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

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Declaration

I, *Waheba Slamang*, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree at this or any other university.

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PROTOCOL

Introduction

Globally, nineteen million children under 15 years are estimated to be visually impaired. The socioeconomic impact of sight threatening illnesses cannot be ignored, since those most affected live in low income countries, where employment opportunities are few and up to 90% who reach adulthood, are unemployed (1).

In 2011, sight disabilities constituted 32% of all disabilities reported in South Africa, of which children older than 5 years comprised 11%. Refractive errors were the most common cause cited but apart from retinopathy of prematurity, the outcome of disease processes (cataracts, raised intra-ocular pressure and corneal scarring) was described (2).

Understanding the underlying causes of visual impairment is essential for prevention, treatment and the improvement of overall visual outcomes.

Uveitis is an important cause of blindness, with children comprising 5–10% of most tertiary uveitis clinic populations (3). Involving inflammation of the iris, choroid and retina, sight threatening complications may result from unrecognized persistent disease activity or the side effects of ongoing treatment. This is particularly devastating in children and may result in severe vision loss in up to 50% of cases (4, 5).

Uveitis aetiology may be classified as either infectious, post infectious or non-infectious, while masquerade syndromes are essential considerations in the differential diagnosis.

The commonly described infectious entities in predominantly adult studies from the developing world include herpes, toxoplasmosis, tuberculosis (TB), cytomegalovirus (CMV) and its association with human immunodeficiency virus (HIV), syphilis and parasites. These comprise around 30% - 50% of all cases described and may present as an acute, painful red eye and with visual disturbance (6).

There is a paucity of literature describing uveitis in children from South Africa, though historically, a study from 1974 showed unknown, idiopathic anterior uveitis to be more common in Black children (7). More recently, HIV as a cause of uveitis, in a case series of 7 children with HIV associated arthritis (8) and streptococcal infection presenting as a post-infectious immune mediated syndrome (9), has been described. Reviews in the adult population, showed infectious aetiology to account for almost 50% of cases compared to 18.2% for non-infectious uveitis (10,11). To date, there are no recent studies reviewing non-infectious uveitis per se, in children from Sub-Saharan Africa.

In developed countries, however, infectious causes contribute significantly less (between 11-20%) to the total uveitis burden, with TB and syphilis accounting for less than 3% (6). Here, non-infectious uveitis is more common and is associated with specific immune mediated disease including juvenile idiopathic arthritis (JIA), HLA-B27 associated diseases, sarcoidosis and Behcet's among others. Additionally, idiopathic uveitis is considered an almost equal contributor in children. Less is known about the associated risk factors for idiopathic uveitis, a diagnosis based on exclusion, but preceding undetected infection may be a trigger (3).

In childhood, JIA an umbrella term for a heterogenous group of disorders, is considered the most common immune mediated disease, with a prevalence rate of 1-4:1000. Uveitis is a well described extra articular manifestation (12) and is the main focus of this review.

The pathogenesis of juvenile idiopathic arthritis associated uveitis (JIA-U) has remained elusive, though a shared antigen with synovial tissue is postulated. Research is predominantly in animal models, mostly due to the lack of adequate human iridectomy and aqueous humour specimens. Anti-nuclear antibody (ANA) positivity appears to be the most consistent feature and while disease activity is attributed to an imbalance between t-regulatory and t-effector cells, research into clarification of the disease pathway is ongoing (13).

The use of the International League of Associations for Rheumatology (ILAR) classification of JIA in conjunction with the Standard Uveitis Nomenclature (SUN) criteria proposed in 2005, has allowed comparisons of presentation, visual complications and outcomes between studies (14, 15).

Current literature describes JIA-U as occurring in about 20% of children with JIA, predominantly in girls of European descent, who present with the oligo-subtype and are ANA positive. JIA-U also occurs in the poly-articular JIA rheumatoid factor (RF) negative subtype. In these subtypes, children often present late, with an asymptomatic chronic insidious onset and more severe, complicated disease than their adult counterparts. An acute anterior uveitis may also be seen in psoriatic JIA and the HLA-B27 associated enthesitis related arthritis (ERA) subtype (16,17).

Children may present with uveitis as the first sign of JIA with no evidence of arthritis at initial diagnosis. JIA may subsequently develop, an indication that ongoing joint assessment is necessary. Alternatively, children could present with JIA and uveitis found incidentally on screening. A mean time to onset of JIA-U of 1.8 years has been described despite concurrent treatment for JIA and a second peak of uveitis activity is also thought to occur around puberty, which necessitates ongoing screening (18).

While the oligo-articular arthritis association with JIA-U is well described, female preponderance and ANA positivity have been questioned (19). Young age also appears to be a risk factor for the development of uveitis in girls but less so in boys. The role of ethnicity on poor visual outcome is uncertain, though it is still suggested that girls of European descent are at higher risk. Additional risk factors for vision loss include the presence of uveitis before arthritis, young age at onset, complications at presentation, short duration between arthritis onset and uveitis, multiple episodes and male sex (14, 20).

Screening algorithms based on the SUN criteria have been developed for JIA-U, taking this into account (21).

Treatment strategies for uveitis have changed since the 1990's. Recent consensus treatment guidelines for JIA-U and idiopathic uveitis in children, advocate the use of biologic therapies to mitigate the side effects of steroids. To achieve optimal control as quickly as possible and improve long-term visual outcomes, these guidelines suggest the use of specific tumour necrosis factor inhibitor treatment, following failure of methotrexate to achieve disease remission within 3 months (21-23).

Despite this, children with JIA-U have shown significant ocular morbidity and up to 50% have visual impairment or blindness of at least one eye and require surgery during the course of the disease. This may be due to active uveitis but also occur as a side effect of treatment. Follow up studies of children with JIA-U have shown persistent activity into adulthood requiring ongoing assessment and treatment (24, 25). The few studies from low and middle income countries tend to support the view that children with JIA have increased morbidity and complications (26). Uncertainty remains regarding the duration of treatment but a minimum of 2 years of remission is advocated before withdrawal is considered (27, 28).

Uveitis associated with other immune mediated diseases are far less common. Behcet's disease is more often seen along the former silk route with a low paediatric prevalence estimated between 0.03 and 0.2 per 1000. Uveitis is listed as one of six criteria for diagnosing Behcet's (though retinal vasculitis is more common) and may be the first presentation in up to 10% of cases, predominantly in boys over 10 years old and can occur up to two years after the initial diagnosis (29-31). Studies from North Africa and the Middle East therefore show a slightly different immune mediated uveitis spectrum to their western counterparts. Behcet's is more commonly described, JIA and sarcoidosis less so (32,33) while idiopathic uveitis comprised up to 50% of studies from elsewhere in Africa (32,34).

While 1 – 3% of paediatric uveitis referrals are due to sarcoidosis, the specific prevalence is not known. Sarcoidosis may affect any part of the eye and the granulomatous uveitis may present with acute anterior chamber inflammation or with posterior chamber involvement. Early age of onset is associated with the familial Blau syndrome, characterised by a triad of uveitis, dermatitis and arthritis (35).

SLE associated uveitis is considered very uncommon with the prevalence estimated at around 0.47 per 1000 in adults. It is rarely reported in children but uveitis may in addition, occur as a result of medication rather than the disease process itself (36).

