DISSERTATION

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TITLE

The common causes of uveitis in different age groups in Universitas Academic Hospital in Bloemfontein (2012 – 2016).

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ABSTRACT

Objectives: to find out the aetiological profile of uveitis among patients that attended the eye clinic at Universitas Academic Hospital from 2012 to 2016. In particular the aetiological profile of uveitis is tailored to differing age groups of patients in our eye clinic population.

Methods: a retrospective review the patients that attended the Universitas Academic Hospital eye clinic from 2012 to 2016 was done.

Results: 71 eyes of 54 patients' clinical files were reviewed. There were three different age group categories, and all three seemed to suffer from different aetiologies, primarily. The paediatric group suffered mostly from JIA and masquerade syndrome, the "youths" group suffered mostly from infective uveitis, as was the adult group, with syphilitic uveitis accounting for above 54% of the cases of uveitis in adults, and about 40.7% overall. Also the occurrence of HIV in this study population was relatively high.

Conclusion: in the local setting, the most common causes of uveitis tend to be infective in nature, and this can be correlated well with the prevalence of HIV in our hospital population. Retinoblastoma also seems to be a significant cause of masquerade syndrome in children.

INTRODUCTION

Uveitis is classically defined as the inflammation of the uveal tract, which is the iris, ciliary body, and choroid. The terms uveitis and intraocular inflammation are used interchangeably and refer to the same entity defined.

Uveitis is a serious public health problem, accounting for approximately 5-20% of legal blindness in the developed countries and is the fourth most common cause of visual disability among the working-age population.[1-3]

Uveitis can affect any/many people in the population, but seems to have a propensity for those in the vulnerable groups, which are children, immunocompromised either by chemotherapeutic agents or by viral means, for example Human Immunodeficiency Virus (HIV), and also the elderly.

The causes of uveitis are vast and vary according to the region and the type of uveitis, and are generally grouped as idiopathic, infective, immune-mediated, collagen disease related, and masquerade syndromes.

Uveitis, if untreated, tends to have unfavourable consequences/results for vision and can lead to glaucoma, cataract, chronic cystoid macular oedema, chroioretinal atrophy, and optic atrophy among other things.

Uveitis is normally treated with steroids, either topical or systemic, depending on the severity and the chronicity, together with mydriatic agents, such as atropine. In some instances uveitis is treated with systemic immunomodulatory agents, such as methotrexate or cyclophosphamide, to suppress the inflammatory process.

Uveitis has been extensively studied in the developed countries of Europe and the United States, while in the underdeveloped and developing countries/ continents for that matter, uveitis has not been extensively studied. This forms the premise for our investigation into the causes of uveitis in our setting, which is a developing country setting.

LITERATURE REVIEW

INTRODUCTION

The history of the uveitis patient is very important as it can yield an option for the differential diagnoses for the patient. The single most important activity to establish the diagnosis in the uveitis patient is a detailed and accurate history. No amount of laboratory testing can substitute the history in the patient with uveitis.

Because uveitis can arise from such a wide variety of causes, the history helps the ophthalmologist in narrowing down the list of possible causes for the uveitis. This can help tailor the specific investigations and treatment strategies for the patient. The history is not used on its own, but in combination to the clinical signs and the special investigations to reach the diagnosis. These facets complement each other to give a full/ more complete picture of the patients' disease.

But because not all uveitis diseases rely on laboratory investigations for diagnosis, and are clinical diagnoses, the history together with the clinical examination comprise the important tools in the assessment of the uveitis patient.

EPIDEMIOLOGY

Most uveitic syndromes occur in the broad, middle-age group of 20-60 years[4-6], and virtually all possible uveitic diagnoses should be considered in this age group. Most of the common uveitic syndromes do not have a specific sex predilection, with the exception of Juvenile Idiopathic Arthritis (JIA) which tends to affect young girls, and HLA-B27 (Human Leucocyte Antigen) associated uveitis which tends to affect young men.[7, 8]

A few uvetitc syndromes have a racial predilection, for example there is an increased prevalence of HLA-B27 associated uveitis[8], ocular Sarcoidosis[9], and systemic lupus[10] in those of African descent; Behcet's syndrome in those of Mediterranean, Middle Eastern and Asian descent[11]; and Vogt-Koyanagi-Harada (VKH) syndrome in Asians, Asian Indians, and Native Americans[12].

CLINICAL PRESENTATION

The assessment of the uveitis patient starts with a thorough history, which will include; after establishing the patient demographics and geographical location or origin - the history of the present complaint, past ocular history, past medical and surgical history, personal (which includes dietary history, sexual history, drug-use history, pet history, and contagion exposure history), and family history. This extensive history is followed by the review of the systems, which is often furnished with the help of a questionnaire. This review of systems is helpful in that it identifies signs and symptoms that might indicate the presence of disease previously unrecognized by the patient, it also provides the ophthalmologist with an opportunity to identify novel uveitic syndromes and associations.

The ocular examination usually follows as described below:

Visual acuity

Visual acuity is usually decreased as a result of many mechanisms, either acting alone or in concert. The patients' refraction has to be obtained in order to establish the patients' best-corrected visual acuity. Also both the uveitis and the use of corticosteroids can accelerate cataract formation, this can lead to myopic shift in the patient with previously known refraction. Also the visual acuity may be decreased as a result of optical media changes: there may be associated keratitis, producing kerato-uveitis, corneal oedema, large kerato precipitates, flare and cells, pupillary seclusion, cataract formation, dense vitritis, and cystoid macular oedema, all these factors lead to decreased vision in the patient with uveitis.

Intraocular Pressure

Intraocular Pressure is important to measure because any form of uveitis can be complicated by ocular hypertension or secondary glaucoma if chronic or recurrent.[13] Ordinarily, however acute uveitis is associated with lowered intraocular pressure. Exceptions to this rule of acute uveitic hypotony include sarcoidosis[9], Herpes simplex keratouveitis[14], Herpes zoster keratouveitis[15], Cytomegalovirus associated anterior uveitis[16], toxoplasmosis[17], syphilis[18], and Posner-Schlossman syndrome[19], which are associated with acute elevation of the intraocular pressure. Although the intraocular pressure rise can be related to the uveitis itself, the rise in intraocular pressure can be as a result of the therapeutic agents, such as corticosteroids, which are known to have a side effect related to increased intraocular pressure and development of glaucoma with the use of corticosteroids.

