

Migraine and frequent tension-type headache are not associated with multiple sclerosis in a Norwegian case-control study

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Multiple Sclerosis Journal –
Experimental, Translational
and Clinical

2: 1–4

DOI: 10.1177/
2055217316682976

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Abstract

Background: Inconsistent results have been obtained with regard to headache comorbidity in multiple sclerosis (MS).

Objective: Investigate the one-year prevalence of migraine and tension-type headache (TTH) in Norwegian MS patients and relate this to clinical parameters.

Methods: A questionnaire concerning headache was administered to 756 MS patients and 1090 controls and used to determine the one-year prevalence of migraine and frequent TTH.

Results: No significant differences were seen between patients and controls or between patients with different disease course. Less migraine was observed in patients with Expanded Disability Status Scale score (EDSS) ≥ 4.0 .

Conclusions: This case-control study does not support an association between migraine or TTH and MS.

Keywords: Multiple sclerosis, migraine, tension-type headache, case-control study

Date received: 13 August 2016; accepted: 15 November 2016

Introduction

The prevalence of migraine among persons with multiple sclerosis (MS) has been reported to be high, varying between 20% and 69%,¹ and a meta-analysis from 2012 concluded that MS patients are more than twice as likely to report migraine as controls.² Migraine has even been suggested as a predictor for MS based on observations from a cohort study.³ On the other hand, a German case-control study did not detect an association between MS and migraine,⁴ and the suggested association between migraine and MS has been debated.⁵ Conflicting results have also been reported for the prevalence of tension-type headache (TTH), but the majority of studies have not detected a higher one-year prevalence of TTH in MS patients compared with controls.¹

We aimed to investigate the one-year prevalence of migraine and frequent TTH in a Norwegian MS cohort and healthy controls and relate this to clinical parameters to increase knowledge of the possible

association between MS and migraine and/or frequent TTH.

Materials and methods

A questionnaire concerning headache was administered to 756 MS patients from the Oslo MS Registry and 1090 controls from the Norwegian Bone Marrow Donor Registry (NBMDR) in 2011/2012. All patients fulfilled the McDonald criteria.⁶ Informed consent was obtained from all participants, and the study was approved by the Regional Committee for Medical and Health Research Ethics. Based on the self-reported information about headache, the diagnosis of migraine and frequent TTH (i.e. TTH ≥ 1 day/month during the last year) were made based on the International Classification of Headache Disorders-II.⁷ The questionnaire had previously been validated against clinical interviews by neurologists with a sensitivity of 67% and specificity of 94% for the diagnosis of migraine (Cohen's kappa = 0.58), and a sensitivity of 96% and specificity of 69% for frequent TTH (Cohen's kappa = 0.44).⁸

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Pearson's Chi-square test was used to analyze the difference in the one-year prevalence of migraine and frequent TTH between patients and controls, between patients with relapsing remitting MS (RRMS) and primary progressive MS (PPMS) and between patients with Expanded Disability Status Scale (EDSS) score ≤ 3.5 and EDSS ≥ 4.0 . All groups were stratified by gender and separate analyses were performed for those < 60 years. Logistic regression was used to calculate the odds ratio (OR) for migraine and TTH with a 95% confidence interval (CI), adjusting for age, gender and smoking status. Analyses were conducted using IBM SPSS version 22 and a significance level of $p < 0.05$ was used for all analyses.

Results

The response rates in patients and controls were 67.5% ($n = 510$) and 83.9% ($n = 914$), respectively. More patients than controls were women, the mean age was higher among patients, more patients than controls reported to be ever-smokers, but the groups did not differ with regard to education level (Table 1).

The one-year prevalence of self-reported headache in general was 52.4% in patients and 54.4% in controls ($p = 0.46$). The one-year prevalence of migraine was 18.2% in patients and 16.3% in controls ($p = 0.35$). Further, 12.7% of patients and 14.9% of controls reported TTH ≥ 1 day/month during the last year (frequent TTH) ($p = 0.27$). Table 2 shows the one-year prevalence of migraine and frequent TTH in patients and controls, as well as in MS subgroups. No significant differences were seen between the clinical subgroups for the one-year prevalence of

migraine and frequent TTH, except when comparing the one-year prevalence of migraine in patients with EDSS ≤ 3.5 with patients with EDSS ≥ 4.0 . Logistic regression analysis adjusting for age, gender and smoking status gave results in accordance with the unadjusted analyses (Table 2), and stratification by gender and age < 60 years gave comparable results with analyses in the total dataset.

