Complications of juvenile uveitis.

Alok Bahl[1*], Sohár Nicolette[2]

[1]Royal Eye Infirmary, University Hospitals Plymouth NHS Foundation Trust, Plymouth, United Kingdom

[2]Department of Ophthalmology, University of Szeged, Szeged, Hungary

Abstract

The International Uveitis Study Group (IUSG) and the Standardisation of Uveitis Nomenclature Working Group (SUN Working Group) have helped define and classify uveitis and reach a global consensus on descriptors and the grading of inflammation. A readily available history taking questionnaire helps to name and mesh the probable uveitic entity, thereby ordering specific investigations tailored to help diagnose a uveitic entity in the most cost effective way.

There are varied uveitic entities that are common in different age groups like infants, toddlers, school children and adolescents, with Juvenile Idiopathic Arthritis Associated Uveitis (JIA-U) being the most common. The knowledge of risk factors for developing uveitis in Juvenile Idiopathic Arthritis (JIA) and poor prognostic indicators has helped in developing screening guidelines.

The better understanding of the pathogenesis of various entities of juvenile uveitis including autoimmunity and genetic associations improved the management of these conditions. There are routine laboratory investigations for all cases and specific ones to diagnose and confirm certain entities.

The main ocular complications of juvenile uveitis include posterior synechiae, cataract, glaucoma, vitreous haze, Cystoid Macular Oedema (CMO), band keratopathy, epiretinal membrane, hypotony and phthisis bulbi.

Corticosteroids usually are the first line of treatment, followed by the use of Disease Modifying Anti-Rheumatic Drugs (DMARD) and then biologic agents to control inflammation. The latter 2 groups of drugs have also played a role as corticosteroid sparing agents as they help control the inflammation through different mechanisms. Periocular steroid injections and intravitreal dexamethasone implants (Ozurdex) have helped to decrease the systemic side effects of corticosteroids in children.

Several factors should be considered in the surgical management of complications of juvenile uveitis, including the risk of irreversible amblyopia, patient age, degree of inflammation, preoperative visual acuity and current therapy. Judicious perioperative use of topical and systemic corticosteroids with addition of immunosuppression leads to improved outcomes. Close collaboration between the ophthalmologist and the treating paediatric rheumatologist is of extreme importance to ensure a successful surgical outcome.

Keywords: Uveitis, Juvenile idiopathic arthritis, Intraocular lens, Glaucoma drainage device, Optical Coherence Tomography (OCT).

Abbreviations:

IUSG: International Uveitis Study Group; SUN Working Group: Standardisation of Uveitis Nomenclature Working Group; JIA: Juvenile Idiopathic Arthritis; JIA-U: Juvenile Idiopathic Arthritis Associated Uveitis; VKH: Vogt-Koyanagi Harada Syndrome; ANA: Antinuclear Antibody; CMO: Cystoid Macular Oedema; IOL: Intraocular lens; IOP: Intraocular Pressure; GDD: Glaucoma Drainage Device; EDTA: Ethylenediaminetetraacetic acid; AC: Anterior Chamber; DMARD: Disease Modifying Anti-Rheumatic Drug; OCT: Optical Coherence Tomography; PCR: Polymerase Chain Reaction; ELISA: Enzyme Linked Immunosorbent Assay; IgG: Immunoglobulin G; IgE: Immunoglobulin E.

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Introduction

Juvenile uveitis is a condition that occurs in children where there is inflammation of the uveal tract, either in part or in whole. Most of the times, there are no symptoms experienced or noticed by the child, and the patient presents to the clinic only when the parents have noticed a change or abnormality in the child's eye. This is often, quite late in the disease process, making the treatment and visual rehabilitation difficult.

More recently, with the better understanding of the immunological processes and pathogenesis, the development of newer treatment is aimed at these immunological processes. This condition requires constant surveillance and monitoring of cases prone to juvenile uveitis, to identify and diagnose the disease early, prevent complications and for better prognosis of the child.

The most common condition associated in children with uveitis is JIA. However, there are many other conditions associated with juvenile uveitis that is less common but equally debilitating. A detailed systemic history is very important and

can lead to the proper recognition of the uveitic entity and appropriate management of the condition.

Medical management needs a multidisciplinary approach with the involvement of the paediatrician and rheumatologist. The use of immunosuppressive drugs in children and their potential systemic side effects needs to be weighed against the need for aggressive treatment of the uveitic condition in children.

Surgical management is fraught with difficulty due to the inflamed eye leading to post-operative complications. All surgeries should be taken up by an experienced paediatric ophthalmic surgeon (Dr. S. Rao, personal communication, December 23, 2017).

Objectives

- The main objectives of this study are:
- To understand the various types of uveitis in children based on anatomical location and aetiology.
- To understand the signs and symptoms of uveitis and the lack of them in many paediatric entities.
- To understand the need for surveillance and early diagnosis.
- To understand the complication of juvenile uveitis and its prevention and management.
- To understand the newer drugs and their mechanisms of action in juvenile uveitis.
- To understand the importance of a multidisciplinary approach to cases of juvenile uveitis.

Definition of uveitis

The International Uveitis Study Group (IUSG) defines uveitis as follows: "Uveitis consists of a group of diseases characterised by significant sight threatening intraocular inflammation primarily involving the uveal tract (iris, ciliary body and choroid), although inflammation of adjacent tissues, such as retina, optic nerve and vitreous humour also occurs" (International Uveitis Study Group, n.d.) [1].

