Outcomes from a Multi-disciplinary Uveitis Referral Clinic in Tasmania, Australia and adaptation during the COVID-19 pandemic

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Abstract

Background: Uveitis is one of the most common causes of visual impairment, accounting for up to 25% of visual loss in the developing world and 10% in developed countries. There are marked regional differences within Australia, particularly in rural and Indigenous populations. There is no published data on uveitis in Tasmania.

Methods: A 5-year retrospective case series review of medical records of all patients reviewed to the clinic was performed.

Results: A total of 95 patients were referred to the clinic. Seventy-six (76) patients (123 eyes) had uveitis and were analysed in detail (see table 1). Nineteen (19) patients had a diagnosis other than uveitis or were on immunosuppressive therapy for another ocular inflammatory disorder (detailed in Table 2). The most common anatomical diagnosis was posterior uveitis (29%), followed by pan-uveitis (20%) and intermediate uveitis (17%). Average follow-up was 36.7 months.

Conclusion:

The most common anatomical diagnosis was posterior uveitis (29%), followed by pan-uveitis (20%) and intermediate uveitis (17%). Telemedicine is a modality that could have application in management of Uveitis in regional areas.

Introduction

Uveitis is one of the most common causes of visual impairment, accounting for up to 25% of visual loss in the developing world and 10% in developed countries. (1-3) It is the second leading treatable cause of vision loss behind diabetic retinopathy in the working age population. (3) There is significant regional variation in the epidemiology of uveitis related to genetic, ethnic, geographic and environmental factors. (1, 4) In the last 20 years a number of studies have investigated the epidemiology of uveitis in Australia, including two regional studies of indigenous Australian populations (5, 6) and studies from tertiary uveitis centres in Sydney (7) and Melbourne (8). The Melbourne study determined that the incidence and prevalence of uveitis in Melbourne is 21.5/100,000 person-years and 36.3/100,000 persons respectively, which is consistent with other Western countries. (4, 8) There are marked regional differences within Australia, particularly in rural and Indigenous populations. There is no published data on uveitis in Tasmania. Tasmania's population of over 500,000 is generally older, of lower socio-economic status and is relatively geographically isolated compared to the rest of Australia. (9)

Rapid control of vision threatening uveitis with systemic corticosteroid therapy followed by early introduction of steroid sparing immunomodulatory therapy has become the standard of care in sub-specialty uveitis clinics. Such clinics typically co-manage these complex patients in multi-disciplinary clinics with Rheumatologists & Immunologists. (10) This practice is supported by a number of high-quality studies and clinical trials. The SITE study was a large retrospective case series that showed immunosuppressive therapy for uveitis was effective in disease control and was not associated with increased malignancy-related mortality. (11) The VISUAL studies were multi-centre, randomised clinical trials, that provided evidence for safety and efficacy of adalimumab over corticosteroid systemic therapy. (12, 13) The Multi-centre Uveitis Steroid Treatment (MUST) trial was a multi-centre, randomised controlled trial, that demonstrated the superiority of treat to target systemic immunosuppressive therapy over sustained release intra-vitreal (local) steroid therapy in the treatment of non-infectious, non-anterior, vision-threatening uveitis. (14)

The current study describes the initial five-year experience from a multi-disciplinary tertiary referral uveitis clinic at Royal Hobart Hospital established to provide local tertiary care for patients with uveitis and other forms of inflammatory eye disease in Tasmania. The clinic provides multi-disciplinary clinical care to manage patients with severe, vision threatening or recalcitrant inflammatory eye disease. The majority of patients seen in the clinic had vision threatening uveitis and this group of patients was analysed in detail. This study also provides insight into models of care for isolated populations requiring subspecialty input during the COVID-19 global pandemic.

