UVEITIS

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CHAPTER CONTENTS

AIMS

This unit aims to outline the diagnosis and management of uveitis via developing:

- A protocol for assessing uveitis
- A framework for the differential diagnosis of uveitis
- A strategic basis for the management of uveitis.

LEARNING OUTCOMES

After completing this unit, students should be able to:

- Conduct a diagnostic assessment of a person with uveitis in one or both eyes
- Differentially diagnose uveitis
- Identify and appropriately refer cases of uveitis
- Manage uveitis to the extent that fits within their legal scope of practice
- Recognize the features of anterior, intermediate, posterior and panuveitis.

INTRODUCTION

Uveitis is a condition that presents as a range of disease entities and is broadly classified into anterior (i.e. anterior chamber), intermediate (i.e. vitreous), posterior (i.e. retina or choroid) and panuveitis (i.e. all).

The anterior presentation, with inflammation of the iris and ciliary body, is the most common form of uveitis with varying incidences reported in different countries. The condition accounts for approximately 10% of blindness worldwide (Agrawal).

Anterior uveitis can be relatively benign in its early presentation but may result in severe morbidity if the treatment regimen is not initiated quickly enough, or is not appropriate for the case.

Inflammation of the anterior uveal tissues may be caused by trauma or the presence of systemic disease, but many cases are idiopathic. Systemic diseases associated with uveitis include e.g. ankylosing spondylitis, Reiter's syndrome, rheumatoid arthritis, tuberculosis and inflammatory bowel conditions.

Any indication of an associated disease, whether determined by history taking, uveitic characteristics, or concurrent systemic signs or symptoms, warrants an in-depth laboratory evaluation.

Anterior uveitis that is idiopathic in nature is not an uncommon presentation in primary care practice and is an important consideration in the differential diagnosis of conditions that cause an acute red eye. In secondary and tertiary care centers, chronic anterior uveitis may be related to conditions such as e.g. seronegative arthropathies, juvenile idiopathic arthritis (juvenile rheumatoid arthritis) and sarcoidosis. Cases of posterior uveitis are commonly associated with, for example, toxoplasmosis, sarcoidosis and systemic lupus erythematosus (SLE) (Rodriguez 1996).

Patients with uveitis require very careful assessment and correct management, including referral to minimize the risk of complications from the uveitis and any associated conditions.

PREVALENCE

The estimated annual incidence rate varies across different populations. The incidence of uveitis in the USA and western or developed countries is of the order of 12 to 23 cases per 100,000 people (Islam 2009). Acute anterior uveitis has the highest prevalence, followed by chronic anterior uveitis.

CLASSIFICATION

ANATOMICAL CLASSIFICATION

Anterior

Inflamed iris (**Iritis):** Inflammation confined to the anterior chamber indicates involvement of the iris and is consequently known as iritis. Cells are found only in the anterior chamber**.**

Inflamed ciliary body (**Cyclitis):** Inflammation confined to the ciliary body. Cells are found only behind the iris upon dilation**.**

Inflamed iris and ciliary body (**Iridocyclitis):** Inflammation of both the iris and ciliary body. Cells are found both in the anterior chamber and just behind the iris.

Intermediate

The term, "intermediate uveitis" is used to describe the location of the inflammation in the eye. The part of the eye affected is the peripheral part of the inner eye in between the posterior and anterior parts. The terms "pars planitis" and "posterior cyclitis" are often used to describe this type of uveitis. Intermediate uveitis typically involves inflammation of the vitreous.

Posterior

Involves inflammation of the retina and/or choroid and may present as e.g. focal, multifocal, or diffuse choroiditis, retinochoroiditis, etc. Floaters and visual disturbances are likely in posterior uveitis.

Panuveitis

Involves inflammation in the anterior ocular structures, vitreous and the retina and/or choroid.

IMPORTANT: When dealing with uveitis that is more posterior in the eye, it is important to consider the following:

- Difficulty of treatment
- Length of time to treat
- Range of complications that can occur
- The chance of systemic disease involvement.

TIME CLASSIFICATION

Onset

The rate of onset of uveitis can be classified as either sudden or insidious.

Duration

Limited: Intraocular inflammation that lasts less than 3 months.
Persistent: Lasts longer than 3 months.

Course

Acute: There is an abrupt onset of uveitis. In general, the more anterior the inflammation (e.g. iritis), the shorter the inflammation lasts. If not treated properly the condition may become chronic in nature.
Chronic: The uveitis may wax and wane over months or years. In general, the more posterior the inflammation is (e.g. cyclitis), the longer the inflammation will persist. In cases of chronic uveitis it is important to rule out any associated systemic disease.

With intermediate or posterior uveitis, it is more likely that the condition will last for a longer time or will be chronic.

IMPORTANT: When dealing with uveitis that is long-lasting it is important to consider the following:

- Posterior ocular involvement
- Difficulty of treatment
- The chance of a systemic disease involvement.

LATERALITY CLASSIFICATION

Unilateral: Anterior uveitis in only one eye. More likely to be an acute event.
Bilateral: Anterior uveitis in both eyes increases the likelihood of chronic systemic disease involvement.

IMPORTANT: When dealing with uveitis that is bilateral it is important to consider the following:

- Difficulty of treatment
- The chance of a systemic disease involvement.

TEMPORAL CLASSIFICATION (THE DISEASE "THROUGH TIME")

Single presentation: A single, unilateral uveitis is at low risk for complications and systemic disease aetiology. If the first-time presentation is bilateral, more posterior location, has intraocular complications, or involves systemic disease symptoms or signs, the practitioner should be very conservative in managing the patient.

Recurrence: Multiple occurrences of the disease. For some people, the uveitis will recur in the future or become chronic and therefore require treatment over a longer period of time. Usually, each episode is heralded by the eye becoming red, sore and watery, with photophobia. Often only one eye is affected at a time, although the particular eye affected can change from episode to episode.

IMPORTANT: When dealing with uveitis that is recurrent it is important to consider the following:

- Increased risk of complications
- The chance of systemic disease involvement
- Difficulty of treatment.

