Journal of Microbiology, Immunology and Infection 55 (2022) 573—580

Available online at www.sciencedirect.com

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Review Article

Step-wise diagnostic approach for patients with uveitis - Experts consensus in Taiwan

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Received 12 July 2021; received in revised form 10 January 2022; accepted 7 February 2022
Available online 18 March 2022

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https://doi.org/10.1016/j.jmii.2022.02.003

KEYWORDS
Evaluation;
Recommendation;
Systemic;
Taiwan;
Uveitis

Abstract Uveitis is a sight-threatening disease that can be associated with many different etiologies. Successful treatment of uveitis relies on accurate diagnosis and prompt efficient therapy. History taking, physical and ocular examinations, systemic evaluations, and response to treatment provide crucial information to differentiate possible etiologies involved in the pathophysiology of intraocular inflammation. This article provides recommendations for a step-wise approach to patients with uveitis in Taiwan based on an expert meeting and consensus. Systemic evaluations for uveitis should be performed step-by-step and include investigation of patients' general systemic conditions, ruling out infectious etiologies, and obtaining evidential biomarkers to diagnose a specific disease entity.

Introduction

Uveitis is defined as an intraocular inflammation involving the iris, ciliary body or choroid.[1] The epidemiology of uveitis is highly variable around the world due to the heterogenicity of the disease and its genetic associations with different ethnicities. Prevalence of uveitis in Asian countries ranges from 40 to 730 cases per 100,000 population.[2] Population-based study has revealed that the incidence is 111 cases per 100,000 person-years in Taiwan and 106 cases per 100,000 person-years in Korea.[3,4] Despite landmark advances in treatments, such as the injectable intraocular corticosteroid implants and systemic biologic disease-modifying anti-rheumatic drugs, uveitis remains a leading cause of irreversible visual impairment, accounting for 5%—20% of legal blindness in developed countries.[5]

Uveitis is a group of disease entities that can be caused by many different etiologies.[6] These entities can be categorized into three groups based on their etiologies: infectious, non-infectious, and masquerade syndrome. "Infectious uveitis" refers to intraocular inflammation that is mainly caused by pathogens that can be identified. Pathogens, including viruses, bacteria, fungi, parasites and mycobacteria, may directly infect intraocular tissues or trigger host immune response, followed by various degrees of uveal inflammation. "Noninfectious uveitis" refers to uveitis resulting from immune-mediated inflammation, which may be associated with systemic rheumatological diseases or may be a solitary ocular disease. Besides, exogenous stimulation such as trauma of the eyeball, intraocular surgical procedures, or medications may also induce uveitis. Masquerade syndrome refers to lymphoma, intraocular foreign body, rhegmatogenous retinal detachment, retinitis pigmentosa, or other causes that may mimic or accompany intraocular inflammation; it should always be considered and ruled out before making the diagnosis.

Given the rapid increase in knowledge of uveitis, ophthalmologists may benefit from a standardized step-wise diagnostic approach that integrates concepts derived from recent advances in clinical trials, molecular studies and imaging technology. With the goal of working toward a consensus regarding the diagnostic approach in Taiwan, an expert panel meeting was held under the auspices of the Taiwan Ocular Inflammation Society. The panel proposed an algorithm for step-wise diagnostic approach to uveitis.

Methods

A panel of 13 Taiwanese physicians with expertise in the management of uveitis were invited to participate and convened to develop consensus recommendations. The panel meeting was held in Taipei, on November 21, 2020. Four of the panelists attended a pre-meeting to formulate statements of recommendation. The expert panel reviewed current evidence for the diagnosis and management of uveitis, which was focused on the efficient and feasible systemic imaging and laboratory examination for differentiating etiologies of uveitis. National health policy and domestic epidemiology were squared up in establishing the consensus. Two algorisms were formulated based on the consensus reached by the experts.

Results

Recommendations

General principles 1:

Ophthalmologists should be aware that uveitis could be caused by infectious pathogens, non-infectious etiologies, or uveitis masquerade syndrome. It may be a sight-threatening disease, despite the etiology and the anatomical classification of the intraocular inflammation.