Materials And Methods

A retrospective analysis of all patients seen at the Royal Hobart Hospital multi-disciplinary Uveitis and Rheumatology Clinic from 2016 to 2020 was performed. Ethics approval was granted by the Tasmanian Health and Medical Human Research Ethics Committee as a Low and Negligible Risk (LNR) study. Patients were identified through clinic lists. All data was captured on a REDCap electronic data capture encrypted database hosted at the University of Sydney. (15, 16) Patients with other forms of inflammatory eye disease receiving systemic immunosuppressive therapy such as scleritis, PUK, ocular cicatricial pemphigus (OCP) and IgG4 orbitopathy were included in the clinic database but excluded from detailed analysis in this study.

Data was obtained by reviewing patient clinic notes stored in electronic medical records. Demographic information including age, gender, ethnicity and comorbidities were collected. Indicators of patient access to care including time to treatment and referral, follow-up and distance travelled were also assessed. Uveitis was characterised using the Standardization of Uveitis Nomenclature (SUN) (17). Data collected included the clinical features of the uveitis, investigations, treatment, side effects, complications, visual

outcomes and relapse rates. It was also noted whether a change in diagnosis or management occurred as a result of a patient's clinic visit.

Snellen visual acuity at initial diagnosis, first clinic visit and most recent follow-up was collected. Snellen visual acuities were converted to LogMAR vision to facilitate analysis. Visual loss was defined as none (LogMAR 0.20, 6/9 or better), mild (LogMAR 0.30-0.60, 6/12 to 6/24), moderate (LogMAR 0.70-0.90, 6/30 to 6/48), and severe (LogMAR $\geq$1.00, 6/60 or worse). Statistical analysis was performed using the STATA 16. Parametric and non-parametric tests were employed, and for binary outcomes logistic regression analysis was performed and odds ratios computed.

Results

A total of 95 patients were referred to the clinic. Seventy-six (76) patients (123 eyes) had uveitis and were analysed in detail (see table 1). Nineteen (19) patients had a diagnosis other than uveitis or were on immunosuppressive therapy for another ocular inflammatory disorder (detailed in Table 2). Average follow-up was 36.7 months. The majority of patients (n=49, 64%) were from the Hobart area, with 11 patients (14%) travelling > 2 hours for review at the clinic.

Table 1 – Patient Demographics

Table 1	n (%)
Age	55 (IQR 36 to 65)
Gender	
Male	37 (39)
Female	58 (61)
Ethnicity	
Caucasian	78 (92)
Indian sub-continent	5 (6)
Indigenous	1 (1)
South Asian	0 (0)
Comorbidities	
Type 2 diabetes	8 (10)
Ischaemic heart disease	4 (5)
Renal impairment	1 (1)
Smoker	4 (5)
Previous or current malignancy	6 (7)

Table 2 Patients excluded from detailed analysis	
Other Inflammatory Eye Disease	
Interstitial keratitis	2
Corneal melt secondary to hyper IgE syndrome	1
Corneal melt secondary to Herpes Simplex Keratitis	3
Peripheral ulcerative keratitis	2
Ocular Cicatricial Pemphigoid	1
IgG4 Orbitopathy	1
Cogan's syndrome	1
Traumatic anterior uveitis response	1
Alternative Diagnoses	
Nyctalopia for investigation	1
Ocular ischaemic syndrome	1
Choroidal melanoma	1
Bilateral sequential CRAO	1
CRVO complicated by a cilioretinal BRAO	1
Bietti crystalline retinopathy	1
Visual snow phenomenon	1

Aetiology and Systemic associations

The most common anatomical diagnosis was posterior uveitis (29%), followed by pan-uveitis (20%) and intermediate uveitis (17%). This is detailed in Table 3. Patients with anterior uveitis (n = 19; 25%) were referred due to frequent multiple relapses, chronic recalcitrant uveitis or for advice regarding peri-operative management. The majority of patients had bilateral disease (n=54, 71%). There was a range of associated systemic diseases and isolated ocular disorders diagnosed. Undifferentiated uveitis was most common diagnosis, followed by inflammatory and then infective aetiology. This is detailed in Table 4.