The Standardisation of Uveitis Nomenclature (SUN) Working Group have helped reach a consensus on classification (based on sites(s) of inflammation and not on presence of structural complications), descriptors of uveitis, grading of Anterior Chamber (AC) cells and flare and activity of uveitis.

The SUN Working Group classifies uveitis according to anatomical site of the inflammation. The first location classified is anterior uveitis and is said to be present when the primary site of inflammation is the AC, which includes iritis, iridocyclitis and anterior cyclitic [2].

Intermediate uveitis is the next location classified and is when the primary site of inflammation is the vitreous and this includes pars planitis and posterior cyclitis. The third location classified is posterior uveitis and it occurs when the retina or choroid is the primary site of inflammation and includes focal, multifocal or diffuse choroiditis, chorioretinitis, retinochoroiditis, retinitis and neuroretinitis.

Panuveitis is the final location classified and is when the primary site of inflammation takes place in the AC, vitreous, and retina or choroid [3,4]. The SUN Working Group classification of descriptors of uveitis is based on the onset, duration and course of the uveitis.

Onset of uveitis can be either sudden or insidious. The duration of uveitis can be classified as limited, when the inflammation lasts for ≤ 3 months, or can be classified as persistent, when the inflammation lasts for a period >3 months. The last category is the course of action of the inflammation. The inflammation is classified as acute, when an episode is characterised by sudden onset and limited duration, or classified as recurrent, when repeated episodes are separated by periods of inactivity without treatment ≥ 3 months in duration, or classified as chronic, when the uveitis is persistent with relapse in <3 months after discontinuing treatment [2,4].

History taking in paediatric uveitis

The importance of detailed history taking cannot be emphasised enough in uveitic cases especially in children. The Massachusetts Eye Research and Surgery Institution developed an Ocular Inflammatory Disease Review of Systems Questionnaire (see Appendix) that includes detailed family history, social history, ocular and systemic medications and allergies, past medical and surgical history. There is a long list of diseases and symptoms of different systems in the body to help diagnose specific diseases associated with uveitis. This kind of systematic collection of information including patient demographics is a major help towards naming and meshing of the uveitic entity [5]. The duration, onset and course of the inflammation, the location of the inflammatory process with detailed clinical examination of the eyes and body, help in differential diagnosis and requesting for specific investigations. This approach is a sensible and practical way to order specific investigations tailored to help diagnose a uveitic entity in the most cost effective way.

In certain cases of known diagnosis like JIA, children do not have any ocular symptoms. In these cases, screening plays an important role.

The most common cause of uveitis in children is JIA. In 73% of these cases considered at risk, uveitis occurs within the first year of the onset of arthritis and could be the first sign of JIA [6]. Despite remarkable progress in the early detection and treatment of inflammation, vision-threatening complications of uveitis still occur in a vast majority of patients. Certain structural complications occur for example band keratopathy and cataracts which make the management of these complications usually more complex and requiring early surgical intervention [7]. This emphasises the need for regular ophthalmic screening and paediatricians and rheumatologists should be reminded to send such cases to the ophthalmologist.

Causes of uveitis in children based on age

According to C.S. Foster, the causes of uveitis (including masquerades) in different age groups among children vary. The most common causes of uveitis in infants include Herpes

Simplex Virus, Toxocara, Congenital Syphilis and Retinoblastoma.

The most common causes of uveitis in toddlers/school children include Toxocariasis, Toxoplasmosis, Leukaemia, Diffuse Unilateral Sclerosing Neuroretinitis and JIA. The most common causes in adolescents include JIA, Toxoplasmosis, HLA-B27-associated sarcoidosis and the presence of an Intraocular Foreign Body [8].

Investigations in juvenile uveitis

The ocular examination includes testing the visual acuity followed by a slit lamp examination of the anterior segment to look for keratic precipitates, AC flare and cells, iris nodules, new vessels on the iris, posterior synechiae and cataract. The measurement of intraocular pressure is important. Gonioscopy is used in cases of raised intraocular pressure to see if the anterior chamber angle is either open or closed with the presence of peripheral anterior synechiae. The examination of the posterior segment is done with either a 90 Dioptre lens on a slit lamp or by indirect ophthalmoscopy.

The ocular investigations include an OCT scan to detect CMO and other macular pathology. Fundus fluorescein angiography is difficult to perform in children and therefore not done. Ultrasound B scan can be done in cases of cataract that obstructs the view of the fundus. The ultrasound B scan can indicate if the retina is detached. It can also indicate the presence of severe vitritis or vitreous haemorrhage and posterior scleritis. Details of the retina cannot be obtained by ultrasound B scan like retinitis, choroiditis and vasculitis (Dr. S. Rao, personal communication, January 29, 2018).

Routine blood investigations include a complete blood count where a raised white cell count may indicate a bacterial infection. Relative lymphocytosis is seen in viral infections and tuberculosis, whereas, eosinophilia helps point us to a diagnosis towards sarcoidosis or parasitic infections.

Erythrocyte sedimentation rate and C-reactive protein are often raised in inflammatory disorders but does not give any specific information about the source of the inflammation. However, a baseline is useful to monitor the disease and response to treatment.