AETIOLOGICAL CLASSIFICATION (CAUSE OF THE UVEITIS)

- **Idiopathic**: A cause or associated conditions are not uncovered after investigation. This is the most common form of anterior uveitis, where at least 50% of all cases of acute anterior uveitis occur in the absence of any systemic disease or positive human leukocyte antigen (HLA) finding.
- **Non-infectious**: Systemic disease or trauma including, for example, eye injury or eye surgery.
- **Infectious**: Bacterial, viral, fungal or parasitic causes for example. It is important to establish whether the cause of the uveitis is infectious or not, as the treatment will be very different.
- **Autoimmune**: In autoimmune disease a part of the body (self) is mistaken as foreign. That part of the body is attacked by its own immune system and the result is inflammation.

PATHOLOGICAL CLASSIFICATION (BASED ON OBSERVATION)

Granulomatous uveitis: Formation of granulomas in tissues such as e.g. iris, choroid, conjunctiva. Appears as a deposition of large, fatty-appearing aggregations of white blood cells known as “mutton-fat” precipitates and may be present on all intraocular tissues. Most commonly the precipitate is seen on the corneal endothelium and is therefore called a keratic precipitate (KP).

- Associated with granulomatous systemic diseases such as Lyme disease, syphilis, sarcoidosis, tuberculosis (TB) and Crohn’s disease.
- More difficult to manage
- More chance of complications
- More chance it will involve other tissues

Non-granulomatous uveitis: Occurs without any evidence of a granulomatous nature and the keratic precipitates will be small and discrete with lymphocytes typically involved.

- Less risk of complications
- Easier to treat
- Typically anterior only
- Associated systemic disease includes e.g. ankylosing spondylitis, Lyme disease and herpes zoster.

The term “posterior uveitis” indicates inflammation of the posterior uveal tract. More specifically, choroiditis is used to describe an inflammation of the choroid. Posterior uveitis is rarely confined to just the choroidal tissue, however, because of the juxtaposition of the retinal and choroidal tissue. The condition is found in such diseases as e.g. toxoplasmosis, syphilis and sarcoidosis.

If the pars plana becomes inflamed it is termed “pars planitis” or intermediate uveitis. Inflammation of the overlying retina, i.e. retinitis, is typical in many cases of choroiditis. Active cases of retinitis often produce inflammation of the overlying vitreous, i.e. vitritis.

In extreme cases of uveitis, all the internal tissues of the eye may become involved –This is known as panuveitis. Many cases are of idiopathic origin but causes of panuveitis include e.g. tuberculosis, Vogt-Koyanagi-Harada (VKH) syndrome and sarcoidosis.

RELATIVE RISK BASED ON CLASSIFICATION SCHEME

On the basis of the above definitions, the relative risk of a systemic disease being associated with a case of uveitis can be predicted to some degree.

The least risk of a systemic disease occurs in a uveitis that is:

- First occurrence
- Unilateral
- Non-infectious
- Acute
- Non-granulomatous
- Anterior involvement (e.g. iritis)

The greatest risk of a systemic disease occurs in a uveitis that is:

- Recurrent
- Bilateral
- Chronic
- Granulomatous
- Posterior involvement (e.g. posterior ciliary body, pars plana, choroid, retina)

PATHOPHYSIOLOGY

In the absence of inflammation, the anterior chamber should be free of cells. Inflammation of the iris causes a breakdown in the blood-aqueous barrier resulting in the migration of protein and polymorphonuclear leukocytes i.e. white blood cells (WBC) into the anterior chamber.

The cells that migrate into the aqueous from the iris or ciliary body are primarily lymphocytes, though there may be a significant number of neutrophils present. The presence of even trace amounts of leukocytes is a strong indicator of anterior uveitis.

Pigmented cells may be present in the anterior chamber in cases of anterior uveitis. These cells originate from the iris pigmentary layer, and may deposit on the corneal endothelium. Pigment may also be released into the anterior chamber from ocular trauma and previous surgery. Any signs of pigment in the anterior chamber or on the endothelium should make the practitioner wary of the potential for pigmentary dispersion syndrome, or pigmentary glaucoma.

Protein in the anterior chamber fluid is described as flare. It may be observed with the slit-lamp biomicroscope. The presence of flare is a significant indicator of a breakdown in the blood-aqueous barrier. This sign is typical in cases of acute, severe iritis, but may be present on a chronic basis after ocular surgery or several bouts of anterior uveitis.

HISTORY

A careful and thorough examination of a patient with uveitis requires the following approach:

- In-depth history
- Ocular examination
- Physical examination – as and when required
- Ancillary investigations - as and when required

A full history is required for the correct diagnosis and management of the patient with uveitis.

History of present illness in terms of onset and progression of symptoms, course and treatment received with special emphasis on corticosteroids therapy should be ascertained.

Past ocular history should elicit recurrent attacks of uveitis and previous response to treatment. Detailed systemic history forms a very important part in the management of uveitis patients. Apart from a review of systems, the social history for pets, dietary history, sexual and drug history should be obtained in detail (Agrawal).

The onset of uveitis is typically fast with the patient waking in the morning with photophobia. The patient, or another person, notices that the eye has turned red very quickly. Patients with anterior uveitis usually consult their practitioner early in the course of the progression – usually within the first 24 hours.

Patients with conjunctivitis typically contact the doctor after three days because the eyelids stick together in the morning. Viral conjunctivitis causes tearing and patients contact the doctor after about a week. In allergic cases with intense itching, about 2-7 days is common.

The majority of uveitis cases seen in primary practice are idiopathic. However, it is important that the practitioner obtain any medical history and other associated symptoms that may be indicative of an underlying systemic cause of the uveitis. Systemic conditions that are associated with active uveitis include e.g. ankylosing spondylitis, multiple sclerosis, sarcoidosis, inflammatory bowel disease, tuberculosis, Behçet's disease and systemic lupus erythematosus (SLE).

Consider sarcoid for pulmonary symptoms, ulcerative colitis for patients with GI symptoms, and SLE for patients with musculoskeletal symptoms. If a patient presents with minimal signs and symptoms, bilateral presentation, a granulomatous response and a posterior extension of uveitis in the eye, be sure to consider systemic causes (Wills Eye Manual).

