Diagnostic approach

The exact diagnosis of uveitis can be extremely challenging given the vast array of presentations and aetiologies. While clinical examination and laboratory testing are important for the diagnosis of uveitis, making a sound differential diagnosis of the underlying aetiology also requires careful attention to the patient's presentation and history, and to demographic information. Bilaterality is more commonly seen in systemic conditions, whereas idiopathic and herpetic uveitis is more commonly unilateral. The non-granulomatous versus granulomatous nature of the presentation will also help to narrow further the differential diagnosis. Early referral to an ophthalmologist with experience in uveitis is essential.

Ocular symptoms

Symptoms in uveitis generally depend on the location of the inflammation in the uvea, which is useful in differentiating between anterior and posterior uveitis. However, a thorough eye examination is the only way to confirm the diagnosis. A patient's symptoms are less useful in further classifying the disease when dealing with possible intermediate or panuveitis.

Patients with anterior uveitis often complain of ocular symptoms, including pain, redness, photophobia, and tearing. Patients may also have unilateral, dull pain that extends from the eye to the surrounding orbit. The area may be tender to palpation through the eyelid. Common causes of anterior uveitis include human leukocyte antigen-B27 (HLA-B27)-associated iritis (including ankylosing spondylitis, psoriatic arthritis, and reactive arthritis), Behçet's disease, juvenile idiopathic arthritis (JIA), Fuchs' heterochromic cyclitis, and masquerade syndrome (disorders that may mimic uveitis).

In contrast, patients with posterior uveitis usually have a painless presentation. Decreased vision, floaters, photopsia (a perception of flashes of light), or asymptomatic presentation may occur in posterior uveitis, although this is highly variable depending on the location, severity, and aetiology of the inflammation. Common causes of posterior uveitis include toxoplasmosis retinochoroiditis, herpes simplex virus (HSV) retinitis, tuberculosis choroiditis, sarcoidosis, and Vogt-Koyanagi-Harada syndrome (a multi-system autoimmune disorder characterised by chronic uveitis with skin, neurological, and auditory manifestations).

Most causes of uveitis result in bilateral disease. However, cases of unilateral uveitis are often seen in post-surgical uveitis, HSV-associated uveitis, and most parasitic diseases. Therefore, a bilateral versus unilateral presentation can assist in determining the aetiology.

Ocular symptom onset and duration

Onset and duration of the ocular symptoms offer clues to the aetiology. Acute uveitis, characterised by sudden onset and limited duration, is seen in certain uveitis-associated diseases. Most forms of anterior uveitis present acutely. The HLA-B27-associated iritis diseases commonly have an acute presentation. Traumatic iritis and post-surgical bacterial endophthalmitis also usually present acutely.

Chronic uveitis is defined as persistent uveitis characterised by relapse within 3 months of therapy termination. Several types of uveitis, such as JIA, tuberculous uveitis, and Fuchs' heterochromic cyclitis, may present this way.

Recurrent uveitis, characterised by periods of disease inactivity alternating with active disease without treatment, may be seen in many types of chronic uveitis, including Fuchs' heterochromic cyclitis and sarcoid-associated uveitis.

Systemic symptoms
Uveitis may occur as a manifestation of a disease with extra-ocular involvement, whether an infectious disease, an autoimmune-mediated systemic disease, or a masquerade syndrome. Other uveitis syndromes may be confined primarily to the eye. Therefore, a good review of systems should help to narrow the possible aetiologies.

Arthritis is an important systemic symptom in relation to uveitis patients. Symptoms such as pain or stiffness of the hands, wrists, fingers, toes, lower back, spine, or any weight-bearing joints should be sought. These symptoms may be found in patients with JIA, HLA-B27-associated disorders, rheumatoid arthritis, and systemic lupus erythematosus.

Rashes can be a systemic sign found in uveitis-associated diseases such as Lyme disease, syphilis, systemic lupus erythematosus, Kawasaki disease, and drug or hypersensitivity reactions.

Gastrointestinal disease, suggested by abdominal discomfort, nausea, vomiting, diarrhoea, or melaena, may point to Crohn's disease or ulcerative colitis. Behçet's disease and Whipple's disease may also have gastrointestinal manifestations.