Discussion

This is to date one of the largest case-control studies performed to investigate migraine and TTH in relation to MS, and the first study to determine the one-year prevalence of migraine and frequent TTH among Norwegian MS patients. The observed prevalence of migraine and frequent TTH were as expected in the Norwegian population,⁹ and no association between MS and these headache types was detected. In contrast, several previous case-control studies have observed a higher prevalence of migraine among MS patients than controls,¹ but most of these studies are relatively small (number of patients included ranging from 50 to 375), and the criteria used for diagnosing migraine are not always specified. The strongest support for an association between MS and migraine has been obtained in the prospective Nurses' Health Study II, where the prevalence of migraine in women with MS at baseline (26%) and women diagnosed with MS after inclusion (29%), was higher than in women without MS (21%).³

In accordance with our findings, a German case-control study did not detect a significant difference in the one-year prevalence of migraine among 491 MS patients and 447 healthy controls (24.6% versus

Table 1. Background characteristics of patients and controls.

	MS ($n = 510$)	Controls ($n = 914$)	<i>p</i> -value
Female gender, <i>n</i> (%)	374 (73.6)	532 (58.3)	$< 0.001^a$
Mean age, years (SD)	50.7 (12.5)	43.9 (6.9)	$< 0.001^b$
College/university, 4 years or more, <i>n</i> (%)	166 (33.3)	289 (32.5)	0.27 ^a
Ever-smoker, <i>n</i> (%)	367 (74.9)	483 (54.5)	$< 0.001^a$
Relapsing remitting MS, <i>n</i> (%)	436 (88.8)	—	—
Mean age at MS onset, years (SD)	32.3 (9.2)	—	—
Mean disease duration, years (SD)	18.4 (11.6)	—	—
Mean EDSS (SD)	3.5 (2.3)	—	—
Mean MSSS (SD)	3.9 (2.7)	—	—

EDSS: Expanded Disability Status Scale; MSSS: Multiple Sclerosis Severity Score; SD: Standard deviation.

^aPearson's Chi-square test, ^bIndependent sample *t*-test.

Missing values are not included.

Table 2. The one-year prevalence of migraine and frequent TTH in patients and controls related to disease course and severity.

	MS (<i>n</i> = 510) <i>n</i> (%)	Controls (<i>n</i> = 914) <i>n</i> (%)	Unadjusted analysis ^a <i>p</i> -value, OR (95% CI)	Adjusted analysis ^b <i>p</i> -value, OR (95% CI)
Migraine, total	93 (18.2)	149 (16.3)	0.35, 1.15 (0.86–1.52)	0.44, 1.13 (0.82–1.57)
<i>Men</i>	10 (7.5)	32 (8.4)	0.73, 0.88 (0.42–1.84)	0.70, 1.18 (0.51–2.72) ^c
<i>Women</i>	82 (21.9)	117 (22.0)	0.98, 1.00 (0.72–1.37)	0.51, 1.12 (0.79–1.59) ^c
Frequent TTH, total	65 (12.7)	136 (14.9)	0.27, 0.84 (0.61–1.15)	0.73, 0.94 (0.67–1.33)
<i>Men</i>	16 (11.9)	55 (14.4)	0.47, 0.80 (0.44–1.46)	0.77, 0.92 (0.47–1.74) ^c
<i>Women</i>	49 (13.1)	81 (15.2)	0.37, 0.84 (0.57–1.23)	0.86, 0.96 (0.64–1.45) ^c
	RRMS (<i>n</i> = 436) <i>n</i> (%)	PPMS (<i>n</i> = 55) <i>n</i> (%)	Unadjusted analysis ^a <i>p</i> -value, OR (95% CI)	Adjusted analysis ^b <i>p</i> -value, OR (95% CI)
Migraine, total	81 (18.6)	9 (16.4)	0.69, 0.86 (0.40–1.82)	0.38, 1.44 (0.64–3.25)
<i>Men</i>	8 (7.6)	2 (7.7)	0.99, 1.01 (0.20–5.07)	0.52, 1.75 (0.32–9.65) ^c
<i>Women</i>	73 (22.1)	7 (24.1)	0.80, 1.13 (0.46–2.74)	0.47, 1.41 (0.56–3.58) ^c
Frequent TTH, total	59 (13.5)	4 (7.3)	0.19, 0.50 (0.18–1.44)	0.34, 0.59 (0.20–1.74)
<i>Men</i>	14 (13.3)	2 (7.7)	0.43, 0.54 (0.12–2.55)	0.55, 0.62 (0.13–3.00) ^c
<i>Women</i>	45 (13.6)	2 (6.9)	0.31, 0.47 (0.11–2.05)	0.55, 0.63 (0.14–2.84) ^c
	EDSS ≤3.5 (<i>n</i> = 291) <i>n</i> (%)	EDSS ≥4.0 (<i>n</i> = 154) <i>n</i> (%)	Unadjusted analysis ^a <i>p</i> -value, OR (95% CI)	Adjusted analysis ^b <i>p</i> -value, OR (95% CI)
Migraine, total	63 (21.6)	16 (10.4)	0.003, 0.42 (0.23–0.76)	0.048, 0.51 (0.26–0.99)
<i>Men</i>	5 (7.7)	4 (7.1)	0.91, 0.92 (0.24–3.62)	0.63, 1.46 (0.32–6.76) ^c
<i>Women</i>	58 (25.7)	12 (12.2)	0.007, 0.40 (0.21–0.79)	0.016, 0.38 (0.18–0.84) ^c
Frequent TTH, total	41 (14.1)	19 (12.3)	0.61, 0.86 (0.48–1.54)	0.58, 1.21 (0.63–2.32)
<i>Men</i>	7 (10.8)	8 (14.3)	0.56, 1.38 (0.47–4.08)	0.50, 1.49 (0.47–4.80) ^c
<i>Women</i>	34 (15.0)	11 (11.2)	0.36, 0.71 (0.35–1.48)	0.82, 1.10 (0.49–2.47) ^c