SYMPTOMS

The severity of the symptoms associated with uveitis ranges from none to very severe. Symptoms of acute anterior uveitis include e.g. photophobia, redness, pain, reduced vision and tearing in the absence of any discharge.

Photophobia

The most common complaint made by patients with acute iritis is photophobia i.e. an aversion to bright light. Photophobia is a significant symptom in the diagnosis of anterior uveitis. Patients describe the photophobia as ranging from mild to painful. Photophobia may be less frequent and severe in cases of chronic uveitis.
In anterior uveitis the patient reports the presence of photophobia when e.g. a pen torch light is shone into the uninvolved eye.

Pain

Pain experienced as a result of non-traumatic, acute uveitis generally develops over a few hours or days. The nature of the pain is most commonly a dull ache within the eye, but can range from mild discomfort to severe pain. Patients sometimes have associated peri-orbital pain or a headache due to involvement of branches of the ophthalmic division of the trigeminal nerve.

The pain/discomfort experienced is usually aggravated by light and may also occur due to the physical contraction of the iris and ciliary muscles.

In cases of chronic uveitis little pain or photophobia is experienced except when there is an acute response (Wills Eye Manual).

Tearing

Tearing is common in acute, anterior uveitis, and may cause some transient reduction in visual acuity. It usually resolves with treatment of the uveitis.

Blurred Vision

Vision is rarely affected by anterior uveitis. In most cases, only a mild subjective complaint of some visual blur is present. The visual blur may be caused by e.g. profuse tearing, corneal deposits, anterior chamber haze or posterior tissue involvement.

SIGNS AND DIAGNOSIS

A careful examination of both the anterior and posterior segments of the eye is of great importance.

Relevant physical examination by the practitioner to rule out any other systemic association is important in cases suspected to have systemic association based on the history. Anterior uveitis can be associated with dermatological, respiratory, rheumatologic, genital, gastrointestinal or neurological findings.

Relevant ancillary investigations include for example:

Ocular investigations

These would be sometimes required, including B-scan ultrasonography, fluorescein angiography, and optical coherence tomography for the assessment of the posterior segment. Ultrasound biomicroscopy would be useful in cases with small pupils and hypotony to assess the status of the ciliary body and presence of cyclitic membranes (Agrawal).

Laboratory investigations

Possible diagnoses should be made from the history and examination. Then, further investigations are used to help confirm the diagnosis. Investigation of a patient with a first episode of anterior uveitis will depend mainly on history and examination. The investigations should be targeted to rule out associated systemic disease and infectious cause of the uveitis.

Investigations are not required in first episode of non-granulomatous anterior uveitis or in Herpes zoster ophthalmicus-associated uveitis and Fuchs' heterochromic iridocyclitis (Agrawal).

Visual Acuity

In most cases of mild anterior uveitis the level of visual acuity (VA) is normal. Any slight reduction in VA may be due to profuse tearing. In more severe cases of uveitis, a reduction in VA may occur.

External Exam

The eyelids and skin around the eyes typically remain unaffected. The palpebral aperture may be reduced as the patient often keeps the eyelids partially closed to minimize the degree of photophobia.

Eye Movement

There is usually no effect on the extraocular muscles and the eye movements remain normal.

Conjunctiva

The classic conjunctival injection pattern observed in a case of acute anterior uveitis is a red circumcorneal flush. This limbal injection may be 360 degrees around the cornea. It represents a reflection on the conjunctival surface of deeper iris or ciliary body inflammation.
The circumcorneal flush is typical in acute iritis but may be absent in chronic anterior and intermediate uveitis.

Cornea

Convection currents are established in the anterior chamber by the aqueous rising up near the warm iris and then falling near the relatively cooler cornea. White blood cells (WBC) in the anterior chamber circulate along these aqueous currents, being driven into the superior anterior chamber and then falling along the corneal endothelium toward the inferior angle.

WBCs may attach to the posterior endothelium and the deposited cells send out chemical messengers to attract other cells to the site. Accumulations of these white blood cells are known as keratic precipitates (KPs). The KPs typically form in the inferior cornea and frequently take on the shape of an inverted triangle (Arlt’s triangle). Neutrophils, macrophages and lymphocytes are typically found within the KP.

The morphology of KPs is very useful to help distinguish non-granulomatous from granulomatous uveitis.
Small diffuse KPs causing dusting of the endothelium are characteristic for non-granulomatous uveitis such as HLA-B27-related acute anterior uveitis (Herbort).

When KPs become larger than endothelial dust they can be individualised and correspond to granulomatous KPs. Medium and large size KPs are called “mutton fat” KPs and have a greasy appearance.

It is useful to distinguish between fresh and chronic (old) mutton-fat KPs. Old mutton-fat KPs tend to be less white, pigmented and less dense in the center (Herbort).

If a significant amount of immune product is deposited on the corneal endothelium, a degradation of the corneal endothelial pump may occur. A reduction in the effectiveness of the pump leads to corneal swelling and cloudiness that patients describe as a visual blur or halos around lights. The patient may describe the vision as “looking through a fog.” The KPs themselves may reduce visual acuity if they are located on the visual axis.

After resolution of the uveitis, KPs may take from weeks to years to clear from the cornea.

Anterior Chamber

White blood cells (neutrophils and lymphocytes) from the inflamed iris or ciliary body are found in the aqueous humor and can be observed on slit-lamp examination. The presence of these cells is pathognomonic of anterior uveitis. The anatomical classification of anterior uveitis can be determined by the position of the cells. White blood cells (WBC) confined to the anterior chamber indicate the presence of an iritis, and if the anterior chamber is clear but cells are present just behind the lens and in front of the vitreous, then a cyclitis is present. Iridocyclitis causes cells to migrate to both positions. If the cells are found more posteriorly in the eye then suspicion of systemic disease should be increased.

Flare is a proteinaceous exudate from the inflamed iris or ciliary body, is typical of acute and traumatic iritis, and is thus not indicative of an associated systemic disease. When the concentration of proteins in the aqueous is very high, they agglomerate and form fibrinous clots, a finding more common in acute non-granulomatous uveitis (Herbort).