Uveitis may be caused by various non-infectious or infectious etiologies. Previous epidemiological study in Asian countries revealed that 10.8%—83.3% of uveitis cases were caused by non-infectious uveitis and 10.0%—64.7% of cases were caused by infectious pathogens.[2,7] In the Chinese population, studies from Taiwan and China reported that 41.2%—83.3% of uveitis cases were non-infectious, whereas 10%—50.8% of uveitis cases were infectious.[8—16] Although

some systemic medical histories and ocular signs may raise suspicion of infectious etiologies, it is always important to rule out infection in all cases since therapy aimed only at non-infectious uveitis may sometimes cause disastrous results in infectious uveitis.

More than one-third of patients experience significant visual decline in the affected eyes.[17,18] Most visual impairment in uveitis patients is the consequential result of various ocular complications, including corneal opacity, glaucoma, cataract, retinal detachment, retinal vascular occlusion, macular edema, and optic atrophy. These complications are highly associated with the severity, duration, and frequency of intraocular inflammation. In addition, irreversible visual loss may also be caused directly by ocular media opacity, tissue ischemia, anatomical atrophy, dysfunction, or death of the neurosensory retinal cells in some specific uveitis entities. Ophthalmologists should be aware of and inform the patients of the risk of visual impairment once they have experienced uveitis with a severe and chronic course.[5,18,19]

General principles 2:

Differentiating the etiology (or entity) of uveitis is important in every case with non-anterior uveitis and patients who have anterior uveitis with a severe or chronic course. Patients who require multidisciplinary efforts for differential diagnosis, treatments, or are at high risk for prominent visual decline are recommended to be referred to sub-specialists in appropriate hospitals.

Population-based studies in Taiwan and Korea showed that 78%—86% of new cases were anterior uveitis.[3,4,9,10] Clinically, most cases can be controlled by topical corticosteroids, but the clinical prognosis and visual outcomes are different if the inflammation is severe, prolonged, or involves the posterior segment of eyeball. The treatment strategy for these patients is to rapidly control the active inflammation and prevent ocular complications.[20—22] Hence, different therapeutic options, duration of treatment, clinical prognosis, and follow-up methods should be considered for different uveitis entities. For example, adequate and long-term immunomodulatory therapy should be administered to patients with ocular Behcet's disease to prevent retinal atrophy following multiple recurrent episodes; anti-viral therapy should be used for some virus-induced anterior uveitis in which the frequent recurrence of elevated intraocular pressure may lead to permanent optic nerve damage.[23,24]

Evaluating the extent of intraocular inflammation carefully by using slit-lamp examination and fundoscopy in every uveitis case is essential.[25] Patients with mild inflammation restricted to the anterior chamber can first be treated with empirical therapy, whereas differentiating the etiology of uveitis is necessary in every patient in whom the ciliary and/or choroid are inflamed, and who have isolated anterior uveitis with severe, chronic or frequently recurrent course. Sometimes, inflammation in the anterior chamber should be managed as non-anterior when the posterior segment cannot be thoroughly evaluated (e.g., caused by severe posterior synechia or exudative fibrin in the anterior chamber), especially when the patient has no history of human leukocyte antigen (HLA)-B27-related acute anterior uveitis.

As for ophthalmologic general practitioners, patients should be referred to appropriate hospitals if comprehensive laboratory/systemic imaging tests are required to differentiate etiology of their uveitis. Urgent referral is also recommended if the patients have recent surgical history, any signs of retinitis, suspected endogenous or exogenous endophthalmitis (fever, systemic infection, recent indwelling catheter overdue, septic abortion), vision-threatening retinal conditions (retinal vasculitis, retinal detachment, choroidal neovascularization, etc.), poor visual acuity (corrected visual acuity $\leq$6/60) or invisible fundus. These histories, symptoms, and clinical signs may suggest several uveitis entities that relate to a higher risk for permanent visual loss.