EDSS: Expanded Disability Status Scale; PPMS: Primary progressive multiple sclerosis; RRMS: Relapsing remitting multiple sclerosis; TTH: tension-type headache.
^aPearson's Chi-square test, ^bLogistic regression adjusted for age, gender and smoking status, ^cNot adjusted for gender.

39.9%, respectively).⁴ In further accordance with our findings, the one-year prevalence of TTH did not differ between patients and controls in the German study.⁴

Interestingly, in the present study fewer patients with EDSS ≥4.0 reported migraine in comparison to patients with EDSS ≤3.5, possibly indicating that migraine is less common among severely affected MS patients. It should be emphasized that the patients with EDSS ≥4.0 had a higher mean age (58.7 versus 47.1). Since the prevalence of migraine is known to be lower in high-age groups,⁹ the age difference between patients and controls could presumably to some degree explain this finding.

Particular strengths of this study are the large study size, high response rates, validated headache questions and clinically well-characterized patients.

The differences in age and gender distribution and smoking status between the groups are potential biases; therefore, age, gender and smoking status were included as covariates in the adjusted analyses with similar results as in the unadjusted analyses. Notably, information on disease modifying treatment (DMT) was not available and could therefore not be adjusted for. This could possibly influence the prevalence of headache in terms of an increase in the patient group, since headache is a potential side-effect of several DMTs, in particular interferons.^{1,5} Finally, it should be acknowledged that inclusion of controls from the NBMDR may have caused a selection bias towards a more than normally healthy control group. However, the one-year prevalence of migraine and frequent TTH among the controls was comparable with the prevalence in the general Norwegian population,⁹ arguing that the control group is representative.

In conclusion, the suggested comorbidity of migraine in MS patients is not retrieved in this relatively large case-control study, and in accordance with the majority of previous reports; no association between TTH and MS was seen.

Acknowledgements

We thank patients and controls for their participation, the Research Council of Norway and the Oslo MS Society for financial support and the Norwegian Bone Marrow Donor Registry, the Genetics of Autoimmunity and Cancer Research Group and the Norwegian Primary Sclerosing Cholangitis Research Center at Oslo University Hospital for collaboration with establishment of the control data set and Anja Bjølgerud, Ragnhild Salvesen, Anneli Reimer and Roy Sieh for help with administration and scanning of the questionnaires.

Conflict of Interest

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: EGC has received grants and personal fees from Novartis and Sanofi and personal fees from Biogen and Almirall. SMM has received speaker honorary and unrestricted research grants from Novartis, unrestricted travel grants and unrestricted research grants from Biogen. PB-H has received unrestricted research grants from Novartis, and funding for travel or speaker's fees from Novartis and UCB. HFH has received unrestricted travel grants or speaker's fees from Novartis, Biogen and Sanofi and unrestricted research grants from Novartis. MWG, BSW, GON, JAZ and BAL declare no conflicts of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/

or publication of this article: This study was supported by a grant from the Research Council of Norway and has received financial support from the Oslo MS Society.

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