Hypopyon is a cellular response and when the quantity of cells is very dense they sediment and cause a build-up in the inferior angle of the anterior chamber. This is a sign more often seen in HLA-B27-related uveitis, Behçet's uveitis and uveitis related to juvenile idiopathic arthritis (JIA) (Herbort).

Hyphema is a deposition of blood in the anterior chamber, and may also be so thick and profuse that it covers the visual axis, thus obscuring the vision of the patient.

The amount of cells and flare needs to be graded (see Table 3 below). This is done to monitor the progression of the disease as well as the success of any treatment.

Grade	Cells	Flare
0	< 1	No flare
½ +	1 – 5	
1+	6 – 15	Faint
2+	16 – 25	Moderate (iris and lens detail clear)
3+	26 – 50	Marked (iris and lens detail hazy)
4+	≥ 50 (snowstorm)	Intense (fibrin deposits, coagulated aqueous)

Table 1. *Grading of cells and flare. Adapted from the Standardization of Uveitis Nomenclature (SUN) Working Group.*

Anterior Chamber Angle

Anterior synechiae (iris to cornea) may be associated with uveitis. A gonioscopic evaluation of the angle is imperative in all cases of anterior uveitis.

Pupils

Anterior uveitis typically produces a miotic pupil on the involved side. Therefore, anisocoria is usually present in cases of acute unilateral anterior uveitis. The miosis is not the result of a neurologic lesion but is an effect of chemical inflammatory mediators on the receptor sites of the pupillary sphincter. Miosis is more common in acute uveitis than in chronic uveitis.

Iris

Anterior synechiae, an abnormal connection between the anterior peripheral iris and the peripheral corneal endothelium, may occur because of iris swelling in anterior uveitis. The iris swells, because of the inflammation, in the anteroposterior axis, thus narrowing the angle of the eye. In extreme but rare cases, the angle may close and cause an acute closed-angle glaucoma attack secondary to the iritis. The synechiae represents a semi-permanent adhesion between the iris and cornea, mostly caused by the presence of fibrin acting as biological glue. Breaking of the anterior synechiae may be accomplished with laser therapy or a surgical approach. Any case of anterior uveitis with elevated IOPs mandates a gonioscopic evaluation of the angles to confirm the presence or absence of anterior synechiae.

Posterior synechiae, the abnormal attachment of the iris to the anterior lens capsule, can cause complications. The adhesion can usually be broken using pharmacological agents within the first 72 hours of formation. If left too long, the pharmacological method of breaking a posterior synechiae is more difficult.

Although the synechiae may not initially represent a significant problem to the functioning of the eye, it may cause a distorted pupil, reduce pupillary function, and be cosmetically unappealing. Furthermore, extensive posterior synechiae may bind down the entire pupil leading to pupillary block with iris bombe. As the iris is pushed anterior by accumulating aqueous behind it, the angle may close down leading to an acute angle closure glaucoma attack secondary to pupillary block. An emergency laser peripheral iridotomy may be necessary to allow appropriate aqueous drainage from the posterior chamber and restore normal IOP.

Two types of iris nodules can develop in granulomatous uveitis. When situated at the pupillary margin (and on the surface of the iris) they are called Koeppe nodules, have a fluffy appearance and a size going from very small, barely visible excrescences to frank, large nodules. When situated in the body of the iris stroma, iris nodules are called Bussaca nodules (Herbort).

In severe and longstanding uveitis, iris rubeosis can develop. It is in fact most often a pseudo-rubeosis that is reversible after introduction of anti-inflammatory treatment. Even when a real rubeosis has developed, it is usually situated at the pupillary border of the iris and is much less aggressive and proliferative than ischemic rubeosis iridis. In Fuchs' uveitis with extensive iris atrophy, iridal vessels can be seen and correspond to a pseudo-rubeosis (Herbort).

Sectorial or widespread iris atrophy is a rather specific sign for herpes simplex or herpes zoster uveitis and is a useful diagnostic help (Herbort). Diffuse atrophy is very often seen in Fuchs' uveitis (Herbort).

Intraocular Pressure (IOP)

Intraocular pressure changes due to uveitis can present either as hypotension or hypertension. The IOP may elevate following the start of an anterior uveitis event. The inflammation that occurs with uveitis results in white blood cells and protein leaking out of blood vessels into the clear, aqueous humor in the anterior chamber. The cells are swept into the anterior chamber angle and block the trabecular meshwork. This effect may be short-lived in some cases and may not be observed by the practitioner, because most patients are not seen within a few hours of the onset of the anterior uveitis. Rather, a patient with uveitis is usually seen a day or two after its onset, by which time the IOP is either normal or slightly below normal.

Hypotony is usually measured in severe uveitis involving the ciliary body such as acute anterior non-granulomatous HLA-B-27-related uveitis (Herbort). The drop in IOP is a result of decreased aqueous humor production due to the inflammation. The IOP returns to normal as the level of inflammation subsides (Wills Eye Manual).

Crystalline Lens

Anterior uveitis can contribute to the formation of cataract. Chronic or recurrent uveitis in particular is disruptive to normal lens physiology and the clarity of the lens decreases.

Topical steroids used to treat anterior uveitis can cause the formation of posterior sub-capsular cataract.

Vitreous

The observation of cells in the vitreous indicates that the uveitis has a posterior component. Causes of visual blur in posterior uveitis include vitritis, retinitis, choroiditis, vasculitis, macular oedema, and disc oedema. Any case of anterior uveitis warrants a dilated posterior evaluation to monitor for any of these conditions. A uveitis that involves posterior structures will be more difficult to treat and has a greater risk of complications.

In cases of intermediate uveitis the presence of floaters is often noticed by the patient and both eyes are usually affected though not to the same degree. The condition may be present for quite some time before it is diagnosed because the patient may not be aware of any problem. The severity of intermediate uveitis varies greatly.

White blood cells arise in the vitreous from the choroid, retina and ciliary body. Protein can also leach into the vitreous, producing a haze. Vitreous haze is a better indicator of inflammation than cells are and is best seen in a binocular indirect view. Inflammation of the vitreous, or vitritis, indicates a posterior extension of the uveitis. Vitritis may be associated with systemic diseases such as e.g. toxoplasmosis. The classic appearance of a vitritis is that of a “headlight in the fog.” In severe cases of vitritis the fundus details may be difficult to visualize through the hazy vitreous humor.

