Paediatric Non-Infectious Uveitis in Cape Town, South Africa:
A Retrospective Review of Disease Characteristics and Outcomes on Immunomodulating Treatment

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ABSTRACT

Background

Non-infectious uveitis is a well-reported cause of blindness in more developed countries, however data from sub-Saharan Africa is lacking. Here we aim to describe the diseases associated with non-infectious uveitis and the impact of currently available treatment in this setting.

Methods

A retrospective observational analysis of children with non-infectious uveitis from January 2010 to December 2017, attending the tertiary paediatric rheumatology and ophthalmology referral units in Cape Town was conducted. Statistical analysis utilizing STATA13 software was performed with p < 0.05 considered significant.

Results

Twenty-nine children were identified: median age at first visit of 74 months (IQR 49–86 months), female to male ratio of 0.9:1, predominantly of mixed race (72.4%).

Juvenile idiopathic arthritis associated uveitis (JIAU) (48.3%) was the most frequent diagnosis. All children with JIAU had chronic anterior uveitis and 3 (21.4%) presented with uveitis before arthritis. There were no differences between children with uveitis and those with arthritis only, for gender (p = 0.68) and race (p = 0.58) but significantly, children with uveitis presented at an overall younger age (p = 0.008), with antinuclear antibody positive (p < 0.001) oligo-articular JIA (p = 0.01). Older age appeared to be protective (p = 0.01 OR1.0 CI 0.6-1.7).

Children with idiopathic uveitis (41.4%) were predominantly male (66.6%), of mixed race (75%), with chronic anterior uveitis (41.7%) and presented with cataracts (100%).
Less commonly, sarcoidosis (6.9%) and Behcet’s disease (3.5%) were diagnosed.

55.2% had complications at presentation, predominantly cataracts (87.5%). 19 children (65.5%) had inactive disease at 12 months from diagnosis. Remission, as assessed at the last clinical visit was achieved in 58.6% on standard initial therapy and in 75% of those on tumour necrosis factor inhibitors. Surgery was needed in 41.4%, primarily in the idiopathic group. Visual acuity improved or was maintained on treatment.

Conclusion

The spectrum and characteristics of immune-mediated non-infectious uveitis are comparable to that reported in more developed countries. Current practice detects children with potentially sight-threatening disease and access to tumour necrosis factor inhibitors has improved outcomes in refractory cases.

KEYWORDS

Non-infectious uveitis children juvenile idiopathic arthritis sub-Saharan Africa
Background

Uveitis broadly describes inflammation of the iris, choroid and retina, occurring when the blood-aqueous and blood-retinal barrier is disrupted by infectious or non-infectious triggers. An important cause of 16–25% of blindness worldwide, the estimated paediatric prevalence of 28:100 000, is at least 4 times lower than in adults (1). However, the sight-threatening consequences due to late presentation and aggressive disease are far-reaching in children, particularly in developing countries where employment opportunities for the visually impaired are limited (2).

Epidemiology studies highlight the paucity of data from Africa and other developing countries, noting potential differences in the prevalence and demographics of underlying aetiologies as well as in outcomes (1,3). Sub-Saharan African countries (SSA) tend to under report uveitis in the context of surveys or studies on blindness, compared to other regions (4-7). In general, active uveitis resulting in visual loss tends to be documented and outcomes including cataracts and glaucoma are recorded, as in South African statistics (8). Additionally, studies predominantly describe adult populations and infectious diseases, where 30 – 50% are caused by herpes, toxoplasmosis, tuberculosis, cytomegalovirus and its association with human immunodeficiency virus (HIV), syphilis and parasites (9-12). Post-streptococcal syndrome and HIV-associated uveitis have also recently been described in children (13-15). Idiopathic uveitis, where an underlying systemic cause cannot be found even when diagnostic ocular paracentesis may be utilized, frequently presents with complications and still accounts for up to 50% of uveitis populations seen at referral centres (16,17,18).