Table 3 – Uveitis by anatomic site

Anatomical diagnosis	**n (%)**
Anterior uveitis	
Acute	9 (12)
Chronic	10 (13)
Intermediate uveitis	13 (17)
Posterior uveitis	22 (29)
Pan-uveitis	15 (20)
Scleritis	7 (9)
Bilateral	54 (71)

Table 4 – Uveitis by aetiology

Aetiology	N (%)
Undifferentiated	41 (54)
Inflammatory	27 (36)
Malignant	1 (1)
Infectious	10 (13)
Inflammatory (systemic)	
Sarcoidosis	6
Ankylosing spondylitis (HLAB27 negative)	2
Psoriatic arthritis (HLAB27 positive)	1
HLAB27 positive (without systemic disease)	2
JIA	1
Behcet's	1
Crohn's disease	1
Dermatomyositis	1
Inflammatory (ocular)	
Birdshot chorioretinopathy	2
MEWDS	1
MFC	6
PIC	1
AZOOR	1
Acute Macular Neuroretinopathy	1
Infectious	
HSV	
Anterior segment	2
Retinitis	1
VZV	
Anterior segment	2
Retinitis	1
CMV retinitis	2
Tubercular	2

Treatment and adverse effects

Fifty-three patients (70%) were co-managed with a physician (rheumatology, infectious diseases, respiratory). All patients on systemic immunosuppressive therapy were co-managed with the rheumatologist. Treatment is detailed in Table 5. Fifty-nine (78%) patients required systemic corticosteroids at some time point and 36 (47%) patients required additional steroid sparing Immunomodulatory therapy (IMT) with methotrexate, mycophenolate or a biologic agent. There was no

relationship between reactivation of inflammation and IMT induction phase (OR 0.72 95% CI 0.26-1.9 p = 0.513). This demonstrated the decision to start IMT was not due to recurrent disease.

Systemic steroid sparing therapy was used in several different circumstances. Eleven patients were commenced on IMT due to a disease with a known, protracted course such as Birdshot choroidopathy or MFC. Ten patients were unable to be tapered to a safe maintenance dose of prednisolone (< 7.5mg) or developed corticosteroid side-effects during their initial induction. Fifty percent of the patients (n=24) on systemic corticosteroids at the time of referral had adverse effects from corticosteroids such as: weight gain (n=24), labile blood pressure (n=8), worsened glycaemic control (n=8), psychological disturbance, exacerbation of peptic ulcer disease and cushingoid habitus.

In the IMT group, a range of mild adverse effects occurred including lymphopaenia (n=1), skin rash (n=1) and flu-like illness (n=1). Rituximab was ceased as a result of hypogammaglobulinaemia in one patient. One patient had disseminated CMV sepsis from IMT requiring suspension for treatment which was re-introduced at a lower dose once systemically stable. One patient had severe flu like symptoms related to infliximab and this was ceased following escalation of local therapies.

There was no significant difference in the rates of relapse of ocular inflammation between patients on combination systemic immunosuppression and those on systemic corticosteroids or local corticosteroids alone (OR 1.3 (95% CI 0.23 – 8.2, p = 0.73). Two patients developed a uveitis relapse while on systemic immunosuppressive therapy. One patient flared while on conventional IMT with the cessation of oral prednisolone. Another patient had a flare of uveitis after self-cessation of biologic due to rash.