Retina

The deposition of an accumulation of white blood cells along the pars plana is known as a ***“snowball”***. Such a presentation may be associated with systemic diseases such as e.g. Lyme disease. Snowballs have also been reported with uveitis secondary to tuberculosis. This form of intermediate uveitis is often found concurrent with anterior uveitis. The snowballs are best seen with a binocular indirect ophthalmoscopic evaluation of the fundus.

Sheathing of the peripheral retinal vessels reflects an inflammatory response within the vessel walls. The presence of sheathed retinal vessels associated with an anterior uveitis may be associated with systemic disease e.g. syphilis or sarcoidosis. In sarcoidosis, the vessels may take a classic appearance of “candle-wax drippings” (Weisinger)

Optic Nerve Head

Optic disc hyperemia, papillitis and papilledema can be associated with anterior uveitis. The finding of any of these optic nerve head changes greatly increases the likelihood of the anterior uveitis being associated with a systemic disease.

Macula

Macular oedema is associated with uveitis and, if present, causes a decrease in visual acuity.

It is very important that any complications associated with uveitis are detected early as they can be more sight threatening than the underlying uveitis. Complications are found by thorough examination which should always include the retina.

COMPLICATIONS

Complications experienced by patients with uveitis may include the following:

COMPLICATIONS OF ANTERIOR UVEITIS

a. **Blurring of vision**

   This can be a result of the inflammation but also can be a temporary problem with drops used to dilate the pupil.

b. **Floaters**

Debris from inflammatory blood cells can be seen in the visual field as wispy dots or streaks. They can be of nuisance value or can sometimes significantly reduce vision.

c. **Persistent pain and redness**

This may be a problem even after a 'flare up' has been treated and no inflammation is present.

d. **Cataracts**

Uveitis sufferers are more likely to develop cataracts and at a younger age than the normal population. This is a problem which can be dealt with but may be more complicated in people with uveitis. The main priority is for the inflammation to be totally under control before and after removal of the cataract.

e. **Rise in intra-ocular pressure (IOP)**

The normal eye has a pressure maintained by the flow of fluid through it. If the pressure is raised this can potentially cause glaucoma and is usually controlled with drops. The pressure is easily measured and uveitis sufferers will always have their eye pressure carefully monitored. Some people's IOP rises as a result of taking steroid drops (i.e. steroid responders).

f. **Posterior synechiae**

Sometimes due to the inflammation, the iris sticks to the crystalline lens (i.e. a posterior synechiae). The synechiae can distort the shape of the iris and adversely influence the IOP.

COMPLICATIONS OF INTERMEDIATE UVEITIS

Intermediate uveitis varies greatly and so, therefore, do the associated complications.

a. **Cataract**

Is the most common complication, affecting up to 40% of patients. Steroid use contributes to this figure.

b. **Macular oedema**

Is the complication which causes the most vision loss in intermediate uveitis.

c. **Glaucoma**

Is not that common, although there is a group of patients who respond to steroids by getting a rise in their intraocular pressure which can lead to glaucoma.

d. **Vitreous opacification** with floaters

Can be a problem as the opacification may lead to a retinal detachment if there is resulting 'traction' where the vitreous 'pulls' at the retina.

COMPLICATIONS OF POSTERIOR UVEITIS

a. **Macular oedema** (also cystoid macular oedema)

This can be acute or chronic. Fluid may build up at the macula which may affect the central vision. Chronic macula oedema can persist in the absence of active uveitis and may be treated with steroid therapy or with immuno-suppressants

b. **Vitritis**

Inflammation in uveitis may affect the vitreous causing a condition known as vitritis. The result of this can be floaters or a more substantial obstruction of vision if a lot of debris is present.

c. **Neovascularization**

Sometimes, as a result of inflammation, small, new blood vessels grow in the retina. These vessels are produced as part of the body's own healing response to injury, but they are unwelcome because they are weak and prone to leak and break down. They can be managed by laser treatment.

Sometimes these new blood vessels form a subretinal neovascular membrane, which can be treated by laser or may even be surgically removed in a few cases.

d. **Loss of visual field**

Inflammation may result in damaged areas of the retina that produce scotoma. These may be in the peripheral vision and hardly noticeable but if near the macula, the central vision can be significantly affected.

It is important to emphasize that it is not always the uveitis directly that dictates the treatment regimen. Sometimes a complication such as glaucoma can 'take over' as the main problem. This is another reason why there is so much variation in the way individual patients will be managed.

SYSTEMIC DISEASE

The following conditions should be considered whenever an anterior uveitis is recurrent, bilateral, granulomatous, proceeds posteriorly in the eye, is resistant to treatment, or becomes chronic:

Infection

- Lyme disease: A bacterial infection spread by the bite of a tick (insect). This disease should be suspected in any patient with uveitis and a rash
- Syphilis: A sexually transmitted bacterial infection that can cause anterior uveitis and a rash
- Tuberculosis: A bacterial infection of the lung that should be suspected in any uveitis patient who presents with a cough. A chest x-ray is required.
- Herpes virus infection: Herpes simplex and zoster keratopathy may cause an anterior uveitis
- Toxoplasmosis: Is caused by infection with a parasitic organism called Toxoplasma gondii, which is carried by cats and is shed in their faeces. Unborn babies may catch the infection if the mother becomes infected during pregnancy; such infection can sometimes have very serious consequences for the health of the child. Infection rarely leads to any problems with vision - most infections lead to tiny scars at the back of the eye that have no effect on eyesight. However, the scars can reactivate up to many years later, causing visual problems. Typically, the vision becomes blurred and floaters are noticed as a posterior uveitis develops; the affected eye can also become red and sore as anterior uveitis may also develop.

Inflammation

- Sarcoidosis: A granulomatous, inflammatory condition of unknown aetiology. It is more commonly observed in African-Americans aged 20-40 years when compared with white Americans. It causes granulomas in the affected regions e.g. the lungs which is diagnosed with a chest-x-ray. This is a condition causing breathing difficulties and skin lumps and rashes, as well as causing a granulomatous acute or chronic anterior uveitis. Treatment of the eye condition often depends on how seriously affected other parts of the body are – steroid drops may be sufficient if there is only an anterior uveitis, but steroid tablets may be required if there is inflammation deeper within the eye or if problems elsewhere in the body require anti-inflammatory treatment.

