

LABORATORY TESTING IN ANTERIOR UVEITIS

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## ABSTRACT

This article is designed to aid the practitioner in determining what type of laboratory testing to order in the treatment of anterior uveitis that has not responded to nonspecific medical management. The major presentations of anterior uveitis will be covered and appropriate laboratory tests recommended. It will be assumed that the practitioner is knowledgeable in the classification, etiology, signs, and symptoms of uveitis.

## INTRODUCTION

Anterior uveal inflammation accounts for about 12 cases per 100,000 population, is four times more common than posterior inflammation(4), and is more likely than posterior to be associated with systemic disease(2). Peak prevalence of anterior uveitis is in persons 20 to 50 years of age. Close to 80% of all anterior uveitis can be successfully treated by nonspecific medical management, the remaining 20% pose a serious and challenging problem to the optometrist. Because there are an infinite amount of laboratory tests and possible etiologies, it is best to design a battery of tests that may identify the most likely systemic causes of anterior uveitis.

Before any type of medical management or laboratory testing is initiated, patients with anterior uveitis should be evaluated for possible infectious cause, which could be effectively treated with the appropriate course of anti-microbials. Though most patients who present with an anterior uveitis do not need laboratory investigation upon initial examination, there are several presentations that do. These presentations include anterior uveitis of unknown etiology in children, any bilateral uveitis, granulomatous uveitis, monocular patients with uveitis, severe vision threatening uveitis, and any recurring or chronic inflammation of unknown etiology.

## GRANULOMATOUS ANTERIOR UVEITIS

Although granulomatous uveitis is more common in the posterior pole, there are several forms that affect the anterior segment(13). The most common causes of granulomatous anterior uveitis include sarcoidosis, syphilis, tuberculosis, Vogt-Koyanagi-Harada syndrome, and Behcet's syndrome.

There are few if any known systemic etiologies that will specifically cause a unilateral granulomatous anterior uveitis. Therefore, when presented with this clinically, one must first consider whether it's an atypical presentation of a bilateral granulomatous inflammation, or an atypical anterior presentation of a posterior granulomatous inflammation. Certainly sarcoid and syphilis must be immediately considered as they are two of the most common causes of granulomatous anterior uveitis. There are several forms of posterior granulomatous inflammation that may

cause a "spillover" anterior reaction, including Toxocariasis, toxoplasmosis, and histoplasmosis; evidence of these can be seen on fundoscopic examination.

Sarcoidosis is a multi-system granulomatous disorder of unknown etiology, mostly affecting young adults, especially black females. It presents most frequently with bilateral hilar lymphadenopathy, pulmonary infiltration, skin, and eye lesions(1). Bilateral, chronic, granulomatous iridocyclitis is by far the most common ocular complication(1). Testing for sarcoid includes a chest x-ray, which is positive in 90% of patients, and serum ACE level, which is probably a reflection of the total granulomatous tissue in the body, and is elevated in about 75% of patients with active, untreated systemic sarcoidosis and about 40% of chronic, untreated patients with sarcoidosis(18).

Syphilitic iridocyclitis occurs in about 4% of patients with secondary syphilis. Inflammation is usually acute and may present nongranulomatously and unilaterally in up to 50% of cases(1) This disease should be suspected in any case of uveitis resistant to conventional treatment(1). Routine serologic testing should include the FTA-Abs study, since this is the most specific test in cases of syphilitic ophthalmic involvement(8). The FTA-Abs test is preferred over the VDRL because the FTA-Abs will remain positive in patients even following successful treatment, unlike the VDRL which may yield negative results following treatment.

Although recent reports indicate that incidence of tuberculosis is rising in association with AIDS cases, it is now a rare cause of uveitis accounting for less than 1% of all cases. It should be considered when the uveitis is unresponsive to topical steroid therapy and findings for other causes of uveitis are negative(1). The uveitis can vary from acute to smoldering, chronic low-grade inflammation(4). Tuberculin skin test aids in identification of the rare case of tuberculosis-induced uveitis.

Vogt-Koyanagi-Harada syndrome (VKH) is an idiopathic multisystem disease affecting pigmented individuals. Signs include alopecia, poliosis, neurological irritation, and encephalopathy(1). In addition to the anterior inflammation, the posterior pole findings may be severe and include papillitis and retinal detachment. Diagnosis is usually based on clinical manifestations.

Behcet's disease is a multisystem disease typically affecting young men who are HLA-B5 positive. There are generally four major lesions: recurrent oral ulceration, genital ulceration, skin lesions, and uveitis(1). About 70% of patients with Behcet's disease develop bilateral inflammation of either the anterior or posterior variety(1). Like Vogt-Koyanagi-Harada syndrome, this disease is most often diagnosed by clinical manifestations.