Peripheral blood smear is used to rule out blood malignancy masquerading as juvenile uveitis. Liver function tests, renal function tests and blood glucose levels are usually done to establish a baseline and monitor patients on corticosteroids and immunosuppressive drugs as these drugs are known to have toxic effects on these particular organs [9].

X-ray chest is requested to exclude tuberculosis and sarcoidosis. X-ray of sacroiliac joints to rule out ankylosing spondylitis. However, this is rare in children but common in adults.

Invasive investigations include anterior chamber paracentesis which is an easy to perform investigation and is used when infectious uveitis and endophthalmitis is suspected. The aqueous drawn is used for direct smear and for culture and sensitivity to detect bacteria, fungus and acid fast bacilli. It is also used for Polymerase Chain Reaction (PCR) [9].

Vitreous biopsy is used in cases of suspected intraocular inflammation, intraocular lymphoma and atypical intraocular inflammation not responding to conventional treatment [9].

Biopsy of iris and ciliary body is performed only if a tumour is suspected. Choroidal biopsy is performed to investigate choroiditis of unknown cause and choroidal malignancies. This procedure has high risk of choroidal haemorrhage and retinal detachment [9].

Retinal biopsy is performed in cases of unknown or atypical retinitis. The junction of the normal and inflamed retina (likely to harbour the infectious agent), superonasal quadrant (less chance of macular damage from retinal detachment and easier tamponade) and less vascular and peripheral location are preferred for the biopsy [9].

PCR is a simple test with higher sensitivity, specificity and quicker results. The presence of deoxyribose nucleic acid or ribose nucleic acid of the pathogen can be directly detected without waiting for culture results. This is helpful in diagnosis of viral uveitis like herpes, in ocular toxoplasmosis and endophthalmitis [9]. Disease specific laboratory investigations are requested based on history and clinical presentation.

Methodology

Conditions causing juvenile uveitis

Juvenile Idiopathic Arthritis (JIA): "JIA is the most common childhood rheumatic disease and is the most prevalent systemic disorder in children with uveitis" [10]. JIA-U its most frequent extra-articular manifestation.

"JIA can be defined as a group of idiopathic arthritides, which occurs before the age of 16 years and persists for at least 6 weeks". Females are more commonly affected than males by a ratio of 3:2 [11].

The most common risk factors for developing uveitis in JIA include, the female sex, Antinuclear Antibody (ANA) seropositivity, Oligoarticular arthritis, Rheumatoid factor seronegativity and early age of onset of arthritis (less than 6 years) [11,12]. There are 3 types of presentation of arthritis based on the onset and extent of joint involvement in the first 6 months [13,14].

Pauciarticular onset JIA which involves four or less joints, accounts for 60% of JIA cases, about 75% of this group of children is ANA positive and uveitis affects 20% of this group. Polyarticular onset JIA which involves 5 or more joints, accounts for 20% of JIA cases, 40% are ANA positive and uveitis affects 5% of this group [12].

Systemic onset JIA (Still disease) that accounts for 20% of JIA cases, no arthritis initially, systemic features include fever, transient maculopapular rash, generalised lymphadenopathy, hepatosplenomegaly and serositis, usually ANA negative, no uveitis in this group [13].

Ocular manifestations usually include typical clinical characteristics of JIA-U include insidious onset, bilateral involvement of eyes (70-80%), non-granulomatous morphology (>90%), chronic course (>90%) and asymptomatic presentation [5].

The Ocular Inflammatory Disease Review of Systems Questionnaire is very useful as the patients have no ocular symptoms and this questionnaire helps to determine the duration of the ocular disease from past ocular and medical history. It also helps to establish the chronicity of the disease and subtype of JIA [5].

Variable AC reaction with inflammatory cells in the anterior vitreous can be seen on slit lamp examination [11]. Keratic precipitates are seen in the Arlt's triangle. Posterior segment involvement in JIA-U is rare except for CMO which can occur quite commonly associated with the anterior uveitis [11].

Specific screening schedules have been recommended by the Royal College of Ophthalmologists, UK with the British Society of Paediatric and Adolescent Rheumatology focused on the highest risk group [15]. Following the initial screening, ongoing screening is of utmost importance to check progression of the disease and the effectiveness of the treatment.

A multidisciplinary approach with paediatric rheumatologist and ophthalmologist in the management of these cases is imperative with good communication between team members to provide the best treatment and outcome for the child.

Sarcoidosis: "Sarcoidosis is a chronic systemic granulomatous disease of unknown aetiology with varied clinical manifestations" [11]. Sarcoidosis is rare in children and seen between 8-15 years. Those below 5 years of age, usually have only anterior segment involvement and older children have anterior, intermediate and posterior segment involvement like adults.

The most common ocular features of paediatric sarcoidosis are chronic granulomatous anterior uveitis with mutton fat keratic precipitates and iris nodules. Moderate to severe intermediate uveitis may be seen with characteristic snowballs and snow banking. When the posterior segment is involved, it is common to see periphlebitis with candle wax dripping, multiple choroid granulomas or sarcoid tubercles [11]. Serum lysozyme levels are raised in sarcoidosis and have better sensitivity and specificity than serum angiotensin converting enzyme in diagnosis of sarcoidosis.

