Association between migraine and asthma: matched case-control study

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SUMMARY

Background: Earlier studies have suggested a link between asthma and severe headache, and also between migraine and wheezing illness. Recent analysis has also shown an increase of asthma among cases with a prior history of migraine but without a history of hay fever, allergic rhinitis or eczema.

Aim: To examine whether there is an association between migraine and asthma in the United Kingdom.

Design of study: Matched case-control study using the General Practice Research Database (GPRD).

Setting: Practices in the United Kingdom providing data on 5,110,619 patients to the GPRD.

Method: The subjects were the patients with one or more diagnoses of migraine plus treatment for migraine. Each case was matched by general practice, sex, and age, with one control who had never been given a diagnosis of migraine. Case and control groups were compared for prevalence of asthma, chronic obstructive pulmonary disease, respiratory symptoms treated with inhalers or hay fever. Investigations were carried out to determine whether the association between migraine and asthma was stronger among patients with hay fever or those without hay fever, and whether patients with migraine had an increased prescription of other (non-migraine and non-asthma) medications.

Results: Among 64,678 case-control pairs, the relative risk of asthma in patients with migraine was 1.59 (95% CI = 1.54 to 1.65) among definite cases, and 0.75 (95% CI = 0.67 to 0.83) among those whose selection as case included β-blocker prophylaxis. Among definite migraine cases, relative risks of chronic obstructive pulmonary disease, respiratory symptoms, eczema, and hay fever (pollinosis), were all raised (at 1.22, 1.85, 1.55, and 1.67, respectively). The association between migraine and asthma was stronger in patients without a diagnosis of hay fever, than in those with hay fever (relative risk = 1.32 and 1.19, respectively). The relative risk of prescription for a range of non-migraine, non-asthma medications was raised, the exception being anti-diabetic medication.

Conclusion: This large case-control study provides evidence for an association between migraine and asthma. Frequent attendance at a general practice surgery may confound this association. Whether the association is real, its elucidation may help the understanding of disease mechanisms shared by migraine and asthma.

Keywords: migraine; asthma; association; hay fever.

Introduction

MIGRAINE is characterised by severe headache accompanied by autonomic and neurological symptoms. A range of underlying mechanisms for migraine have been postulated, including ‘neurogenic inflammation’, defects in arachidonic acid or serotonin metabolism, cyclical changes in ovarian steroids concentrations, food allergy, and atopy.

Asthma has been described as ‘pulmonary migraine’ or ‘acephalic migraine’. Case reports and a few population-based studies have reported an association between migraine and asthma. Observational evidence of inter-generational association has been found in hospital-based studies. Parental history of migraine was found to be more common among asthmatic children than among age and sex-matched controls in a small hospital-based study in Turkey (odds ratio [OR] = 5.5, 95% confidence interval [CI] = 1.3 to 25.0). The United States Collaborative Perinatal Project found that asthma was more common in children of mothers with migraine than in those whose mothers were migraine-free.

An early population-based cross-sectional study suggested an association between asthma and severe headache in men. An association between migraine and wheezing illness was also found in a cross-sectional study of schoolchildren in the United Kingdom.

More recently, analysis of a 1958 British birth cohort identified an increased incidence of asthma among subjects with a prior history of migraine at one or more follow-ups (at 7, 11, 16, 23 or 33 years). This association was confined to subjects without a history of hay fever, allergic rhinitis or eczema (‘non-atopics’).

These results suggest a link between migraine (vascular reactivity) and asthma (bronchial reactivity) that is independent of allergic mechanisms. A shared functional abnormality of smooth muscle in blood vessels and airways offers a plausible explanation for this link.

This study sought to confirm an association between migraine and obstructive airways disease, by testing whether patients consulting with migraine had an increased prevalence of asthma, chronic obstructive pulmonary disease (COPD), respiratory symptoms treated with inhalers, or hay fever. Investigations were made to find whether the association between migraine and asthma was stronger among patients with migraine than in those with hay fever, and whether patients with migraine had increased prescription of other (non-migraine and non-asthma) medications.

Method

A matched case-control study was designed using the
HOW THIS FITS IN

What do we know?

Case reports and a few population-based studies have reported an association between migraine and asthma

What does this paper add?

The association between migraine and asthma was confirmed in a very large case-control study. This association was stronger in patients without a diagnosis of hayfever, consistent with non-atopic mechanisms. However, there were also associations of migraine with other chronic diseases, suggesting that frequent attendance at a GP surgery may increase the probability that migraine is diagnosed.

General Practice Research Database (GPRD). The GPRD is a national database comprising anonymised medical records on about 6% of residents of England and Wales. Demographic, morbidity and prescription data are recorded by general practices and data quality has been established in previous studies. Cases were permanently registered by general practices and data quality has been established. Demographic, morbidity and prescription data are recorded on about 6% of residents of England and Wales. A national database comprising anonymised medical records on about 6% of residents of England and Wales. Demographic, morbidity and prescription data are recorded by general practices and data quality has been established in previous studies.