- Crohn's disease: A granulomatous disease of the bowels, this condition should be suspected in any patient with anterior uveitis and stomach pain or diarrhea

Collagen-Vascular Disease

- Ankylosing spondylitis (AS): An inflammation of the spinal joints, sacro-iliac joint and intervertebral spaces, AS most often occurs in white males aged 20-40, who present with lower back pain. It is often diagnosed with X-ray and lab testing. Acute anterior uveitis is often seen in patients with undiagnosed AS
- Reiter's syndrome (Reactive Arthritis (RA)): Is a reaction to bacterial infection in the body (e.g. intestines, genitals, urinary tract). Typically results in inflammation of the wrist, knees and ankles. Occurs typically in white males aged 20-40, who complain of distal joint pain. There is no direct test for RA but assessment of suspect patients involves blood analysis and lab testing e.g. chlamydia. Treatment is usually conducted by a rheumatologist.
- Juvenile rheumatoid arthritis (JRA): An inflammation of several joints in the child, most commonly the knee. Any anterior uveitis in a child should warrant an immediate rheumatology consult to rule-out JRA.

Other medical conditions associated with posterior uveitis include e.g.

- Behçet's disease
- Idiopathic retinal vasculitis
- Vogt-Koyanagi-Harada syndrome
- Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)
- Presumed ocular histoplasmosis syndrome (POHS)
- Birdshot choroidopathy
- Multiple sclerosis
- Sympathetic ophthalmia

This list is not complete and has no particular order or classification.

WORKUP FOR NON-GRANULOMATOUS ANTERIOR UVEITIS

Herbort recommends the following strategy:

In a case of simple, fibrinous or hypopyon non-granulomatous uveitis, the only first-line work-up test to perform is the detection of the HLA-B27 antigen. **HLA-B27 testing** is performed even if the inflammation is only moderate. If the test is positive it avoids further unnecessary testing during a subsequent episode and it is reassuring for the patient and the doctor to know the specific diagnosis, especially when it is a benign disease. In case of a positive result, no further investigation is performed at the ophthalmological level.

It is, however, recommended to take an **oriented history** that allows, with the help of the internist or rheumatologist, to sub-classify the condition as ankylosing spondylarthritis, Reiter's syndrome, Crohn's disease, ulcerative colitis or simply into HLA-B27 uveitis without systemic associated disease when necessary. About 50‑55% of acute anterior non-granulomatous uveitis is HLA-B27 positive in Europe, but this varies from one geographical area to another, being for instance quite low in Japan. In the remaining 45‑50% of cases a specific diagnosis is more difficult to establish.

No further investigation is performed if the episode of HLA-B27 negative non-granulomatous uveitis is of limited severity and/or responds readily to topical corticosteroid therapy.

In case of an anterior uveitis with hypopyon, signs and symptoms found in **Behçet's syndrome** should be investigated, in particular oral and/or genital ulcerations, cutaneous signs such as erythema nodosum and pustules, arthralgies, thrombophlebitis or central nervous system involvement. If Behçet's uveitis is suspected we find it useful to look for the HLA-B51 antigen which, when present, represents an additional argument for the diagnosis of Behçet's uveitis, especially in the milder forms of Behçet's uveitis seen in the Caucasian European population. Isolated anterior Behçet's uveitis can occur but posterior involvement should be searched for by fundoscopy and is best investigated by performing a fluorescein angiography to look for retinal vasculitis.

In case of non-granulomatous uveitis in children (with or without band keratopathy), history should be directed towards **juvenile idiopathic arthritis (JIA)**. Inflammatory symptoms can be completely absent, contrasting with the severe signs of uveitis such as hypopyon and extensive synechiae that can characterize JIA-related uveitis. Uveitis is usually associated with the pauciarticular form of JIA and testing should include anti-nuclear antibodies (ANA) that are present in up to 70% of JRA patients with uveitis. In elderly children it is also useful to test for the presence of HLA-B27 antigen.

Bilateral non-granulomatous uveitis in children, but also in adults, should prompt to search or exclude **tubulointerstitial nephritis and uveitis syndrome (TINU)**, an often-neglected diagnosis. Renal function should be tested, starting with the dosage of creatininemia sometimes requiring renal biopsy. Urinalysis should be performed looking for glucosuria and dosage of beta-2-microglobulin which is found to be elevated in TINU.

In children, pars planitis can initially present with a pronounced anterior participation and can be mistaken for an anterior uveitis if the posterior segment is not carefully analyzed.

In case of non-responding HLA-B27 negative anterior uveitis or in case of recurrence, pursue the work-up in the same fashion as for a granulomatous uveitis (Herbort).

WORKUP FOR GRANULOMATOUS ANTERIOR UVEITIS

Herbort recommends the following strategy:

Before starting the work-up of granulomatous uveitis, it is important to **exclude Fuchs' uveitis,** as this condition, when sufficiently typical, does not need any work-up. Further, corticosteroid treatment should be withheld in Fuchs' uveitis to avoid the side-effects of a treatment that usually has no impact on the inflammatory process. Characteristic findings of Fuchs' uveitis include fine stellate granulomatous keratic precipitates which usually do not accumulate inferiorly by gravitation but are more uniformly distributed over the whole surface of the endothelium, fine Koeppe nodules at the pupillary edge of the iris, prominent vessels in the irido-corneal angle seen by gonioscopy and absence of posterior synechiae.

Spill-over anterior granulomatous uveitis can occur in very inflammatory toxoplasmic retino-choroiditis which has to be excluded by performing a detailed examination of the posterior segment with fundoscopy.

The first-line laboratory tests performed to investigate granulomatous uveitis are **serum angiotensin converting enzyme (ACE) and lysozyme** – products indicating the presence of granulomatous lesions. ACE can be normally elevated in children and serum lysozyme levels tend to be progressively more elevated in elderly persons. It is therefore important to perform both tests.