Depending on the site and severity of the intraocular inflammation, the primary treatment is topical, periocular or systemic corticosteroids. Immunosuppressive agents like methotrexate and azathioprine can be used in cases of long standing chronic inflammation who do not respond to steroids [11].

Ocular tuberculosis: Tuberculosis is caused by Mycobacterium tuberculosis and is commonly seen in developing countries. It can cause anterior, intermediate and posterior uveitis.

Anterior uveitis is granulomatous with mutton fat keratic precipitates, iris nodules and formation of posterior synechiae. Intermediate uveitis is usually mild to moderate with snowballs, peripheral vasculitis and snowbanking. The most common presentation in posterior uveitis is multifocal, yellowish white choroidal tubercles. Large subretinal abscess with exudative retinal detachment can also occur [11].

Laboratory diagnosis of ocular tuberculosis is difficult. Mantoux test is of limited value in children due to cross reactivity with the Bacillus Calmette-Guerin vaccine (BCG). Interferon-gamma release assays including the QuantiFERON-TB Gold In-Tube offer several advantages over the Mantoux test, including improved specificity (particularly in Bacillus Calmette-Guerin vaccinated populations). Computerised tomography of chest is helpful when a systemic focus is suspected [16].

Toxocariasis

"*Toxocara canis* or *Toxocara cati* are parasitic nematodes that are found in the small intestine of dogs, cats, and wild carnivores." Contaminated food and soil that contains larval eggs can cause infection in humans [11].

One of the syndromes associated with toxocariasis is visceral larva migrans, which is the systemic form of the toxocara infection and is usually seen in children between the age of 6 months to 5 years [11]. The other syndrome is called ocular toxocariasis and occurs in children older than the age of 5 and is unilateral in 90% of cases.

Ocular toxocariasis is classified into three types

Type 1: Peripheral inflammatory granuloma which is the most common of the three, where the granuloma is white in colour, elevated and measures two-thirds to three disc diameters in size. In severe cases of inflammation heterotropia of the macula occurs leading to extensive loss of vision.

Type 2: Posterior pole granuloma presents as a white chorioretinitis patch with ill-defined margins and severe overlying vitritis.

Type 3: Endophthalmitis like picture where there is peripheral inflammation and a yellowish white mass. This endophthalmitis is painless and not associated with redness and photophobia [11].

Diagnosing ocular toxocariasis is difficult and is based on clinical presentation of symptoms. Leukocytosis and eosinophilia are seen in patients with systemic toxocariasis or visceral larva migrans. ELISA with toxocara excretory-secretory antigen is highly specific for toxocara infection. An increase of anti toxocara antigen IgE level indicates an acute toxocara infection or progressive inflammation, whereas an increase of IgG level confirms a past or present infection with minimal inflammation. Treatment is with systemic benzimidazole derivatives like albendazole, thiabendazole and mebendazole [11].

Ocular toxoplasmosis

Toxoplasma gondii is the organism responsible for causing ocular toxoplasmosis which is a major cause of uveitis in children. Toxoplasma gondii" is an obligate intracellular parasite, ubiquitous in nature and its definitive host is the cat [11].

The hallmark of ocular toxoplasmosis is focal necrotizing retinochoroiditis, with secondary involvement of the choroid. The active lesion is seen as yellowish white in colour, with a variation in size and usually circular or oval in shape located mainly in the posterior pole. "Necrotizing retinochoroiditis is usually accompanied by severe vitritis, producing the classic 'headlight in the fog' appearance" [11].

Some of the signs include increased IOP, neuroretinitis and papilitis. Complications include choroidal neovascularisation in children.

Diagnosis of ocular toxoplasmosis is based on the measurement of intraocular parasite-specific antibody production, which indicates an indirect proof of the presence of the parasite within the eye [11].

The main goal of treatment is to prevent the multiplication of the protozoa. The combination of pyrimethamine and sulfadiazine is used for the treatment of ocular toxoplasmosis. Other drugs are trimethoprim/sulfamethoxazole, clindamycin, and azithromycin [11].

Lyme disease

Lyme disease also known as Borreliosis is an infection caused by a flagellated spirochete bacterium *Borrelia burgdoferi*.

Uveitis is not very commonly seen but when it manifests it can be seen in the form of anterior or intermediate uveitis, peripheral multifocal choroiditis, retinal periphelbitis and neuroretinitis. Some of the other ocular manifestations include follicular conjunctivitis, episcleritis, keratitis, scleritis, orbital myositis, optic neuritis, ocular motor nerve palsies and reversible Horner syndrome.

Investigations include PCR and ELISA. Treatment involves the use of oral doxycycline or amoxicillin [13].

Sympathetic ophthalmia

Sympathetic ophthalmia is an autoimmune disease of the eye and a cause of bilateral anterior granulomatous uveitis in children [11]. It is most commonly caused by trauma and ocular surgical intervention and presents as bilateral panuveitis.

On slit lamp examination, some of the common findings include "bilateral anterior granulomatous uveitis associated with mutton-fat keratic precipitates, moderate-to-severe vitritis, exudative retinal detachment, papillitis, and choroiditis. Sub-retinal pigment epithelium yellowish white nodules are seen in the peripheral retina and are known as Dalen-Fuchs nodules." [11].

