Queen Mary University of London

Preventive Neurology Unit
Wolfson Institute of Preventive Medicine

A systematic review and meta-analysis of the prevalence of multiple sclerosis in patients with uveitis and characterisation of the phenotype of patients with both conditions

Thomas RP Taylor[1,2], Sara Leddy[1,3], Benjamin Meir Jacobs[1,2], Gavin Giovannoni[1,2,4], Harry Petrushkin[5], Ruth Dobson[1,2]

1. Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London, UK. 2. Royal London Hospital, Barts Health NHS Trust, London, UK. 3. Brighton and Sussex University Hospital Trust, Brighton, UK. 4. BartsMS, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, UK. 5. Moorfields Eye Hospital NHS Foundation Trust, London, UK

Introduction

Uveitis describes inflammation of the uveal tract. It may occur in the absence of a predisposing underlying condition or it may be secondary to a systemic autoimmune disease or infection. There is a known association between uveitis and multiple sclerosis (MS)[1]. Estimates for the prevalence of uveitis associated with MS range from 0.65% to 1.1% in large cohorts[2,3] compared to 0.06% in the general population[4].

Recently, anti-TNFα therapies have been licensed for the treatment of refractory uveitis. Anti-TNFα monoclonal antibodies have previously been associated with de novo demyelination and exacerbations of pre-existing demyelinating disease[5]. Accordingly, it is becoming increasingly important to understand the relationship between uveitis and MS in order to potentially identify subgroups at higher risk of demyelinating events and to inform risk-benefit discussions and direct treatment options.

This systematic review and meta-analysis seeks to estimate the prevalence of MS in patients with uveitis worldwide, and the characteristics of patients with both diagnoses.

Methods

This study was conducted in accordance with MOOSE guidelines[6]. MEDLINE and Embase databases were searched – 1411 studies identified from 1/1/1988 to 1/1/2020. After review, 109 patient cohorts were included from 103 separate studies.

Inclusion criteria: studies with a base population of patients with uveitis (of all types, or intermediate uveitis only), or MS, and a stated or deducible prevalence of the other condition in that cohort.

Exclusion criteria: non-English language, cohort based on a treatment subgroup, duplicate data sets.

Prevalence, and corresponding 95% confidence intervals (CIs), were calculated for each study. Meta-analyses of these prevalence calculations were conducted in R Version 3. 6. 2 (R Core Team (2019)). All analyses were meta-analyses of proportions using a random-effects model and inverse variance weighting. A random-effects model was used due to the high inter-study heterogeneity.

Results

The global prevalence estimate of MS in patients who have had uveitis:

Global pooled estimate of the prevalence of MS in patients with all types of uveitis: **0.60/100** (95% CI 0.39-0.84/100). 59497 patients included.

Subgroup analysis:

Not significant: size of cohort (<1000 vs >1000), year of publishing (2003 and before vs post-2003), study design (prospective/retrospective/cross-sectional).

Significant: geographic location of study (Europe and Northern America vs rest of the world).

Pooled prevalence estimates by geographic region of **0.20/100** (Asia), **1.32/100** (Europe), **0.88/100** (Northern America), **0.19/100** (Oceania), **0.00/100** (South America).

Global prevalence estimate of MS in patients who have had intermediate uveitis

Pooled prevalence estimate: **3.71/100** (95% CI 2.45 – 5.15/100). 7061 patients included.

Global prevalence estimate of uveitis in patients with MS

Pooled prevalence estimate: 2.00/100 (95% CI 0.89 – 3.46/100). 32681 patients included.

Additional Results

Pooled proportions of characteristic features of patients with both MS and uveitis

Intermediate uveitis is the most common type of uveitis associated with MS (pooled proportion of **66.82%**) of cases compared to **6.01%** for anterior uveitis, **6.09%** for posterior uveitis and **4.64**% for panuveitis.

Patients are more likely to be female (**71.77%**) and Caucasian (**84.90%**) as well as having bilateral eye disease (**71.09%**).

Uveitis was more likely to be the first presenting complaint than MS or simultaneous presentation (**45.83%** compared to **41.17%** and **13.74%** respectively).

Characteristic	Number of Studies	Number of patients	Pooled prevalence (%)	95% CI	Hetero-geneity (%)	95% CI
Demographic						
Female	25	425	71.77	67.08 - 76.02	7.4	0.0 - 40.2
Caucasian	5	50	84.90	55.44 - 96.21	62	0.0 - 85.7
Uveitis type						
Anterior	35	509	6.01	2.78 - 10.00	13.6	0.0 - 43.1
Intermediate	35	509	66.82	53.33 - 79.30	81.3	74.7 - 86.2
Posterior	35	509	6.09	1.22 - 13.12	63.6	47.8 - 74.6
Panuveitis	35	509	4.64	0.60 - 10.91	64.4	49.0 - 75.1
Uveitis features						
Bilateral	16	346	71.09	62.48 - 78.41	46.4	4.0 - 70.1
Uveitis presented first	12	274	45.83	39.95 - 51.83	0	0.0 - 36.2
MS presented first	12	274	41.17	32.60 - 50.32	36.4	0.0 - 67.9
Simultaneous presentation	12	274	13.74	9.98 - 18.63	0	0.0 - 39.8

Table 1. Pooled proportions of characteristic features of patients with both MS and uveitis.

Discussion

Limitations

There was high heterogeneity in the study designs included (some specifically looked at MS/uveitis relationship, some assessed all causes of uveitis). Additionally, anatomical classification of uveitis subtype was commonly limited to one type only when in reality, multiple subtypes may be present. Finally, there was significant variability in study numbers per region, and non-English language studies were excluded.

Conclusions

Our estimate of the global prevalence of MS in patients who have had uveitis (0.60/100) is significantly higher than the estimate for the global prevalence of all cases of MS, reported as 0.03/100[7]. The highest estimate of prevalence of MS was in patients with intermediate uveitis, at 3.71/100 globally, therefore the possibility of MS should be considered in patients referred with intermediate uveitis, particularly those who are female and Caucasian with bilateral, intermediate uveitis.

It is clear from our analysis that there is substantial geographic variation in the prevalence of multiple sclerosis in patients with uveitis. Estimates were particularly low at 0.00 – 0.20/100 in Asia, Oceania and South America, and higher in North America (0.88/100) and Europe (1.32/100).

This combined analysis helps to strengthen previous observations from individual studies and may be helpful when risk-stratifying patients and when discussing the merits and disadvantages of further investigations with them.

Conflict of Interest Statement

The authors report no conflicts of interest relevant to this report.

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