



Prevalence and demographics of multiple sclerosis-associated uveitis: a UK biobank study

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ABSTRACT

Background: Uveitis describes intraocular inflammation of the uveal tract. It may occur in the absence of a predisposing underlying condition, or may be secondary to a systemic autoimmune disease or ocular infection. An association with Multiple Sclerosis (MS) has also been observed.

Objectives: To investigate the association between MS and uveitis in UK Biobank.

Methods: 1696 individuals with MS were identified within UK Biobank using ICD-10 code G35 and 626 individuals with uveitis were identified using ICD-10 codes H20, H30, and H22.1. Participants who had a comorbid autoimmune condition that could also be associated with uveitis were excluded from analysis, as were those in whom MS was diagnosed prior to uveitis. 1568 individuals with MS and 470 individuals with uveitis were included in the final analysis. We used multivariable logistic regression to model uveitis diagnosis on MS status and control for confounding factors (age, sex, and socio-economic status). We also examined phenotypic and genetic characteristics of individuals with both conditions.

Results: Uveitis prevalence in people with MS was 0.51%, compared to 0.10% in controls. The adjusted odds ratio (OR) of MS given a diagnosis of uveitis was OR 5.25, 95% CI 2.6 - 10.6, $p=0.00024$. 87.5% of people with both diagnoses were female and 87.5% identified as White. 25.0% were DRB1*15 heterozygotes, while 75.0% carried no copies of the DRB1*15 risk allele.

Conclusions: These findings support the suggested association of these two conditions and demonstrate a comparable predominance of white females with both conditions.

1. Background

Uveitis describes intraocular inflammation of the uveal tract. Clinically, uveitis is subdivided into anterior, intermediate, posterior and pan-uveitis depending on the affected structures. Uveitis may occur in the absence of a predisposing underlying condition, or may be secondary to a systemic autoimmune disease or ocular infection.

Observational studies have suggested an association between uveitis and multiple sclerosis (MS), an autoimmune disease affecting the central nervous system (Breger and Leopold, 1966). Ocular and neural tissues share common embryological origins and the two diseases have been linked to the HLA-DRB1*15 allele (Raja et al., 1999). Estimates for the prevalence of uveitis associated with MS vary but range from 0.65%

to 1.09% in large cohorts (Le Scanff et al., 2008, Shugaiv et al., 2015) compared to 0.058% in the general population (Acharya et al., 2013). Given the common embryological origins, it may be that this overlap can be used to inform research regarding processes leading to MS development.

Recently, adalimumab - a monoclonal antibody which inhibits the action of Tumour Necrosis Factor alpha (TNF α) has been licensed for the treatment of refractory uveitis. Anti-TNF monoclonal antibodies and soluble TNF-alpha receptors (Lenercept) have previously been associated with *de novo* demyelination and exacerbations of pre-existing demyelinating disease. (Bosch et al., 2011) There are clinically significant safety concerns about the use of TNF antagonists in at least some of the uveitis population. As a result, patients in whom clinicians

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are considering starting anti-TNF α therapy may be referred to neurologists for assessment of the risk of developing demyelination, particularly if there is a history of neurological symptoms or a family history of MS. Evaluating this risk is extremely difficult; therefore a better understanding of the characteristic features of those at risk of both diseases has the potential to inform risk-benefit discussions and direct treatment options.

2. Methods

We set out to examine the relationship between MS and uveitis using UK Biobank, a longitudinal cohort study of volunteers aged 40-69. (UK) UK Biobank incorporates genotyping data, questionnaire data, biological samples, imaging, and linked healthcare records (from Hospital Episode Statistics).

MS was defined using the ICD-10 code G35 (Multiple Sclerosis). Uveitis was defined using ICD-10 codes H20 (iridocyclitis), H30 (chorioretinal inflammation), and H22.1 (iritis in the context of systemic illness). Self-reported uveitis was excluded, as the rarity and temporal nature of the disease were considered likely to affect the accuracy of recall and potentially bias results. Self-reported MS without a corresponding ICD-10 code was also not included for similar reasons. In both disease groups, participants who had a comorbid autoimmune condition that could also be associated with uveitis were excluded. Ethnicity data was taken from UK Biobank field ID 21000 which was collected as a self-reported questionnaire during initial assessment of participants. Classical HLA alleles were imputed by UK Biobank using HLA:IMP*2 (field ID 22182). Allele dosages were classified as 0, 1, or 2 by thresholding at a posterior probability threshold of <0.7 (=0 alleles), 0.7-1.4 (1 allele), and >1.4 (2 alleles), as recommended by UK Biobank (UK).