Lids, conjunctiva and sclera

The palpebral, forniceal and bulbar conjunctiva are examined for the presence of nodules, which occur in granulomatous uveitis such as sarcoidosis and tuberculosis. Ciliary injection usually accompanies iritis, whereas deep episcleral injection with oedema represents scleritis.

Cornea

Evidence of past or present keratitis is related to various infectious organisms. Active stromal keratitis is seen in both herpes simplex and herpes zoster infections, with keratic precipitates seen under the site of corneal inflammation. Reduced corneal sensation must prompt suspicion of herpes simplex or herpes zoster infection. Band keratopathy results from long standing uveitis and is seen frequently In JIA and sarcoidosis[9]. Inferior corneal thickening and annular stromal infiltrates have been described in sarcoidosis. Keratic precipitates are aggregations/ clumps of inflammatory cells and/or inflammatory debris on the corneal endothelial surface.

Keratic precipitates are also noted and described regarding number, size, distribution, and appearance[20]. Keratic precipitates are characterized as follows – pigmented, often old and inactive; white or yellow, recently or currently active; granulomatous, larger and greasy in appearance; nongranulomatous, smaller; stellate, often distributed over the entire endothelial surface.
Most keratic precipitates are found on the inferior corneal endothelium, occurring between 4 o'clock and 8 o'clock, these form what is termed the *Arlt Triangle*.

Gonioscopy

The angle is examined for granulomas, called *Berlin nodules.* The angle is also examined for peripheral anterior synechiae and the presence of angle neovascularization, which occur in chronic and/or recurrent uveitis.

Anterior chamber

The anterior chamber is examined for shallowing of the anterior chamber which results from extensive peripheral anterior synechiae with contraction, extensive posterior synechiae with pupil seclusion, or inflammatory infiltration of the anterior choroid producing anterior rotation of the iris root and ciliary body. The presence of cells and flare is graded carefully using the Standardization of Uveitis Nomenclature (SUN) [21], and these are graded on a scale from 0 to 4+.

Table 1. Anterior chamber cells grading[21].

Grade	Cells in 1X1mm slit beam field
0	0 cells
0.5+	1-5 cells
1+	6-15 cells
2+	16-25 cells
3+	26-50 cells
4+	>50 cells

Table 2. Anterior chamber flare grading[21].

Grade	Description
0	0
1+	Faint
2+	Moderate (iris/lens details clear)
3+	Marked (iris/lens details hazy)
4+	Intense (fibrin, plastic aqueous)

The formation of hypopyon indicates severe anterior inflammation, as seen in Behcet's syndrome, HLA-B27 associated uveitis and in endophthalmitis. Haemorrhagic hypopyon in the setting of chronic uveitis suggests the possibility of iris or angle neovascularization.

Pseudohypopyon may represent tumour cells either from a primary tumour such as retinoblastoma or from a metastatic carcinoma. Anterior chamber bleeding in the setting of acute uveitis is seen mostly with herpetic uveitis or with masquerade syndromes such as retinoblastoma or juvenile xanthogranuloma.

Iris

The iris is examined for irregularity, which occurs in the presence of posterior synechiae, or if there was trauma with iris sphincter injury/tear, or in the presence of herpetic uveitis with iris sphincter damage. The pupil is usually miotic in the inflamed eye. Iris precipitates occur in granulomatous uveitis, and are termed *Koeppe nodules* (when located in the pupillary margin), *Busacca nodules* (when located between the pupillary margin and the angle), and *Berlin nodules* (when located in the anterior chamber angle). Posterior synechiae tend to occur in chronic or recurrent uveitis, and when extensive, may result in pupil seclusion with development of secondary angle closure glaucoma. With retroillumination, iris atrophy can be visualized, as seen in cases of Fuchs uveitis syndrome and herpetic uveitis. Rubeosis can occur in severe or chronic anterior uveitis, but its occurrence in the setting of diffuse uveitis should prompt a search for retinal nonperfusion or ocular ischaemia[22].

Lens

The lens is inspected for anterior lens capsule pigment clumps which may represent broken anterior synechiae from previous episodes of uveitis. Posterior subcapsular cataract formation is a frequent/common complication of both uveitis and corticosteroid therapy for the treatment of uveitis. In the pseudophakic patient, the posterior lens capsule should be inspected carefully for the presence of residual lens matter which may contribute/cause the development of lens-induced uveitis. Also in the pseudophakic patient the posterior capsule bag should be inspected carefully for the presence of white plaques which can be indicative of infection with the slow growing organisms such as *Propionibacterium acnes* or *Staphylococcus epidermidis*, which can cause a chronic form of endophthalmitis.

Vitreous

The vitreous humour is examined for inflammation which may be anterior, posterior or diffuse. “Spillover” of anterior segment cells into the anterior vitreous humour causing anterior vitreous inflammation is seen in the setting of iridocyclitis. Posterior vitritis occurs with retinal, choroidal and optic nerve head inflammation. Diffuse vitreous cells obscure the view of the posterior pole. Vitreous cells may aggregate to form “snowballs”, “strings of pearls”, or “snowmen”. In intermediate uveitis the vitreous cells aggregate and form an opaque band in the inferior periphery, called a “snowbank”. Anterior vitreous cells and diffuse vitreous cells are graded on a scale of 0-4, as in the anterior chamber cells, but the former are graded with direct slit beam on the slit lamp, while the latter are graded with the use of indirect lenses, either Hruby, or diagnostic lens, or with the aid of the direct ophthalmoscope.

Table 3. Vitreous cells grading[23].

Grade	Vitreous inflammation
0	No opacities.
1+	Opacities present; mildly obscured fundus details.
2+	Opacities present; moderately obscured fundus details.
3+	Marked blurring of fundus details; barely visible disc and vessels.
4+	Severe blurring; no view of disc or vessels.

