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An up-to-Date Literature Review on Uveitis

Author: Abdullaev Shakhzodbek
Andijan State Medical Institut

Abstract:

Uveitis is a broad term of inflammation of the uveal tract, which also may affect other intraocular structures including retina, retinal vessels, vitreous body, and optic disk. The Standardized Uveitis Nomenclature (SUN) classified uveitis on a morphological basis, focusing on iris/ciliary body, vitreous, and retina/choroid involvement [1].

Keywords:

Corticosteroid, therapy, uveitis, panuveitis, periocular, intravitreal.

Classification

The etiological classification differentiates uveitis into 2 different types: infectious and non-infectious (autoimmune/inflammatory).

Uveitis is classified anatomically as:

Anterior uveitis: Localized primarily to the anterior segment of the eye, includes iritis (inflammation in the anterior chamber alone) and iridocyclitis (inflammation in the anterior chamber and anterior vitreous)

Intermediate uveitis: Localized to the vitreous cavity and/or pars plana (part of the ciliary body that extends posteriorly beyond the junction of the iris and sclera)

Posterior uveitis: Any form of retinitis, choroiditis, or inflammation of the optic disk

Panuveitis: Inflammation involving anterior, intermediate, and posterior structures

Uveitis is also classified by onset (sudden or insidious), duration (limited or persistent), and course (acute, recurrent, or chronic).

Posterior uveitis is the rare form of the disorder and is the type of uveitis most associated with loss of vision. Uveitis can affect one or both eyes and it affects people of all ages, including children. Posterior uveitis can cause further complications if it is not treated, such as blindness.

People with certain genes may be more likely to develop posterior uveitis. Patients who have a weakened or impaired immune system (immunocompromised) such as those with HIV or AIDS are at higher risk for viral posterior uveitis. People with a normally functioning immune system may also develop viral posterior uveitis. Cigarette smoking has been associated with a harder to manage disease.

Etiology

- Causes of anterior uveitis include

Idiopathic or postsurgical (most common cause)
Trauma
Spondyloarthropathies
Juvenile idiopathic arthritis
Herpesvirus infection (herpes simplex virus [HSV], varicella-zoster virus [VZV], and cytomegalovirus [CMV])

-Causes of intermediate uveitis include

Idiopathic (most common)

Multiple sclerosis
Sarcoidosis
Tuberculosis (TB)
Syphilis
Lyme disease (in endemic regions)

- Causes of posterior uveitis (retinitis) include

Idiopathic (most common)
Toxoplasmosis
CMV (in immunocompromised patients)
HSV/ VZV
Sarcoidosis

- Causes of panuveitis include

Idiopathic (most common)
Sarcoidosis
TB

Infrequently, systemic drugs cause uveitis (usually anterior). Examples are sulfonamides, bisphosphonates (inhibitors of bone resorption), rifabutin, cidofovir, and checkpoint inhibitors such as nivolumab and ipilimumab.

Symptoms and signs may be subtle and vary depending on the site and severity of inflammation.

- Anterior uveitis tends to be the most symptomatic (especially when acute), usually manifesting with

Pain (ocular ache)
Redness
Photophobia
Decreased vision (to a variable degree)

Chronic anterior uveitis may have less dramatic symptoms and present with irritation or decreased vision.

Signs include hyperemia of the conjunctiva adjacent to the cornea (ciliary flush or limbal injection). Slit-lamp findings include keratic precipitates (white blood cell clumps on the inner corneal surface), cells and flare (a haze) in the anterior chamber (aqueous humor), and posterior synechiae. With severe anterior uveitis, white blood cells may layer in the anterior chamber (hypopyon).

Uveitis (Anterior)

- Intermediate uveitis is typically painless and manifests with

Floaters
Decreased vision

The primary sign is cells in the vitreous humor. Aggregates and condensations of inflammatory cells often occur, appearing as "snowballs." Vision may be decreased because of floaters or cystoid macular edema, which results from fluid leakage from blood vessels in the macula. Confluent and condensed vitreous cells and snowballs over the pars plana (part of the ciliary body that extends posteriorly beyond the junction of the iris and sclera) may cause a classic "snowbank" appearance, which can be associated with neovascularization of the retinal periphery.

Uveitis (Intermediate)

- Posterior uveitis may give rise to diverse symptoms but most commonly causes floaters and decreased vision as occurs in intermediate uveitis. Signs include

Cells in the vitreous humor
White or yellow-white lesions in the retina (retinitis), underlying choroid (choroiditis), or both
Retinal vasculitis
Optic disk edema

- Panuveitis may cause any combination of the previously mentioned symptoms and signs.