There is a strong correlation between uveal injury and sympathetic ophthalmia that has led to strong suspicion of the pathogenic role of the uvea, citing the presence of antiuveal antibodies in a large percentage of patients with sympathetic ophthalmia [14]. Treatment with corticosteroids and immunosuppressant drugs should be initiated as soon as possible in order to prevent irreversible loss of vision [11].

Results and Discussion

Complications of juvenile uveitis

Complications are more often seen in delayed presentations. Early diagnosis and prompt initiation of treatment to achieve complete quiescence is the mainstay of management of juvenile uveitis patients for prevention of sight threatening complications [11].

Due to the lack of treatment or in cases of inadequate treatment certain complications can include formation of, cataract (40-80%), band keratopathy (30-80%), CMO (30-50% in chronic cases), vitreous haze/debris (20-30%), glaucoma (10-30%), chronic hypotony and phthisis (5-20%) and other posterior pole complications (e.g. disc neovascularization, macular hole) that are rare [5].

Complications from treatment of the uveitis may include ocular complications like cataracts, keratitis, and steroid-induced glaucoma from topical steroids, whereas regional corticosteroids cause complications like lid abnormalities, orbital socket contraction, and globe perforation [13].

Treatment complications may also include certain systemic complications like gastrointestinal bleeding from the use of non-steroidal anti-inflammatory drugs, growth retardation, weight gain, acne, mood swings, and infections from systemic corticosteroids. Immunosuppressive therapy with the use of methotrexate, cyclosporine-A, cyclophosphamide, chlorambucil can lead to certain dangerous complications, for example bone marrow suppression and pancytopenia [5].

Medical management of juvenile uveitis

The goal of treatment in uveitis is to immediately control and clear the intraocular inflammation. Corticosteroids usually are the first line of treatment whether used topically, regionally or systemically [17]. This is followed by the use of DMARD's and then biologic agents as needed. Table 1 shows the different classes of immunosuppressive drugs and their mechanism of action. Corticosteroids are the first line of treatment for juvenile uveitis.

Class	Mechanism of Action	Generic name	Trade name
Corticosteroids (topical, systemic, regional)	Nonspecific anti-inflammatory	Topical prednisolone acetate 1%	Pred forte
		Topical difluprednate	Durezol
		Oral prednisolone	Deltasone

		Intravitreal dexamethasone implant	Ozurdex
		Periocular triamcinolone acetonide	Kenalog
Antimetabolites	Inhibit purine synthesis	Methotrexate	Rheumatrex
		Mycophenolate mofetil	Cellcept
		Azathioprine	Imuran
T-cell inhibitors	Inhibit T-cell activation and interleukin-2 (IL-2) production	Cyclosporine	Sandimmune Neoral Gengraf
Biologics TNF inhibitors	Inhibits tumour necrosis factor-alpha(TNF-α)	Etanercept	Enbrel
		Infliximab	Remicade
		Adalimumab	Humira
		Golimumab	Simponi
Lymphocyte inhibitors	Inhibits CD20	Rituximab	Rituxan
	Inhibits CD80 and CD86	Abatacept	Orencia
IL-6 antagonists	Inhibits IL-6	Tocilizumab	Actemra

Table 1. *Immunosuppressive drugs used to treat juvenile uveitis, with their mechanism of action [17].*

Corticosteroids can be classified as either topical, systemic or regional. Antimetabolites like methotrexate are the second line of drugs used in the treatment of juvenile uveitis. If the inflammation is still unresolved then the third line of drugs are administered.

These include the biologic agents like adalimumab which is a tumour necrosis alpha factor inhibitor. Topical cycloplegic agents like tropicamide or cyclopentolate 0.5%-1% eye drops are used in conjunction to reduce the pain caused by ciliary spams, keep the pupil mobile to prevent formation of posterior synechiae and to break any previously formed posterior synechiae [15].

Types of corticosteroids

Topical corticosteroids like prednisolone acetate 1%, dexamethasone phosphate 0.1% or its equivalent is prescribed [17]. Based on the severity of uveitis on presentation, the frequency of administration of the eye drops ranges from hourly instillation to three to four times a day. The topical corticosteroids are gradually tapered off based on the response of the ocular inflammation to the treatment until there is no reactivation of the inflammation.

Systemic corticosteroids are indicated if poor prognostic indicators like poor visual acuity, hypotony, cataract, glaucoma, macular oedema and dense opacities of the vitreous are present on initial presentation. Either oral prednisolone 1–2 mg/kg/day or intravenous pulse methylprednisolone 20–30 mg/kg/day for 1–3 days is given. Methotrexate, a DMARD is the first choice of second-line therapy [15].

Regional corticosteroids like posterior sub-Tenon injection or orbital floor injection of triamcinolone acetate can be considered with severe anterior uveitis, vitritis and CMO that have shown a good response to topical and systemic corticosteroids.

Intravitreal dexamethasone implant has been used in paediatric uveitis with a good safety profile, with few patients having cataract progression and raised IOP compared to other regional corticosteroid injections [18]. Intravitreal dexamethasone implants are mostly indicated in cases of vitritis and CMO. The effect of intravitreal dexamethasone implants lasts for up to 6 months following a single injection and the decision to repeat treatment is based on recurrence of CMO on OCT. However, the need for repeated general anaesthesia to administer these injections and its cumulative risk needs to be considered.