Retina

Retinitis can be manifested as retinal whitening, haemorrhage, and vasculitis. The location, pattern and extent of the retinitis should be noted carefully, particularly in regard with major landmarks such as the arcade vessels, optic disc, and fovea. Taking into account the depth of the retinitis is important as some of the retinal lesions may occur at certain layers while others may affect the whole thickness of the retina. For example Cytomegalovirus (CMV) and toxoplasma cause full thickness retinitis, while neuroretinitis and acute multifocal retinitis cause superficial inflammation, which is also focal, whereas acute multifocal placoid pigment epitheliopathy, acute retinal pigment epitheliitis, multiple evanescent white-dot syndrome, and progressive outer retinal necrosis tend to affect the outer layers of the retina including the retinal pigment epithelium. Retinal vasculitis may affect primarily arterioles causing arteriolitis such as occurs in acute retinal necrosis and bechet's syndrome, whereas in some cases the vasculitis may primarily affect venules causing phlebitis such as occurs in sarcoidosis, syphilis and toxoplasmosis. In addition the vasculitis may be exudative, causing sheathing or occlusive. Arteriolitis is often associated with occlusive disease whereas phlebitis is associated with exudative disease and also haemorrhagic disease. Exudative retinal phlebitis is typically seen in sarcoidosis and is termed *tache de bougie*, or "candle wax drippings". Microvasculitis is inflammation of the retinal capillaries and postcapillary venules, and it produces cotton wool spots and intraretinal haemorrhages, and is characteristic of collagen-vascular diseases and behcet's syndrome.

Retinal neovascularization occurs in response to both intraocular inflammation and retinal ischaemia. Neovascularization typically starts at the optic nerve head or along the arcades, but can start in the midperiphery as well. Because development of neovascular fronds depends on an adherent posterior hyaloid surface, which acts as a scaffold, the presence of posterior vitreous detachment allows for the development of rubeosis without the presence of retinal neovascularization.

Cystoid macular oedema is the most common cause of visual loss in patients with uveitis[24], and reflects the degree of vitritis and/or the proximity of associated retinal or optic disc inflammation. Cystoid macular oedema is best investigated with Optical coherence tomography (OCT) and Fundus Fluorescein Angiography (FA), as the OCT may miss mild foveolar fluid from leakage, which are best seen with the FA. Exudative retinal detachment is infrequent in uveitis patients, and is secondary to choroidal inflammation such as occurs in VKH, posterior scleritis and sympathetic ophthalmia. The main complication after resolution of the subretinal fluid is Retinal Pigment Epithelium (RPE) changes and RPE atrophy.

Choroid

Active choroidal inflammation is usually white or yellow, depending on the underlying choroidal and RPE pigmentation. Common causes of choroiditis in immunocompetent patients are sarcoidosis, tuberculosis, syphilis, and sympathetic ophthalmia, while in the immunocompromised patients the causes are likely opportunistic infections such as pneumocysticosis, histoplasmosis, and cryptococcosis. Choroidal neovascularization is rare but can occur in chronic uveitis, especially if the inflammation involves the outer retina or the choroid.

Optic nerve

Optic disc oedema is a common finding in patients with uveitis. It is usually secondary to adjacent vitritis or surrounding choroiditis. This optic disc oedema is called “uveitic papillopathy”, and must be differentiated from optic disc oedema that occurs with papillitis/optic neuritis, as the latter is a primary inflammation of the optic disc. The latter can also be differentiated from the former by its objective evidence of optic nerve dysfunction such as afferent pupillary defect or colour vision loss.

CLASSIFICATION

To categorize uveitis, several classification schemes have been used, none of which are solely adequate in isolation. They are based on demographic information, severity, chronology, laterality, pathology, location, and pattern of the intraocular inflammation, associated ocular and systemic findings, and predisposing factors.

Classification according to severity – mild, moderate, and severe.

Classification according to laterality – unilateral and bilateral.

Classification according to location – anterior, intermediate, posterior, and diffuse.

Anatomical classification – iritis, iridocyclitis, cyclitis, pars planitis, retinitis, retinochoroiditis, chorioretinitis, choroiditis, panuveitis, and endophthalmitis.

Pathological classification – granulomatous, and nongranulomatous.

Classification according to pattern – focal, multifocal, diffuse, and disseminated.

Predisposing factors – trauma, surgery, immunosuppression, drug use, occupation, and travel

Table 4. SUN Working Group Descriptors of Ueitis[21].

Category	Descriptor
Onset	Sudden Insidious
Duration	Limited: ≤3 months duration Persistent: >3 months duration
Course	Acute: episode characterized by sudden onset and limited duration Recurrent: repeated episodes separated by periods of inactivity without treatment ≥3 months in duration Chronic: persistent uveitis with relapse in <3 months after discontinuing treatment

The classification usually leads to considerable narrowing down of the range of diagnostic possibilities.

INVESTIGATIONS

Investigations for the uveitis patient are usually reserved for the patient with more serious/ complicated disease, which is the patient with moderate to severe disease, or even mild bilateral disease. The investigations are usually tailored in accordance to the suspected causative factor, dependent on information obtained from the history and the ocular/physical examination. The investigations are generally separated into investigations to establish the cause, investigations to rule out or establish a systemic/syndromic disease, and investigations aimed at establishing the presence or absence of any complications.

In our setting the investigations are usually carried out in accordance with regional, national and international norms, with the proviso of the resources available to us.

For example the patient suspected of having an immune-mediated uveitis such as sarcoidosis, in addition to the history and clinical signs – Serum Angiotensin Converting Enzyme (SACE), chest radiography (either chest X ray or CT scan of the chest), and CD_4:CD_8 ratio would be done to ascertain the suspected cause; a conjunctival or skin biopsy would be done on suspicious granuloma lesion, both to confirm the diagnosis of sarcoidosis and to rule out caseating necrosis in the granuloma that is caused by tuberculosis; OCT and/or FA would be done to rule out the presence or absence of cystoid macular oedema, as this is the known complication of chronic or recurrent uveitis[24], blood tests such as liver function and kidney functions would done to rule out any hepatic or renal dysfunction as a result of these organs' infiltration by the inflammatory process.

With investigating the patient suspected of having an infective type of uveitis such as CMV retinitis, in addition to the history and clinical signs – although the diagnosis of CMV retinitis is largely clinical, the CMV IgG and IgM are usually taken to support the clinical diagnosis; the CD_4 count (which is usually below 100 cells/ml) is taken as well as chest radiograph (chest X ray) in order to rule out immune mediated uveitis, which is a complication of rapid immune reconstitution in patients that began antiretroviral therapy with very low CD_4 counts[25], and to rule out interstitial pneumonitis which is a complication of the systemic CMV viremia.