The second step is to **differentiate between sarcoid, tuberculous or other granulomatous causes**. In order to differentiate between tuberculosis and sarcoidosis, multiple skin tests measuring delayed type hypersensitivity reaction to several antigens to which the adult patient should be normally reacting (MultiMérieux® containing tuberculin, streptococcus, diphtheria, tetanus, tricophyton and candida antigens) are performed to search for anergy (i.e. absence of the normal immune response to a particular antigen or allergen) – this provides a strong argument for sarcoidosis.

In a patient vaccinated for tuberculosis or known to have been exposed to a tuberculous infection, a PPD skin test which has become negative has the same diagnostic value. We find it also useful to look for polyclonal antibody activation that is present in up to 85% of the patients with sarcoidosis and was also found in patients with ocular sarcoidosis. For this purpose, serologies to four herpes viruses to which most of the adult population has been exposed (herpes simplex, herpes zoster, cytomegalovirus and Epstein-Barr) are performed. ELISA serology detects exposure to these viruses and complement fixation serology is done to establish whether the antibody titers are elevated. An isolated elevated titer to only one virus might be indicative of a viral aetiology.

Polyclonal activation, however, is an additional element for sarcoidosis. This non-specific antibody elevation is the cause of some of the false-positive diagnoses of presumed infectious uveitis, relying only on a serology such as Lyme borreliosis. A positive serology is not a confirmation of ocular Lyme disease. We followed five cases with uveitis and a positive Lyme serology that had negative anterior chamber antibody ratios (Goldmann-Witmer coefficient) and for whom

the diagnosis was finally sarcoidosis. Patients with a compatible clinical picture and positive ACE and lysozyme tests in presence of cutaneous anergy have a probability of over 95% to have ocular sarcoidosis.

On the other hand, when the PPD tuberculin skin test is hyper-positive, this should raise the suspicion of a tuberculous granulomatous uveitis. The next test to be performed is one of the gamma-interferon releasing assays which test blood lymphocytes of patients in order to detect lymphocytes reacting ***in vitro*** when put in the presence of specific proteins from ***Mycobacterium tuberculosis***. When the patient's lymphocytes release gamma-interferon, it means that the patient has been exposed to the bacteria and tuberculosis should be actively researched.

Syphilis serology is performed either routinely or in case of a positive history. In case of undefined diagnosis, serology for Lyme borreliosis is performed with the known limitations of the value of a positive serology. Toxoplasmic retinochoroiditis can sometimes present as a granulomatous (hypertensive) anterior spill-over uveitis. The presence of a retinal focus orients clearly into this direction. In order to make the diagnosis possible toxoplasmic serology should be performed to show the presence of IgG antibodies indicating that the patient has been in contact once in his life with ***Toxoplasma gondii***.

In case of negative ACE/lysozyme test and a non-contributory skin test, a herpetic uveitis should be suspected. Clinical signs that are very suggestive of herpes simplex/zoster uveitis are ocular hypertension and iris atrophy (found both in herpes simplex and varicella-zoster uveitis). Laboratory confirmation of herpes simplex/zoster anterior uveitis can be obtained by the detection of intraocular production of antibodies in the aqueous humor (Goldmann-Witmer coefficient). Aqueous paracenthesis is, however, not performed routinely in these cases but reserved for sight-threatening diseases such as necrotic herpetic retinopathies (NHR) that include acute retinal necrosis. It is also performed in uveitis suspected to be herpetic but that does not respond to classical combined systemic antiviral and topical steroidal therapy to detect CMV DNA in the aqueous.

A condition that can be associated with anterior granulomatous uveitis is multiple sclerosis (MS). In most cases, posterior segment findings such as periphlebitis and vitritis are usually present (Herbort).

LABORATORY TESTING

According to Bansal, recent advances in the understanding of the pathogenetic mechanisms of uveitis have changed the diagnostic and therapeutic approach to patients with uveitis.

Random screening with a full battery of tests is needless and Bansal routinely orders from the following laboratory tests:

- Full blood counts
- Erythrocyte sedimentation rate
- Mantoux test
- Chest X-ray (Computed tomography if required) for tuberculosis and sarcoidosis
- Syphilis serology (***Treponema pallidum*** haemagglutination test)

The following tests are ordered only when relevant to the particular disorder (Bansal):

- Serum Angiotensin-Converting-Enzyme (ACE) levels for sarcoidosis
- Human leukocyte antigen (HLA) typing (B51, DR4) for Behçet's disease (BD) or VKH syndrome
- Antinuclear antibody (ANA) for juvenile idiopathic arthritis
- Anti-neutrophil cytoplasmic antibody for vasculitis associated with Wegener granulomatosis
- X-ray of sacro-iliac joint for ankylosing spondylitis
- Antibodies against ***Toxoplasma gondii***

Other laboratory testing should include:

- Urinalysis (psoriatic arthritis, proteins)
- Lyme titers

- HLA-B27 (ankylosing spondylitis and other seronegative spondylarthropathies)

TREATMENT

The basis of uveitis treatment and management is as follows:

- Alleviate the patient's symptoms
- Control inflammation
- Preserve vision
- Prevent systemic morbidity
- Rule out any infectious condition

Topical steroids are the mainstay of treatment for the majority of uveitis conditions, but steroid injections and oral steroids are often needed in cases of intermediate and posterior conditions. Steroids should always be used aggressively to treat and suppress the inflammatory response with the initial dose ranging from q1h to q.i.d.

The treatment of uveitis can be divided into following steps (Bansal):

- Diagnosis and treatment of the specific causative agent
- Non-specific treatment
- Treatment of related conditions
- Supportive therapy

Uveitis due to infectious agents is treated by specific antimicrobial therapy (antibiotic, antiparasitic or an antiviral) for appropriate duration, with or without corticosteroids.

The mainstay of treatment of non-infectious uveitis is anti-inflammatory therapy. Severe or refractory panuveitis needs immuno-suppressive agents (Bansal).

Optimal treatment of uveitis should achieve the following:

- Relief from pain and discomfort
- Prevention of visual loss due to the disease or its complications
- Treatment of the cause of the disease where possible
- Minimization of any side effects

All drugs and other treatments used in uveitis are powerful in their action and may have significant side effects. It is necessary to balance the benefits of the treatments against the possible harmful effects.

