Meta-Analysis of the Relationship between Multiple Sclerosis and Migraine

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Abstract

Background: Studies investigating a proposed association between multiple sclerosis (MS) and migraine have produced conflicting results and a great range in the prevalence rate of migraine in MS patients. By meta-analysing all available data we aimed to establish an overall estimate of any association in order to more accurately inform clinicians and care-givers about a potential association between MS and migraine.

Methods: Pubmed and EMBASE were searched to identify suitable studies. Studies were included if they were a case-control study or cohort study in which controls were not reported to have another neurological condition, were available in English, and specified migraine as a headache sub-type. The odds ratio (OR) of migraine in MS patients vs. controls was calculated using the inverse variance with random effects model in Review Manager 5.1.

Results: Eight studies were selected for inclusion, yielding a total of 1864 MS patients and 261563 control subjects. We found a significant association between migraine and MS (OR = 2.60, 95% CI 1.12–6.04), although there was significant heterogeneity. Sensitivity analysis showed that migraine without aura was associated with MS OR = 2.29 (95% CI 1.14–4.58), with no significant heterogeneity.

Conclusions: MS patients are more than twice as likely to report migraine as controls. Care providers should be alerted to ask MS patients about migraine in order to treat it and potentially improve quality of life. Future work should further investigate the temporal relationship of this association and relationship to the clinical characteristics of MS.

Introduction

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) characterized by myelin loss, varying degrees of axonal pathology, and progressive neurological dysfunction. The clinical features of MS encompass an extremely wide range of neurological symptoms but migraine is not typically included [1]. Migraine is a common chronic debilitating condition, with an estimated 1-year period prevalence of 11.7%, which reduces the quality of life in many sufferers [2,3].

Within Europe, migraine has a high economic impact, with headaches (including migraine) estimated to cost €43.5 billion per capita in 2010 [4]. MS and migraine have a number of demographic similarities including a female preponderance and relatively young age at onset [5,6]. Epidemiological similarities also exist, as both conditions have a higher prevalence in Caucasian as compared to African or Asian populations [7,8]. In 1952 Compston and McAlpine found that 2% of MS sufferers experienced migraine within 5 months of MS onset [9]. This finding stimulated further studies but limitations, including small sample sizes, has resulted in conflicting results and a great range in the prevalence rate of migraine in MS patients [10–18]. In this meta-analysis we sought to provide an overall estimate of the relationship between MS and migraine by comparing the occurrence of migraine in MS patients vs. controls in order to accurately inform clinicians.
| First author & year of publication | Type of study | MS diagnostic criteria | Migraine diagnostic criteria | Cases | Controls | OR (95% CI) | F/M ratio | Case source | Control source | Age range and mean age of MS patients (years) | MS subtype | Mean MS duration (years) | Median EDSS score | Migraine ascertainment |
|----------------------------------|--------------|------------------------|-------------------------------|-------|----------|-------------|-----------|------------|--------------|---------------------------------|-------------|---------------------|-----------------------|----------------------|
| Watkins 1969                    | Case-control | Definite/probable MS, McDonald criteria | Critchley 1967 | 100   | 100      | 2.71        | 1.78      | Hospital (prevalent) | Hospital | Range 15–50 | N/a       | N/a       | N/a       | Interview             |
| Zorzon 2003                     | Case-control | Definite MS, McDonald criteria |  | 140   | 131      | 20.41       | 1.8       | Multiple Sclerosis Center (prevalent) | Blood Transfusion Center | Range 17–65, mean 42.1 | 71.4% RRMS, 19.3% SPMS, 9.3% PPMS | 10.9   | 2                     | Questionnaire in interview |
| Vacca 2007                      | Case-control | Definite MS, McDonald criteria | International Classification of Headache Disorders 2004 (2nd edition) | 238   | 238      | 3.19        | 1.9       | Hospital (prevalent) | Friends | Range 24–61 | 75.6% RRMS, 24.4% SPMS | N/a       | 2.5                  | Interview             |
| Nicoletti 2008                  | Case-control | Definite/probable MS, Poser criteria | International Headache Society criteria, 1988 | 101   | 101      | 1.31        | 1.81      | Cohort (incidence and prevalence) | Cohort | Mean 43.6 | 75.2 RRMS, 19.0 SPMS, 2.0 PPMS | 9.9         | N/a                  | Standardised questionnaire in interview. If doubtful diagnosis, underwent neurological examination |
| Putzki 2009                     | Case-control | Definite MS, Poser or McDonald criteria | International Headache Society criteria | 491   | 447      | 0.49        | 2.13      | Hospital (prevalent) | Cohort | Mean 45.3 | 63.7 RRMS, 20.2 SPMS, 9.2 PPMS, 51.1% uncertain | 11.5       | Median n/a, EDSS mean 3.17 | Validated questionnaire |
| Kister 2010                     | Case-control | Definite MS, McDonald criteria | International Classification of Headache Disorders, 2nd edition | 204   | 162576   | 6.47        | N/a       | MS Care Center (prevalent) | Cohort | Mean 45 | N/a       | 12.5      | N/a                  | Validated questionnaire |
| Katsiari 2011                   | Case-control | Definite MS, McDonald criteria | ICHD-II, 2004 | 48    | 72       | 1.04        | 25.32     | Hospital (prevalent) | Hospital | Mean 37.8 | N/a       | 7.5       | Median n/a, EDSS mean 3.0 at the 1 year follow up | Standardised questionnaire in interview. If positive response, underwent neurologic examination |
| Kister 2012                     | Cohort        | Definite/probable MS, Poser or McDonald criteria | Physician-diagnosed migraine | 542   | 97898    | 5.65        | All female | Cohort (incident & prevalent) | Cohort | Range 25–42 | N/a       | N/a       | N/a                  | Questionnaire/medical record |