In some instances the diagnosis can be evasive to laboratory investigations, and as such the diagnosis is only attainable through a thorough history and clinical examination. For example in sympathetic ophthalmia, no amount of laboratory investigations can aid in pinning down the exact diagnosis except for the history and the clinical examination. In these instances the diagnosis can only be confirmed with the aid of histological examination of biopsied tissue, in the case of sympathetic ophthalmia, the enucleated eye for histological examination.

General tests[4,26]

Several nonspecific tests are helpful. A complete blood count with differential count will help identify systemic infection (with leucocytosis), parasitic infestation (with eosinophilia), leukaemia, or immunocompromised states. A comprehensive metabolic panel will help identify renal or hepatic dysfunction, and undiagnosed hyperglycaemia. The results of these tests are essential for initiating therapy with corticosteroids and steroid-sparing medications. Chest X ray is useful in workup for sarcoidosis and tuberculosis. Nonspecific tests for inflammation (such as CRP- C reactive protein) are rarely useful in the diagnosis of uveitis.

Infective uveitis

Syphilis: Caused by the spirochete *Treponema pallidum*. *Treponema pallidum* is very difficult/impossible to culture in the laboratory, under normal conditions.The mainstays of testing are direct and indirect treponemal antibody tests. The direct tests are – the fluorescent treponemal antibody (FTA-ABS), *Treponema pallidum* particle agglutination assay (TPPA), and microhaemagglutination assay (MHA-TP/TPHA). These teste serve as seroconversion markers, and remain positive forever once the patient has been exposed to syphilis, even if it was completely treated. These tests are more useful in ruling out syphilis than in establishing the diagnosis. The indirect tests are – the rapid plasma reagent (RPR) and the Venereal Disease Research Laboratory (VDRL). The titres of these indirect tests vary with the disease load and become undetectable in fully treated disease. Thus for active syphilis the patient has a positive TPHA and a positive RPR, while the patient with latent, neurosyphilis or previously treated syphilis will have a positive FTA-ABS with a negative RPR. It is important to note that because ocular syphilis implies neurosyphilis, the patient with ocular syphilis usually presents with a positive FTA-ABS and negative RPR, without a prior history of treatment for syphilis. Also these patients require lumbar puncture to perform VDRL on the cerebrospinal fluid to rule out neurosyphilis. The polymerase chain reaction (PCR) diagnostics are capable of detecting *Treponema pallidum* DNA in biopsy specimens, such as vitreous. This is particularly useful in posterior segment or panuveitic syphilitic disease.

Tuberculosis: More than 2 billion people worldwide have been infected with *Mycobacterium tuberculosis*. Like *treponema pallidum*, *mycobacterium tuberculosis* is very difficult to culture in the laboratory. Definitive diagnosis of tuberculosis is through observation of mycobacterium tuberculosis on biopsy specimen with acid-fast stains or by PCR amplification of mycobacterium tuberculosis DNA. These are rarely achieved in the clinical setting, so the diagnosis is usually achieved through indirect testing. An elevated ESR (approaching 100) and a Chest X ray are important adjuncts to the diagnosis of tuberculosis. It is important to note that most cases of uveitic tuberculosis for paucibacillary or military disease are not accompanied by pulmonary disease. The QuantiFERON TB-GOLD test (Cellistis, Valencia, California) and the T-SPOT TB test (Oxford Immunotec, Marlborough, Massachusetts) are FDA-approved interferon gamma release assays (IGRAs). The patients' peripheral blood leucocytes are purified and mixed with a very specific set of mycobacterium tuberculosis peptides that do not include BCG (Baccile Calmette-Guerin) cross-reacting proteins. The resulting lymphocyte gamma interferon production is the quantified. These tests are considerably much more expensive, compared to the TST (tuberculosis skin testing). In our population TST is not as reliable as almost the entire population was immunized with BCG at birth, and tuberculin skin testing may reveal false positives in our population.

Lyme disease: Testing for Lyme disease is not regularly done in South Africa[27]. It is caused by the spirochete *Borrelia burgdorferi*. It is more common in the northeastern and northern Midwest regions of the United States, which correspond to the habitat of its vector tick of the *ixodes* genus. Serologic testing, with screening ELISA (Enzyme Linked Immunosorbent Assay) followed by confirmatory testing with Western blot screening, are the mainstay of diagnosis.

Viral testing: The diagnosis for CMV retinitis is clinical, as CMV retinitis has a typical appearance, and no additional confirmatory testing is generally necessary. The other types of viral infections such as acute retinal necrosis (ARN) caused by varicella-zoster or herpes zoster infection, the same rule applies. When confirmatory tests are required, varicella-zoster or herpes simplex DNA PCR is done, and can detect fewer than 10 viral DNA copies in the aqueous or vitreous fluid. Viral DNA PCR is incapable of differentiating active from previous/ latent infection, in this case quantitative real-time PCR can provide tier-like data on the amounts of viral DNA in the sample.

Parasitic testing: Toxoplasma uveitis is suspected in the patient with retinochoroiditis, dense vitritis, and choroidal scars of variable pigmentation. The finding of positive anti-*toxoplasma* IgG is not sufficient to make the diagnosis, as about 30% of the American population are seropositive for *toxoplasma gondii*[26]. Negative serology effectively rules out the diagnosis. In cases of acquired toxoplasmosis IgM tiers rise before IgG seroconversion. Definitive diagnosis of toxoplasmosis is accomplished through DNA PCR of either vitreous or aqueous. The larger t.*gondii* organisms do not readily enter the anterior chamber, therefore vitreous sampling has better yield.

Toxocara canis and *toxocara catis* serum antibody titers are considered positive if greater than or equal to 1:8. DNA PCR has got no role because the worm is usually sequestered in the choroid or choriocapillaries, and thus definitive diagnosis is rarely achievable. The finding of eosinophilia is only supportive of the diagnosis.