Usually, the multidisciplinary care of ophthalmologists and physicians is more efficient and beneficial for most uveitis cases. Patients for whom all infectious etiologies of uveitis have been ruled-out and combinations of systemic rheumatoid diseases are suspected are suggested to be co-cared with rheumatologists. Patients for whom the uveitis entities are associated with systemic infections are suggested to be co-cared with infectious specialists. Oncology consultation is advised if the patient is diagnosed with intraocular malignancy.

Differential diagnoses of uveitis can be made based on various information, including systemic and ocular history, review of system, disease course, intraocular signs, results from ophthalmic ancillary examinations, laboratory examinations, and clinical response to previous treatment.[25—28] Each specific component is important for exploring the etiology that may have caused the uveitis (Fig. 1.).

General principles 3:

Differentiating the etiology of uveitis mainly based on systemic/ocular history, review of system, disease course, signs obtained by detailed ocular examinations, the classifications of the intraocular inflammation, and support from laboratory/imaging examinations.

Taking a comprehensive history of systemic disease/medication, ocular disease, ocular surgery, trauma, pet/animal contact, traveling or clustering, and course of uveitis is important for differentiating the etiology of uveitis. Infectious uveitis should always be considered and ruled out if the patient is in a systemic immunocompromised status (e.g., having acquired immunodeficiency syndrome, under chemotherapy for systemic malignancy, or receiving long-term immunosuppressive therapy for rheumatic disease or post-organ transplant status), has received ocular or major

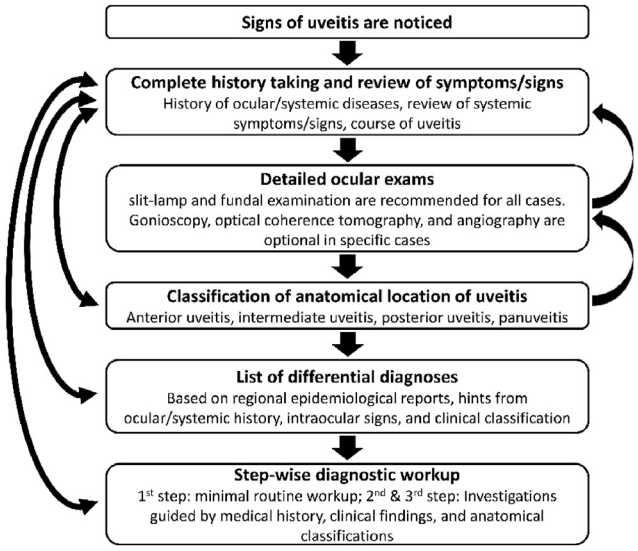

Figure 1. General algorithm for differentiating etiology of uveitis.

systemic surgery, has been hospitalized, or has undergone recent delivery/abortion.

The course of uveitis can be divided into different dimensions. The affected eyes may be unilateral or bilateral. The onset can be sudden or insidious. The duration of intraocular inflammation can be classified as limited if it lasts for no longer than 3 months, or persistent if it lasts for longer than 3 months. It could be acute with sudden onset and limited duration, recurrent if there are repeated episodes separated by periods of inactivity without treatment for equal to or more than 3 months in duration, or chronic if the uveitis is persistent and relapses in less than 3 months after discontinuing treatment.

Carefully reviewing the systemic symptoms and signs is also crucial for diagnosing those uveitis entities associated with systemic diseases. For example, patients with Behcet's disease or syphilis may frequently develop oral ulcers or genital ulcers; patients with spondyloarthritis may experience neck stiffness or low back pain; patients with inflammatory bowel disease may experience diarrhea, abdominal pain, or bloody stool; skin eruptions or lesions may be noticed in patients with Behcet's disease, sarcoidosis, psoriasis, or Lyme disease; endogenous endophthalmitis should be ruled-out if the patient has experienced fever or chills recently; and chronic cough may be present in patients with sarcoidosis or pulmonary tuberculosis. Systemic symptoms and signs should be checked based on initial impression. However, the experience of oral ulcers (including frequency, site, and duration), skin lesions (size, location, color, and three-dimensional shape), arthralgia (low back pain, neck stiffness, plantaris fasciitis, calcaneal tendinitis, etc.), and fever are suggested to be reviewed for all patients whose etiology of uveitis remains to be identified.

