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Clinical paper

Epidemiology of Adult Uveitis in a Northern Ireland Tertiary Referral Centre

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ABSTRACT.

Uveitis is inflammation of the middle layer of the eye, called the uveal tract. It can be classified by anatomic location of the focus of inflammation inside the eye: intermediate, posterior or pan-uveitis. These types are less common than anterior uveitis (iritis), but more often have underlying aetiologies that require identification. Some aetiologies are infective, while others require systemic immunosuppression. Underlying aetiologies vary in different regions in the world, and so local data is important to guide clinicians. This study describes the aetiology of 255 cases of intermediate, posterior and pan-uveitis in adults. The most common non-infectious causes, after idiopathic, were sarcoid, Birdshot chorioretinopathy, demyelination-related and Behçet's, whereas toxoplasmosis and herpes simplex and zoster related retinitis were the common infectious causes. Neither age nor sex of the patient were related to aetiology.

INTRODUCTION.

Uveitis is inflammation of the middle layer of the eye; iris, ciliary body and choroid. Uveitis can be classified by anatomical location in the eye, as anterior (iritis), intermediate (focus of inflammation is in the vitreous), posterior (focus of inflammation is chorioretinal) or panuveitis (all segments of the eye affected). Intermediate, posterior and panuveitis present specific challenges, as there is a diverse range of underlying aetiologies, which are important to distinguish but which have common presenting features. Typically cases present with blurred vision, floaters, pain and redness, and on examination iritis, vitreous haze, chorioretinitis and macular oedema may be present. Usually systemic immunosuppression is needed, but not before infectious or neoplastic causes are excluded. Non-infectious cases may be idiopathic or may be associated with a systemic disease.

When a patient presents with uveitis, determination of the aetiology is needed to guide investigations and treatment. Prevalence of types of uveitis varies with geographic location.[1] Knowledge of the local epidemiology of uveitis is necessary to aid and guide clinical assessment, in determining the aetiology by giving the clinician prior probabilities of the likely causes. The purpose of this study is to determine the pattern of aetiologies underlying intermediate, posterior and pan-uveitis adult cases attending tertiary uveitis clinics in Belfast.

METHODS.

Data were collected on consecutive new and review patients attending two tertiary uveitis clinics in the Belfast Health and Social Care Trust from February 2016 for 12 months (study is ongoing). Permission was given by the Belfast Health and Social Care Trust audit department, and the tenets of the Declaration of Helsinki were followed. A short form was designed, piloted, and then disseminated to the relevant clinics. The form was filled in by hand by a member of the clinical team once for each patient, during or immediately after the clinical encounter, entering data based on their clinical judgement. Data collected were patient identifiers including age, along with clinical data based on the Standardisation of Uveitis Nomenclature (SUN) Working Group terms, specifically on the primary location of the inflammation in the eye (anterior, intermediate, posterior, pan-uveitis, scleritis and orbital), and aetiology.[2] Data were entered into Excel, and transferred to SPSSv25 for data cleaning (e.g. removing duplicates) and analysis. In July 2018, data on aetiology, which may not have been apparent initially, were updated for all cases.

RESULTS.

Data were collected on 255 cases: 19.4% (52) were intermediate uveitis cases, 203 posterior and pan uveitis cases. Posterior and pan uveitis cases were analysed together, as often the distinction between them is a matter of clinical judgement and marginal, depending on the degree of severity of anterior segment and vitreous signs.

The mean age of intermediate uveitis cases was 49.8 years (range 16-85, sd 17.0) a histogram of age showed a normal distribution: 46.2% (24/52) were female. The aetiology is shown in Table 1. There was no significant association of aetiology with sex ($\chi 2=4.2$, $p=0.6$), nor was there association of aetiology with age ($F=1.0$, $p=0.4$).

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Table 1.

Aetiology of intermediate uveitis cases.

Aetiology of intermediate uveitis cases	Percentage of intermediate cases (frequency) (total = 52)
Idiopathic	61.5% (32)
Multiple sclerosis	13.5% (7)
Sarcoid	11.5% (6)
Isolated HLA B27-related	7.7% (4)
Tubulointerstitial nephritis uveitis ('TINU')	1.9% (1)
Mycobacterium related	1.9% (1)
Under investigation (Sep. 2018)	1.9% (1)

For the 203 posterior and pan-uveitis cases, the mean age was 59.6 years (range 17-92, sd 16.5): 51.9% were female. There were 47 infectious cases of posterior and pan-uveitis (23.2%). The mean age of infectious cases was 51.0 years (range 17-92, sd 18.6): 42.6% were female. The aetiology is shown in Table 2. There was no significant association of the specific infectious aetiology with sex ($\chi 2=6.0$, $p=0.5$) or age ($F=0.6$, $p=0.7$).

For 153 non-infectious cases of posterior or pan-uveitis, the

Table 2.

Aetiology of infectious posterior or pan-uveitis cases.