Immune-mediated uveitis

Sarcoidosis: Definitive diagnosis of sarcoidosis requires histopathological demonstration of noncaseating granulomata in biopsied tissues, the easiest of which to biopsy is suspicious conjunctival nodules. The chest X ray remains the core diagnostic test, with radiographic features of hilar adenopathy or interstitial fibrosis, necessitating pulmonary function tests, bronchoscopy, or mediastinoscopy. High resolution chest CT also has high sensitivity for detection of pulmonary sarcoidosis, as well as gallium scan or even ^{18}F-labeled fluorodeoxyglucose positron emission tomography, but should be followed up by tissue biopsy. The angiotensin converting enzyme (ACE) measures serum concentration of this enzyme which is produced by macrophages, and is present in high concentrations in patients with high systemic granuloma load. ACE levels can be decreased by treatment with immunosuppressants (for example systemic corticosteroids), and in patients taking ACE-inhibitors for their treatment for hypertension. The same can be said for serum lysozyme and urinary 24-hour calcium testing, in that their sensitivity is about 84% while their specificity is about 95%, as the ACE. But combining these serum tests with the radiologic investigations increases the diagnostic accuracy significantly.

Human Leucocyte Antigen Testing: Human Leucocyte Antigen-associated disease is defined as the statistically increased frequency of an HLA haplotype in persons with that disease as compared to the frequency in a disease-free population. HLA testing can provide supportive evidence for a particular diagnosis but cannot make a definitive diagnosis. HLA-B27 positivity is associated with a number of autoimmune diseases, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease. The presence of this allele in the general population is approximately 8%. HLA subtying is accomplished with either a serologic approach or a molecular biologic approach that amplifies the HLA-B locus and identifies the alleles present. Approximately 40% to 50% of acute uveitis cases are associated with HLA-B27. Acute, unilateral, sudden onset, nongranulomatous, anterior uveitis, typically with hypopyon is characteristic of HLA-B27 positive uveitis. Such patients have a history of axial arthritis, particularly low back stiffness and pain worse on awakening. Sacroiliac X ray films can be diagnostic of ankylosing spondylitis, they are relatively nonspecific. Birdshot chorioretinitis, characterized by bilateral multifocal choroiditis associated with visual field loss and reduced electroretinogram (ERG) and cystoid macular oedema, occurs exclussiely in patients who are HLA-A29 positive. HLA-B51 is associated with a 6-fold increase risk of Behcet's disease. Tubulointerstitial nephritis and uveitis syndrome has a very strong association with HLA-DRB1*0102. It can be screened by urinalysis and β-2 microglobulin, which is a coreceptor for HLA class 1 and spills into the urine in the patient with interstitial nephritis. It usually presents as a bilateral anterior uveitis in older children and young adults.

Rheumatologic disease:

As a group rheumatologic diseases are associated with acute anterior uveitis, scleritis, and retinal vasculitis. The mainstay of testing is serology and radiographic analysis. Although Rheumatoid Arthritis is most often associated with anterior scleritis than with anterior uveitis, the rheumatoid factor and anti-IgG antibody are useful in ruling out the disease than in confirming it. Rheumatoid factor can also be falsely positive in Sjogren syndrome, chronic viral infection, hepatitis, and systemic lupus erythematosus (SLE). The anti-citrullinated protein antibody (ACPA) has been recently used as a biomarker for rheumatoid arthritis because of its increased specificity.

Chronic anterior uveitis is often associated with juvenile idiopathic arthritis (JIA), and is typically bilateral and asymptomatic, but is associated with high rates of complications. Uveitis is most commonly found in the pauci-articular (fewer than 5 joint involvement) form, and the majority of patients have positive antinuclear antibody (ANA) titers but negative rheumatoid factor.

The diagnosis of SLE is clinical and is based on 11 diagnostic criteria of which the ANA test is one. Approximately 5% of the population are ANA positive, but anti-dsDNA and Antihistone antibodies are more specific for SLE. Ideally the patient suspected of having SLE should be referred to the rheumatologist for evaluation.

Masquerade syndromes:

The presence of leucocoria in an otherwise white eye in a child should alert the physician to the likelihood of retinoblastoma. Diagnosis is through clinical (with leucocoria, vitreous seeding, and pseudohypopyon in advanced disease) and radiologic modalities. With B scan ultrasonography demonstrating a posterior segment mass containing echodensities form calcium and CT scanning demonstrating typical intralesional calcifications.

Workup for intraocular lymphoma in adults is more complex, most intraocular lymphoma is due to primary central nervous system lymphoma (CNS). The mainstay of diagnosis for intraocular lymphoma is vitreous biopsy, with the specimen undergoing cytology, flow cytometry for lambda chain clonality and lymphocyte markers, and immunohistochemical staining. Lumbar puncture is useful, especially in the patient that has neurologic symptoms. Ancillary testing with magnetic resonance imaging (MRI) of the head is useful in suspected intraocular lymphoma. Aqueous humour interleukin-10 (IL-10) and interleukin-6 (IL-6) have shown promise as an adjective means in diagnosis but have not gained popular clinical usage.

Special considerations:

In the patient with intermediate uveitis (pars planitis), a high level of suspicion must be maintained for demyelinating disease such as mulptiple sclerosis, as multiple sclerosis is present in 15 – 20% of those patients with intermediate uveitis. A brain MRI is therefore indicated to rule out demyelinating white matter lesions in the brain. With regard to panuveitis, behcet's disease, Vogt-Koyanagi-Harada disease, sympathetic ophthalmia, and multifocal choroiditis, may all present with panuveitis. For these disease entities there are laboratory tests to establish the diagnosis. Also the white dot syndromes (acute posterior multifocal placoid pigment epitheliopathy, serpiginous choroiditis, punctate inner choroidopathy, and multiple evanescent white dot syndrome) do not have a specific test to establish diagnosis.

Neuroretinitis, either unilateral or bilateral, is typical of cat scratch disease caused by *Bartonella henselae* and *Bartonella quintana*, both of which serologic testing helps to direct specific therapy.

TREATMENT

The mainstay of treatment in uveitis revolves around reduction of the inflammatory process inside the eye, or systemically if the cause is found to be systemic. The major available anti-inflammatory drugs by far are still the corticosteroids. The corticosteroids can be administered either topically, regionally (as in subtenons or intraorbital), or they can be administered systemically. Systemic corticosteroid therapy is generally reserved for the more severe types of uveitis, and the usual dose of intravenous corticosteroids is 10mg/kg/day. The same dose is used for enteral corticosteroid therapy. In cases where the anti-inflammatory effect is not substantially reducing the inflammation or when there is anticipated long term use of corticosteroids, other immunomodulatory drugs are sought, in order to avoid the unwanted side effects of the corticosteroids. These “steroid-sparing”, for example methotrexate or cyclophosphamide are not without systemic side effects in themselves, and should therefore be used very judiciously and with the collaboration of the relevantly qualified specialist in that specific field, in most cases the internist or the rheumatologist.