Detailed ocular examination and classification of intraocular inflammation are crucial to **list** differential diagnoses. A precise classification of uveitis may help ophthalmologists to narrow the range of differential diagnosis, facilitate the diagnostic workup with a better positive/negative predictive value of tests, and improve the planning of treatment. Identifying the primary location of the intraocular inflammation is one of the most practical and efficient classifications for making the list of differential diagnoses for uveitis entities. Common uveitis entities in Taiwan are listed in Table 1.

Clinicopathological classification (granulomatous versus non-granulomatous inflammation), findings from other ancillary ophthalmic examinations (optical coherence tomography, optical coherence tomography angiography, fluorescence angiography, Indocyanine green angiography, etc.), and other signs such as intraocular pressure, macular edema, or retinal vasculitis may also contribute to the listing of differential diagnoses.[29–33] It is noteworthy that recent studies have shown that fluorescence angiography with ultra-wide field imaging technique may provide more information for observing peripheral retinal lesions and vasculitis in uveitis patients.[34–37]

Indeed, many uveitis entities can be diagnosed based on patients' histories and results from clinical exams. For those cases, systemic investigation is usually done for confirming diagnosis, excluding systemic infection, and evaluating the general condition before systemic therapy. For the other cases, systemic laboratory and imaging tests should be done in accordance with the list of all possible differential diagnoses.

General principles 4:

Systemic investigations should be done step-by-step based on the list of differential diagnoses for each uveitis patient individually. The evaluations should include routine systemic workup and specific exams guided by the anatomical classification of uveitis, clinical or preclinical findings, and medical histories of the patients.

Systemic evaluations for uveitis patients should include investigations for checking patients' general conditions, tests for ruling out infectious etiologies, and image or laboratory biomarkers to obtain evidence for diagnosing a specific disease entity. For every patient who needs systemic corticosteroid/immunomodulatory therapy, patients' general conditions should be checked at baseline to avoid contraindications for systemic therapy, and monitoring for systemic side effects after treatments. For those patients with uveitis for whom the etiology needs to be differentiated, a step-by-step investigation, including routine systemic workup and specific exams guided by the anatomical classification of uveitis, clinical or preclinical findings, and medical histories of the patients is recommended.[38,39] (Table 2.) In this algorithm, the first step contains minimal routine workup when evaluating every patient with uveitis. The second step contains less invasive or less costly workups based on anatomical classifications, clinical or preclinical findings and medical history. The third step was to adopt advanced diagnostic approaches, including invasive diagnostic procedures for specific disease entities.

Table 1 Common uveitis entities in Taiwan.

Anatomical Classifications	Common uveitis entity	
Anterior uveitis	**Infectious etiology**	**Syphilis and masquerade syndrome can manifest as any anatomical type of uveitis*
	Viral anterior uveitis caused by cytomegalovirus, herpes simplex virus, or varicella zoster virus	
	Non-infectious etiology	
	Human Leukocyte Antigen-B27 related uveitis	
	Glaucomatocyclitic crisis	
	Psoriasis-related uveitis	
	Fuch'sheterochromic iridocyclitis	
	Juvenile idiopathic arthritis-related uveitis	
	Reiter's syndrome	
	Behcet's disease (uncommon manifestation)	
	Sarcoidosis (uncommon manifestation)	
Intermediate uveitis	**Infectious etiology**	
	Ocular tuberculosis	
	Non-infectious etiology	
	Pars planitis	
	Sarcoidosis	
Posterior uveitis	**Infectious etiology**	
	Ocular Toxoplasmosis	
	Acute retinal necrosis	
	Cytomegalovirus retinitis	
	Ocular tuberculosis	
	Non-infectious etiology	
	Sarcoidosis	
	Multiple evanescent white dot syndrome	
	Punctate inner choroiditis	
	Serpiginous choroiditis	
	Acute posterior multifocal placoid pigment epitheliopathy	
	Multifocal choroiditis	
	Idiopathic retinal vasculitis	
Panuveitis	**Infectious etiology**	
	I*nfectious endophthalmitis*	
	Ocular tuberculosis	
	Non-infectious etiology	
	Vogt-Koyanagi-Harada syndrome	
	Behcet's disease	
	Sarcoidosis	
	Sympathetic ophthalmia	