Aetiology of infectious posterior or pan-uveitis cases	Percentage of infectious cases (frequency) (total = 47)
Toxoplasmosis	34.0% (16)
Acute retinal necrosis due to HSV or VZV	29.8% (14)
Mycobacterium-related	23.4% (11)
CMV retinitis	4.3% (2)
Presumed varicella zoster (related to shingles)	2.1% (1)
Syphilis	2.1% (1)
Bartonella	2.1% (1)
Toxocara	2.1% (1)

mean age was 58.9 years (range 18-86, sd 15.9); 55.5% were female. The most common aetiologies are shown in Table 3. Less common aetiologies were Fuchs Heterochromic Cyclitis-related retinal vasculitis, Punctate Inner Choroidopathy, systemic or cerebral vasculitis (2.6% or 4 cases each), sympathetic ophthalmia (1.9% or 3 cases), and 1 case each of tubulo-interstitial nephritis uveitis, HLA B27 associated uveitis, Vogt Koyanagi Harada disease, Acute Zonal Occult Outer Retinopathy, post-streptococcal uveitis, Multifocal Choroiditis and other white dot syndrome. Three cases were under investigation at the time of writing, and 2 attended for screening or treatment of drug-related posterior uveitis (for example related to pembrolizumab). There was no significant association of specific non-infectious aetiology with sex ($\chi 2=16.4$, $p=0.6$). Visual inspection of mean age for each of the more common aetiologies showed similar average ages for each, with no category standing out.

Table 3.

Aetiology of non-infectious posterior or pan-uveitis cases.

Aetiology of non-infectious posterior or pan-uveitis cases	Percentage of non-infectious cases (frequency) (total = 153, excluding 3 under investigation)
Idiopathic	43.1% (66)
Sarcoid	17.0% (26)
Birdshot chorioretinopathy	7.2% (11)
Behçet's disease	5.9% (9)
Cancer-associated or autoimmune retinopathy confirmed or suspected	4.6% (7)
Multiple sclerosis (not optic neuritis)	3.3% (5)
Inflammatory bowel disease	3.3% (5)
Other	15.7% (24)

DISCUSSION.

Uveitis is an important set of conditions as blindness can result. The first step in clinical assessment of a case of uveitis is to define the location. Then a determination of likely aetiology should be undertaken, primarily assessing whether infection or neoplasm (such as lymphoma) is present or not. In our sample, no cases of intermediate and approximately one fifth of cases of posterior or pan-uveitis were infectious.

Age and sex were similar for infectious and non-infectious cases, with the extremes of age being present in both categories. Similarly neither age nor sex were a guide to the specific type of infectious aetiology, although numbers were relatively small. Thus there is no evidence from this Northern Ireland sample that age or sex should influence the clinician's judgement of the probability of infection, or the type of infection, in uveitis. The mean age, of approximately 50 years, for all groups of our sample, and the wide range of ages, illustrates that amongst those affected by uveitis are those of working age. Though less prevalent overall than age-related eye conditions like macular degeneration or glaucoma, uveitis therefore has a potential personal and societal economic impact.[3] Indeed anecdotally we are acutely aware of the difficulties many patients with uveitis have in balancing their hospital attendances, treatment, visual loss on occasion and work.

Comparisons across studies should be done with the knowledge that different patterns of uveitis will be seen in general and subspecialty services, as well as in different

geographical regions. Geographical location is an interesting factor. For example Behçet's disease was reported as the commonest cause of non-infectious uveitis in a prospective study in Iraq (8% of 318 cases of anterior, intermediate, posterior and pan-uveitis uveitis cases, grouped together), most cases coming from Northern Iraq (part of the 'Silk Road'), [4] while a Vienna study found 4.9% (33/671) of posterior and pan-uveitis cases to be related to Behçet's, [5] in comparison to our finding of 5.9%.

Infectious causes too vary by region. The most common infectious causes of uveitis are reported in a systemic review as toxoplasmosis and herpes, [1] and this was true in our sample. A study from Virginia looked retrospectively at 30 years of uveitis patients, and found toxoplasmosis and herpetic retinitis (acute retinal necrosis, or 'ARN') to be the commonest aetiologies amongst 38 eyes with infectious posterior or pan-uveitis.[6] Toxoplasmosis was also the commonest cause of uveitis in samples from India (40.2% of 92 posterior uveitis cases).[7] The next most common aetiology in our sample was 'mycobacterium-related', meaning tuberculosis (TB) (in all but one case, which was atypical mycobacterium). In the Iraqi study, toxoplasmosis and "presumed ocular TB" were the commonest infectious causes.[4] In India, ocular TB is said to be increasing in incidence.[7] Studies from Manchester also report the incidence of TB related uveitis to be increasing in the UK, perhaps partly because of increasing recognition of TB as a possible cause.[8] Our sample illustrates that in Northern Ireland, clinicians should enquire about symptoms and risk factors for TB, and test for exposure if appropriate. Uveitis can occur in association with TB either due to direct infection, or in association with an auto-immune uveitis. It is clinically impossible to distinguish these two mechanisms. It should be clarified that the TB-related cases in this database do not include those patients whose tests indicated latent TB and who therefore required TB treatment merely as they started immunosuppression for non-TB related uveitis.