In the case of infective uveitis, the treatment is aimed at eradicating the causative agent. In cases of bacterial infection, the appropriate antibacterial agent(s) is (are) used, in cases of viral infection, antiviral agents are used, and in cases of parasitic infestation the appropriate antimicrobial agents are employed. In general most patients with uveitis do get a dose of a strong topical steroid such as prednisolone acetate 1%, except in cases of herpetic keratouveitis. These patients are also treated with moderately strong mydriatic/cycloplegic agent such as homatropine or atropine, in order to break the posterior synechiae.

METHODOLOGY

This is a retrospective study that was conducted at the Universitas Academic Hospital, approved by the Health Sciences Research Ethics committee of the Faculty of Health Sciences of the University of the Free State and by the Health Sciences Research Ethics Committee of the Department of Health of the Province of the Free State, South Africa. Permission was also granted by the Head of Department of the provincial Department of Health and also the Hospital Chief Executive Officer (CEO). This study followed the tenets of the declaration of Helsinki, and no informed consent was required for the study. The patients' details and identities were kept confidential and were delinked in order to ensure the patients' information could not be traced back. The study ran over 1 year (12 calendar months).

Included in the study were all the patients that were seen, investigated (and diagnosed) and treated at the Universitas Academic Hospital eye clinic over 5 years (that is from 1/1/2012 to 31/12/2016). These patients received specific diagnoses based on their history, clinical examination, and laboratory results.

Excluded from the study were all the patients that were "proven" to be having idiopathic uveitis (with a clinical picture that does not "fit in" with any of the common uveitis syndromes and after extensive investigations the cause was still not found), toxic/drug induced uveitis, traumatic/postsurgical uveitis, and phacogenic uveitis. A special group of uveitis deserves special mention, as with time this group tends to make up most of the idiopathic uveitis. This is "simple anterior uveitis" which is first episode of acute, unilateral, mild to moderately severe nongranulomatous iritis or iridocyclitis occurring in an otherwise healthy young to middle-aged adult[22]. These patients are treated empirically without any further investigations.

The age groups were categorized as follows[28] : 0 – 14 years = children

: 15 – 24 years = youths

: 25 – 64 years = adults

: ≥65 years = seniors

The HIV status was already known in the majority of cases. Those that were not aware of their status were either tested at the eye clinic, local clinic, or refused testing without knowing their HIV status.

The statistical analysis was done by the Department of Biostatistics of the University of the Free State. With quantitative variables the analysis included observed minimum and maximum values, calculated mean, and standard deviation and median; with qualitative variables the absolute and relative frequencies were calculated to assess homogeneity, the chi square test was used at the significance threshold of 5%.

The minimum follow up period of these patients as recorded on the clinical files was 12 months follow up.

RESULTS

Demographics:

In the population of the study there were 54 patients, with 71 eyes analysed. All 54 patients were of Black African ethnicity, and were of lower working class in terms of socio-economic status. There were 27 males and 27 females, with an equal frequency of both genders in the study population. There were 14 patients in the subgroup of children (minimum age = 1 years, median age = 5.5 years, and maximum age = 13 years); 6 in the youths subgroup (minimum age = 15 years, median age = 19 years, and maximum age = 23 years); 33 in the adult subgroup (minimum age = 24 years, median age = 42 years, maximum age = 56 years); and only 1 in the seniors subgroup (age 70 years).

With regards to HIV status 23 patients (42.59%) tested positive, 23 patients (42.59%) tested negative, and 8 patients (14.81%) remained unknown. Predictably the majority of patients that were HIV positive came from the adults' age group (19 patients, 35.18%).

22 of the patients (40.47%) were smokers, while 32 patients (59.25%) were non-smokers.

Anterior uveitis was diagnosed in 17 patients (31.48%), and of these 15 patients (27.77%) had unilateral disease, while 2 patients (3.7%) had bilateral disease.

Intermediate uveitis was diagnosed in 5 patients (9.25%) all of whom had unilateral disease.

Posterior uveitis was diagnosed in 4 patients (7.4%), of whom 2 (3.7%) had unilateral disease and the other 2 (3.7%) had bilateral disease.

Panuveitis was diagnosed in 28 patients (51.85%), of whom 15 (27.77%) had unilateral disease and 13 (24.07%) had bilateral involvement.

Granulomatous uveitis was diagnosed in 3 patients (5.55%), 2 (3.7%) had bilateral disease, while 1 (1.85%) had unilateral involvement. Thus 51 patients (94.44%) were diagnosed with nongranulomatous uveitis.

Acute disease was diagnosed in 17 patients (31.48%), while chronic involvement was diagnosed in 37 patients (68.51%).

When it comes to the presentation, 53 patients (98.14%) presented with decreased vision; 46 patients (85.18%) presented with ocular discomfort; 45 patients (83.33%) presented with ocular pain; 39 patients (72.22%) presented with redness; and 10 patients (18.51%) presented with foreign body feeling. The presentation with floaters was very rare, presumably because the patients with panuveitis, intermediate uveitis and posterior uveitis presented with poorer vision.

Visual acuity was graded according to the Snellen chart, at the index entry/ on presentation, and the worst vision was recorded (visual acuity for the worst eye in the case of bilateral disease). 7 patients (12.96%) presented with visual acuity ≥20/70; 10 patients (18.51%) presented with visual acuity between <20/70 and 20/200; and 37 patients (68.51%) presented with visual acuity less than 20/200.

At the final recorded visual acuity (Snellen chart) – in the group >20/70 there were 20 patients (37.03%); in the group ≤20/70 to 20/200 there were 16 patients (29.62%); and in the group <20/200 there were 18 patients (33.33%). It is important to note that in this last subgroup (<20/200), 9 patients (50% of this subgroup) were having advanced retinoblastoma. They presented with NLP visual acuity, and those eyes were eventually enucleated as they were not salvageable, and therefore these patients could not regain vision in those eyes.

