008. Since prescription data were available for the period 1995–2008, this design allowed a minimum 1-year opportunity for exposure to penicillin before clinical onset of MS.

Selection of population controls

For each MS case included in the study, we selected 10 controls from the entire Danish population through the Civil Registration System. This registry, which is updated daily, keeps records on the vital status (dead or alive), date of death, and residence of all Danish citizens. We used risk set sampling (9) and matched the controls to cases on sex and birth date (±6 months). We defined the index date for controls as January 1 of the year of their matched case’s first MS symptom.

Use of antibiotics

Data on penicillin prescriptions were obtained through the National Prescription Database. This database, which is maintained by the Danish Medicines Agency, retains key information on all prescribed drugs dispensed from all pharmacies in Denmark. The information includes the civil registration number of the patient, the type of drug prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system, and the date of prescription. We used the ATC codes J01C xxx (except J01CA08 and J01CA11) to identify penicillin prescriptions redeemed before the date of clinical onset of MS symptoms for cases or the index date for controls. Penicillin is available only by prescription in Denmark. We similarly identified all prescriptions for any antibiotic (ATC code J01), pivmecillinam (ATC codes J01CA08 and J01CA11), macrolides (ATC code J01F), tetracyclines (ATC code J01A), nitrofurantoin (ATC code J01XE01), and sulfamethizole and/or trimethoprim (ATC code J01E) redeemed before the date of clinical onset of MS symptoms for cases or the index date for controls.

Statistical analysis

We computed the frequencies and proportions of cases and controls within categories of antibiotic exposure and the co-variates. We used conditional logistic regression analysis to estimate the odds ratio associating MS with antibiotic use according to time since last exposure to antibiotics (<1 year, 1–2 years, 3–4 years, or ≥5 years) and category of number of prescriptions. Given the density sampling of controls, odds ratios in conditional logistic regression are valid estimates of the corresponding incidence rate ratios. We repeated this analysis to estimate the odds ratio associating other types of antibiotics (defined as at least 1 prescription redeemed before the date of clinical onset of MS or the index date) with MS. Analyses were performed using SAS, version 9.2 (SAS Institute Inc., Cary, North Carolina).

The study protocol was approved by the Danish Data Protection Agency.

RESULTS

The case-control analysis included 3,259 MS cases and 32,590 population controls. Descriptive characteristics are shown in Table 1. Two-thirds of the cases were women, as expected, and approximately two-thirds were younger than age 40 years at diagnosis.

Of the 3,259 MS patients, 1,922 (59%) had redeemed at least 1 prescription for penicillin during the years 1995–2008 and before their first MS symptom. Among the 32,590 controls, 17,906 (55%) had redeemed at least 1 prescription for penicillin during the years 1995–2008 and before their index date.

Any use of penicillin preceding the date of clinical onset of MS symptoms or the control’s index date was associated with MS (odds ratio = 1.21, 95% confidence interval: 1.10, 1.27). Table 2 shows the odds ratios for MS by time between prescription and year of first MS symptom/index date and by number of prescriptions for penicillin. All odds ratio estimates were above 1.0, and use of penicillin 5 or more years before the first MS symptom had the highest odds ratio. We observed no dose-response for number of penicillin prescriptions.

Use of any type of antibiotic preceding the date of clinical onset of MS symptoms or the control’s index date was associated with an increased risk of MS (odds ratio = 1.41, 95% confidence interval: 1.29, 1.53). Use of other subtypes of antibiotics was similarly associated with an increased risk of MS, with most odds ratios being approximately equal to 1.3 (Table 3).

DISCUSSION

In this nationwide population-based case-control study, we found a nearly 20% increased risk of MS associated with use of penicillin and a 30% increased risk associated with use of most other types of antibiotics. Thus, our findings did not replicate the finding of a decreased risk of MS associated with use of penicillin reported by Alonso et al. (4). However, Alonso et al. did find a 30% increased risk of MS among persons who had used penicillin for a short duration (8–14 days) during the 3 years before the index date in comparison with no use (4), which is consistent with our results. We lacked information on dosage and number of treatment days in our study. Oral penicillin in Denmark is usually given for at least
penicillin prescriptions, and we assume that this proportion is of similar magnitude in Denmark. Moreover, Alonso et al. found that the association between penicillin use and MS risk did not differ between persons whose antibiotic treatment was prompted by a respiratory infection and those whose treatment was prompted by another indication (4).