The prevalence of paediatric immune-mediated systemic diseases and the associated uveitis, varies by underlying disease, disease subtype, as well as geographically (23-26).
Notably BD is reported more frequently from countries around the Mediterranean basin and the Far East (1). In JIA, where the highest prevalence is seen in European and western countries, up to 20% of chronic anterior uveitis occurs in the oligo-articular subtype in young girls under 7 years old of Caucasian race, who are ANA positive. Associations with race as a predictor of more aggressive disease and poorer outcomes has been described, although research in this area is ongoing. Acute anterior uveitis may also be seen in enthesitis-related arthritis and psoriatic JIA, as well as in other HLA B27 associated diseases (27-31). The limited data for immune-mediated uveitis in SSA children, describe the association with juvenile idiopathic arthritis (JIA) (19-22).

The potential risk of amblyopia and poor long-term outcomes secondary to persistent disease activity and prolonged corticosteroid treatment in children is recognized. The standard uveitis nomenclature (SUN) working group classification and screening guidelines, though not formally validated in children, has improved cross-study comparisons. This has aided monitoring of treatment responses and decisions to escalate therapy (32,33) further elaborated in recent management guidelines (34-45)

Understanding the underlying causes of non-infectious, immune-mediated uveitis is essential for appropriate management and to improve overall visual outcomes. However, to date there are no studies reviewing the impact of non-infectious uveitis per se, in children from SSA.

Aim

Here we aim to describe the disease characteristics and outcomes on immunomodulatory treatment, of children with non-infectious uveitis managed at a tertiary paediatric referral center in Cape Town, South Africa.
Methods

Study design

A retrospective case file review of all children ≤16 years managed for non-infectious uveitis by the paediatric ophthalmology and rheumatology units in Cape Town from 1 January 2010 to 31 December 2017 was conducted.

Setting and population

The paediatric rheumatology and ophthalmology tertiary referral units in Cape Town are based at Groote Schuur and Red Cross Children’s Hospitals. These hospitals are the main tertiary referral centers for the Western Cape as well as other provinces in South Africa, where these paediatric services may be minimal or absent. The Western Cape population numbers around 6.2 million and children <15 years constitute 26%. Statistically, the racial profile of the Western Cape region reflects 47.5% people of mixed race and differs from the rest of South Africa, where the black African race group is more common (46). For the purposes of this study, mixed race refers to everyone not identifying themselves as either black African or Caucasian. Race is considered here, as associations with potentially higher risk and poorer outcomes have been described (28,30).

Data collection

1. Children were identified from a review of paediatric rheumatology (PR) and ophthalmology case files which were correlated with clinic attendance books and confirmed on the hospital electronic booking system.

2. Data of patients identified with non-infectious uveitis included
   - Demographics: age, gender, race (self-reported)
   - Clinical presentation
• Date of first presentation, anatomical location of uveitis, visual acuity, (VA) and complications.

• For uniformity, VA was converted from the recorded Snellen (feet, meters or decimal) annotation to the log of the minimal angle of resolution (LogMAR), based on the conversion by Schulze et al (47).

  o Disease characteristics and laboratory investigations
  o Data of children with JIA additionally included JIA subtype, time to uveitis diagnosis and whether JIA remission was achieved on treatment.

Disease definitions

  o **JIA**: as per International League of Associations for Rheumatology criteria (48)
  o **Idiopathic uveitis**: after exclusion of infective and other immune mediated diseases by clinical assessment and laboratory tests including but not limited to:

    • Toxocara and toxoplasma serology, HIV Elisa or polymerase chain reaction (PCR), ANA, anti-double stranded DNA, anti-streptolysin O (ASO) and, anti-deoxyribonuclease B (Anti-DNase B) titres, serum angiotensin converting enzyme, Treponema Pallidum Haemagglutination test and/or Venereal Disease Research Laboratory test, urine dipstix.