Since there are typically only several systemic conditions which can cause a granulomatous uveitis, it makes the laboratory investigation somewhat more simple. We have discussed the five

most commonly associated systemic causes: Syphilis, Sarcoidosis, Tuberculosis, Vogt-Koyanagi-Harada syndrome, and Behcet's disease. Since VKH and Behcet's syndrome are usually diagnosed by clinical manifestations, it is best to refer for a medical consult if either of these conditions are suspected. In the rare event that undiagnosed tuberculosis is suspected, a skin test can be ordered. From a diagnostic standpoint, this leaves syphilis and sarcoidosis as the two main disease entities causing bilateral, granulomatous anterior uveitis in which testing is almost always indicated. Therefore, first line testing for this type of uveitis should include an FTA-Abs for syphilis, ACE level testing, and possible chest x-ray for sarcoidosis.

#### NONGRANULOMATOUS ANTERIOR UVEITIS

Nongranulomatous anterior uveitis is frequently caused by trauma and infections including herpes simplex keratitis, herpes zoster ophthalmicus, and fungal infections such as candidiasis. The more common systemic causes include ankylosing spondylitis, Reiter syndrome, and juvenile rheumatoid arthritis. In addition, recent studies have shown Lyme disease to cause a nongranulomatous anterior uveitis. The majority of the noninfectious cases of this type of inflammation usually present as an isolated occurrence, respond well to nonspecific topical steroidal/cycloplegic management, and do not necessitate laboratory investigation. When the inflammation is in a child, vision threatening, recurrent, or not responsive to topical management laboratory investigation should be considered.

Ankylosing spondylitis is a chronic inflammatory arthritis of unknown etiology that predominantly affects males of 20 to 40 years. The typical complication is an acute, recurrent, nongranulomatous iridocyclitis. As high as 90 percent of AS patients will be positive for HLA-B27 (versus 8% for the general population), and most will have an elevated ESR(1). X-ray of the sacroiliac joints is recommended in all young adult males with acute unilateral iridocyclitis irrespective of low back symptoms(1).

Reiter's syndrome is one of the most commonly associated systemic illnesses in anterior uveitis(2). The disease consists of a triad of nongonococcal urethritis, conjunctivitis, and seronegative arthritis and is more prevalent in males(1)(4). Ocular complications include an acute/recurrent, bilateral, nongranulomatous iridocyclitis(13). Laboratory tests yield an elevated erythrocyte sedimentation rate (ESR), positive HLA-B27, and sacroiliac joint X-rays much like those found in ankylosing spondylitis(13).

Juvenile rheumatoid arthritis (JRA), sometimes called juvenile chronic arthritis (JCA), is a "seronegative" idiopathic inflammatory arthritis in children less than 16 years of age(1). There are three subgroups: Polyarticular, affecting five or more joints, and systemic onset (Still's disease) combine to make up

half of JRA patients. Pauciarticular JRA, affecting four or less joints, accounts for 50% of JRA cases and represents the subgroup most likely to develop anterior uveitis at 20%(1). These children are rheumatoid factor negative (unlike their adult counterparts). Approximately 75% of children with JRA and uveitis test positive for antinuclear antibodies (ANA) as opposed to just 30% in JRA patients without uveitis. In addition, the sedimentation rate (ESR) can be elevated in these patients. Characteristically, the eye is white, keratic precipitate formation (if any) is small and mild, and posterior synechia formation is common(1). fifty percent of the cases of uveitis in JRA patients are moderate to severe and last over four months. Because early diagnosis may better the prognosis of the disease, ANA and ESR testing is indicated in all children with idiopathic uveitis regardless of evidence of arthropathy.

Lyme disease is caused by a tick born spirochete that can cause a multitude of systemic features including skin lesions, cardiac abnormalities, arthritis, multiple sclerosis, and ocular complications such as iridocyclitis, hemorrhagic conjunctivitis, keratitis, and optic neuritis(6). Because several systems are likely to be involved, diagnosis of Lyme disease on ocular signs alone is unlikely. However, there are several laboratory tests for this disease. Either ELISA or indirect IFA tests for IgG and IgM directed at the causative agent, *Borrelia burgdorferi*, are available(18).