Oral lesions (Behçet's disease, inflammatory bowel disease), genital lesions (Behçet's disease, syphilis), headache (Behçet's disease, VKH), neurological symptoms (multiple sclerosis, Behçet's disease), and pulmonary findings (tuberculosis) may also be useful in diagnosis.

The absence of systemic symptoms may also prove useful in diagnosis. A lack of systemic findings is seen in uveitic syndromes confined primarily to the eye, including acute posterior multifocal placoid pigment epitheliopathy (APMPPE), Fuchs' heterochromic cyclitis, birdshot choroidopathy (a bilateral inflammatory disease affecting the choroid layer), and pars planitis.

### Medical, ocular, and medication history

The patient's past medical history (including past ocular history, previous illnesses, and medications) and family history may provide crucial information. Any previous episode and treatment of uveitis should be documented to determine the duration of the disease and/or to determine if the current presentation is a relapse of an existing condition. Documentation of previous disease course and treatments may help to classify the disease and guide treatment. History of past ocular surgeries or trauma that may be associated with the current presentation is also important. Existing ocular conditions including glaucoma, cataracts, and cystoid macular oedema should also be discussed and may be related to the current presentation.

It is important to know if a patient has been diagnosed with any prior illness known to be associated with uveitis, because the presentation could be a manifestation of the underlying disease. History of any autoimmune disease, infectious disease, or neoplastic and paraneoplastic disorders with possible associated uveitis should be sought.

Uveitis secondary to an inflammatory response to medications is rare, but a careful review of a patient's medications may help with the diagnosis. Drug-induced uveitis is most commonly seen with the use of rifabutin, used to treat tuberculosis and other atypical mycobacterial infections. Cidofovir, an antiviral agent used to treat cytomegalovirus in AIDS, has also been shown to cause uveitis. Protease inhibitors used in the treatment of AIDS, particularly indinavir, have also been associated with uveitis. Because all of these drugs are used in patients with HIV, which is itself a potential cause of anterior uveitis, determining the exact aetiology may be difficult in these patients. However, most drug-related uveitis responds well to topical corticosteroid treatment, often making the diagnosis of drug-induced uveitis possible shortly after initiation of treatment.

### Family history

Family history is important since many autoimmune disorders have a genetic predisposition and are seen more commonly in family members. In addition, many infectious diseases can be transmitted congenitally and may underlie the uveitis.

HLA-B27-associated iridocyclitis as seen in ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease is seen in families with HLA-B27 encoded in the major histocompatibility complex on chromosome 6. Birdshot retinochoroidopathy is associated with HLA-A29. Patients with known HLA correlations or those with a family history of an HLA-related disease may be at increased risk for associated conditions.

TORCH (Toxoplasmosis, Other agents, Rubella, CMV. Herpes simplex virus) syndrome covers the common list of perinatal infections associated with congenital infection and associated ocular manifestations. Toxoplasmosis is an example of a disease causing uveitis by congenital transmission. This disease may be passed from mother to child, leading to ocular disease in the child. Additional common congenital infections include syphilis and HIV.

### Demographic information in relation to disease risk

Age, sex, ancestry, social habits, sexual habits, and geographic and occupational exposure risks are important factors.

- Age

The age of a patient may be the most useful demographic consideration when classifying uveitis, given that certain diseases often present in certain age groups:

- Childhood uveitis, although less commonly seen than uveitis in older patients, may be seen in the paediatric population associated with JIA, HLA-B27-associated disorders, Lyme disease, toxocariasis, and retinoblastoma. [16]
- In young adults, uveitis most often occurs in HLA-B27-associated uveitis, Fuchs' heterochromic iridocyclitis, multiple sclerosis, Behçet's disease, APMPPE, and pars planitis.
- Middle-aged patients with uveitis often have ocular disease associated with sarcoidosis, systemic lupus erythematosus, birdshot retinochoroidopathy, and VKH.
- Older adults rarely present with primary uveitis. This may be related to the overall decreased immune response in the older population. One of the rare instances of an autoimmune disease in older adults is giant cell arteritis. In patients with chronic persistent intra-ocular inflammation with poor response to treatment, intra-ocular lymphoma, other malignancies, and masquerade syndromes should be high on the list of possible causes.