Periocular administration of depot corticosteroids not only controls the intraocular inflammation but avoids the need for increasing or commencing systemic immunosuppression which can cause significant morbidity in children. It can also help in reducing or stopping systemic corticosteroids and other immunosuppressive agents [18].

Side effects of corticosteroids

Side effects seen due to the use of corticosteroids can vary from patient to patient on the basis of the dosage administered, the type of the steroid, the length of the treatment and their current medical problems.

Ocular side effects

The ocular side effects of corticosteroids include cataract, raised IOP, glaucoma and an increased risk of ocular infections like viral keratitis. The mechanism by which corticosteroids cause posterior subcapsular cataract is thought to be because of covalent binding of the steroid to lens proteins, resulting in the oxidation of the protein structure. The cause of steroid induced raised IOP and glaucoma is uncertain but it may be mediated by an increase in trabecular meshwork cell myocilin production [18].

Systemic side effects

Growth suppression occurs *via* inhibition of linear growth by an unknown mechanism and is more likely to occur if the patient has used the steroids for greater than 6 months. Fluid and electrolyte balance occurs due to the mineralocorticoid effect of glucocorticoids. Salt and water is reabsorbed leading to formation of oedema, weight gain and increased blood volume that causes hypertension.

Metabolic disturbances due to increased corticosteroid use causes an increase in blood sugar levels *via* gluconeogenesis and glycogenolysis that occurs due to a reduced sensitivity to insulin. Fat redistribution occurs when the excessive use of glucocorticoids triggers the process of lipolysis from adipose

tissue and causes the liver to increase production of lipids, thereby, increasing the total serum level of lipids, which leads to the Cushingoid effect [19].

Osteoporosis is caused by the suppressive effect of glucocorticoids on osteoblastogenesis in the bone marrow causes decreased bone formation [19]. The patient should be given calcium and calcitriol and should do regular exercise in order to prevent the symptoms [19]. Myopathy is another complication that can be found in children due to excessive use of corticosteroids.

The manifestations of steroid withdrawal symptoms after chronic therapy are mainly due to the failure of the body to produce endogenous steroids due to suppression of the hypothalamic pituitary axis. The symptoms include weakness, fatigue, weight loss, nausea and vomiting, hypoglycaemia, dehydration, electrolyte imbalance, hypotension, abdominal, joint and muscle pain, headache and fever.

It is important to taper the dose gradually and even more important to increase the dose during stress, surgery or severe medical illness [19].

Disease modifying anti-rheumatic drugs

Methotrexate, which is the first drug of choice as a second line of therapy is given once there is no noted improvement of 2 grades of AC cells or worsening of symptoms even after glucocorticoid treatment. Methotrexate is a folic acid antagonist that inhibits cytokine production and purine nucleotide biosynthesis, leading to immunosuppressive and anti-inflammatory effects [20]. Methotrexate is administered either orally or subcutaneously at a dose of 10-15 mg/m^2 with a typical dose being 7.25-25 mg weekly [21]. Patients that are on methotrexate are usually given folic acid supplementation of 1 mg daily to reduce the severity of adverse effects such as macrocytic anaemia and oral ulcers. The current recommendation is to continue methotrexate for at least 12 months once uveitis is inactive and for 24 months in those with poor visual prognosis provided there is improvement and grade 0 AC cells [15]. Though its potential side-effects are gastro intestinal upset, fatigue, hepatotoxicity and pneumonitis, it is effective and safe for chronic anterior and intermediate uveitis in children [21].

Mycophenolate mofetil is another immunosuppressive drug that acts by inhibiting inosine-5 monophosphate dehydrogenase, thereby inhibiting purine synthesis. Mycophenolate mofetil can be used as an alternative to a biologic drug in the presence of active uveitis and inactive arthritis. It is given at a dose of 300 mg/m^2 twice a day [15]. Diarrhoea, nausea, hair loss and leukopenia are the potential side effects [21].

Cyclosporine is another choice of immunosuppressive drug and is the most commonly used T-cell inhibitor, the next being tacrolimus. They both work as calcineurin inhibitors blocking T cell proliferation. Gastrointestinal disturbance, hypertension, renal and liver dysfunction are the potential side effects [15]. If methotrexate or other DMARD is not effective in controlling the inflammation, then adding a biologic agent like adalimumab should be considered.

Biological agents

Biological agents are monoclonal antibodies that reduce inflammation by inhibiting specific pro-inflammatory cytokines like tumour necrosis factor, antigens like B-cell surface antigen CD-20 or receptors like interleukin receptors. Due to lack of evidence most of the biological agents remain off label in the treatment of JIA uveitis and are restricted to selected patients under the guidance of a uveitis specialist and a rheumatologist [17].

Adalimumab is the preferred choice of drug as the fully humanised antibody adalimumab has a lower risk of anti-drug antibody formation compared to infliximab which is a chimeric (mouse-human) monoclonal antibody, also, because it is administered *via* subcutaneous injection compared to intravenous infusion for infliximab lowering the rate of infection [17]. Adalimumab is given at a dose of 24 mg/m^2 subcutaneously once every two weeks [15].