Other immune mediated uveitis associated with anti-neutrophil cytoplasmic antibody mediated vasculitides and Kawasaki's disease are also rare. Recent reports have considered anterior uveitis as an aid in the diagnosis of incomplete Kawasaki's disease (37,38) although uveitis is not part of the current diagnostic criteria.

These comorbidities impact further on overall treatment and long-term outcome.

Non-infectious immune mediated uveitis, particularly when associated with JIA, may thus be sight-threatening, complications arising from the underlying disease and potentially the treatment.

To our knowledge, this will be the first description of children with non-infectious uveitis, co-managed at a paediatric rheumatology service from Sub-Saharan Africa.

This study may be useful in defining associated co-morbidities, reassessing currently available screening guidelines and may be used to inform treatment strategies in our resource limited setting.

Aim

To describe the presentation, associated disease characteristics and treatment outcomes of children with non-infectious uveitis, co-managed at a tertiary paediatric rheumatology (PR) service in Cape Town

Objectives

1. To describe the overall spectrum of children co-managed with non-infectious uveitis at the PR service in Cape Town
2. To describe the presentation, disease characteristics and treatment outcomes of children with non-infectious uveitis

Methods

Study Setting and Population

The paediatric rheumatology and ophthalmology tertiary referral service in Cape Town are based at Groote Schuur and Red Cross Children's Hospitals. These hospitals are the main referral units for the Western Cape as well as other provinces in South Africa, where paediatric rheumatology services may be minimal or absent. Referred children are from a broad ethnic spectrum and varying socioeconomic circumstances.

Sample Size

An estimated sample size of 150-200 children diagnosed with JIA is expected, based on PR clinic attendance statistics

JIA-U prevalence is estimated at 10 -20% in reported literature. An estimated sample size of 15-40 children is anticipated.

Data Collection (Appendix A)

Inclusion criteria

1. Data will be extracted from case files of all patients reviewed at the paediatric rheumatology and ophthalmology service for non-infectious uveitis and JIA from 1 January 2010 to 31 December 2017.
2. Children with uveitis will be identified from a systematic review of paediatric rheumatology (PR) case files, correlated with clinic attendance books, ophthalmology clinic attendance records and confirmed on Clinicom.
3. Similarly, children with JIA will be identified from PR clinic attendance books and confirmed on Clinicom.

This will minimise missed records and allow maximum relevant data collection.

4. Data of patients identified with non-infectious uveitis will include age, gender, date of diagnosis, time to diagnosis as well as:
    - Clinical presentation: visual acuity and complications
    - Disease characteristics: associated diseases, antibody profile, anatomical location of uveitis
    - Treatment modalities utilized
    - Treatment outcome defined according to SUN (15) criteria
    - Remission defined as ≥ 3months of inactive disease on treatment
5. Data of patients with JIA will additionally include JIA subtype, time to uveitis diagnosis and whether JIA remission was achieved.

6. Primary Outcome considered as inactive disease on treatment
7. Secondary outcome considered as improvement in visual acuity

Exclusion Criteria

All children assessed at the PR service prior to 1 January 2010 to 31 December 2017, with infectious chronic uveitis will be excluded.

Those treated for less than 3 months or were lost to follow up during the study period, will be excluded from outcomes analysis.

Selection Bias

Children referred to the PR service have a high likelihood of an immune mediated disorder, which may influence the overall analysis.

Limitations

This is a retrospective case file review and will depend on the availability and accuracy of the medical records included in the study.

Patient records may be missed if clinic appointments were not booked or recorded.

Key data may therefore not be present in the case files and impact on the overall accuracy of analysis

Statistical Analysis

Statistical analysis will be done utilizing STATA13.

Descriptive statistics will be employed for categorical variables to determine measures of central tendency e.g mean, median, mode. Chi- squared or Fisher exact testing and t- tests for comparisons between groups, will be used as appropriate to evaluate associations with $p<0.05$ considered significant.

Privacy and confidentiality

Data protection and storage

Approval for data collection from Red Cross Children's Hospital and Groote Schuur Hospital was sought .

Data will be anonymised and collected in accordance with the principles of Helsinki and Good Clinical Practice.

Data will be transcribed onto a password protected electronic data sheet with identifying data removed. Data will then be stored in a password protected database to which only the PI and sub-investigator will have access.

On completion, the data will be made available for further study as part of the paediatric rheumatology database and repository.

The completed study will be submitted to the School of Paediatrics and Child Health, University of Cape Town in partial fulfilment of the MPhil Paediatric Rheumatology (sub-speciality training) and be made available for publication.

There are no conflicts of interest

This is a non-funded study.

Minor costs will be covered by the researcher.

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Chapter 1: Introduction

1.1 CONTEXT

Uveitis is an important cause of blindness worldwide and may be classified by anatomical location, histopathology or by aetiology as infectious, post infectious or non-infectious. These terms encompass a range of underlying diseases, the clinical presentation depending on which areas of the uveal tract and adjacent structures are most affected.

Non-infectious uveitis is associated with systemic immune mediated disorders including juvenile idiopathic arthritis (JIA), human leukocyte antigen (HLA) B27 associated diseases, sarcoidosis and Behcet's disease (BD) in children. Idiopathic uveitis, an isolated ocular presentation with no evidence of systemic disease is often reported, as well as Fuch's heterochromic iridocyclitis (FHI), Vogt-Koyonagi-Harada syndrome (VKH) and tubulointerstitial nephritis with associated uveitis (TINU) (1-3).

Additionally, the acknowledged management difficulties in frequently asymptomatic children and the resultant long-term morbidity and complications, underscores the need for expertise in uveitis management (4,5).

Objectives

Here, we aim to review the epidemiology, characteristics and treatment of diseases associated with non-infectious uveitis in African children.

Literature search strategy

- A literature search was performed in the MEDLINE (PUBMED), Scopus and Cochrane library databases (Appendix C)
- Search terms included: Non-infectious uveitis child Africa, epidemiology non-infectious uveitis child, non- infectious uveitis child treatment Africa, juvenile idiopathic arthritis Africa, paediatric SLE Africa
- Inclusions
    - Only articles in English with titles and abstracts deemed appropriate published up to October 2019 were considered
    - 18 articles including relevant case series, case reports and reviews were considered
- Exclusions
    - Duplicate studies due to overlapping search terms
    - Literature only relating to infectious uveitis
    - Literature where the paediatric subset was not well defined in combined adult-paediatric studies
- A narrative data synthesis was compiled

Literature Review

Epidemiology

In tertiary referral centres in developed countries, the ocular manifestations of non-infectious immune mediated diseases are well-described and infectious causes do not contribute significantly to the total uveitis burden (2). Gender may influence the type of inflammation, where a male preponderance in HLA B27 associated acute anterior uveitis is seen, although the influence of race and ethnicity needs further elucidation (5-7).

This is in contrast to Africa and other developing countries, where infectious diseases cause up to 60% of uveitis and depending on geographic location, may be due to parasites, leptospirosis, tuberculosis and herpes virus among others. Syphilis, toxoplasmosis, onchocerciasis, cytomegalovirus and its association with human immunodeficiency virus (HIV) are considered in posterior uveitis, as well as human T-cell leukaemia virus type-1 in intermediate uveitis. Panuveitis is also frequently described. Here a male preponderance is often reported and ascribed to health seeking behaviour and access. Non-infectious causes are less frequently reported, though recent data have suggested an increasing trend (1,2,8).