    • Ebstein Barr Virus, cytomegalovirus (CMV) and Lyme disease (not endemic in the Western Cape region of South Africa) serology are not routinely requested but may be
Sarcoidosis: Clinical presentation, histology +/- raised serum angiotensin levels

Behcet’s disease: Clinical diagnosis based on Paediatric BD criteria 2015 (49)

Treatment modalities

- Standard Initial Treatment includes corticosteroids (topical and/or systemic) and Methotrexate 10–20mg/m² (maximum dose 20mg orally or 25mg subcutaneously)
- Additional disease modifying anti-rheumatic drug therapy includes azathioprine (1–3mg/kg) and mycophenolate mofetil (250–500mg/m² bd)
- Biologics include TNFi Infliximab 6–10mg/kg iv infusion monthly (after loading) and Adalimumab 20–40mg subcutaneously every second week

Outcome

- Primary Outcome was considered as clinically inactive disease on treatment.
- Ophthalmology assessments were performed at weekly to 3-monthly intervals depending on severity of disease. Disease activity at 12 months and at the last clinical visit was evaluated. Treatment outcome was recorded as at the last clinical visit.
- Anterior chamber disease was assessed utilising the Standard Uveitis Nomenclature (SUN) criteria (33)
  - Response to treatment defined by the SUN criteria as a two-step decrease in inflammation or decrease to Grade 0
  - Active disease defined by the SUN criteria as ≥ Grade 1 (6–15 cells/slitr lamp field and faint anterior chamber flare)
  - Inactive disease defined by the SUN criteria as Grade 0 (<1...
cell/slit lamp field and no anterior chamber flare)

- Remission was defined as ≥ 3 months of inactive disease on treatment
- Secondary Outcome was considered as improvement in visual acuity

Exclusion criteria

- Children managed for < 3 months or were lost to follow-up
- Children with infectious uveitis

Statistical analysis

Statistical analysis was performed utilising STATA13 software.

The frequencies of categorical variables were recorded, and descriptive statistics employed to determine measures of central tendency. Chi squared (or Fisher exact tests if frequencies were <5) and t-tests (or Wilcoxon sum rank tests for non-parametric data) for comparisons between groups, were used as appropriate to evaluate associations with p < 0.05 considered significant. Odds ratios for statistically significant variables were calculated to evaluate associated risk. Cox regression model was used to assess time to inactive disease and time to uveitis from JIA diagnosis.

Results

Thirty-four children were referred for management of uveitis. One with toxocariasis, 2 with post-streptococcal syndrome and 2 with HIV-associated uveitis were excluded, resulting in 29 children meeting inclusion criteria. The overall group had a 0.9:1 female to male ratio, median age at first visit of 74 months (IQR 49–86 months) and were predominantly of mixed race (72.4%). Bilateral (75.9%), chronic anterior uveitis (72.4%) was most frequent. Complications
at presentation (55.2%) were predominantly cataracts (87.5%) and there was an overall clinical improvement in visual acuity (VA) (Table 1). The median time to inactive disease was 7 months (IQR 6-15 months) (Fig. 1.a.). There was no statistical difference ($p = 0.28$) between JIAU and idiopathic uveitis for overall time to inactive disease (Fig. 1.b.). Nineteen (65.5%) children had inactive disease at 12 months after commencement of treatment, including 3 who had been started on TNFi subsequent to failure of earlier therapy (Fig. 1.c.). Twenty-seven (93.1%) children achieved remission, 1 (3.5%) had clinically inactive disease for <3 months and 1 (3.5%) had ongoing active disease at the last clinical visit (Table 2).
JIAU (48.3%) was the most common diagnosis in a female to male ratio of 1:0.75, at a median age of 55 months (IQR 34–86 months), in children predominantly of mixed race (71.4%), with chronic anterior uveitis (100%).