Table 5 – Treatment Breakdown per patient

Treatment type	n (%)
Specialist physician co-management	53 (70)
Treatment modality	
Topical	54 (71)
Regional	12 (16)
Systemic corticosteroids	59 (78)
Systemic IMT	46 (61)
Anti-microbials	9 (12)
Regional corticosteroid treatment	
Orbital floor injection	8 (10)
Dexamethasone implant	2 (2)
Systemic immunosuppression	
Prednisolone alone	25 (33)
Prednisolone + Methotrexate	17 (22)
Prednisolone + Mycophenolate	6 (8)
Prednisolone + Biologic	11 (14)
TNF-alpha	9 (12)
Rituximab	1 (1)
Tocilizumab	1 (1)
Immunosuppression alone	9 (12)
Methotrexate	7 (9)
Mycophenolate	1 (1)
TNF-alpha alone	1 (1)
3 or more agents	3 (4)

Surgical interventions were required in 20 patients and are detailed in Table 5. The majority (29 eyes) were cataract surgery. Two patients (3 eyes) required glaucoma surgery. Two patients (4 eyes) had undergone vitrectomy prior to referral to the clinic for persistent cystoid macula oedema and epiretinal membranes.

Table 6 – Surgical interventions for management of complications

	Number of patients	Number of eyes
Glaucoma surgery	2	3
Cataract surgery	16	29
Vitreoretinal surgery	2	4

Visual outcomes and complications

Visual acuity was maintained and trended towards improvement from time of diagnosis to last review (per eye analysis n = 119; mean difference 0.06 95% CI -0.004 to 0.12 p = 0.07).

Table 7 – Comparison of visual loss at initial and final review

Visual loss	Uveitis review	Final review
None (LogMAR £ 0.20, 6/9 or better)	40	45
Mild (LogMAR 0.30-0.60, 6/12 to 6/24	21	16
Moderate (LogMAR 0.70-0.90, 6/30-6/48)	9	10
Severe (LogMAR 1.00, 6/60 or worse)	6	5

For those patients who had lost vision prior to referral to the clinic, there was an overall improvement in grading of visual loss (x^2 = 13.8 with 4 df; p = 0.008). In most patients, this was due to improved control of intraocular inflammation and cystoid macula oedema. Figure 1 details the ocular complications during the period of clinic follow up.

Virtual clinics in the setting of COVID-19

During the course of the study, the COVID-19 pandemic prompted international and inter-state border closures in Australia. As a result, the uveitis clinic transitioned to a virtual telemedicine format. Clinical assessment by local Ophthalmologists and Rheumatologist, as well as medical records and multi-modal imaging, were conveyed through internet-based video communication to the offsite uveitis specialist. A total of 34 patients were reviewed during the two virtual clinics (6 new patients and 28 review patients). Five patients had an escalation of treatment (2 increased doses of IMT, 2 commenced biologics, 1 dexamethasone implant prior to planned cataract surgery). Three patients underwent a reduction in treatment during the virtual clinics.

Discussion

Uveitis can cause significant visual morbidity particularly in the working age group. This is the first study to investigate the patterns of uveitis in a Tasmanian population, highlighting differences with mainland Australia. The geographic isolation of Tasmania requires a plane flight or ferry to mainland Australia. (9) Demographically, Tasmania has a female predominance (61%), a low rate of ethnic diversity (92% of patients identifying as Caucasian) and lower rates of immigration compared to mainland Australia. The Royal Hobart Hospital Uveitis Clinic team involves a visiting uveitis specialist from Sydney, several local ophthalmologists, a local rheumatologist, ophthalmology trainees, nurses,

orthoptists and administrative staff. Referrals are received from across the state and triaged via webinar prior to each clinic which occurs 3-4 times each year. The multidisciplinary clinic allows multiple specialist reviews and consensus management decisions in a single visit.

Predictably, the most common uveitis phenotype seen in this sub-specialist clinic was posterior uveitis, as these patients are at risk of significant vision loss and often require systemic therapy. The most common aetiology was idiopathic, followed by inflammatory then infectious. The frequency of idiopathic uveitis (54%) was higher than that seen in the Sydney study, but lower than that in the Melbourne study. (7, 8). The most common identifiable systemic inflammatory disorder was sarcoidosis, followed by seronegative spondyloarthritis and two patients with HLA-B27 associated uveitis without systemic disease. Other studies have shown HLA-B27 is the most common systemic association in Western countries. (1, 7, 8) Toxoplasmosis has been identified to be the most common cause of posterior infectious uveitis in the Western population. (1, 7, 8) There were no cases of toxoplasmosis and lower numbers of B27 related uveitis than expected seen in the Hobart clinic, which likely reflects the inherent referral bias of this study as such patients are adequately managed in the community and did not require tertiary input.