There are differences between the treatment strategies for posterior, intermediate or anterior uveitis. The main difference arises from the ease with which the drugs used to treat the condition can be delivered to the area of inflammation.

- In anterior uveitis, eye drops can reach the source of the inflammation.
- In intermediate uveitis, eye drops reach the area of inflammation but sometimes injections are used to "deliver" the drugs where they are needed most.
- In posterior uveitis, the inflammation is at the back of the eye and drops can't reach the affected area. This requires a different approach and this is why drugs (usually a steroid) are taken systemically (in tablet form).

The medical intervention required to treat anterior uveitis is guided by three goals:

1. The first and foremost goal is reduction and eventual elimination of intraocular inflammation. Timely intervention reduces the chance of serious complications such as massive KP formation, cataract, glaucoma, and permanent visual reduction.
2. The second goal involves the mitigation of the pain and photophobia associated with anterior uveitis. The ocular irritation associated with intraocular inflammation is a significant concern and should not be overlooked. Symptomatic relief is imperative in the therapeutic management of uveitis. The alleviation of photophobia also helps improve compliance with the medication regimen.
3. The third goal is for the clinician to prevent the formation of posterior synechiae and/or break any existing adhesions. This reduces the possibility of permanent pupil dysfunction and minimises the risk of IOP increase and subsequent pupillary-block glaucoma.

Inflammation

Steroids (e.g. Prednisolone forte 1%)

Amelioration of the inflammatory response is the primary goal of uveitis therapy. The inflammatory response of anterior uveitis is undesirable as it can lead to permanent intraocular changes and possible visual loss.

Topical corticosteroid eye drops act to reduce the intraocular inflammation by reversing the increased capillary permeability and reducing white blood cell migration.

Steroids are administered in a variety of ways including e.g.

- Eye drops
- Periocular injection
- Systemically, via the blood stream, either by oral (tablets) or intra-venous injection or infusion (drip) delivery

The method used to present the steroid depends on the severity of the uveitis and where the inflammation occurs.

Typically, steroid eye drops are used every hour for the first day as a loading dose. Then, when appropriate, they are reduced to the recommended schedule and the patient is followed to observe the efficacy of the treatment regimen. At an appropriate time a slow tapering regimen is commenced whereby the frequency of drug use is reduced to zero.

The use of topical steroids increases the risk of elevating intraocular pressure, developing glaucoma and forming a cataract. As long as the pressure is continuously monitored and treated when indicated, the benefits of steroid treatment outweighs the risks involved.

When considering IOP lowering agents, use caution with prostaglandin analogues because they may exacerbate the inflammatory response.

In addition, topical steroids may delay wound healing or epithelialization, reactivate latent herpes simplex infections and potentiate bacterial, fungal or acanthamoeba infections. Prior to the application of steroids, the presence of herpes keratitis must be ruled out.

If the uveitis is severe then injections or use of steroid tablets may be necessary. Cyclosporin is often used in combination with topical steroids to reduce the required dosage of the steroid or if side effects of the medication are a problem.

Injectable steroids should only be administered to patients who do not have an untreated infectious condition, such as e.g. syphilis, Lyme disease, toxoplasmosis or tuberculosis.

It is important that the patient use the medications correctly and continue to take them for the whole of the prescribed course (usually at least 6 weeks) and not to stop them even if the eyes feel better. Steroids should not be ceased abruptly otherwise a rebound reaction is likely.

Make sure the patient is followed up appropriately to ensure that:

- The medication is used as intended
- The eye is responding to treatment after a uveitis attack.

Relief of Photophobia

Cycloplegia (e.g. Atropine or Homatropine)

Photophobia is produced by the biochemical cascade that is responsible for the inflammatory response of the eye. Any movement of the iris produces pain. When the eye is exposed to light, the pupil quickly constricts and the irritation and pain that result can be unbearable.

Cycloplegia acts to paralyze the sphincter muscle by use of a parasympatholytic agent that renders the iris immobile and dilated. Preventing movement of the iris ameliorates photophobia, and the patient obtains symptomatic relief. Typically, a cycloplegic agent (e.g. homatropine 5%) will be used once or several times daily for a few days until the anterior uveitis begins to resolve.

Make sure to inform the patient that the mydriasis does not necessarily guarantee analgesia. Just because the patient stays dilated for a day or two, depending on the drug used, it does not mean the pain will subside for that long.

Posterior Synechiae

Dilation (e.g. Homatropine 5%)

Topical homatropine acts to dilate the iris and therefore break the posterior synechiae and minimize the risk of new adhesions.

Side effects

It is possible that the treatment regimen may have some side effects on the patient. Make sure that the patient is given all the necessary information about potential drug side effects and ensure that they know to contact their doctor about any concerns they have regarding their treatment. It is important that the patient report any and all side effects of the uveitis treatment regimen.

Monitoring of response to treatment must include assessment of the visual acuity and repeat grading of cells and flare. A decrease in the cells and flare indicates a positive response to the treatment regimen. If at follow-up, the anterior chamber reaction is improving, the clinician may continue or reduce medications, depending on the severity of the initial reaction. Cycloplegic drugs may be discontinued when the cellular reaction is subsiding and flare is absent.

The schedule of follow-up should depend on the severity of initial inflammation, potential for sequelae and type of therapy instilled. Patients should be carefully monitored for side effects of corticosteroids and immunosuppressive agents.

Chronic anterior uveitis may require long-term use of low-dose topical steroids. When the patient is a steroid responder (i.e. increased IOP), concurrent treatment with a beta-blocker is advised unless contraindicated.

Once the patient's condition has stabilized, follow-up should be every one to six months. The longer the eye is quiet, the longer can be the interval between follow-up visits.

The patient should be informed about the serious nature of uveitis. Compliance with the therapeutic regimen and keeping all follow-up appointments are essential to achieve the therapeutic goals. The treating practitioner should advise the patient of the potential side effects of long-term corticosteroid use (i.e. glaucoma and posterior sub-capsular cataracts). It is important that this advice be well-documented in the medical record, and the patient should be reminded periodically throughout the course of treatment (Agrawal).

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