Respiratory disorders, minor infections and gastrointestinal disorders were some of mild side effects noted with the use of adalimumab. Adalimumab can also now be prescribed by ophthalmologists in Europe due to the results of the Sycamore Study Group [22]. 3 months following the administration of methotrexate and adalimumab, if there is noted improvement and grade 0 of cells in the AC, then maintenance therapy should be continued for 24 months [15].

If, however, there is worsening of symptoms, the recommended course of action is to switch the adalimumab to infliximab, tocilizumab or abatacept. Infliximab, tocilizumab and abatacept are the other biological agents used as an alternative to adalimumab [15].

Management of ocular complications of juvenile uveitis

Management of cataract and posterior synechiae: The risk factors for development of cataract in juvenile uveitis are posterior synechiae, or adhesion of the capsule to the iris of the lens, excessive systemic corticosteroid therapy, topical corticosteroid therapy exceeding 3 drops/day and active, ongoing inflammation of the eye [23].

Several factors should be considered in the decision of performing cataract surgery, including the risk of irreversible amblyopia, patient age, degree of inflammation, preoperative visual acuity and current therapy.

Judicious perioperative use of topical and systemic corticosteroids with addition of immunosuppression leads to improved outcomes. It is important that uveitis be quiescent, typically for at least 3 months prior to surgery [23]. Close collaboration between the ophthalmologist and the treating paediatric rheumatologist is of extreme importance to ensure a successful surgical outcome.

The use of a posterior sub-Tenon injection of triamcinolone acetate may be considered at the end of surgery [23]. This reduces the chances of development of CMO post operatively. However, raised IOP after the injection will need to be dealt with anti-glaucoma medication.

Cataract surgery can be challenging due to limited surgical exposure from posterior synechiae and fibrinous membranes overlying the anterior lens capsule. The posterior synechiae are released during surgery with the help of viscoelastic and a blunt spatula. Iris hooks may be needed for retract the iris and visualise the cataract [23].

It is preferred to perform a posterior capsulorhexis with anterior vitrectomy to ensure that the visual axis is not eventually obscured with posterior capsular opacification. Pars plana anterior vitrectomy and anterior approach through the cornea or sclera have been described and are both associated with safe and effective management of the posterior capsule in paediatric cataract surgery [23].

The controversy regarding leaving the patient aphakic or pseudophakic remains unresolved. The age of the child is an important consideration in this decision. Complications due to intraocular lens (IOL) implantation include, synechiae from fibrin deposition, pupillary membrane formation, hypotony and the possible need for IOL explantation, if the visual axis is compromised by IOL pigmentation or secondary fibrinous membranes. Improved surgical techniques, better and finer instruments, superior quality of IOL implants and better postoperative management of inflammation with newer drugs have provided better results in pseudophakes. Heparin coated polymethylmethacrylate and silicone IOLs are the preferred choice of IOL's. In children who are left aphakic, it is essential to provide early refractive correction with contact lenses or glasses to prevent deprivation amblyopia [23].

The management of postoperative complications such as uncontrolled inflammation, early posterior capsular opacification, glaucoma, CMO, epiretinal membrane, hypotony, and phthisis bulbi requires meticulous care [23].

Management of glaucoma

The management of glaucoma in juvenile uveitis is challenging as both the disease and its treatment can cause glaucoma.

The uveitis can cause glaucoma by various mechanisms. In the early stages, the cells and proteins leaked into the aqueous clogs the trabecular meshwork and causes raised IOP. In chronic inflammation, the trabecular meshwork gets scarred from repeated inflammatory assaults leading to sustained elevation of IOP and secondary open angle glaucoma. In cases where the inflammation causes posterior synechiae, peripheral anterior synechiae and secondary angle closure develop, leading to raised IOP and glaucoma. In extreme cases, new vessels develop in the angle and iris due to chronic inflammation leading to neovascular glaucoma [24].

The management of glaucoma includes treatment of the inflammation itself with corticosteroids and corticosteroid sparing agents. Topical corticosteroids help to reduce the inflammation but themselves can cause glaucoma (steroid induced glaucoma) when used at high dose for a prolonged period of time. Oral corticosteroids can also cause glaucoma. The use of topical and regional steroids has a higher risk of inducing glaucoma whereas the oral steroids have a higher risk of developing cataract. Posterior sub-Tenon injection, orbital floor injection and more recently intravitreal dexamethasone implants are used. Intravitreal dexamethasone implant is known to cause raised IOP after 4-8 weeks of injection and most patients need IOP lowering agent for a few months to maintain normal IOP. Usually the raised IOP is transient and can be managed medically. Rarely, surgical management of glaucoma is needed due to intravitreal dexamethasone implant alone.

The medical management of glaucoma includes use of topical and systemic carbonic anhydrase inhibitors. Beta blockers and alpha agonists are avoided in children.

The medical management of glaucoma is limited and surgical intervention is needed frequently. The surgery of choice in paediatric uveitis is goniotomy. This procedure works well in cases with open angles and phakic patients. Goniotomy involves incising the trabecular meshwork, creating a cleft, and presumably removing inflammatory debris blocking the outflow pathway. This procedure requires excellent preoperative control of the uveitis to help avoid inflammation-mediated synechiae formation and cleft closure. Goniotomy requires a relatively clear cornea; a gonioscopic view of the angle, and surgical expertise, but this relatively non-invasive procedure preserves the conjunctiva and can be repeated for additional IOP-lowering effect [24].