OR (95% CI) = odds ratio with 95% confidence intervals, F = female, M = male, N/a = not available, RRMS = relapsing-remitting MS, SPMS = secondary-progressive MS, PPMS = primary progressive MS.

Historical controls used.

Age range of all individuals in the Nurses’ Health Study II.

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Methods

Article Search

PubMed was searched by JP and AEH for abstracts using the terms (“multiple sclerosis”[MeSH Terms] OR (“multiple”)[All Fields] AND “sclerosis”[All Fields]) OR “multiple sclerosis”[All Fields] AND (“migraine disorders”[MeSH Terms] OR (“migraine”)[All Fields] AND “disorders”[All Fields]) OR “migraine disorders”[All Fields] OR “migraine”[All Fields] and (“multiple sclerosis”[MeSH Terms] OR (“multiple”)[All Fields] AND “sclerosis”[All Fields]) OR “multiple sclerosis”[All Fields] AND (“headache”[MeSH Terms] OR “headache”[All Fields]). EMBASE was searched for abstracts using the terms “multiple sclerosis”[All fields] AND migraine[All fields]. No limitations or time period restrictions were applied; the latest search was undertaken on the 17th December 2011. We were not familiar with any study currently in progress to be considered for inclusion. Published conference abstracts were eligible for inclusion and so were both prospective and retrospective studies. Studies were subsequently excluded if they were not a case-control study or cohort study, if the article was not available in English, or if migraine was not specified as a headache sub-type. Studies where controls had other neurological conditions were also excluded. The abstracts of the resulting articles were hand-searched in order to select studies. Attempts to identify further articles were done by searching the references of the studies. Data on study type, raw numbers of MS patients and controls who had and had not experienced migraine and their sex; diagnostic criteria of MS and migraine used; method of migraine ascertainment; source of cases and controls; age range and mean age of patients and controls; MS patient subtype, mean diseases duration and median EDSS score was extracted independently from included articles. Any discrepancy on the suitability for inclusion of a study between the authors was resolved by consulting a third author (SVR).