* Common etiologies of uveitis in Taiwan are listed in this table. Other etiologies, including uveitis-glaucoma-hyphema (UGH) syndrome, tubulointerstitial nephritis and uveitis (TINU), multiple sclerosis-associated uveitis, Human T-lymphotropic virus 1 (HTLV-1)-related uveitis, Lyme disease, ocular leptospirosis, toxocariasis, etc., are seldom reported. However, those diagnoses should still be considered if the clinical presentations are typical and the other etiologies are ruled-out.

Minimal routine workup is suggested as the first step of the investigation. This workup should at least include complete blood count, erythrocyte sedimentation rate, C-reactive protein, treponemal and non-treponemal assays for syphilis, and chest X-ray. Results from these exams are usually fast and can help us quickly rule-out some infectious etiologies or even detect masquerade syndrome caused by systemic malignancy.[40] The proposed minimal routine workup rendered skin tuberculin test as the optional test, because the Bacillus Calmette-Guerin vaccine, or BCG, is administered to all children in Taiwan. A positive skin test might not indicate a TB infection.

The second step of the investigation should be arranged in accord with the list of differential diagnoses for each individual uveitis patient. The list should be made based on the anatomical classification of uveitis, clinical or preclinical findings, and medical histories of the patients. For example, the genetic test for HLA-B27 could be checked for patients with anterior uveitis but no signs of herpetic infection; serologic test of serum immunoglobin could be checked for patients in whom parasitic infection is suspected, such as toxoplasmosis or toxocariasis; chest computed tomography can be arranged for patients in whom sarcoidosis was suspected; polymerase chain

Table 2 Recommended step-wise systemic workup for uveitis patients in Taiwan.

Step 1[a] Minimal routine workup	Step 2[b] Investigations guided by 1. Anatomical classifications 2. Clinical or preclinical findings 3. Medical history	Step 3 Investigations guided by 1. Anatomical classifications 2. Clinical or preclinical findings 3. Medical history
⇨ Complete blood count (CBC) ⇨ Treponemal and Nontreponemal assays for syphilis (e.g., TPPA + RPR) ⇨ Chest X-ray ⇨ ESR ⇨ CRP	⇨ HLA-B27 (if no sign for herpetic infection) ⇨ Serology for Toxoplasma ⇨ Chest CT for Sarcoidosis ⇨ ANA/Anti-phospholipid Ab/ ANCA (for isolated retinal vasculitis) ⇨ PCR for CMV/VZV/HSV (for steroid-resistant anterior uveitis or patients with recurrent/chronic anterior uveitis but negative for genetic test of HLA-B27)	**Image study** ⇨ Brain MRI ⇨ PET or whole-body gallium scan **Histopathology** For sarcoidosis ⇨ Bronchial lavage ⇨ Conjunctival/Lacrimal gland ⇨ Skin granuloma biopsy ⇨ VATS/EBUS For lymphoma ⇨ Vitrectomy