Disease profiles

A detailed review of the immune mediated diseases associated with non-infectious uveitis has been reported previously (9-11). Here the main focus is on JIA and the immune mediated diseases associated with uveitis described in African children.

Juvenile Idiopathic Arthritis

JIA, a heterogenous group of disorders currently classified according to the International League of Associations for Rheumatology (ILAR) criteria, is the most common immune mediated disease in children, with a prevalence of 1-4:1000 (12). Although JIA associated

uveitis (JIAU) is well researched in developed countries (13-15), the pathogenesis has remained elusive. A shared antigen with synovial tissue is postulated and disease activity attributed to an imbalance between t-regulatory and t-effector cells. Antibody production, as evidenced by ANA positivity, appears to be the most consistent feature (16,17).

Current developed country literature describes up to 20% of JIAU as an asymptomatic chronic insidious anterior uveitis, occurring more frequently in oligo-articular and poly-articular rheumatoid factor (RF) negative children. An acute anterior uveitis may be seen in psoriatic JIA and the HLA-B27 associated enthesitis related arthritis (ERA) subtype (18).

JIA and JIAU data from Africa are summarised in Table 1.

Difficulties in comparison occurred when data was not defined according to the ILAR criteria (12). However, varying frequencies of JIA subtypes, notably 7-52% oligo-articular and 7-21% RF negative poly-articular JIA, which may influence the frequencies of JIAU, are apparent. Three studies from North Africa report JIAU frequencies of 6.25% (not included in Table 1 as JIA data is not further detailed) to 19.7%, with ANA positivity of up to 50% in two. Seven JIA studies from SSA indicate JIAU frequencies of 1.5 – 12.8% but of three South African studies, only two from Kwazulu Natal reported JIAU. Also, only two studies provided details of the anatomical location of uveitis where most were chronic anterior and were correlated with ANA positivity and JIA subtype. Different to developed country studies, sub-Saharan African (SSA) children were predominantly male, were invariably ANA negative or not tested and did not have oligo-articular but polyarticular JIA. RF and HLAB27 were minimally reported, however the availability and cost of diagnostic testing is specifically mentioned by the respective authors as reasons for waiving testing (19-27, 32).

Table 1: Summary of JIA and JIAU data from Africa

	Sub Saharan Africa							**North Africa**	
Country	**South Africa (Kwazulu Natal)(19)**	**South Africa (Kwazulu Natal) (20)**	**Nigeria (Lagos) (26)**	**South Africa (Western Cape) (21)**	**Zambia (Lusaka) (22)**	**Kenya (Nairobi) (23)**	**Nigeria (24)**	**Morocco (25)**	**Egypt (Sharkia) (27)**
Year	1984	2008	2010	2011	2013	2016	2017	2013	2012
Tertiary Single/ Multicentre	Single Cohort	Single	Single	Two	Single	Single	single	Single	Single
Total N	60	97	23	78	85	68	28	30	132
JIA subtypes (%)									
Oligo	36.7	39	7	26	32.1	23.5	39.3	30	52.2
Poly RF-	26.6	30	13	14	34.6	38.2	42.8	16.7	21.2
Poly RF+	21.6	9		26.9	11.5	17.6	7.1		8.3
ERA	0	5	0	23	6.4	5.9	0	26.7	4.5
Psoriatic	0	0	0	1.3	1.3	0	0	0	0
SJIA	15	16	3	7.7	14.1	14.7	17.9	23.3	13.6
Undifferentiated	0	0	0	0	0	0	0	0	0
Uveitis (%)	8.3	4	8.7	0	12.8	1.5	7.1	13.3	19.7

HLA B27 associated diseases

HLA B27 associated uveitis is the second most common cause of uveitis in the developed world. The acute anterior uveitis is most frequently seen in young males with ankylosing spondylitis (28). However, the frequency of HLA B27 is reported as <1% in SSA and despite higher frequencies in West African populations, ankylosing spondylitis is rarely seen (29, 30). Khairallah et al reported 2.8% HLAB27 associated uveitis and one child with uveitis and Crohn's Disease from North Africa in another study, where HLAB27 was not reported (31, 32). Importantly, an increasing number of HLA B27 negative spondyloarthropathies have been seen in association with HIV from Africa. Data in SSA children is limited to two case series of children with HIV associated polyarthritis and uveitis (20, 33).

Behcet's Disease

BD disease has a high association with HLAB51, is more often seen around the Mediterranean basin, Middle and Far East and has a low paediatric prevalence estimated between 0.03 and 0.2 per 1000. Uveitis may be the first presentation in up to 10% of cases, predominantly in boys over 10 years old or may occur up to two years after the initial diagnosis (5, 34). Few adult studies from Africa and paediatric uveitis studies from North Africa, show worse disease activity and poorer outcomes (32,35-38). There are however, no reports of BD in children from SSA.

Sarcoidosis

While 1 – 3% of paediatric uveitis referrals are due to sarcoidosis, the specific prevalence is not known. Early age of onset is associated with the familial Blau syndrome and late onset with more systemic systems (39,40). Studies in adults have reported an increased risk based on ethnicity (41) however, there are no similar studies in children. A French cohort involving mostly African American and SSA immigrant children with pulmonary sarcoidosis, reported 17.1% as having ocular manifestations but

this was not further elucidated (42). There are no African studies of sarcoidosis nor associated uveitis in children, as far as we were able to ascertain.

Systemic Lupus Erythematosus (SLE)

SLE associated uveitis is very uncommon and is rarely reported in children. A large retrospective cohort study from Brazil showed 0.8% of children with uveitis, notably with higher SLE disease activity scores. However, no uveitis was reported in two significant paediatric case series from South Africa and one from Nigeria (43-46, 86).

Vogt Koyanagi Harada (VKH)

VKH syndrome, is a rare T-helper cell 1 lymphocyte mediated anti-melanocyte disease affecting Asian, Middle Eastern, Hispanic and Native Americans and is rarely reported from Africa. The global incidence of VKH varies from 1-7% and usually presents in the second to fifth decades, although children may also be affected. Only one child with VKH has been reported in a North African study (31).

Post streptococcal syndrome

Post infectious streptococcal immune mediated uveitis has historically been described by Cokingtin and Han and a large case series from South Africa once again highlighted the importance of this disease. A case series from Northern Ireland reported the successful use of tumour necrosis factor inhibitor treatment for refractory cases but similar data from Africa has not been published (47- 49).

Other

Uveitis presenting in TINU (associated with common infections and medication) and FHI (recently associated with the rubella virus), comprise 2-7% of uveitis clinic referrals in North America. Uveitis

in anti-neutrophilic cytoplasmic antibody associated vasculitides, Kawasaki's disease and auto-inflammatory syndromes are rarely described (50-55).

No paediatric cases have been reported in African literature.

In summary, some data for immune mediated diseases, particularly JIA in SSA children, has emerged from Africa in recent years with limited focus on the ocular manifestations and its treatment.