Statistical Analysis

The inverse variance model in Review Manager 5.1 was used to calculate the overall odds ratio (OR), 95% confidence interval (95% CI) and test statistic for the relationship. Statistical significance was set at \( p < 0.05 \). Statistical heterogeneity of studies was assessed through the calculation of \( \tau^2 \) and \( I^2 \). A random effects model was applied unless the \( I^2 \) was \( \leq 25\% \) in which case a fixed effects model would be used. In attempting to dissipate any heterogeneity, sensitivity analysis was done by excluding individual studies to see if there was a notable reduction in heterogeneity and further, subgroup analysis was performed on studies which differentiated between migraine with and without aura. Generation of a funnel plot and the Egger p-value allowed determination of the potential publication bias of included studies. Further, the quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS).

| Study          | Selection (max 4 ✓) | Comparability (max 2 ✓) | Exposure (max 3 ✓) |
|----------------|---------------------|-------------------------|-------------------|
| Katsiari 2011  | ✓✓                  | ✓✓                      | ✓                 |
| Kister 2010    | ✓✓                  | ✓                       | ✓                 |
| Kister 2012    | ✓✓✓✓                | ✓                       | ✓                 |
| Nicoletti 2008 | ✓✓                  | ✓                       | ✓                 |
| Putzki 2009    | ✓✓✓✓                | ✓                       | ✓                 |
| Vacca 2007     | ✓✓✓✓                | ✓                       | ✓                 |
| Watkins 1969   | ✓✓✓✓                | ✓                       | ✓                 |
| Zorzon 2003    | ✓✓✓✓                | ✓                       | ✓                 |

Table 2. Newcastle-Ottawa Scale (NOS) assessment of the quality of the studies.

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Figure 1. Forest plot of comparison: MS patients vs. control, outcome: migraine.

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Results

Included Studies

Our Pubmed search initially yielded 654 studies (of which some studies appeared under more than one search term) and the EMBASE search 705 studies. In total, 8 studies were selected for inclusion according to the described inclusion criteria [11–18], yielding a total of 1864 MS patients and 261563 control subjects. However, it should be noted that Kister et al 2010 and Nicoletti et al 2008 used historical controls [15,18]. Information about the included studies can be found in table 1 and the assessed quality of each study using NOS is indicated in table 2.

Migraine in MS Patients vs. Control

Migraine was more common in MS patients than controls. The overall OR upon inclusion of all 8 studies was 2.60 (95% CI 1.12–6.04), fig 1, however, significant statistical heterogeneity was identified (I² = 97% Chi² = 247.10, P<0.00001). Publication bias assessment is shown using a funnel plot, fig 2. No selective reporting of outcomes was found for any study when comparing methods of studies to results. There was no significant indication of publication bias, Egger p-value = 0.64. The results of subgroup analyses of studies investigating migraine with and without aura showed a significant co-morbid association between MS and migraine without aura (OR = 2.29 (CI = 1.14–4.58)) without any significant heterogeneity (Table 3 and Figure 3).

Discussion

This meta-analysis has shown that there is a significant association between migraine and MS, with MS patients being more than twice as likely to report migraine as controls. Limitations of this study include the nature of the studies included and study heterogeneity [20]. Of note, in subgroup analyses, migraine without aura was significantly increased in patients with MS (OR = 2.29 (CI = 1.14–4.58)) without any significant heterogeneity. The heterogeneity may be in part explained by variation in the demographic characteristics (as shown in table 1), recall/reporting/interviewer bias of migraine in some studies as this data was largely collected by questionnaire/interview and ascertainment/selection bias of MS patients and controls. As indicated in Table 2, we found some discrepancy in the quality of the studies and the potential for bias. Bias may result in an over or under-estimation of ORs depending on whether the bias is differential or non-differential with respect to MS patients and controls. It can be speculated that MS patients are more likely to be in contact with a