Diagnoses:

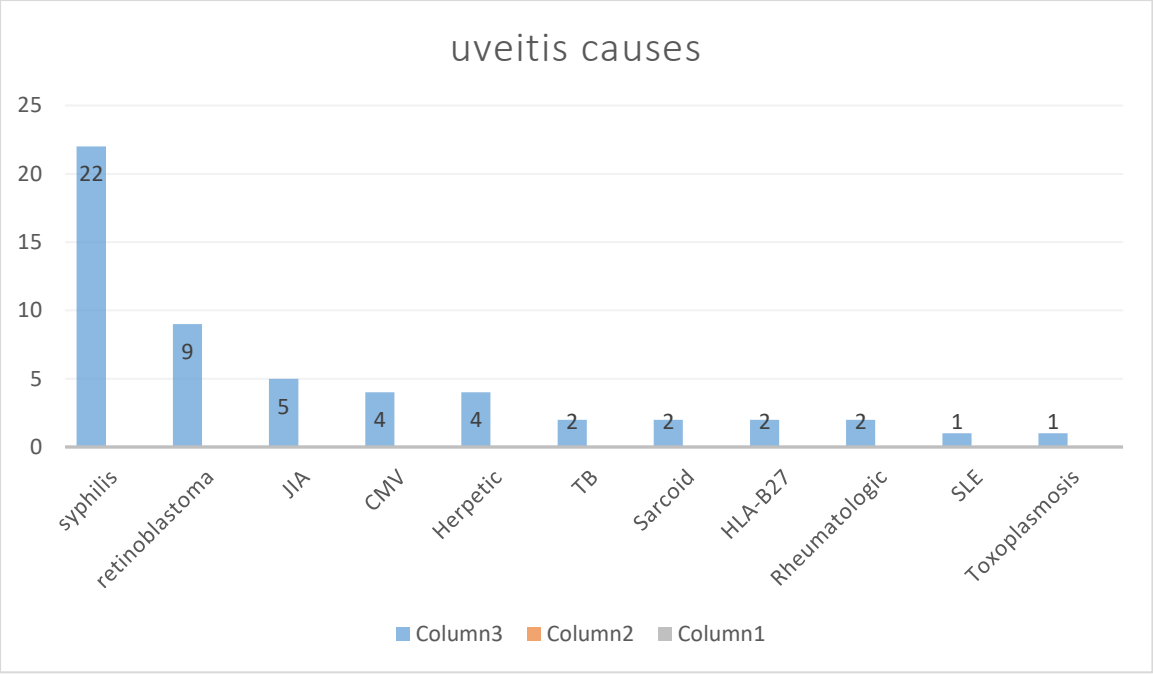
Children age group: 9 patients (64.28% of subgroup, 16.66% of study population) were diagnosed with the masquerade syndrome, Retinoblastoma. These children presented with advanced retinoblastoma with pseudohypopyon; 4 patients (28.57% of subgroup, 7.4% of study population) were diagnosed with JIA; and 1 patient (7.14% of subgroup, 1.85% of study population) was diagnosed with syphilis (Non-congenital).

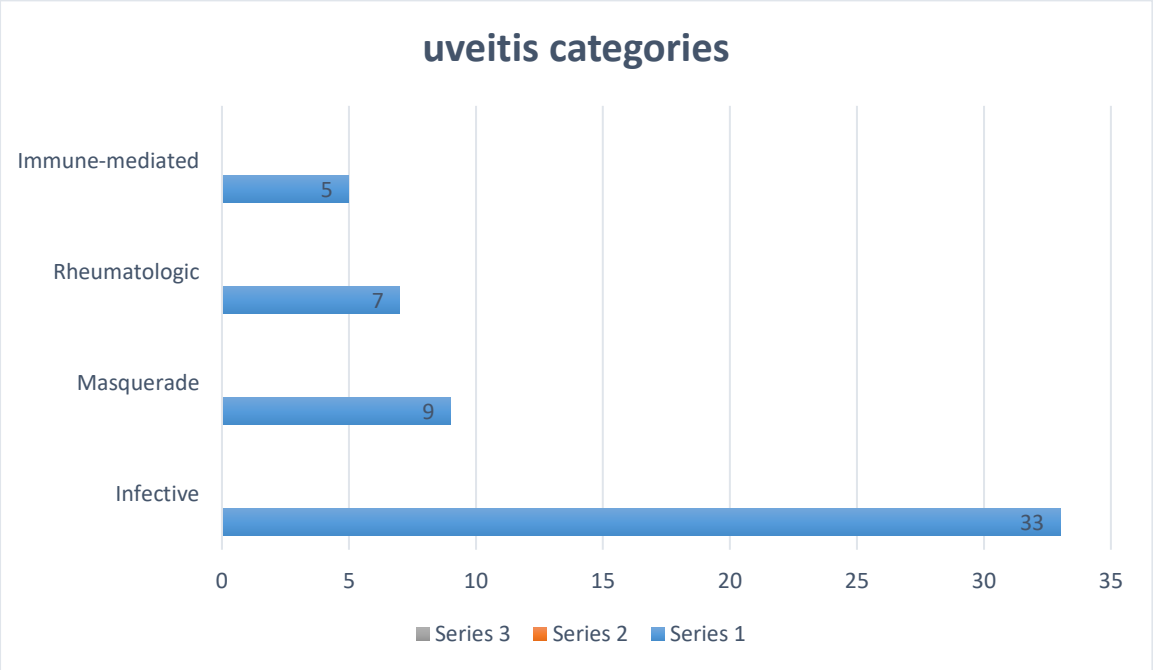
Youths group: the most frequent diagnosis was/were syphilis with 2 patients (33.33% of subgroup, 3.7% of study population); herpetic uveitis in 2 patients (33.33% of subgroup, 3.7% of study population) as well; JIA with 1 patient (16.66% of subgroup, 1.85% of study population); and sarcoidosis with 1 patient (16.66% of subgroup, 1.85% of study population) as well.