In this study, dose-limiting corticosteroid side effects were the most common reason for commencing steroid-sparing immunosuppression. Corticosteroid side effects were seen in 50% of patients, most commonly weight gain and worsening glycaemic control. Patients treated with IMT showed lower rates of side-effects with only two significant adverse events, namely hypogammaglobulinaemia and flu-like illness. The frequent corticosteroid complications are best minimised by management in a multi-disciplinary clinic with experienced physicians. Non-uveitis trained ophthalmologists often do not initiate and do not have the expertise to manage systemic immunosuppression monitoring. (10)

Although patients requiring systemic IMT often have more severe or aggressive uveitis, the rates of active inflammation and relapse in these patients were no greater than in those not requiring systemic immunosuppression. Further, visual acuity stabilised once IMT was introduced, with the number of eyes with logMAR of 0.30 or worse reducing from 30.3% to 26.1%. Patients who had poor visual outcomes (LogMAR ³ 1.0, 6/60 or worse) developed irreversible vision loss early in their disease course. Overall, the Hobart clinic results support the safety and efficacy of IMT in line with the VISUAL studies. (18)

As seen in the current study, present-day treat to target IMT using of biologics and conventional systemic immunosuppressive drugs has considerably reduced ocular and systemic morbidity (10) Visual loss in uveitis most commonly results from cystoid macular oedema or lens opacity. (2, 19) In studies from

tertiary uveitis referral centres in 1996 & 2004, significant visual loss (defined as £ 6/18 Snellen visual acuity in at least one eye) was found in 70%, while 38% of their patients ended with 6/60 or worse. (19) Bilateral disease was a predictor of poorer outcomes. The highest rates of visual loss was in pan-uveitis (84%) followed by posterior uveitis (64%). (2) In the current study, although 68% had bilateral uveitis and 49% had posterior or pan-uveitis, only 7% of our patients developed severe visual loss (BCVA £ 6/60).

The management of complex uveitis patients in an area with limited subspecialist uveitis expertise like Tasmania is a challenge that is best managed by developing a well-functioning multi-disciplinary team that can function not only in a conventional clinic setting but can also function remotely via telehealth when required. (3) During the COVID-19 pandemic, onsite clinical assessment by local specialists combined with internet transmission of multi-modal imaging and web-based video-communication software enabled high standard patient care to be maintained. This clinic model and the potential for off-site input from subspecialists may be adaptable to other communities with limited uveitis or other subspeciality resources elsewhere in Australia. This has become more relevant during the COVID-19 pandemic, where ongoing travel restrictions may adversely affect patient care and outcomes if feasible alternatives are lacking.

There are many limitations and biases inherent in a retrospective study such as this study. The ascertainment and referral bias have been discussed earlier. The bias and limited patient numbers underestimates the prevalence and pattern of uveitis within the Tasmanian population. (4, 7) Children were excluded from the study population. Nonetheless, this study provides real world clinical data on the phenotypes and causes of severe uveitis, as well as data on the visual outcomes of patients with vision threatening uveitis.

Conclusion

Despite differing demographics, the disease pattern and spectrum is similar to that seen in the rest of Australia and has been managed to achieve similar outcomes to those seen nationally and internationally. This study provides evidence of the efficacy and safety of systemic immunotherapy in regional populations with the support of a multi-disciplinary team. The study further demonstrates that telemedicine is an effective medium for uveitis outreach to areas without a uveitis sub-specialist, which is invaluable in these times of the coronavirus pandemic.