[a] Optional test for Step 1: Tuberculin test, antinuclear antibody (ANA), rheumatic factor (RF), C3, C4, IgG or IgM for cytomegalovirus, herpes simplex virus and varicella-zoster virus, HLA-B27, HLA-B51, IgG or IgM for Toxoplasma.
[b] Optional test for Step 2: Angiotensin-converting enzyme level, PCR tests for *Mycobacterium* or universal pathogens.
Abbreviations: ESR: Erythrocyte Sedimentation Rate; CRP: C-reactive protein; ANA: antinuclear antibody. ANCA: anti-neutrophil cytoplasmic antibodies. AST: aspartate transaminase. CMV: cytomegalovirus. CT: computed tomography. EBUS: endobronchial ultrasound. HSV: herpes simplex virus. MRI: magnetic resonance imaging. PCR: polymerase chain reaction. PET: Positron emission tomography. VATS: video-assisted thoracic surgery. VZV: varicella-zoster virus.

reaction (PCR) test of aqueous fluid for herpes simplex virus type 1/2, varicella-zoster virus, or cytomegalovirus can be done for patients with anterior uveitis resistant to steroid-therapy or in whom the genetic test HLA-B27 was negative; anti-nuclear antibodies, anti-phospholipid antibodies, and anti-neutrophil cytoplasmic antibodies are suggested to be checked in patients with retinal vasculitis but no significant chorioretinitis.[41,42] Most hospitals can perform these tests, and the results can usually be obtained within 1—2 weeks.

If a diagnosis cannot be made with previous tests, further advanced examinations should be arranged for several disease entities. For example, brain magnetic resonance imaging may be arranged when multiple sclerosis or lymphoma is suspected; whole body gallium scan or positron emission tomography (PET) can be arranged for patients who are suspected to have systemic sarcoidosis; histopathological tests of bronchial lavage fluid or biopsies from lesions, granulomas, or lymph nodes can be performed to diagnose sarcoidosis; diagnostic vitrectomy should be done for cases with the suspicion of intraocular lymphoma.[42,43] All of these tests should also be considered based on the anatomical classification of uveitis, clinical or preclinical findings, and medical histories.

Lastly, regional epidemiology of each disease entity should always be considered before making the final diagnoses.[44] In a study of 258 non-infectious uveitis cases at a tertiary referral center in Taiwan, HLA-B27-associated uveitis was most commonly seen, followed by Vogt—Koyanagi—Harada disease and Posner—Schlossman syndrome.[9] While the prevalence of HLA-B27 is higher in Taiwan than in Japan or Southern China (5% in Taiwan, 1% and 2% in Japan and China, respectively); the prevalence of toxoplasmosis is relatively lower in Taiwan than that in Western countries.[9,16,45—49] In a study of 823 uveitis cases at a medical center in Northern Taiwan, 123 patients were diagnosed to have rheumatic diseases. The most frequent rheumatic diseases included ankylosing spondylitis (5.8%), followed by Behçet's disease (2.8%), sarcoidosis (1.4%), psoriasis (1.1%), and juvenile idiopathic arthritis (1.1%).[8] A positive serologic test of serum immunoglobin for *Toxoplasma gondii* in Taiwan would be very informative for making a diagnosis of ocular toxoplasmosis, especially in patients with suggestive clinical findings such as "headlight in a fog" or "active chorioretinitis lesion with satellite pigmentary scar."

Discussion

It is critical that all ophthalmologists should understand that uveitis could be vision-threatening and associated with various infectious and non-infectious etiologies. Accurate diagnosis is crucial for planning an appropriate treatment regimen for every case. In this article, we have proposed four principles and a stepwise systemic evaluation for making the differential diagnoses for uveitis. However, ophthalmologists should know that all systemic laboratory and imaging tests should be arranged based on clinical suspicion and followed by history taking, systemic review, and detailed ophthalmic exams. We have only listed the exams for several uveitis entities that are commonly seen in Taiwan. Some specific tests for other diseases not

mentioned in this article should be checked if those diseases are suspected clinically. Last but not least, every diagnosis of uveitis entity based on laboratory investigations must correspond with clinical manifestations. The diagnosis should always be re-evaluated when the disease course and/or treatment response is not as expected.

Declaration of competing interest

All authors declare that there is no conflict of interest related to the subject matter or materials discussed in this article.

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