Further analysis in relation to the overall JIA cohort managed during the study period was undertaken (Table 3). 229 patients were assessed for JIA of which 12 were excluded according to ILAR criteria. 217 were evaluated, with a consequent JIAU clinic prevalence of 6.5%. Three children had uveitis for 12, 9 and 4 months prior to the diagnosis of JIA, the majority developed uveitis within a year (Figure 1.d.). Comparisons for gender (p = 0.68) and race (p = 0.58) were not statistically significant. No children older than 144 months were diagnosed (p = 0.01) with uveitis but young age ≤84 months (p = 0.01), oligo-JIA subtype (p = 0.01) and positive ANA (p < 0.001) were significant. Univariate analysis showed odds ratios (OR) for possible risk factors associated with uveitis as oligo-articular subtype (OR 4.45 CI 1.35–14.7) and positive ANA (OR 33.3, CI 6.83–162.09). Older age at diagnosis, 145–192 months (OR1.0 CI 0.6– 1.7) appeared to be protective. Reduced VA at presentation was mostly due to cataracts (71.4%).

Seven (50%) children had complications with no statistical difference between those diagnosed pre-JIA and on screening (p = 0.28). At 12 months from diagnosis, 9 (64.3%) children on standard initial treatment and one on TNFi had inactive disease. 57.1% achieved uveitis remission on standard initial treatment, 14.3% on additional DMARDs and the refractory 28.6% on TNFi treatment. Three were originally commenced on Infliximab and 2 were switched to Adalimumab due to lack of efficacy. Of these, one was diagnosed 12 months before arthritis. All children in the Adalimumab group achieved remission. Three children had surgery including one pars planar vitrectomy/ lensectomy.
Idiopathic uveitis (41.4%) was the next frequent diagnosis, presenting in males (66.6%), median age 76.5 months (IQR 49–156 months) of mixed race (75%). Both eyes were affected in 66.6% with chronic anterior uveitis (50%). All children presented with cataracts with median VA LogMAR 0.95 (0.55–2.45). Four children (33.3%) had inactive disease on standard initial treatment and 2 (16.7%) on TNFi at 12 months. Remission was achieved in 50% on standard initial treatment, 16.6% on Infliximab and 33.3% on Adalimumab as assessed at the last clinical visit. 75% of children required surgery. One child did not respond to therapy, was ANA positive and needed evisceration of one eye due to painful glaucoma. The overall improvement in VA for the remaining children was statistically significant (p = 0.001).

Sarcoidosis (6.9%) was diagnosed in 2 females. One presented at 49 months, was of mixed race and had posterior uveitis. The other, presented at 156 months, was black African and presented with acute anterior uveitis. Both had bilateral uveitis and no complications at presentation. Both had inactive disease by 12 months, achieved remission on standard initial therapy and had preserved vision.

The 120-month old male of mixed race with BD presented with unilateral chronic anterior uveitis, had no complications and responded to standard therapy within 3 months.

**Table 1: Comparison of JIA arthritis only and JIAU**

**Discussion**

Non-infectious immune-mediated uveitis remains an important cause of ocular morbidity in children and despite some advances in the understanding of the underlying pathophysiology, sight-threatening complications are still frequently reported (50,51). The dearth of literature from Africa and other developing countries, reinforces the perception that these diseases are rare or non-existent in children from this setting.
Although this assumption has recently been challenged (52-54), advocacy for treatment strategies deemed too expensive, regardless of proven efficacy elsewhere, is still hindered.

Here, we have shown that the spectrum and disease characteristics associated with non-infectious uveitis are comparable to that of developed countries, yet dissimilar to reports from North Africa, where BD (23,24) is more common. Importantly, 54.5% of our cohort presented with easily identifiable cataracts and posterior synechiae, attesting to significant delays in diagnosis.

**Juvenile Idiopathic Arthritis**

Comparison with two studies from developed countries (Table 4), the large multicentre Canadian Research in Arthritis in Canadian Children emphasizing Outcomes (ReaCCH-out) study cohort and a single centre Atlanta study (27,55), shows similarities in median age of JIA presentation, relative frequencies of poly-articular RF negative JIA subtype and ANA positivity. However, an older age at JIAU presentation and a lower frequency of oligo-articular JIA is seen in our cohort. The prevalence of JIAU here (6.5%) is also lower than reported in those studies (8.5% and 18%), as well as other developed country descriptions of up to 20% (31). However, our clinic prevalence seems to be in keeping with the few published studies from SSA (15, 20, 21, 56).