Treatment

Uveitis management involves treatment of the underlying disease, the ocular inflammation and the complications. Initial treatment of anterior uveitis typically includes topical corticosteroids and cycloplegics. Systemic corticosteroids are initiated when topical therapy fails or in the context of severe ocular or systemic disease.

JIAU and idiopathic uveitis

Recent consensus treatment guidelines for chronic anterior uveitis in JIA-U and idiopathic uveitis, advocate a step-up approach if control is not achieved within 3 months of initiating a new therapy. Limited evidence for the efficacy of methotrexate, other DMARD's and biologics, support their use to mitigate the side effects of steroids (56-62).

Intra-ocular and intravitreal corticosteroid injections are utilised in the management of intermediate and posterior uveitis. However, while evidence from two small case series on intravitreal dexamethasone implants showed improvement of visual acuity, raised intraocular pressure and relapse in 36.4% of children were noted (63-65).

Ongoing research for additional biologics used in cases refractory to TNFi, are summarised in Appendix D (66-81, 87).

As yet, uncertainty remains regarding the duration of treatment but a minimum of 2 years of inactive disease is advocated before withdrawal is considered. In addition, children often require surgery during the course of their disease (25,82,83).

Other diseases

Treatment options for other diseases include early systemic corticosteroids and DMARDs in BD and VKH, as well as tumour necrosis factor and interleukin 1 inhibitors in refractory sarcoid uveitis.

In children with FHI, a poor response to topical steroids with the development of raised intraocular pressure may occur and surgery required earlier in the disease course (40,52,84,85).

These treatment options are predominantly based on developed countries data and expert opinion. There are no studies or clinical trials from Africa for the management of non-infectious uveitis.

Limitations

The review is limited by:

- One reviewer's selection bias as to relevance
- Exclusion of articles in languages other than English, as French in particular is the official language of at least 21 countries in Africa

Gaps in literature

Non-infectious uveitis is well reported in developed countries with scant data available from Africa. Literature from North Africa shows a different disease spectrum to developed countries and importantly, the data for post infectious immune mediated syndromes and the uveitis related to

HLAB27 negative spondyloarthropathies associated with HIV infection, suggests the need for further investigation. Despite more publications on immune mediated diseases in children from SSA becoming available, the data for their ocular manifestations are limited and relatively poorly defined.

Conclusion

Further study of the presentation and treatment of non-infectious uveitis in African children is needed to better assess the burden of disease and to develop context specific acute and long-term management strategies.

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1.2 ETHICAL CONSIDERATIONS

Ethics approval

Ethics approval for data collection was obtained from the University of Cape Town human research ethics committee HREC no: 692/2018, prior to the commencement of research.

HREC approval letter appended (Appendix B)

Privacy and confidentiality

Data collection and storage

No human or animal subjects were involved, as a retrospective case file review was performed.

Specific consent/assent was therefore not required from patients.

Data was anonymised and collected in accordance with the principles of Helsinki and GCP. Data was transcribed onto a password-protected electronic data sheet with identifying data removed. Data is stored in a password-protected database to which only the PI and sub-investigator has access.

1.3 AUTHOR GUIDELINES

The journal article has been formatted to the requirements as set out by *Paediatric Rheumatology ISSN: 1546-0096,* the official publication of the Paediatric Rheumatology European Society, published by Biomed Central

Paediatric Rheumatology enjoys a wide international and local readership and would be the ideal journal to raise awareness of the immune mediated diseases, associated manifestations, treatment and challenges faced by African children with these conditions.

This research work falls within the scope and aims of the publication

The scopes and aims as well as the submission requirements are appended (Appendix E and F)

Chapter 2: Publication-ready manuscript

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

Uveitis is a known cause of blindness in the developed world, where non-infectious diseases dominate the spectrum of underlying aetiologies. 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 utilising STATA13 software was performed with $p < 0.05$ considered significant.

Results

Twenty-nine children were identified with a 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 ($p = 0.01$) and 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 and 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 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 Africa (SSA) data tend to under report uveitis in the context of surveys or studies on blindness in a specific region (4-7). Only active uveitis resulting in visual loss is 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 recently been described in children (13-15). Idiopathic uveitis, where an underlying systemic cause cannot be found, frequently presents with complications and still accounts for up to 50% of uveitis populations seen at referral centres (16). The utility of microbial polymerase chain reaction and culture as well as cytospin of fluid obtained by ocular paracentesis, has been established in determining a cause for up to one third of previously reported cases of idiopathic uveitis (17,18). However, the technical aspects of the procedure in children and analysis of the small amounts of fluid obtained, remains a challenge in many under resourced countries.

The limited data for immune mediated uveitis in SSA children describe the association with juvenile idiopathic arthritis (JIA) (19-22). Reports from North Africa, additionally describe uveitis in Behcet's disease (BD) (23-25). However, uveitis presenting in other immune mediated diseases are not featured.

In developed countries, non-infectious uveitis is a more recognized ocular manifestation of systemic immune mediated diseases and in children, is frequently described in JIA, HLA-B27 associated diseases, sarcoidosis and BD among others. Here, infectious diseases contribute significantly less to the total uveitis burden, with TB and syphilis accounting for under 3% (1,3).

The prevalence of paediatric immune mediated systemic diseases and the associated uveitis, varies by underlying disease, disease subtype, as well as geographically (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 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). Management by experienced ophthalmologists and rheumatologists is thus advocated, as refractory disease often requires the addition of disease modifying anti-rheumatic drugs (DMARDs) and biologics. The recent Single Hub and Access point for paediatric Rheumatology in Europe (SHARE), Childhood Arthritis and Rheumatology Research Alliance (CARRA) and American College of Rheumatology (ACR) consensus guidelines, for chronic anterior uveitis in JIA and idiopathic uveitis, are based on expert opinion and evidence from developed countries (34-37). These consider DMARDs including azathioprine, mycophenolate mofetil and cyclosporine rescue therapy in conjunction with methotrexate, within 3 months of failure to achieve optimal control of inflammation with corticosteroids. Tumour necrosis factor inhibitors (TNFi) have

proven efficacy in recent clinical trials (38,39) and are also advocated in these treatment algorithms. Smaller case series for other biologics, including rituximab, tocilizumab and abatacept have yielded promising results in cases refractory to TNFi (40-45). No data for the use of biologics for non-infectious uveitis in SSA children has been published, although in South Africa, biologic treatment in the last 10 years despite limitations of cost and availability, is noted anecdotally.

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 centre 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 centres 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

<15years 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 systematic 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, metres or decimal) annotation to the log of the minimal angle of resolution (LogMAR), based on the conversion by Schulze et al (47).
    - Disease characteristics and laboratory investigations
    - Data of children with JIA additionally included JIA subtype, time to uveitis diagnosis and whether JIA remission was achieved on treatment.