Adults group: the most frequent diagnosis was syphilis with 18 patients (54.54% of subgroup, 33.33% of study population); CMV retinitis with 4 patients (12.12% of subgroup, 7.4% of study population); Tuberculosis with 2 patients (6.06% of subgroup, 3.7% of study population); herpetic uveitis with 2 patients (6.06% of subgroup, 3.7% of study population); HLA-B27 associated uveitis with 2 patients (6.06% of subgroup, 3.7% of study population); rheumatologic disease with 2 patients (6.06% of subgroup, 3.7% of study population) as well; sarcoidosis with 1 patient (3.03% of subgroup, 1.85% of study population); systemic lupus with 1 patient (3.03% of subgroup, 1.85% of study population); and toxoplasmosis with 1 patient (3.03% of subgroup, 1.85% of study population).

Seniors group: there was 1 patient (1.85% of study population) with unilateral moderately severe syphilitic uveitis.

Results chart

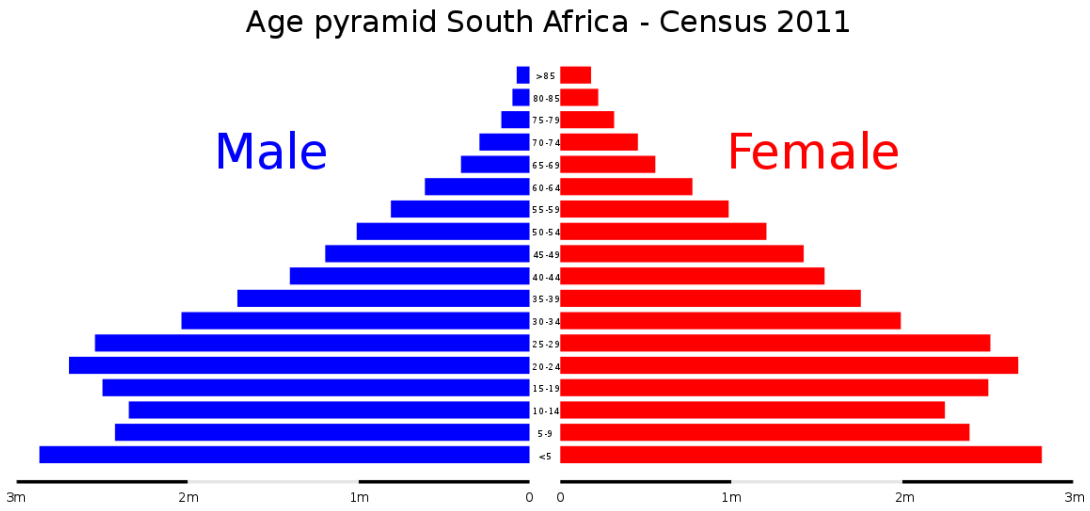




DISCUSSION

The data from the study suggest that the eye clinic population is a "young" population, as evidenced by the rarity of uveitic patients that are above the age of 60 years. This correlates with the general South African population[29], as well as the population of Africa in general.

Figure 1[29].



The results of the data show that the main problem of uveitic patients in our study population is infective type of uveitis (such as syphilis, CMV retinitis, and Herpetic uveitis), as shown by the high occurrence of syphilitic uveitis and CMV retinitis in adult patients, and herpetic uveitis and syphilitic uveitis in youths in this study. This might be related to the occurrence of HIV in this study population, which is high in comparison to the general population[29-31].

After infective uveitis, the most common type is collagen disease/Rheumatologic type (such as JIA and Rheumatoid arthritis) and HLA-B27 associated uveitis in the adult group, with both occurring in similar frequency in the adult group; while collagen disease and immune mediated uveitis occur in similar frequency in the youths group, second to infective causes.

In the children group masquerades (Retinoblastoma) dominated the group, followed by JIA. JIA is as expected in this group, but retinoblastoma presented a disproportionately frequency as these children presented initially with a pseudohypopyon due to advanced (at least stage V retinoblastoma) on initial evaluation.

The seniors group was uncharacteristic in that there was only 1 patient, who was HIV negative, and this patient had unilateral infective form of uveitis, which is not in keeping with the vast majority of current literature,[32,33] as the most common cause of uveitis in the elderly is mostly autoimmune diseases like sarcoidosis. This perhaps correlates well with the fact that the African population is of adult and young age in general[29].

Overall infective type of uveitis accounted for 61.11% of the cases in this study; with syphilitic uveitis accounting for 40.74%; CMV and herpetic uveitis accounting for 7.4%, each/individually; tuberculosis accounting for 3.7%; and toxoplasmosis accounted for 1.85%.

The Masquerade syndrome, retinoblastoma, accounted for 16.66% of the cases in this study.

Rheumatologic disease accounted for 12.96% of the total number of cases in this study; with JIA accounting for 9.25% and Rheumatoid arthritis accounted for 3.7%.

Immune mediated uveitis accounted for 9.25% of the cases in this study; with sarcoidosis and HLA-B27 associated uveitis accounting for 3.7%, each/individually; and Systemic Lupus accounted for 1.85% of the cases.

There was also a recorded gross increase in the visual acuity of the patients in this study at the last recorded visual acuity. It is important to note that half the number of patients in the poor visual acuity group (<20/200), were retinoblastoma children with non-salvageable eyes/ or vision.

The limitations of this study comprise those of a static cross-sectional design, whereby we might be missing a number of mild uveitis cases from our tertiary public healthcare bounded population that may have been seen exclusively in private clinics/practices and primary, and secondary healthcare level that were not referred to the tertiary institution.

CONCLUSION

The study finding are in general in keeping with the current literature on uveitis. And as predictable by our population, the main problems with uveitis in our population tend to be infective causes. This might be related to the high occurrence of HIV and the poor/low socio-economic standing of our population.

In our population the high index of suspicion for advanced retinoblastoma in childhood uveitis cannot be overstated. These children typically present with a pseudohypopyon, in an eye that is not inflamed or red. This pseudohypopyon is often mistaken for inflammatory hypopyon. Because these children tend to present with advanced disease, they also present with a red and painful eye due to the secondary closed angle glaucoma (with neovascularization in the angle), which can prompt the physician to make an assessment of uveitis.

The limitations of this study comprise those of a static cross-sectional design, whereby we might be missing a number of mild uveitis cases from our tertiary public healthcare bounded population that may have been seen exclusively in private clinics/practices and primary, and secondary healthcare level that were not referred to the tertiary institution.

As such other secondary studies may be appreciated, in order to include the patients seen in private clinics and practices. Also other secondary studies to look at other related issues not included in this study may be appreciated, for example to look at the profile of complications from these patients or to look at the visual outcomes of these patients.

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