The chronic anterior uveitis, presenting at a younger mean age, significantly in the ≤ 84-month age group (p = 0.001), also fits developed country descriptions. Potentially increased risk associated with female gender, Caucasian race, oligo-arthritis subtype and positive ANA, need further prospective studies to elucidate the role of these variables in our cohort. The majority of children with JIAU were ANA positive (78.6%). However, this is in contrast to previous studies from South Africa, where children with uveitis had...
polyarthritis and were ANA negative. The differences could possibly be ascribed to race as the children in our study were predominantly of mixed race, compared to the other South African studies, where race was reported as black African (15,19).

A high percentage (21.4%), compared to the 3–7% generally described (57), developed uveitis before arthritis was diagnosed. Eleven were detected on screening and half presented with complications, 71.4% of which were cataracts. This raises further concerns of diagnostic delays in our setting. Notably, treatment was escalated to manage uveitis as arthritis was in remission.

**Idiopathic**

In our study, idiopathic uveitis (36.3%) had a relatively lower frequency, reflecting the small number of referred patients. As in other descriptions, refractory disease (58%) with chronic anterior and panuveitis, complications and the need for surgery (75%) is noted (58,59). Similar severity and poorer outcome were reported in black South African children in a historical study by Freedman et al (60), prior to the availability of TNFi. Here, children with refractory disease showed significant improvement in disease activity and VA on TNFi treatment.

**Sarcoidosis**

Sarcoidosis is rare in children, may affect the uveal tract and while African American females have a ten times increased risk for the development of sarcoidosis, information for African children is lacking. In our cohort, both cases were female. The early onset case was diagnosed on bone marrow biopsy. NOD2 testing was not available at the time. The second case, a black African female presented with late onset sarcoidosis diagnosed by clinical features and persistently raised serum angiotensin converting enzyme levels.
Biopsy results could not be found for this case. Both responded well to systemic corticosteroid treatment and methotrexate. TNFi except etanercept, are used in refractory sarcoid uveitis as a second or third line agent. In limited data, most cases show an overall improvement in disease activity, although follow up times are relatively short. Escalation to TNFi was not needed here (61-64).

**Behcet’s disease**

North African studies in adults, describe a high prevalence of BD (6.25–13%) compared to North American and other European populations (0–0.7%) and case series from SSA, highlight severe skin and ocular manifestations (24,25,65). Paediatric BD, however, is rarely reported from countries outside the geographical area of the former silk route. The case of clinical BD in our cohort partially fulfilled paediatric BD 2015 criteria (49). HLAB51 testing was not done and as far as was known, he was not of Mediterranean nor Eastern descent. In contrast to case series from North Africa, (25,66,67), our patient had few recurrences, no complications and near normal vision at the last clinical assessment.

Other immune mediated diseases including Vogt Koyanagi Harada syndrome, tubulointerstitial nephritis associated uveitis, uveitis with SLE and other autoinflammatory disorders- were not represented in this study.

**Treatment outcome**

Overall, remission on standard initial uveitis treatment (58.6%) endorses its use as first line therapy in our resource limited setting. Azathioprine and MMF were used less frequently due to gastrointestinal adverse effects and perceived lower efficacy. Neither cyclosporine nor intraocular corticosteroid injections were used in our cohort, as low
evidence and side effect profile in young children were considered to outweigh the benefit (36,45,68,69). TNFi were only used in refractory cases due to availability and cost and showed good efficacy. Adalimumab was used in conjunction with methotrexate in all our patients and while outcomes appeared better than that reported in meta-analyses of previous studies (26,38), this may be due to small sample size. Further research into the use of these agents in our setting is needed.
Selection bias

Not all children with immune-mediated uveitis may have been referred, thus community prevalence is not reflected. Children with JIA are routinely assessed for uveitis screening and may be over-represented in this sample.

Limitations

This retrospective case file review was dependent on the availability and accuracy of the medical records reviewed. The small sample size limits inferences that can be made from these results.