Disease definitions

- **JIA**: as per International League of Associations for Rheumatology criteria (48)
- **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, ASOT, AntiDNASe B, 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 done in individual cases

- **Sarcoidosis**: Clinical presentation, histology +/- raised serum angiotensin levels
- **Behcet's disease**: Clinical diagnosis based on Paediatric BD criteria 2015 (49)

Treatment modalities utilised

- Standard Initial Treatment includes corticosteroids (topical and/or systemic) and Methotrexate 10–20mg/m^2 (maximum dose 20mg orally or 25mg subcutaneously)
- Additional disease modifying anti-rheumatic drug therapy includes azathioprine (1–3mg/kg) and mycophenolate mofetil (250–500mg/m^2 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/slit 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 ≥ 3months of inactive disease on treatment
- Secondary Outcome was considered as improvement in visual acuity

Exclusion criteria

- All children assessed at the PR service prior to 1 January 2010 and after 31 December 2017
- Children managed for <3 months or were lost to follow up
- Children with active infectious uveitis

Statistical analysis

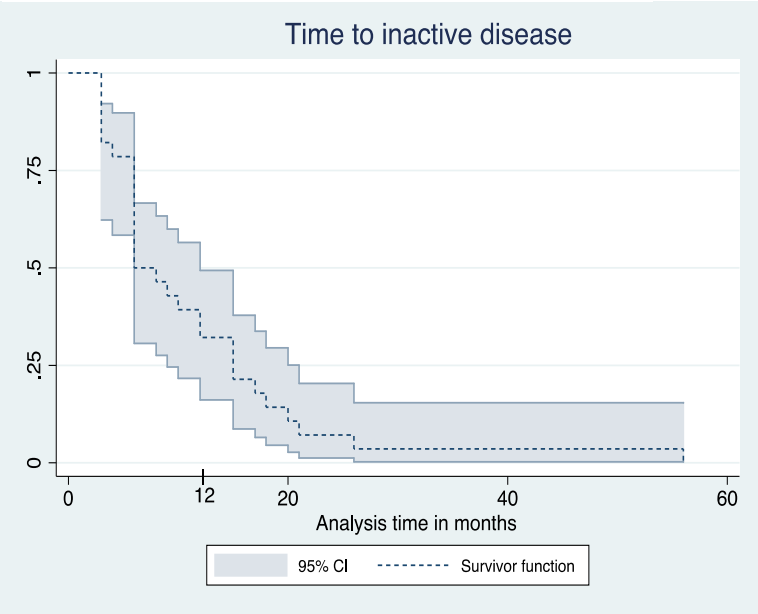
Statistical analysis was performed utilising STATA13 software.

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 non-infectious 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 2). The median time to inactive disease was 7 months (IQR 6-15 months) (Fig. 1). There was no statistical difference ($p = 0.28$) between JIAU and idiopathic uveitis for overall time to inactive disease (Fig. 2). 19 (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. 3). 27 (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 3).

Fig 1: Time to inactive disease



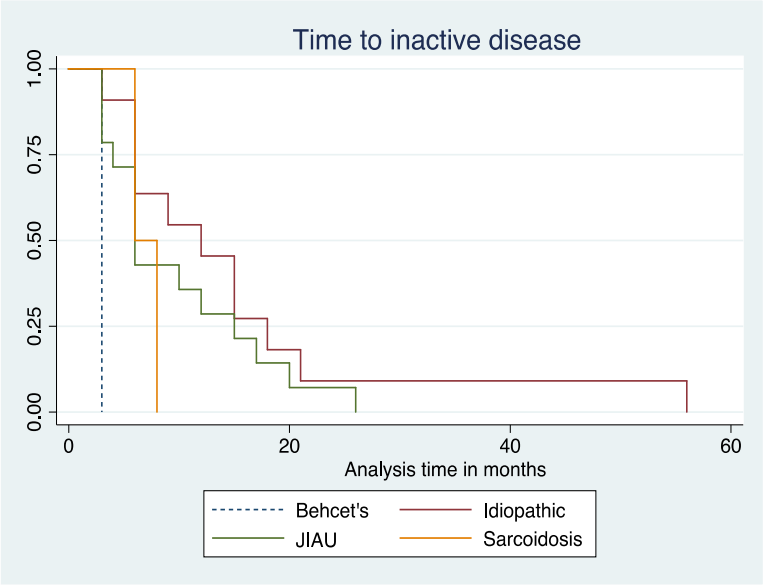
N=28
Median time to inactive disease: 7 months
IQR: 6-15 months

Table 2: Disease characteristics

Diagnosis	**JIAU**	**Idiopathic**	**Sarcoidosis**	**Behcet's Disease**
Total N (%) (CI: 1.4–2.0)	N=14 (48.3)	N=12 (41.3)	N= 2 (6.9)	N= 1 (3.5)
No. of affected eyes (CI: 1.6–1.9)	26	20	4	1
Demographics				
Presentation age (months) Median (IQR) (CI: 62.6–87.8)	55 (34–86)	76.5 (67–85)	102.5 (49–156)	120 -
Female N (%) (CI: 1.3–1.7)	8 (57.1)	4 (33.3)	2 (100)	0
Race N (%) (CI: 1.1–1.6)				
Mixed	10 (71.4)	9 (75)	1 (50)	1 (100)
Black African	2 (14.3)	2 (16.7)	1 (50)	0 (0)
Caucasian	2 (14.3)	1 (8.3)	0 (0)	0 (0)
Anatomical Location (CI: 1.3–2.2)				
Acute Anterior	0	1 (8.3)	1 (50)	0
Chronic Anterior	14 (100)	6 (50)	0	1 (100)
Intermediate	0	1 (8.3)	0	0
Posterior	0		1 (50)	0
Panuveitis	0	4 (33.4)	0	0
Laterality				
Unilateral	2 (14.3)	4 (33.3)	0 (0)	1 (100)
Bilateral	12 (85.7)	8 (66.7)	2 (100)	0 (0)
Complications (CI 1.0 – 1.9)				
No. affected children N (%)	7 (50)	9 (66.6)	0 (0)	0 (0)
Cataracts	5 (71.4)	9 (100)	0	0
Posterior synechiae	3 (42.9)	3 (33.3)	0	0
Band Keratopathy	2 (28.6)	2 (22.2)	0	0
Raised intra- ocular pressure	3 (42.9)	4 (44.4)	0	0
VA at presentation (Median) LogMAR (IQR)	0.1 (0.0–0.3)	0.95 (0.55–2.45)	0.0 (0.0–0.0)	0.3 (-)
VA at last visit Median LogMAR (IQR)	0 (0.0–0.2)	0.3 (0.0–0.6)	0 (0–0)	0.1 (-)
Change in VA: p-value	0.06	0.001	-	-

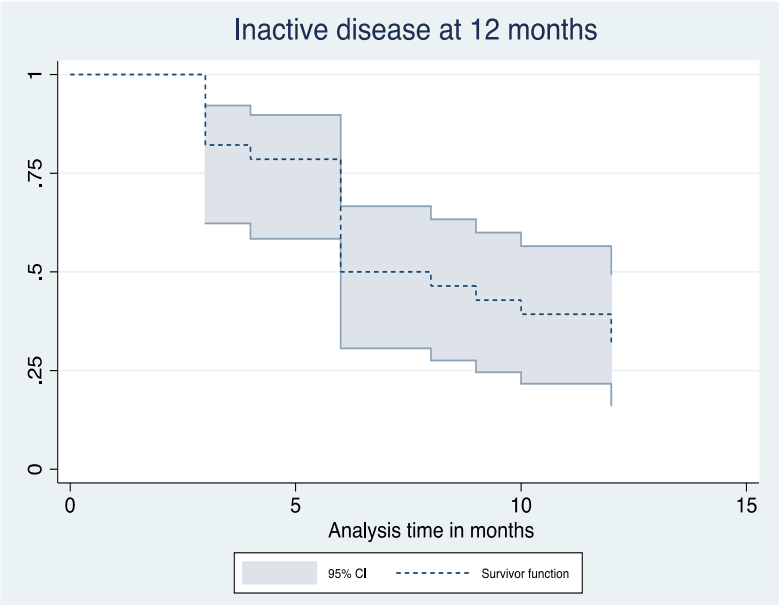
***JIAU**: Juvenile Idiopathic Arthritis associated Uveitis, **CI**: 95% confidence interval, **VA**: Visual Acuity, **LogMAR**: Log of minimal angle of resolution, where LogMAR 0.0 ~ Snellen 6/ 6, LogMAR 0.5 ~ Snellen 6/19 and LogMAR 1.0 ~ Snellen 6/60*