Glaucoma Drainage Devices (GDD) like Baerveldt and Ahmed valves are less frequently used in paediatric uveitis to reduce IOP compared to adult uveitis. When goniotomy which rarely cannot be performed due to peripheral anterior synechiae, GDD is considered. However, the GDD is associated with complications of migration and exposure as well as corneal endothelial damage, cataract formation, increased inflammation, pupillary abnormalities and strabismus. Despite problems related to hardware in and around the eye, GDDs can be useful in cases of JIA-associated uveitic glaucoma, especially in eyes in which goniotomy has failed or in eyes that are not amenable to angle surgery [24].

Cycloablation is commonly reserved for eyes that have late or end-stage glaucoma. External or internal approach can be used but both are not very successful in reducing IOP. Overtreatment can result in hypotony and subsequent phthisis bulbi. Cycloablation also causes a significant intraocular inflammatory response that can exacerbate the uveitis. Cycloablation should therefore be used sparingly, if at all, in children with JIA-U [24].

Management of cystoid macular oedema

The preferred option of management of CMO is by periocular corticosteroid injections as described in detail under medical management with regional corticosteroids. Triamcinolone

acetonide can be given as an intravitreal, posterior sub-Tenon or orbital floor injection.

Intravitreal dexamethasone implants have largely replaced intravitreal use of triamcinolone as it has a longer duration of action up to 6 months against 6 weeks of triamcinolone. Also, intravitreal dexamethasone implants have fewer incidences of ocular side effects like cataract and raised IOP [25]. Intravitreal injections are intraocular injections as opposed to sub-Tenon and orbital floor injections that are periocular injections and therefore has a greater risk of endophthalmitis. However, administration of intravitreal dexamethasone implant is easier and safer due to direct visualization of the needle as compared to posterior sub-Tenon injection that is a blind procedure (i.e. cannot see the needle while injecting). Having said that, both single and repeated injections of a dexamethasone-containing implants are safe and effective for the treatment of non-infectious intermediate and posterior uveitis in children. However, more data needs to be acquired in order establish a true and reliable safety profile of the implant in children [26]. Another study has shown results of a promising nature and comprise the use of dexamethasone implants in children which showed improved retinal thickness and reduction in ocular inflammation, with improved inflammation for several months. Repeat implantations resulted in continued control of the inflammation, allowing for a reduction of systemic immunosuppression therapy with few or insignificant ocular complications [25].

Management of band keratopathy

Band keratopathy occurs due to calcium deposition on the cornea which accumulates just beneath the epithelium. It causes irritation, foreign body sensation, blurred vision and photophobia. Superficial keratectomy and lamellar keratopathy is used to treat the band keratopathy. Ethylenediaminetetraacetic acid (EDTA) is used as a chelating agent. The epithelium is debrided and EDTA applied. The calcium is then scraped off to clear the central visual axis. A topical antibiotic and a nonsteroidal agent are used with a bandage contact lens until the epithelium heals in 1-2 weeks. In some cases, chelation may be needed before cataract extraction to allow better visualisation to perform the surgery [5,27].

Conclusion

There are several causes for juvenile uveitis as described above and conditions that mimic it. The uveitis can affect different parts of the uvea and can be classified as either anterior, intermediate or posterior uveitis and/or pan-uveitis. The onset can be sudden or insidious and the course can be acute, recurrent or chronic. The aetiology of juvenile uveitis can be infectious or non-infectious.

A careful and detailed history with relevant investigations helps to diagnose the condition and give the appropriate treatment to the patient. Since juvenile uveitis is a rare condition, there are no clear-cut guidelines for its management. Apart from the screening schedule for juvenile idiopathic arthritis, no firm guidelines are in place. A regular follow up of all patients of juvenile uveitis is essential to prevent complications of the condition.

It is the experience of the uveitis consultant and the help of the rheumatologist and paediatrician that aids in proper and complete management of the child. The side effects of corticosteroids and better understanding of the pathogenesis of the various uveitic entities has led to newer drugs being developed for the treatment of juvenile uveitis for example biologic agents like adalimumab. The periocular and intraocular steroid injections and newer drugs have helped reduce the side effects of systemic corticosteroids in children.

The main ocular complications of juvenile uveitis are posterior synechiae, cataract, glaucoma, vitreous haze, CMO, band keratopathy, hypotony and phthisis bulbi. Cataract is treated surgically with several modifications to deal with a small pupil from posterior synechiae and to deal with the refractive outcome to prevent amblyopia. Treatment of glaucoma mainly is with carbonic anhydrase inhibitors medically and with goniotomy surgically. The most common treatment for CMO is periocular steroid injections. First line of treatment of band keratopathy is chelation with EDTA.

Despite advances in medical management with the availability of biologic agents, many eyes still develop complications needing surgical intervention. Advances in surgical techniques have given us better outcomes but some eyes are lost despite all efforts due to the relentless progression of the inflammation. There is scope for further improvement in the medical and surgical management of juvenile uveitis and its complications for better outcomes in future.

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*Correspondence to

Dr. Alok Bahl

Department of Ophthalmology

University Hospitals Plymouth

NHS Foundation Trust

Plymouth

United Kingdom

E-mail: alok.bahl@nhs.net