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Declarations

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Figures

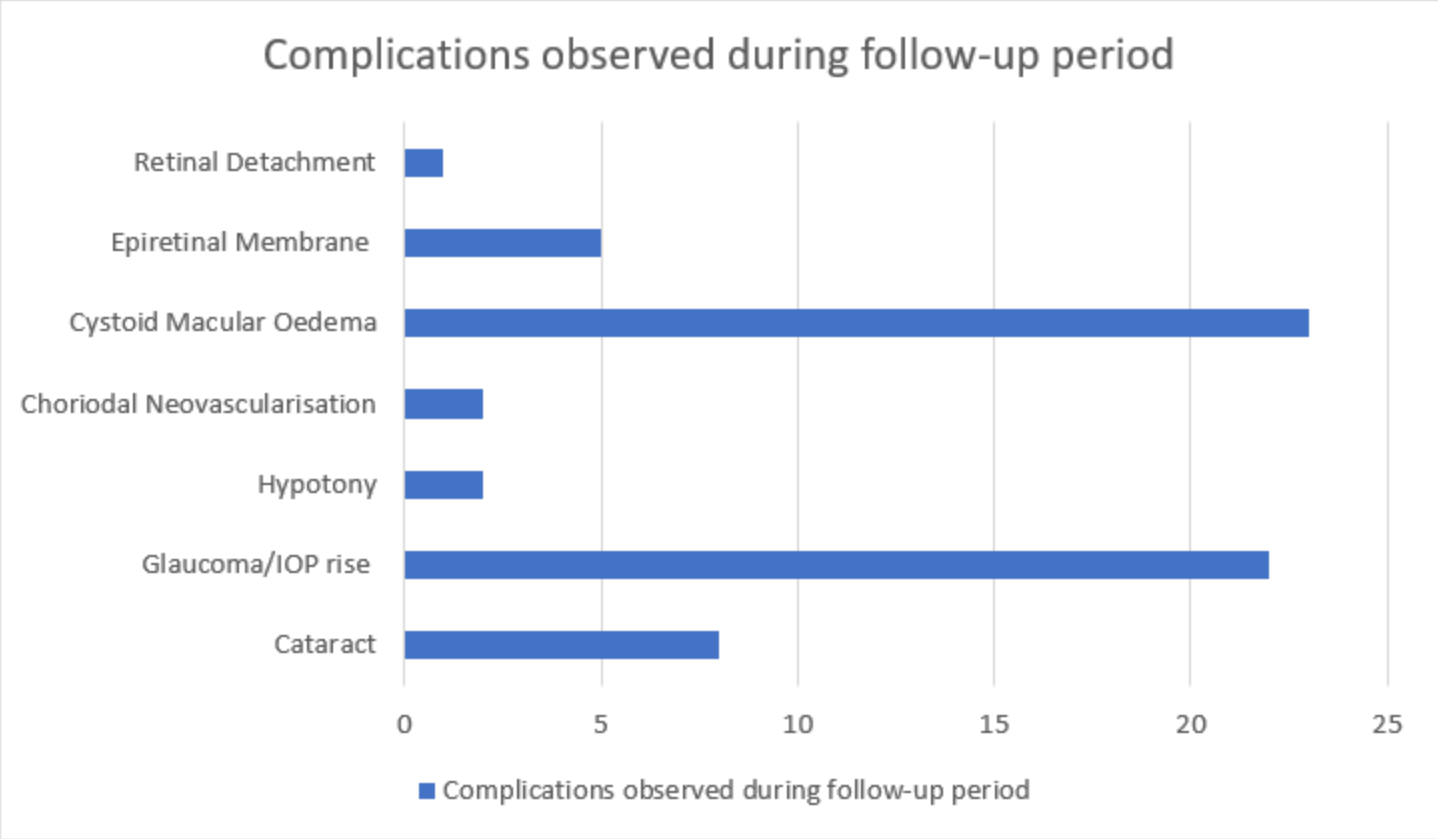

Figure 1

Complications during the period of observations (per patient analysis)