MS may come to medical attention in a number of ways, making MS diagnosis difficult (12, 13). Insidious onset of MS is a challenge in risk factor studies, because causal exposures necessarily must precede the disease. Because of our access to the Danish Multiple Sclerosis Registry, we were able to use year of first symptom as the index date instead of date of diagnosis. We included only cases with a confirmed diagnosis. Exposures incurred between the first symptom and the ultimate diagnosis date are not etiologically relevant for the clinical onset of MS but could occur as consequences of disease onset, thereby presenting as inverse causation. For example, changes in medication use or lifestyle changes may be a consequence of the onset of MS symptoms preceding a recorded diagnosis and may affect the rate of disease progression, but they could not affect the disease causally. Alonso et al. (4) similarly evaluated exposures incurred before the first symptom, so a difference in study design does not explain the protective association they reported.

It is possible, however, given the diagnostic complexity of the disorder, that the date of the first symptom is also an inaccurate measure of MS onset. Use of magnetic resonance imaging has demonstrated the presence of demyelinating lesions in asymptomatic persons, and the concept of preclinical MS is now recognized (14). Still, when we examined different time periods between last prescription and first MS symptom, we found the highest odds ratio in persons who had used penicillin at least 5 years prior to the first MS symptom, which provides some evidence against reverse causation as an explanation for the present findings.

Since we observed an association with different types of antibiotics used for different indications, our findings suggest that the underlying infections are causally associated
with MS. Viral infections have long been suspected of playing a role in MS, and accumulating evidence supports a causative role for Epstein-Barr virus (15, 16). Still, the mechanism of how infections may initiate MS remains elusive. On the one hand, the innate immune system may prevent autoimmunity by differentiation of regulatory T cells. On the other hand, the immune system probably promotes relapses in MS (17). Our finding of an increased risk of MS following exposure to penicillin and other types of antibiotics is compatible with the hypothesis that a nonspecific response to bacterial infections in the preclinical MS phase could play a role in promoting the first MS symptom.

In conclusion, we found a nearly 20% increased risk of relapses in MS (17). Our finding of an increased risk of MS associated with exposure to other antibiotics. This increased risk may be related to the underlying infections for which the antibiotics are prescribed.

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Conflict of interest: none declared.

REFERENCES


Table 3. Odds Ratio for Multiple Sclerosis According to Use of Any Type of Antibiotic and Different Types of Nonpenicillin Antibiotics in 3,259 Multiple Sclerosis Cases and 32,590 Population Controls, Denmark, 1996–2008a

<table>
<thead>
<tr>
<th>Type of Antibiotic</th>
<th>No. of Cases</th>
<th>No. of Controls</th>
<th>Odds Ratiob</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any antibiotic</td>
<td>2,292</td>
<td>20,802</td>
<td>1.41</td>
<td>1.29, 1.53</td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>168</td>
<td>1,265</td>
<td>1.35</td>
<td>1.14, 1.59</td>
</tr>
<tr>
<td>Macrolides</td>
<td>918</td>
<td>7,514</td>
<td>1.31</td>
<td>1.21, 1.42</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>302</td>
<td>2,318</td>
<td>1.33</td>
<td>1.18, 1.51</td>
</tr>
<tr>
<td>Sulfonamides/trimethoprim</td>
<td>507</td>
<td>4,150</td>
<td>1.26</td>
<td>1.14, 1.40</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>76</td>
<td>425</td>
<td>1.83</td>
<td>1.42, 2.34</td>
</tr>
<tr>
<td>Quinolones</td>
<td>115</td>
<td>1,066</td>
<td>1.08</td>
<td>0.89, 1.32</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>298</td>
<td>2,389</td>
<td>1.27</td>
<td>1.12, 1.44</td>
</tr>
</tbody>
</table>

a Use of penicillin was recorded from 1995 through the calendar year before the date of clinical onset of multiple sclerosis/index date.

b Conditional on date of birth and sex.