A crude odds ratio (OR) for diagnosis of both diseases was calculated; logistic regression was then used to calculate the adjusted OR of MS given a diagnosis of uveitis, controlling for age, sex, and Townsend deprivation index (a measure of socioeconomic status).

3. Results

We identified 1696 people with ICD-coded diagnoses of MS and 626 people with ICD-coded diagnoses of uveitis from a total pool of 488,276 UK Biobank volunteers. After exclusion of 18929 individuals with ICD-coded diagnoses of other autoimmune disorders, a pool of 469,347 participants remained, of whom 1597 had an ICD-coded diagnosis of MS, 480 had an ICD-coded diagnosis of uveitis, and 9 had both MS and uveitis. 1 individual did not have a coded date of uveitis diagnosis, and 20 individuals did not have a coded date of MS diagnosis and were excluded. Of the 9 individuals with diagnoses of both uveitis and MS and a date of diagnosis, 5 individuals were coded as having uveitis prior to their MS diagnosis and three were coded as having uveitis and MS simultaneously. One individual was excluded as the MS diagnoses preceded the uveitis diagnosis. The final numbers included were 1568 individuals with MS, 470 with uveitis and 8 with both diagnoses.

The prevalence of coincident or prior uveitis among people with MS (8/1576, 0.51%) exceeded that of the general UKB population (470/467749, 0.10%), yielding a crude odds ratio (OR) for MS given a prior or coincident diagnosis of uveitis of 5.07 (95% CI 2.52 - 10.22). In a multivariable logistic regression model adjusting for age, sex, ethnicity, and Townsend deprivation index, MS was strongly associated with uveitis, with a similar effect estimate and precision to the crude OR (OR 5.25, 95% CI 2.6 - 10.6, $p=0.00024$).

Of the 8 pwMS who had a previous or coincident diagnosis of uveitis, and no other potential underlying autoimmune disease, 7/8 (87.5%) were female, 7/8 (87.5%) were White, median age at recruitment was 56.5 (IQR 17), median age at MS diagnosis was 44.7 (IQR 2.22), and median age at uveitis diagnosis was 43.2 (IQR 9.26). Further demographic details are given in Table 1.

Table 1

Comparison of patients from UK Biobank with MS, uveitis and MS-associated uveitis.

Trait	Multiple Sclerosis (n = 1568)	Uveitis(n = 470)	MS and Uveitis (n = 8)
Age			
• Median Age at Recruitment	56.0 (IQR 13.0)	60.0 (IQR 12.0)	56.5 (IQR 17.0)
• Median Age at Diagnosis of MS	38.4 (IQR 10.3)	NA	44.7 (IQR 2.2)
• Median Age at Diagnosis of Uveitis	NA	41.2 (IQR 9.1)	43.2 (IQR 9.3)
Sex			
• Female	1131 (72.1%)	253 (53.8%)	7 (87.5%)
Ethnicity			
• White	1525 (97.3%)	417 (88.7%)	7 (87.5%)
• BAME	27 (1.72%)	41 (8.7%)	1 (12.5%)
• Other/unknown	16 (1.0%)	12 (2.6%)	0
DRB1*15[†]			
• 0	796 (50.8%)	351 (74.7%)	6 (75.0%)
• 1	669 (42.7%)	109 (23.2%)	2 (25.0%)
• 2	103 (6.6%)	10 (2.1%)	0
A*02[†]			
• 0	983 (62.7%)	263 (55.9%)	6 (75.0%)
• 1	499 (31.8%)	177 (37.7%)	1 (12.5%)
• 2	86 (5.5%)	30 (6.4%)	1 (12.5%)
B27			
• Negative	1460 (93.1%)	440 (93.6%)	7 (87.5%)
• Positive	108 (6.9%)	30 (6.4%)	1 (12.5%)

BAME: Black, Asian and Minority Ethnic

[†] 1 = heterozygous carriage; 2 = homozygous

We examined the distribution of MS HLA risk alleles among pwMS who had a diagnosis of uveitis and no other potential underlying autoimmune disease. 2/8 individuals (25.0%) were DRB1*15:01 heterozygotes, while 6/8 (75.0%) carried no copies of the DRB1*15:01 risk allele. Six out of 8 (75.0%) lacked a copy of the protective A*02:01 allele (Table 1).