Table 3. Odds ratio and 95% confidence intervals for subgroup studies.

| Subgroup of studies       | Odds ratio with 95% CI | P-value | Number of studies | Heterogeneity                  |
|---------------------------|-----------------------|---------|------------------|--------------------------------|
| Migraine with aura        | 0.8 (0.29–2.16)       | P = 0.65 | 3[16–18]         | Tau² = 0.34; Chi² = 3.55, df = 2 (P = 0.17); I² = 64% |
| Migraine without aura     | 2.29 (1.14–4.58)      | P = 0.02 | 3[16–18]         | Tau² = 0.21; Chi² = 4.62, df = 2 (P = 0.10); I² = 57% |

Abbreviations: CI = confidence interval, df = degree of freedom. Tau² estimates the between-study variance and I² describes the proportion of variation estimated to be due to heterogeneity.

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neurologist and may thus be more likely to report migraine and/or have migraine detected, resulting in an overestimated OR. Similarly, an MS patient may be more attentive to the frequency and severity of migraine.

Whereas the occurrence of migraine without aura but not migraine with aura was found to be significantly more frequent in MS patients, it is plausible that small sample sizes in studies investigating migraine with aura meant there was insufficient power to detect significance.

Further, the study by Rolak and Brown, which was not included in this investigation as the controls had neurological disorders, found migraine reported in 22/104 MS patients vs. in 10/100 control neurological patients, OR 2.41 (CI 1.08 - 5.40) [10].

The mechanism behind any association between MS and migraine remains to be determined but a number of hypotheses exist. Nicoletti et al compared the age of onset of both conditions which was 33.6 -10.8 years for MS and 19.5+- 7.4 years for migraine [18]. Since migraine often precedes MS by numerous years, as also shown by Kister et al, another potential explanation is that migraine could be a potential risk factor for MS [11]. However, cortical demyelination has been shown to accelerate cortical spreading depression in rodent models of autoimmune induced cortical demyelination, a key aspect in migraine pathophysiology [21]. Migraine may therefore result from early MS lesions. Importance of lesion location in MS patients has also been suggested following observations that lesions within the midbrain are more commonly associated with co-morbid migraine in MS patients. This may be explained by the presence of the periaqueductal gray matter (PAG) within the midbrain which is suspected to have a role in migraine aetiology [22,23].

Immune therapies used to treat MS may also have a role as evidence for a migraine-inducing role of interferon beta exists [24], however, immune therapies could only ever provide a small part of the complete explanation due to the fact that migraine often precedes MS. Interferon beta treatment is also thought to worsen pre-existing migraine, suggesting it may not be implicated in the aetiology of the migraine itself [25]. Notably, evidence suggests that the other disease modifying therapies glatiramer acetate and natalizumab do not appear to worsen migraine, and indeed some patients may want to take this into consideration as switching from interferon beta may help reduce both frequency and severity of migraine [26-27]. Furthermore, stress and anxiety, which often accompany MS, are thought to be very likely causes of increased migraine frequency and chronification [28]. One further suggestion is that instead of one condition causing the other, both conditions have a common pathway in their underlying cause.

Before any of the above hypotheses can be confirmed, more studies specifically investigating whether MS precedes migraine or vice versa would be necessary to determine the temporal relationship of the demonstrated association and clarify whether migraine is as a risk-factor, co-morbidity or symptom of MS. Regardless, the key aspect of this study is the potentially underappreciated finding of migraine being more common in MS patients and as a major potential cause of poorer quality of life, it should be actively looked for and treated.

Author Contributions

Conceived and designed the experiments: SVR. Performed the experiments: JP. Analyzed the data: JP AEH GG RD SVR. Wrote the paper: JP AEH GG RD SVR.

Figure 3. Forest plot of comparison: MS patients vs. control.

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