Fig 2: Time to inactive disease by diagnosis



N=28	*Behcet's disease:*	*3 months*
	Sarcoidosis:	*median 7 months IQR: 6-8 months*
	JIA:	*median 6 months IQR: 4-15 months*
	Idiopathic:	*median 10.5 months IQR: 6-16.5 months*

Fig 3: Inactive disease at 12 months



N=19
Standard initial treatment N=16: JIA (9) Idiopathic (4) BD (1) Sarcoidosis (2)
TNFi N=3: Idiopathic (2) JIA (1)

Table 3: Treatment

Treatment N (%)	Total treated N (%)	Response (R) / No Response (NR)	JIAU N=14		Idiopathic N=12	Sarcoidosis N=2	Behcet's Disease N=1	Total N(%)
			Screening N =11	Pre-JIA N=3				
Standard Initial Rx	29 (100)	R	7 (24.1)	1(3.5)	6 (20.7)	2 (7.0)	1 (3.6)	17 (58.6)
		NR	4 (13.8)	2 (7.0)	6 (20.7)	0	0	12 (41.4)
Azathioprine	8 (72.7)	R	1 (12.5)	-	0	-	-	1 (12.5)
		NR	3 (37.5)	-	4 (50)	-	-	7 (87.5)
Mycopheno- late Mofetil	3 (27.3)	R	1 (33.3)	-	0	-	-	1 (33.3)
		NR	1 (33.3)	-	1 (33.3)	-	-	2 (66.6)
Infliximab	6 (54.5)	R	1 (16.7)	0	2 (33.3)	-	-	3 (50)
		NR	1 (16.7)	1 (16.7)	1 (16.7)	-	-	3 (50)
Adalimumab	8 (72.7)	R	1 (12.5)	2 (25)	4 (50)	-	-	7 (87.5)
		NR	0	0	1 (12.5)	-	-	1 (12.5)
Surgery N (%)			2 (18.2)	1 (33.3)	9 (75)	0	0	12 (41.4)
Cataract			2 (18.2)	0	6 (50)	0	0	8 (27.5)
Pars Planar vitrectomy/ lensectomy			0	1 (33.3)	4 (33.3)	0	0	5 (17.2)
Chelation			0	0	2 (16.7)	0	0	2 (6.8)

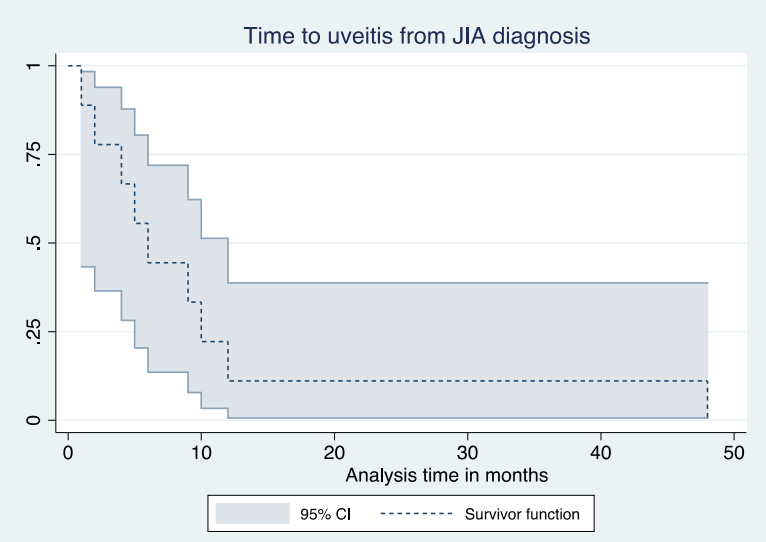
Responders (R) had inactive disease on treatment. In non-responders (NR), treatment was escalated to one of the additional DMARDs then a TNFi or directly to a TNFi

Disease characteristics

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 5). 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 4). 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%).

Fig 4: Time to uveitis from JIA diagnosis



N=11
2 children were diagnosed at first screen
8 children developed uveitis within 1 year of JIA diagnosis, detected at routine screening
1 child developed uveitis 4 years after initial JIA diagnosis, detected at routine screening
(3 children had uveitis before JIA diagnosis and were excluded from the model)

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. 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 4: Comparison of JIA only and JIAU

Diagnosis	**JIA Total N=217**	**JIA only N=203**	**JIAU N=14**	**p-value**	
Median Age months (IQR)	111 (54–148)	114.5 (59–152)	55 (34–86)	†p = 0.008	
Age groups (months) N (%)					**Odds Ratio 95% CI**
0–84	70 (32.3)	60 (29.6)	10 (71.4)	†p = 0.01	0.46 CI 0.25–0.83
85–144	73 (33.6)	69 (33.9)	4 (28.6)	p = 0.78	0.71 CI 0.22–2.35
145–192	60 (27.7)	60 (29.6)	0	†p = 0.01	1.0 CI 0.6–1.7
Female N (%)	135 (62.2)	127 (62.5)	8 (57.1)	p = 0.68	0.78 CI 0.26–2.34
Race N (%)					
Mixed	124 (57.1)	114 (56.2)	10 (71.4)	p = 0.40	0.72 CI 0.39–1.3
Black African	37 (17.1)	35 (17.2)	2 (14.3)	p = 1.00	1.25 CI 0.27–5.8
Caucasian	56 (25.8)	54 (26.6)	2 (14.3)	p = 0.53	0.46 CI 0.10–2.1
JIA subtype N (%)					
Oligo-articular	83 (38.3)	73 (35.9)	10 (71.5)	†p = 0.01	4.45 CI 1.35–14.7
Poly articular RF +	18 (8.3)	18 (8.8)	0	p = 0.61	0.08 CI 0.04–0.13
Poly articular RF –	43 (19.8)	40 (19.7)	3 (21.4)	p = 1.00	1.05 CI 0.54–2.04
Psoriatic	16 (7.4)	15 (7.4)	1 (7.1)	p =1.00	0.99 CI 0.59–1.66
Systemic Onset JIA	17 (7.8)	17 (8.4)	0	p = 0.61	-
Enthesitis Related Arthritis	38 (17.5)	38 (18.7)	0	p = 0.14	-
Undifferentiated	2 (0.9)	2 (1)	0	p =1.00	-
Lab Parameters N (%)					
ANA tested Hep2 Positive Elisa Positive	147 (67.7) 15 (10.2) 15 (10.2)	136 (67) 10 (7.4) 9 (6.6)	11 (78.6) 5 (45.5) 6 (54.5)	†p < 0.001	33.29 CI 6.83–162.09
RF tested Negative Positive	125 (57.6) 107 (85.6) 18 (8.3)	116 (57.1) 98 (84.4) 18 (8.9)	9 (64.3) 9 (100) 0	p = 0.36	-
HLAB27 tested Present	63 (29) 4 (1.8)	62 (30.5) 4 (1.9)	1 (7.1) 0	p =1.00	-