Complications

Serious complications of uveitis include profound and irreversible vision loss, especially when uveitis is unrecognized, inadequately treated, or both.
The most frequent complications include
Cataract (secondary to the disease process and/or to corticosteroid treatment)
Glaucoma (secondary to the disease process and/or to corticosteroid treatment)
Retinal detachment
Neovascularization of the retina, optic nerve, or iris
Cystoid macular edema (the most common cause of decreased vision in patients with uveitis)
Hypotony (an intraocular pressure that is too low to support the health of the eye)

Diagnosis

Slit-lamp examination
Ophthalmoscopy after pupil dilation
Uveitis should be suspected in any patient who has ocular ache, redness, photophobia, floaters, or decreased vision. Patients with unilateral anterior uveitis have ocular ache in the affected eye if light is shined in the unaffected eye (true photophobia), which is uncommon in conjunctivitis.
Diagnosis of anterior uveitis is by recognizing cells and flare in the anterior chamber. Cells and flare are seen with a slit lamp and are most evident when using a narrow, intensely bright light focused on the anterior chamber in a dark room. Findings of intermediate and posterior uveitis are most easily seen after dilating the pupil. Indirect ophthalmoscopy (usually done by an ophthalmologist) is more sensitive than direct ophthalmoscopy. (NOTE: If uveitis is suspected, patients should be referred immediately for complete ophthalmologic evaluation.)
Many conditions that cause intraocular inflammation can mimic uveitis and should be considered in the appropriate clinical settings. Such conditions include severe conjunctivitis (eg, epidemic keratoconjunctivitis), severe keratitis (eg, herpetic keratoconjunctivitis, peripheral ulcerative keratitis), and severe scleritis.
Acute angle-closure glaucoma can cause redness and severe pain similar to that of uveitis, which is why it is important to check intraocular pressure at every visit. Uveitis is often (but not always) associated with a low intraocular pressure, whereas pressure is typically high in acute angle-closure glaucoma. Uveitis also can be distinguished from angle-closure glaucoma by the absence of corneal haze and the presence of a deeper anterior chamber.
Other masqueraders include intraocular cancers in the very young (typically retinoblastoma and leukemia) and in older people (intraocular lymphoma). Much less commonly, retinitis pigmentosa can manifest with mild inflammation, which may be confused with uveitis.

Treatment

Corticosteroids (usually topical) and sometimes other immunosuppressive drugs
Cycloplegic-mydriatic drugs
Sometimes antimicrobial drugs
Surgical therapy

Treatment of active inflammation usually involves corticosteroids given topically (eg, prednisolone acetate 1% one drop every hour while awake) or by periocular or intraocular injection along with a cycloplegic-mydriatic drug (eg, homatropine 2% or 5% drops [if available] or cyclopentolate 0.5% or 1.0% drops, either drug given 2 to 4 times/day depending on severity). Antimicrobial drugs are used to treat infectious uveitis. Particularly severe or chronic cases may require systemic corticosteroids (eg, prednisone 1 mg/kg orally once/day), systemic noncorticosteroid immunosuppressive drugs (eg, methotrexate 15 to 25 mg orally once/week, adalimumab 40 mg subcutaneously every 1 to 2 weeks, or infliximab 4 to 10 mg/kg IV every 4 weeks), laser phototherapy, cryotherapy applied transsclerally to the retinal periphery, or surgical removal of the vitreous (vitrectomy) [5-7].

Corticosteroids

Corticosteroids, also abbreviated as “steroids,” are considered the gold standard for treatment. Corticosteroids resemble cortisol (stress hormone) which work by reducing the activity of the immune system by decreasing inflammatory chemicals and migration of the white blood cells to the inflamed area. Thus, steroids are able to lower the amount of inflammation, redness and itching. Giving steroids on a long-term basis can cause changes in the blood cell counts and hormone levels. For example, corticosteroids can reduce the amount of white blood cells that generally stick to the blood vessels or are in the circulation, which can lead to greater infection risk. In addition, fluctuations in hormone levels upon long-term use of systemic corticosteroids can increase the risk of increased pressure in the eye (glaucoma) and cataracts, so the patient must be followed closely.

There are three different classes of steroids that can be given.

Periocular steroids

Periocular steroids are injected directly into the eye and are known to reduce the systemic spread of the drug.

Intravitreal steroids

Intravitreal steroids bypass the blood-retinal barrier and lead to greater availability of the drug. The effects of the medication typically last for 6-8 weeks. Intravitreal implants can deliver the steroid by an insert over time and several different types of implants are available.

Systemic steroids

Systemic steroids are given in the oral or intravenous (IV) formulations. These steroids affect the whole body and are dosed based on body weight. Generally, the daily dose should be less than 10mg of prednisolone that is given orally and are tapered slowly. An increased amount of systemic steroids may be given if the patient has vision threatening diseases.

Long term safety concerns of taking steroids have led to the development of other therapies. Immunomodulator Therapy Overtime, if a patient stops responding to systemic steroids and needs to continue therapy, off-label medications may be prescribed. Immunomodulator therapies can help lower inflammation in the body and help suppress the immune system.

Immunomodulatory medications used for posterior uveitis:

Voclosporin
Cyclosporin A

Tacrolimus
Azathioprine
Mycophenolate mofetil
Cyclophosphamide
Chlorambucil

Biologic Response Modifiers (BRM)
These medications are bioengineered molecules that inhibit the activity of the immune response. They target specific cytokines, interleukins, proteins and analogues. BRM are also used if the patient is unable to take other treatments.
Biologic response modifiers used for certain posterior uveitis conditions include:
Adalimumab (FDA approved)
Infliximab
Ocular Gene Therapy
Ocular gene therapy works by injecting small amounts of adeno-associated virus (AAV) and lentivirus which act as vectors. These vectors have either direct or indirect anti-inflammatory properties.

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