4. Conclusions

We report that the prevalence of a uveitis diagnosis among pwMS in UK Biobank is 0.51%, once patients with other potentially autoimmune conditions are excluded. We also report an association between uveitis and MS, with a diagnosis of uveitis conferring a higher risk of subsequent/coincident diagnosis of MS (OR 5.25, 95% CI 2.6 - 10.6, $p=0.00024$). It was felt to be important to exclude other autoimmune conditions, as diseases such as psoriasis, inflammatory bowel disease and ankylosing spondylitis have a stronger association with uveitis than multiple sclerosis and the objective of this research was to specifically examine the relationship between MS and uveitis (Acharya et al., 2013, Suhler et al., 2008). The prevalence observed in UK Biobank is lower than published estimates from comparable cohorts (0.65 - 1.09%) (Le Scanff et al., 2008, Shugaiv et al., 2015, Biousse et al., 1999) but significantly higher than the prevalence among individuals without MS. This provides further evidence supporting an association between these two diseases. The patient characteristics are also in keeping with established observations of patients with both diseases; whilst gender and ethnicity broadly mirror the demographic traits of MS patients, the HLA type of patients with both diseases appears more in keeping with the uveitis population. This information may be useful for clinicians to consider if they are asked to stratify the risk of developing demyelination in patients with uveitis as it reinforces the possibility that patients may be predisposed to both conditions.

It is interesting to note that the proportion of patients who had a copy of the HLA-DRB1*15 MS risk allele was lower in our cohort of patients with MS who had a diagnosis of uveitis (25.0%) when compared to a previous study on this genetic relationship where the

proportion was 60.0% (Raja et al., 1999). In both studies however the number of patients in each group is small and it is also relevant to note that Raja and colleagues were only investigating patients with pars planitis, a subgroup of intermediate uveitis known to have a stronger association with MS than other types.

The use of UK Biobank for the analysis of the relationship between two relatively rare diseases has limitations. The small numbers of patients with both diagnoses prevent meaningful conclusions being drawn regarding the characteristics of these patients. Selection of individuals was a further challenge as the ICD-10 coding for uveitis does not match the Standardisation of Uveitis Nomenclature (SUN) criteria for the categorisation of uveitis type based on affected structures. (Jabs et al., 2005) Furthermore, we did not include self-reported diagnoses. The self-reported diagnosis of uveitis in UK Biobank is limited to only iritis, a subset of anterior uveitis, and so is unlikely to represent the true range of uveitis subtypes associated with MS, particularly as intermediate uveitis has the strongest known association. (Messenger et al., 2015) It is also not possible within the UK Biobank data to assess whether patients had a single episode of uveitis which resolved, or if they had multiple or chronic episodes of the disease.

Diagnostic and recall biases may also create a spurious association between MS and uveitis. People with MS are more regularly assessed by health professionals than individuals without chronic health conditions and may be diagnosed with milder forms of uveitis than would normally present to eye services. In addition, subtle visual disturbances caused by optic neuritis (in the context of MS) may be misattributed to uveitis, and vice-versa. Misdiagnoses may not be subsequently corrected in Hospital Episode Statistics data, and so this association could be purely due to diagnostic uncertainty in the early stages of MS.

In conclusion, the prevalence of uveitis in pwMS in UK Biobank is significantly higher than in controls and a diagnosis of uveitis confers a higher risk of subsequent/coincident diagnosis of MS, supporting the association between the two diseases and thus updating and strengthening the data regarding this relationship. As the availability of information from larger cohorts of rare diseases becomes more readily available, there may be increased opportunity to investigate the relationship between these two conditions and given the increasing concern regarding use of anti-TNF α for uveitis, there may be a need to conduct further prospective research to investigate the risk of developing MS in patients with uveitis.

Declaration of Competing Interests

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

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CRediT authorship contribution statement

Thomas RP Taylor: Conceptualization, Writing - original draft. **Benjamin M Jacobs:** Software, Data curation, Methodology, Investigation. **Gavin Giovannoni:** Writing - review & editing. **Harry Petrushkin:** Writing - review & editing. **Ruth Dobson:** Writing - review & editing, Funding acquisition, Supervision.

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