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. However, it is dissimilar to reports from North Africa, where BD (23,24) is more common, largely explained by the geographic location of this study cohort outside the Mediterranean basin. 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 5), 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 in JIA subtype and ANA positivity could possibly be ascribed to race. The children in our study were predominantly of mixed race, reflecting the racial demographics of the Western Cape region of South Africa, 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 and may affect the uveal tract. African American females have a ten times increased risk for the development of sarcoidosis but information for African children is lacking. In our cohort, both cases were female. The early onset case of mixed race 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 systemic symptoms, acute anterior uveitis 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, as has been described in other case series was not needed here (61-64).

Behcet's disease

Adult studies from North Africa, 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 adults with 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 but increased prevalence is noted in immigrant children from high prevalence areas compared to the local population. The case of clinical BD in our cohort partially fulfilled paediatric BD 2015 criteria, as he presented with recurrent uveitis and skin lesions but had less than 3 attacks of oral aphthosis per year (49). HLAB51 testing was not done and as far as was known, he was not of Mediterranean nor Eastern descent. The chronic anterior uveitis responded well to standard initial therapy, in contrast to other case series from North Africa, where posterior uveitis, severe ocular complications and poor visual outcome are described in up to 75% (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, Fuch's heterochromic uveitis, 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.

Table 5: Comparison of JIA and JIAU studies from SSA and developed countries

Country	Current study South Africa	South Africa (15)	Zambia (20)	Kenya (56)	Nigeria (21)	Canada (55)	Atlanta (27)
Single / Multicentre	Single	Single	Single	Single	Single	Multi	Single
Total N	217	97	85	68	28	1183	287
JIA subtypes (%)							
Oligo	38.3	39	32.1	23.5	39.3	40	46
Poly RF–	19.8	30	34.6	38.2	42.8	20	24.4
Poly RF+	8.3	9	11.5	17.6	7.1	4	4.5
ERA	17.5	5	6.4	5.9	0	14	12.9
Psoriatic	7.4	0	1.3	0	0	6	3.5
SJIA	7.8	16	14.1	14.7	17.9	6	7.7
Undifferentiated	0.9	0	0	0	0	10	0.7
Uveitis (%)	6.5	4	12.8	1.5	7.1	8.5	18.2

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 is a retrospective case file review and was dependent on the availability and accuracy of the medical records included in the study.

The SUN working group criteria were applied retrospectively to cases diagnosed prior to 2016 and required an accurate assessment of clinical notes.

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 is needed.

Abbreviations

ANA	Anti-Nuclear Antibody
ANA HEp2	Anti-Nuclear Antibody Human Epithelial cell indirect immunofluorescence test
AntiDNAse B	Anti-Deoxyribonuclease B
ASOT	Anti-Streptolysin O titres
ARVs	Antiretroviral therapy
BD	Behcet's Disease
CMV	Cytomegalovirus
DMARDs	Disease Modifying Anti-Rheumatic Drugs
ERA	Enthesitis Related Arthritis
FHI	Fuch's Heterochromic Iridocyclitis
HIV	Human Immunodeficiency Virus
HLAB27	Human Leukocyte Antigen B27
IL	Interleukin
ILAR	International League of Associations for Rheumatology
IQR	Interquartile Range
IRIS	Immune Reconstitution Syndrome
ISG	International Study Group
JIA	Juvenile Idiopathic Arthritis
JIAU	Juvenile Idiopathic Arthritis associated Uveitis
LogMAR	Log of the minimal angle of resolution
MMF	Mycophenolate Mofetil
ReaCCH-out	Research in Arthritis in Canadian Children emphasizing Outcomes
RF	Rheumatoid Factor
SSA	sub-Saharan Africa
SUN	Standard Uveitis Nomenclature
TB	Tuberculosis
TINU	Tubulo-Interstitial Nephritis associated Uveitis
TNFi	Tumour Necrosis Factor Inhibitors
VA	Visual Acuity
VKH	Vogt Koyonagi Harada Syndrome

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

Funding

This is a non-funded study

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, management expertise and reviewed the manuscript.

Acknowledgements

We would like to thank Drs K. Webb, L. O'kongo, A. Fadmolela, Y. Fuseini, S. Akhalwaya and N. Freeman, as well as the administrative and nursing staff at Red Cross War Memorial Children's Hospital for their ongoing assistance in the management of our patients.

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Appendices

A. Protocol Data Collection Sheet

Data Collection Sheet												
	Patient 001		**Patient 002**		**Patient 003**		**Patient 004**		**Patient 005**		**Patient 006**	
Folder no:												
Gender												
Age at presentation JIA (where applicable)												
Age at presentation Uveitis (where applicable)												
Time to Uveitis diagnosis from JIA												
Associated diseases												
JIA Oligo-arthritis												
JIA Poly-arthritis RF-												
JIA Poly-arthritis RF+												
JIA ERA												
JIA Psoriatic												
JIA undifferentiated												
JIA systemic												
Behcet's												
Sarcoidosis												
Other												
Anatomical Location: Anterior												
Posterior												
Intermediate												
Pan												
Antibody Profile												
ANA												
Rheumatoid Factor												
HLA B27												
Visual Acuity	**Initial**	**End**	**Initial**	**End**	**Initial**	**End**	**Initial**	**End**	**Initial**	**End**	**Initial**	**End**
Right eye												
Left eye												
Complications Right eye												
Band Keratopathy												
Posterior Synechiae												
Cataracts												

Glaucoma						
Surgery						
Other						
Complications Left eye						
Band Keratopathy						
Posterior Synechiae						
Cataracts						
Glaucoma						
Surgery						
Other						
Treatment						
Topical Steroids						
Topical cycloplegics						
Oral Steroid						
Intravenous Steroids						
Methotrexate						
MMF						
Azathioprine						
Adalimimab						
Infliximab						
Other						
Surgery						
JIA Remission (Y/N)						
Uveitis Remission (Y/N)						

B. HREC Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
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26 October 2018

HREC REF: 692/2018

A/Prof Chris Scott
Rheumatology
J-floor, OMB

Dear A/Prof Chris Scott

PROJECT TITLE: THE SPECTRUM OF PAEDIATRIC NON-INFECTIOUS UVEITIS IN CAPE TOWN: CLINICAL PRESENTATION, DISEASE CHARACTERISTICS AND TREATMENT OUTCOME (MPhil Candidate - Dr W Slamang)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30 October 2019.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

The HREC acknowledge that the student, Dr Waheba Slamang will also be involved in this study.