15,16 Cases were permanently registered by general practices and data quality has been established. Demographic, morbidity and prescription data are recorded on about 6% of residents of England and Wales. A national database comprising anonymised medical records on about 6% of residents of England and Wales. Demographic, morbidity and prescription data are recorded by general practices and data quality has been established in previous studies.

"Definite" migraine cases were those with one or more prescriptions for migraine prophylaxis; "possible" cases were those with one or more diagnoses with one or more prescriptions for migraine prophylaxis; "possible" cases were those with one or more diagnoses with one or more prescriptions for migraine prophylaxis; "possible" cases were those with one or more diagnoses with one or more prescriptions for migraine prophylaxis; "possible" cases were those with one or more diagnoses with one or more prescriptions for migraine prophylaxis. Case reports and a few population-based studies have reported an association between migraine and asthma.

2.4 (named in 4.7.4.2)

β-blockers for prophylaxis of migraine Pizotifen, clonidine hydrochloride, methysergide Propranolol, metoprolol, nadolol, timolol

What does this paper add?

The specificity of selection of migraine cases was confirmed by comparison with clinical review of the patient records of 100 randomly selected cases. For each case, a control who had never had a diagnosis of migraine was matched by general practice, sex, and year of birth. Thirty-two cases could not be matched by exact year of birth and were subsequently matched within a ten-year age band. Asthma, chronic obstructive pulmonary disease, respiratory symptoms, and hay fever were defined according to combinations of OXMIS codes developed and validated earlier. Disease outcome was defined in three ways: diagnosis alone, relevant therapy alone, and diagnosis plus relevant therapy. Statistical Analysis Software was used for data manipulation. For each disease outcome, the relative risk (RR) of migraine if the outcome was present to the risk of migraine if the outcome was absent was calculated as the ratio of discordant pairs (case affected, control unaffected; case unaffected, control affected). A 95% CI was calculated for each relative risk, and differences between discordant pair ratios were tested for significance using 2 x 2 tables and a Yates’ corrected $\chi^2$ test.

Results

We identified a total of 64,678 potential cases (48,571 females and 16,107 males; ratio 3.02:1). Migraine diagnosis category is tabulated against year of birth among cases in Table 1.

Relative risks of a range of disease outcomes were calculated by category of migraine diagnosis. When calculating relative risk of asthma, category 4 (β-blocker prophylaxis) was considered separately for the reasons given under the Method. Relative risk of asthma in those with a diagnosis of migraine was raised in categories 1, 2 and 3, but not in category 4. The effect of restricting the analysis to case-control pairs followed up for a minimum of three years was checked to explore for possible diagnostic bias, but this had no material effect on the relative risk (Table 2). There was no significant variation in relative risk of asthma by age of the case-control pair for pairs born from 1941 onwards, but lower relative risks occurred in older age groups.

<table>
<thead>
<tr>
<th>OXMIS code</th>
<th>Diagnostic term</th>
<th>Percentage cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>3459M</td>
<td>Epilepsy migraine</td>
<td>0.02</td>
</tr>
<tr>
<td>346A</td>
<td>Migraine</td>
<td>91.67</td>
</tr>
<tr>
<td>346B</td>
<td>Migraine abdominal</td>
<td>1.16</td>
</tr>
<tr>
<td>346C</td>
<td>Migraine headache</td>
<td>3.60</td>
</tr>
<tr>
<td>346CL</td>
<td>Migraine classic</td>
<td>0.66</td>
</tr>
<tr>
<td>346CD</td>
<td>Migraine common</td>
<td>0.33</td>
</tr>
<tr>
<td>346D</td>
<td>Migraine visual disturbance</td>
<td>0.67</td>
</tr>
<tr>
<td>346E</td>
<td>Migrainous neuralgia</td>
<td>0.68</td>
</tr>
<tr>
<td>346EP</td>
<td>Peroxysmal migrainous neuralgia</td>
<td>0.12</td>
</tr>
<tr>
<td>346F</td>
<td>Migraine facial</td>
<td>0.19</td>
</tr>
<tr>
<td>346GB</td>
<td>Migraine basilar</td>
<td>0.12</td>
</tr>
<tr>
<td>346HT</td>
<td>Histamine headache</td>
<td>0.02</td>
</tr>
<tr>
<td>346PH</td>
<td>Ophthalmic migraine</td>
<td>0.15</td>
</tr>
<tr>
<td>346MH</td>
<td>Migraine hemiplegic</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Box 1. OXMIS codes used for assignment of first migraine diagnosis.