The most common aetiology of non-infectious posterior or pan-uveitis was 'idiopathic' (43.1% of non-infectious cases and 33.0% of all posterior and pan-uveitis cases). It may be that idiopathic cases have a specific underlying aetiology that will emerge with time or future investigations, but in keeping with our sample, idiopathic is reported as the aetiology of 30 to 50% of all uveitis cases.[9] It is unlikely these cases were infective, as infective cases typically worsen over days or weeks, and their infective nature thus becomes evident. Occasionally uveitis is the presenting feature of a systemic disease. Sarcoid was the 2nd most common aetiology for non-infectious cases in our sample (17.0% of non-infectious posterior or pan uveitis cases in our sample). It is not known in how many of these cases, the diagnosis of sarcoid was established prior to uveitis, but it is important to identify sarcoid, if present, and not just to monitor lung function but also other organs including cardiac function.[10] The next most common aetiology in our sample was 'birdshot chorioretinopathy' (7.2% in our sample). In the Virginia study, 11.3% of 62 patients with posterior uveitis had birdshot chorioretinopathy-related uveitis. 'Birdshot' is an uncommon ocular condition, with no known systemic manifestations, diagnosed by recognition of characteristic ocular signs, confirmed by testing for HLA-A29 heterogeneity. As it usually requires long-term systemic immunosuppression and monitoring, its identification is important to enable appropriate management and counselling. Behçet's was the aetiology in 5.9% of our non-infectious posterior and pan-uveitis cases. In a study from Iran, Behçet's disease was the most common cause of non-infectious posterior and pan-uveitis [11] as it was in the Iraqi study [4], with sarcoid and birdshot chorioretinopathy accounting for 1.5% and 0.7% of posterior uveitis cases. Behçet's is important as biologics could be considered as first line therapy for Behçet's-related uveitis. [12] Other conditions were less common in our sample, such as VKH: interestingly, 45.2% of 31 cases of panuveitis were due to VKH in an Indian sample.[7]

The most common cause of intermediate uveitis was idiopathic, followed by sarcoid and multiple sclerosis (MS). Most medical students are aware that optic neuritis is an ophthalmic manifestation of MS, but ophthalmologists should be aware of MS as a cause of intermediate uveitis as apparent in our sample, classically causing peripheral retinal periphlebitis and inflammatory debris around the pars plana. Systemic questioning should be directed with this in mind, and anti-TNF agents, if being contemplated, should not be started if MS is suspected.

This study captured the aetiology of review and new cases, so the present data will not be able to detect changes with time. However the contemporaneous nature of data entry and extensive checking and updating of the database helped to ensure our data accurately reflected the given diagnoses. The SUN Working Group has published a mapping of clinical features and diagnoses based on the consensus of uveitis experts internationally.[13] SUN mapping closely reflects our local clinical practice, although SUN criteria are not intended to aid diagnosis making but to allow clear communication between clinicians.[14] No comment can be made on incidence or prevalence of these conditions in Northern Ireland, as a small but unknown number of intermediate, posterior and pan-uveitis cases may be attending other hospitals in the region and so prevalence measures are likely to be under-estimates. Furthermore, cases managed outside the regional centre may be less severe. Also, this sample only captures adult patients, excluding those aged under 16 years with uveitis, who attend a different service.

It is important in any region to ascertain local patterns of uveitis. Visual impairment registration figures in the UK may underestimate the prevalence of uveitis as a cause, due to the categories used on the registration form.[15] Indeed in Northern Ireland from 2015-17, only 3.1% of registrations of severe sight impairment (n=4/1294) and 0.2% of sight impairment registrations (n=1/554) had uveitis as the primary or secondary cause (personal communication, Prof Jonathan Jackson), figures which do not correspond with our anecdotal

clinical experience. A report on the Republic of Ireland's causes of blindness register of 1996 does not mention uveitis.[16] It is thought that the categories used for blindness registration in the UK and the Republic of Ireland may capture *complications* of uveitis as causes of blindness, such as cataract and glaucoma, rather than the condition of uveitis *per se*. It is also possible that clinicians are not discussing registration with suitable patients, although this should be no more true of uveitis than other conditions. In the USA, uveitis is the reported cause of between 10 and 15% of blindness, reflecting the impact of uveitis on a population.

This database gives a picture of the relative causes of uveitis in Northern Ireland in a tertiary clinic. As uveitis cases initially present to any and all ophthalmic services, such as Eye Casualty and the general on call team, this data helps clinicians to assign prior probabilities to the most likely causes of a patient's uveitis in Northern Ireland. Furthermore large datasets offer the potential for hypothesis generation. Our database serves as a tool for the future to dissect out specific aspects of interest for deeper study. The Royal College of Ophthalmologists has been taking steps towards a standardised dataset for uveitis, and our growing data may facilitate generation of a rolling UK-wide or all-Ireland uveitis database, examining diagnosis, management and outcomes for specific aetiologies.[17]

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