Yours sincerely

Signature Removed

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

C. Summary of literature search

Search Terms	Pubmed	SCOPUS	Cochrane Library	Included
Epidemiology non-infectious uveitis child	19	1	1	1
Non-infectious uveitis child Africa	1	1	0	1
Non-infectious uveitis child treatment Africa	0	0	0	0
Uveitis rheumatic diseases Africa	4	17	0	3
Juvenile idiopathic arthritis associated uveitis Africa	2	3	0	3
Juvenile Idiopathic Arthritis Africa	29	17	0	7
Biologics juvenile idiopathic arthritis uveitis associated uveitis Africa	0	0	18	0
Paediatric SLE Africa	14		0	3

A literature search was performed using the Pubmed (Medline), Scopus (documents) and Cochrane Library databases

18 published articles were reviewed and data relevant to non-infectious immune mediated uveitis analysed. Of these, 2 reported the clinical spectrum of uveitis in children and further data on uveitis in association with specific diseases were extracted from 16 articles.

The strength of evidence for non-infectious immune mediated uveitis in African children is low and currently relies on few case series/ cohort studies which have other descriptive objectives and aims. There is no evidence for the treatment of children in Africa

D. Summary of evidence for other biologics

Tocilizumab				
Author, Country (year)	**Multi/ Single Centre**	**No. of patients**	**Treatment Dose**	**Outcome**
Ramanan, APTITUDE study (2015- 2019) UK (66)	Phase II Trial		Tocilizumab	Results Pending
Case report Di Pasqale Italy (2019) (87)	Single	2	8mg/kg every 4 weeks	Inactive disease within 2 weeks and discontinuation of prednisone after 1 month and methotrexate after 1-1.5 years
Calvo-Rio, Spain (2017) (67)	Multi centre	25	Tocilizumab 8 mg/kg every 4 weeks	79% improvement in AC cells after 6 weeks, 88% after 1 year and central retinal thickness improvement
Tappeiner, Switzerland (2016) (68)	Retrospective single centre	17	Tocilizumab 8mg/kg every 4 weeks	Inflammatory macula oedema responds to TCLZMB
Tappeiner, Switzerland (2012) (69)	Single	3	Tocilizumab	Improvement in macular oedema
Case reports Babu, India (2019) (70) Tsang, Canada (2014) (71) Adan et al (2013, 2014) (72, 73)	 Single Single Single	1	 Tocilizumab 10mg/kg Tocilizumab 8mg Every 2- 4wks	 Improved macular oedema Remission with Tocilizumab after Abatacept, Rituximab and TNF alpha failure
Rituximab				
Author, Country (year)	**Multi/ Single Centre**	**No. of patients**	**Treatment Dose**	**Outcome**
Miserocchi, Italy (2016) (74)	Single	8	Rituximab 1g D1/ D15 then every 6 months	Uveitis control achieved 4-5 months after infusion, except 2 discontinued due to ineffective arthritis TX Mean follow up 4 years
Heiligenhaus, Duisberg-Essen (2011) (75)	Multi centre	10	As above	One rituximab cycle follow-sup 1 year 7/10 inactivity, uveitis recurred in 3 and responded to second Ritux

Abatacept				
Author, Country (year)	**Multi/ Single Centre**	**No. of patients**	**Treatment Dose**	**Outcome**
Birolo, Russia 2016 (76)	Multi	35	500mg iv infusion after loading	Comparison of ABA as first line and after 1 or more TNFi – No difference between groups
Tappeiner Munster, Milan, Paris, Helsinki, Heidelberg 2015 (77)	Multi	21	As above	Refractory cases, 7/18 responded but was not sustained
Case report: Kenawy et al India 2010 (78)	Single	2	500mg weeks 0, 2, 4 then monthly	Refractory cases - Improvement in inflammation and macular oedema
Case report Elhai 2011 Paris (79)	Single	2	As above	Sustained response in refractory uveitis
Zulian, 2010 (80)	Single	7	As above	Refractory disease failed ≥ 2 TNFi Sustained improvement in 6/7 cases
Case report Angeles Han, New York 2008 (81)	Single	1	As above	Sustained response

Case reports and case series from predominantly developed countries, where these biologics are more readily available, include small numbers of children and show promising results in cases refractory to TNFi, for tocilizumab, rituximab and abatacept

E. Aims and scope *Paediatric Rheumatology*

Pediatric Rheumatology is the official publication of the Pediatric Rheumatology European Society (PReS). Submissions on the evaluation and treatment of non-surgical musculoskeletal syndromes and diseases in children and adolescents, particularly autoimmune and rheumatic diseases are welcomed.

Diseases and syndromes of particular interest include musculoskeletal pain syndromes, rheumatic fever and post-streptococcal syndromes, juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis, local and systemic scleroderma, Kawasaki disease, Henoch-Schonlein purpura and other vasculitides, sarcoidosis, inherited musculoskeletal syndromes, autoinflammatory syndromes, and others. Pediatric Rheumatology encourages submissions on educational advances, drug studies, laboratory and radiological evaluations, and outcome measures.

Pediatric Rheumatology began publishing as Pediatric Rheumatology Online Journal in 2003. For access to articles published prior to 2006, contact the Editorial team.

PReS are providing financial support to aid any authors who require assistance with the article processing charge (APC). Applicable authors would be charged a discounted article processing charge of £350 payable for articles accepted for publication. Authors who would like to apply for the reduced APC should contact the contact the Editorial team. Applicable authors can request this support during the submission process, stating payment via the PReS Shared Support option.

Pediatric Rheumatology

ISSN: 1546-0096 Contact us: info@biomedcentral.com

F. Author submission guidelines

Submission Guidelines

Research article

Research articles should report on original primary research.

Pediatric Rheumatology strongly encourages that all datasets on which the conclusions of the paper rely should be available to readers. We encourage authors to ensure that their datasets are either deposited in publicly available repositories (where available and appropriate) or presented in the main manuscript or additional supporting files whenever possible. Please see Springer Nature's information on recommended repositories. Where a widely established research community expectation for data archiving in public repositories exists, submission to a community-endorsed, public repository is mandatory. A list of data where deposition is required, with the appropriate repositories, can be found on the Editorial Policies Page.

Preparing your manuscript

The information below details the section headings that you should include in your manuscript and what information should be within each section.

Please note that your manuscript must include a 'Declarations' section including all of the subheadings (please see below for more information).

Title page

The title page should:

- present a title that includes, if appropriate, the study design e.g.:
    - "A versus B in the treatment of C: a randomized controlled trial", "X is a risk factor for Y: a case control study", "What is the impact of factor X on subject Y: A systematic review"
    - or for non-clinical or non-research studies a description of what the article reports
- list the full names and institutional addresses for all authors
    - if a collaboration group should be listed as an author, please list the Group name as an author. If you would like the names of the individual members of the Group to be searchable through their individual PubMed records, please include this information in the "Acknowledgements" section in accordance with the instructions below
- indicate the corresponding author

Abstract

The Abstract should not exceed 350 words. Please minimize the use of abbreviations and do not cite references in the abstract. Reports of randomized controlled trials should follow the CONSORT extension for abstracts. The abstract must include the following separate sections:

- **Background:** the context and purpose of the study
- **Methods:** how the study was performed and statistical tests used
- **Results:** the main findings
- **Conclusions:** brief summary and potential implications
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