Despite these guidelines, it is important to consider that certain causes may present at any age.

- Sex

Although many causes of uveitis affect the sexes equally, certain types show predominance in either men or women. Reactive arthritis, ankylosing spondylitis, and Behçet's disease are more commonly seen in men. As a result of lifestyle differences, men are also more commonly found to have traumatic iritis, fungal endophthalmitis, and sympathetic ophthalmia, resulting from trauma or intravenous drug use. In contrast, JIA and systemic lupus erythematosus are 2 to 3 times and 7 to 15 times more common, respectively, in females than in males.

- Ancestry

Some systemic diseases associated with uveitis are found to be much more common in certain ethnic groups. Examples include HLA-B27-associated iritis, including ankylosing spondylitis, reactive arthritis, and psoriatic arthritis, which are more common in white people. Sarcoidosis is 3 to 4 times more common in black people. Behçet's disease is seen most commonly in the Turkish population and is very common in Asia and Middle Eastern countries compared with North America and Europe. VKH is the second leading cause of uveitis in Japan after Behçet's disease and is seen most commonly in Asian and Native American patients.

- Sexual and social habits

Consideration of sexual and social habits may uncover conditions that could have exposed the patient to infectious causes of uveitis.

Sexual behaviour is important because homosexual and young, sexually active males are more likely to contract HIV and other AIDS-related opportunistic infections. Common HIV-associated manifestations include cytomegalovirus (CMV) retinitis, Pneumocystis carinii choroiditis, tuberculosis-associated uveitis, toxoplasmosis retinochoroiditis, and candida endophthalmitis.

Sexually active people are more likely to acquire sexually transmitted infections, such as syphilis, gonorrhoea, and HSV, that can cause a primary infectious uveitis. Chlamydia, the most common sexually transmitted infection, may trigger the HLA-B27-associated iritis in reactive arthritis. In these cases, it is important to gather a full sexual history, including sexual practices, current genitourinary symptoms, and previous sexually transmitted infections.

Other social habits may reveal further exposure risks of a uveitis patient. Intravenous drug users are at increased risk for HIV and all opportunistic infections. Patients with a history of ingesting raw or undercooked pork are at increased risk of ocular toxoplasmosis. Patients who have ingested unpasteurised milk may be exposed to Brucella. Patients with cats are at increased risk of exposure to faeces containing Toxoplasma gondii. Ocular toxocariasis may also be contracted from cats or dogs carrying this parasite. Bartonella henselae, which causes cat scratch disease, may also be transmitted to patients with exposure to cats.

- Environmental exposure

Environmental exposures, whether due to geographic location, recent travel, occupation, or contact with an infected person, are important when considering several infectious causes of uveitis.

Geographic location and history of recent travel may be important. Histoplasmosis is endemic to the Mississippi-Ohio-Missouri River valleys and must be considered in patients from that area and in those who have recently travelled there. Coccidioidomycosis can be acquired visiting or living in the south-western parts of the US. Dysentery, tuberculosis, malaria, and leprosy are other examples of infectious diseases that may be acquired during travel or in endemic countries.

Occupational exposures to infectious organisms known to cause uveitis are also important to consider. Patients who work on farms or work closely with animals are at higher risk for certain infectious diseases, including leptospirosis (seen in sewer or laboratory workers exposed to rat urine or contaminated water), brucellosis (seen in farm or slaughterhouse workers), and cat scratch disease and toxoplasmosis (seen in patients who work with felines).

Another environmental exposure to consider is an infected human being. Tuberculosis is an example of a disease that is commonly acquired from person-to-person transmission. Tuberculosis is easily spread through air droplets from a person with active disease.