Although Fuch's heterochromic iridocyclitis is not considered to be a systemic illness or diagnosable by routine laboratory testing, it is worth mentioning because it is frequently misdiagnosed. It is a chronic, nongranulomatous anterior uveitis which has an insidious onset and usually does not respond to steroidal therapy. It is usually unilateral and predominantly affects middle age adults(4). This type of uveitis accounts for about 2% of all uveitis and is considered the most often misdiagnosed and mistreated anterior inflammation(1). Heterochromia is often the first sign(4), but is often absent or difficult to identify, making diagnosis more difficult. Although there is no laboratory testing for Fuch's heterochromic iridocyclitis, evaluation of iris color, characteristic lattice-like keratic precipitates, and a very mild anterior chamber reaction accompanying this disorder permit the clinician to make this diagnosis with routine examination(8).

Laboratory testing in nongranulomatous uveitis should include HLA-B27 testing, an ESR, and possible sacroiliac joint x-ray to help rule out Reiter's syndrome and ankylosing spondylitis. In the case of a child, ANA testing and an ESR should be performed to insure the prompt diagnosis of an arthropathy. If the inflammation is not responsive to steroids, an FTA-Abs should be ordered to rule out syphilis.

## MASQUERADING SYNDROMES

When evaluating a patient with uveitis, it is important to be familiar with several conditions which can mimic the appearance of a uveitis and perhaps lead to misdiagnosis. These "masquerading syndromes" include: pseudohypopyon in a patient with a retinoblastoma, juvenile xanthogranuloma involving lesions of the iris, leukemia in which leukemic cells infiltrate the iris and float freely in the anterior chamber, and peripheral retinal detachments(8,P).

## CONCLUSION

It must be kept in mind that anterior uveitis has been separated into granulomatous and nongranulomatous inflammation for organizational purposes. When presented with inflammation clinically, it is not always this simple. For example, early granulomatous inflammation may present nongranulomatously or diseases that characteristically present with a certain type of inflammation may present with another. Diagnosing inflammation as granulomatous or nongranulomatous gives the clinician an excellent start toward accurate diagnosis and management, but should not be thought of as absolute.

Because anterior uveal inflammation is a relatively common finding in any eyecare facility, it is important for the treating practitioner to have an intelligent and methodical approach to proper diagnosis. This paper is meant to aid the practitioner in formulating first line testing depending on the presentation. It must be kept in mind we are often required to go well beyond this initial stage of tests and will often be frustrated with cases in which further testing and appropriate referrals reveal no apparent etiology. Many times in these cases, the systemic etiology may be still subclinical but still sufficient to induce an inflammation.

Table 1. Quick referrance guide to diagnoses and relevant information.

Type of Uveitis	Gran. (G) Non- gran. (N)	Chro- nicity	Male (M) Fe- male (F)	Uni- lat- eral (U) Bi- lat- eral (B) *	Laborarory Tests Special Tests
Sarcoidosis	G	C-R	F-m	B	ACE Chest X-Ray
Syphilis	G	A-r	--	B	FTA-Abs,
Tuberculosis	G	C A-R	--	B	Skin Test, Med. Consult
Vogt-Koyanagi- Harada Syn- drome	G	A-R C	--	B	Med. Consult
Behcet's Syndrome	G	A-R	M	B	Med. Consult
Ankylosing Spondylitis	N	A-R	M	B	ESR, HLA-B27 S-I jt x-ray
Reiter's Syndrome	N	A-R	M	B	ESR, HLA-B27 S-I jt x-ray
Juvenile Rheumatoid Arthritis	N	C	--	B	ANA, ESR
Lyme Disease	N	A-R	--	B	ELISA or indirect IFA

A=acute, R=recurrent, C=chronic, ELISA=enzyme linked immunosorbant assay  
Adapted from Uveitis a Clinical Approach to Diagnosis and Management.  
R.E. Smith, R.M. Nozik 1983 Williams and Williams.

\* Author's note: Laterality is based on highest probability but not absolut

Table 2. Common laboratory tests and expected normal ranges.

TEST	NORMAL RANGES
ACE	Adult: 8-52 U/L    PEDIATRIC: 0-2 years 5-83 U/L 2-7 years 8-76 U/L 8-14 years 6-89 U/L
ESR	Adult                      Adult *Males = age/2         Females = (age + 10)/2
ANA	<1:40 = negative, 1:40 to 1:80 = low antibody level >1:160 = elevated levels
FTA-Abs	**This test yields "reactive", meaning positive, or "nonreactive", meaning negative.
HLA-B27	This test yields either a "positive" or "negative" result

\* This formula is a quick assessment of ESR normals. Consult the laboratory document for more precise expected values.  
 \*\* Must be reactive on two consecutive trials to be diagnostic.



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