Conclusion

The spectrum of immune mediated non-infectious uveitis is comparable to that reported in developed countries. While current practice detects children with potentially sight-threatening disease, delays in diagnosis are a concern. Here, access to tumour necrosis factor inhibitors has improved outcomes in refractory cases. Further prospective studies to establish the role of associated risk factors, particularly in JIAU and the efficacy of biologics are needed.
|   | Abbreviations                                                                 |
|---|-----------------------------------------------------------------------------|
| 18 | **ANA** Anti-Nuclear Antibody                                               |
| 451| **ANA HEp2** Anti-Nuclear Antibody Human Epithelial cell indirect immuno-    |
| 453| fluorescence test                                                            |
| 454| **AntiDNAse B** Anti-Deoxyribonuclease B                                      |
| 455| **ASOT** Anti-Streptolysin O titres                                          |
| 456| **ARVs** Antiretroviral therapy                                              |
| 457| **BD** Behcet’s Disease                                                      |
| 458| **CMV** Cytomegalovirus                                                      |
| 459| **DMARDs** Disease Modifying Anti- Rheumatic Drugs                            |
| 460| **ERA** Enthesitis Related Arthritis                                         |
| 461| **FHI** Fuch’s Heterochromic Iridocyclitis                                    |
| 462| **HIV** Human Immunodeficiency Virus                                         |
| 463| **HLAB27** Human Leukocyte Antigen B27                                       |
| 464| **IL** Interleukin                                                           |
| 465| **ILAR** International League of Associations for Rheumatology             |
| 466| **IQR** Interquartile Range                                                  |
| 467| **ISG** International Study Group                                            |
| 468| **JIA** Juvenile Idiopathic Arthritis                                        |
| 469| **JIAU** Juvenile Idiopathic Arthritis associated Uveitis                    |
| 470| **LogMAR** Log of the minimal angle of resolution                            |
| 471| **MMF** Mycophenolate Mofetil                                               |
| 472| **ReaCCH-out** Research in Arthritis in Canadian Children emphasizing Outcomes |
| 473 | RF | Rheumatoid Factor |
|-----|----|------------------|
| 474 | SSA | sub-Saharan Africa |
| 475 | SUN | Standard Uveitis Nomenclature |
| 476 | TB | Tuberculosis |
| 477 | TINU | Tubulo-Interstitial Nephritis associated Uveitis |
| 478 | TNFi | Tumour Necrosis Factor Inhibitors |
| 479 | VA | Visual Acuity |
| 480 | VKH | Vogt Koyonagi Harada Syndrome |
| 481 |    |                  |
Declarations

Ethics approval
Ethics approval for data collection was obtained from the university of Cape Town human research ethics committee, HREC no: 692/2018

Consent for publication
Not applicable

Availability of data and material
Privacy and confidentiality
Data was anonymised and collected in accordance with the principles of Helsinki and GCP.

Data is stored in a password-protected database to which only the PI and sub-investigator has access.

The data is available from the corresponding authors upon reasonable request and is stored as part of the paediatric rheumatology database and repository at the University of Cape Town.

Competing interests
WS has received sponsorships from Pfizer and Abbvie for conference attendance
CS has received conference attendance sponsorships and speaker fees from Abbvie, Pfizer and Roche
CT and NB declare no competing interests

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Authors Contributions
WS conceptualised the study, drafted the protocol, performed data collection, statistical analysis and prepared the manuscript.

CT and NB provided diagnostic and management expertise.

CS supervised the study, reviewed the protocol, provided input and management expertise.

All authors reviewed the final manuscript.

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Fig. 1.c: Inactive disease at 12 months: n=19; Standard initial treatment n=16: JIA(9)
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  JIA(1)

Fig.1.d: Time to Uveitis from JIA diagnosis: n=11 Two children were diagnosed at first screen, Eight children developed uveitis within 1 year of JIA diagnosis detected at routine screening, one child developed uveitis 4 years after initial JIA diagnosis, detected at routine screening. Three children had uveitis before JIA diagnosis and were excluded from the model.