Physical examination

In order to determine the appropriate laboratory work-up in anterior uveitis, granulomatous uveitis must be differentiated from non-granulomatous uveitis. The appearance of the keratic precipitates (KPs) aids in differentiation. Granulomatous uveitis has large ‘mutton fat’ KPs as well as clusters of cells in the anterior chamber (Busacca nodules), trabecular meshwork (Berlin's nodules), or pupillary border (Koepp's nodules), whereas non-granulomatous uveitis has fine keratic precipitates over the corneal endothium. These changes can be seen on dilated fundoscopic examination. Intermediate and posterior uveitis requires a dilated fundus examination to look for signs of vitritis (retinal exudates in the vitreous) and retinitis (retinal vascular sheathing, macular oedema, optic disc swelling, and retinal haemorrhages). In cases of chronic inflammation, a posterior subcapsular cataract may be visualised as well.

Upon slit-lamp examination with tonometry, anterior uveitis may show conjunctival injection with exacerbation around the limbus (ciliary flush), a slight decrease in visual acuity, a decrease in intra-ocular pressure (rarely increased), lymphocyte aggregates in the corneal endothelium (keratic precipitates), corneal oedema, and WBCs or protein in the anterior chamber (flare). In non-granulomatous disease, fine cells are seen, but in granulomatous disease,
mutton fat precipitates are found. Synechiae (iris adherence) to either the cornea (anterior synechia) or lens (posterior synechia) typically form during acute inflammation and can also be seen on slit-lamp examination. In cases of chronic inflammation, a posterior subcapsular cataract and band keratopathy may be visualised as well. A constricted, non-reactive pupil may also be seen.

## Laboratory testing

The list of potential laboratory tests for uveitis is very extensive. The initial focus is to narrow the work-up based on the location of the uveitis (anterior, intermediate, posterior, panuveitis) as well as the type of uveitis (non-granulomatous versus granulomatous). A greater emphasis is placed on finding infectious aetiologies, since they are often more aggressive and may lead to permanent blindness long term. Once infectious aetiologies are ruled out, the ophthalmologist can often collaborate with a rheumatologist and other medical specialties to investigate the autoimmune-mediated aetiologies.

In patients with a first-episode unilateral, non-granulomatous uveitis without symptoms or systemic manifestations, no further evaluation is warranted. This is also true for patients with a recent history of trauma or surgery or with clinical signs of HSV or herpes zoster virus infection.

If the patient presents with bilateral, recurrent, or granulomatous uveitis, further evaluation is needed. FBC, angiotensin-converting enzyme (ACE) level (elevated in sarcoidosis), syphilis serology, and HLA-B27 should be ordered to help identify a related systemic disease. Testing for rheumatoid factor and anticyclic citrullinated peptide (anti-CCP) antibodies should be done in the setting of possible rheumatoid arthritis. Antidouble-stranded DNA levels and complement levels may be elevated in SLE. Other HLA antigens may point to the presence of specific disorders. Elevated levels of antineutrophil cytoplasmic antibodies point to the presence of a vasculitic condition. ESR, CRP, and urinalysis can be useful non-specific tests.

Rapid plasma reagin (RPR), venereal disease research laboratory (VDRL), and fluorescent treponemal antibody (FTA-ABS) testing can help to identify syphilis infection. Ocular manifestations of syphilis involve secondary, tertiary, and neurosyphilis, and RPR and VDRL are usually positive in these patients. A positive FTA-ABS test result does not necessarily indicate active syphilis but a history of syphilis at some point, since the test remains positive for life after syphilis infection. False-positive results may occur in Lyme disease, leprosy, and diseases with high antinuclear antibody (ANA) levels. False-negative results may occur in tertiary syphilis.

If the patient has a history of known exposure or is suspected to be at high risk as a result of occupation, lifestyle, or hobbies, relevant tests should be performed: Lyme titre for Borrelia burgdorferi; purified protein derivative (PPD) skin testing for those with HIV, history of alcohol abuse, or suspected TB; toxoplasma titre; Bartonella henselae titre if cat-scratch disease is suspected. Special considerations should be taken when interpreting a PPD in patients who have had a previous BCG vaccination or who are immunosuppressed. In patients with retinal vasculitis, ANA and antineutrophil cytoplasmic antibodies are needed. ANA is likely to be positive in JIA and so may be a particularly useful test in children.

Vitrectomy (removal of vitreous humour) for cytological analysis, flow cytometry, and culture is not widely used at present, but when available it can be used to assist in identifying the aetiology and thus guide treatment.

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