<table>
<thead>
<tr>
<th>BNF code</th>
<th>Description</th>
<th>Therapy included (generic or proprietary name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.7.4.1</td>
<td>Treatment of acute migraine attack</td>
<td>Migraleve, Migravess, Paramax, Domperamol, dihydroergotamine mesylate, ergotamine tartrate, isometheprine mucate, naratriptan, rizatriptan, sumatriptan, zolmitriptan, tolfenamic acid</td>
</tr>
<tr>
<td>4.7.4.2</td>
<td>Prophylaxis of migraine</td>
<td>Pizotifen, clonidine hydrochloride, methysergide</td>
</tr>
<tr>
<td>2.4 (named in 4.7.4.2)</td>
<td>β-blockers for prophylaxis of migraine</td>
<td>Propranolol, metoprolol, nadolol, timolol</td>
</tr>
</tbody>
</table>

Box 2. British National Formulary codes used for assignment of migraine therapy.
For other conditions, migraine diagnosis categories 1 to 4 were combined. Relative risks of COPD, "respiratory symptoms," eczema, and hay fever were raised significantly in all categories (Table 3).

In those who did not have a diagnosis of hay fever, the association between asthma and migraine was stronger (RR = 1.32, 95% CI = 1.28 to 1.37) than among those in the smaller group with a diagnosis of hay fever (RR = 1.19, 95% CI = 1.05 to 1.36), though this difference was not significant ($\chi^2 = 2.2, P = 0.14$). These risks were not materially changed if diagnosis and relevant therapy were used as the outcome measure. The rates of prescription of several categories of non-migraine, non-asthma medication were compared between definite migraine cases and controls, to investigate the specificity of the relationship with asthma and the potential for diagnostic bias. The relative risk was raised for most medications except for anti-diabetic medication (Table 4).

### Discussion

This large case-control study provides evidence for an association between migraine and asthma. A number of factors indicate that the raised relative risk of 1.59 represents a real association, but others suggest caution in attributing it to a causal relationship.

One major strength of the GPRD is its size, comprising data on over five million patients. This, together with the relatively high prevalence of migraine (such that we based the analysis on 64 678 case-control pairs), gave the study huge statistical power. Thus, the relative risk for the association between asthma and migraine could be calculated with precision. An important limitation, however, is the lack of information on potential confounding variables, such as socio-economic status. Although some information on smoking habits is recorded by GPRD practices, this is known to be incomplete and was not available for our analysis. However, in the British birth cohort study, asthma and migraine were associated even after adjustment for a range of confounding variables, including social class and smoking habit.14

The female:male ratio (3:1) among migraine cases is consistent with those calculated in other studies and reviews.119 Similarly, peak age prevalence between 30 and 50 years is
consistent with that reported in other sources.\(^1,18\) Both these observations indicate that the case definition used in this study has external validity. Finding a significantly reduced relative risk of asthma among migraine cases that were prescribed \(\beta\)-blocker prophylaxis, provides evidence for internal validity.

Certain findings shed doubt onto the specificity of the association between migraine and asthma. Relative risks of COPD, respiratory symptoms, hay fever and eczema were all raised among patients with migraine compared with those without. In a similar way, relative risks of prescription of a range of non-migraine, non-asthma medications were raised in patients with migraine compared with those without. These findings may be explained by postulating that patients with migraine attend their general practitioners more frequently than those without, making them more likely to be diagnosed with a range of conditions and more likely to be prescribed a range of medications. Frequent attendance would therefore act as a confounder in the migraine–asthma association.

We included two chronic conditions — epilepsy and diabetes — where patients might be expected to attend their doctor regularly regardless of personal and cultural determinants of consulting behaviour. Interestingly, no association with migraine was observed for diabetes, but there was an excess of antiepileptic medication prescribed to patients with migraine (Table 4). Prescriptions for carbamazepine are included in the latter group, and some of these may have been for trigeminal neuralgia, a condition which may sometimes be confused with migraine, and where the threshold of awareness and non-medical factors may influence the patient’s consulting behaviour.

Differential attendance could explain the finding that the association between migraine and asthma was stronger in those without hay fever than those with hay fever. Patients with hay fever would be expected to be more frequent attenders than those without, thus the effect of migraine in increasing attendance (and hence likelihood of diagnosis with asthma) would be diminished in comparison with those without hay fever. On the other hand, the relative risk of migraine is lower among patients prescribed anti-diabetic medication (another group who would be expected to attend frequently), so frequent attendance may not entirely explain the association of migraine with other diseases and therapies. Furthermore, the finding is consistent with that in a British birth cohort,\(^14\) where migraine, asthma and atopic diseases were ascertained by questionnaire, independent of consultation with a doctor.

An alternative explanation would be that migraine is more strongly associated with non-atopic asthma, which might also account for the raised risk of COPD in migraine patients. More detailed clinical and epidemiological studies of the association between migraine and asthma may aid the identification of shared disease mechanisms.

### References