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Review

Uveitis: Diagnostic work-up. A literature review and recommendations from an expert committee

Pascal Sève [a,b,*], Patrice Cacoub [c,d], Bahram Bodaghi [e], Salim Trad [f], Jérémie Sellam [g], David Bellocq [h], Philip Bielefeld [i], Damien Sène [j,k], Gilles Kaplanski [l], Dominique Monnet [m], Antoine Brézin [m], Michel Weber [n], David Saadoun [c,d], Christophe Chiquet [o], Laurent Kodjikian [g]

[a] Service de Médecine Interne, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, 103 grande rue de la Croix-Rousse, 69317 Lyon Cedex 04, France
[b] Faculté de Médecine Lyon-Sud, Université Claude Bernard-Lyon 1, France
[c] Service de Médecine Interne et Immunologie Clinique, Hôpital Pitié Salpetrière, Université Paris 6, AP-HP, Paris, France
[d] DHU I2B, Inflammation, Immunopathology, Biotherapy, UPMC, Paris VI, France
[e] Service d'Ophtalmologie, Hôpital Pitié Salpetrière, Université Paris 6, AP-HP, Paris, France
[f] Service de Médecine Interne, Hôpital Ambroise Paré, 92100 Boulogne-Billancourt, France
[g] Service de Rhumatologie, Hôpital Saint-Antoine, AP-HP, UPMC Univ Paris 06, INSERM UMRS 938, DHU i2B, 75012 Paris, France
[h] Service d'Ophtalmologie, Hôpital Pitié Salpetrière, Université Paris 6, AP-HP, Paris, France
[i] Service de Médecine Interne et Maladies Systémiques, CHU Dijon Bourgogne, 21000 Dijon, France
[j] Service de Médecine Interne, Hôpital Lariboisère, AP-HP, GH Saint-Louis Lariboisière Fernand-Widal, France
[k] Université Sorbonne Paris Cité- Paris Diderot, Paris, France
[l] Service de Médecine Interne et Immunologie Clinique, Hôpital de la Conception, 147 Boulevard Baille, 13005 Marseille, France
[m] Service d'Ophtalmologie, Hôpital Cochin, Université Paris-Descartes, Assistance Publique – Hôpitaux de Paris, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France
[n] Service d'Ophtalmologie, Hôtel Dieu, Centre Hospitalo-Universitaire de Nantes, 1 place Alexis Ricordeau, 44093 cédex 1, France
[o] Service d'Ophtalmologie, Hôpital Albert Michalon, Université de Grenoble, F-38009 Grenoble, France

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ABSTRACT

Purpose: Diagnosis of uveitis is difficult. Etiologic investigations should take into account the epidemiology of uveitis and should focus on the most severe forms of the disease and those which can be treated. This study was undertaken to establish recommendations for the diagnosis of uveitis.
Methods: Recommendations were developed by a multidisciplinary panel of 14 experts, including internists, ophthalmologists, and rheumatologists, and are based on a review of the literature and the results of the ULISSE study, which was the first prospective study to assess the efficacy of a standardized strategy for the etiologic diagnosis of uveitis. The following groups of patients are not included in these recommendations: children, immunocompromised patients, patients with severe retinal vasculitis, and those with specific eye diseases diagnosed by ophthalmologic examination only.
Results: Diagnosis should be guided by the medical history of the patient and physical examination. Serologic screening for syphilis is appropriate in all forms of uveitis. If uveitis is not diagnosed at this stage, investigations oriented by the anatomic characteristics of uveitis are proposed. These consist of assays for HLA-B27 (in unilateral acute anterior non-granulomatous uveitis), serum angiotensin-converting enzyme, interferon-gamma release, chest computed tomography (chronic uveitis), cerebral magnetic resonance imaging and anterior chamber tap with interleukin-10 analysis (intermediate or posterior uveitis in patients >40 years-old). Other investigations prescribed in the absence of orientation are usually unhelpful.
Conclusions: A strategy is proposed for the etiologic diagnosis of uveitis. The benefit of more invasive investigations remains to be determined.

Abbreviations: ACE, angiotensin-converting enzyme; ACT, anterior chamber tap; BAL, bronchoalveolar lavage; BMSG, biopsy of the minor salivary gland; CNS, central nervous system; CSF, cerebrospinal fluid; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; FDG-PET-TDM, fluorodeoxyglucose positron emission tomography tomodensitometry; GWC, Goldmann-Witmer coefficient; IGRA, interferon-gamma release assay; IL, interleukin; MRI, magnetic resonance imaging; MS, multiple sclerosis; NPV, negative predictive value; PC, platelet count; PCR, polymerase chain reaction; PIOL, primary intraocular lymphoma; POCL, primary ocular-cerebral lymphoma; PPV, positive predictive value; TST, tuberculin skin test; WB, Western blot.

* Corresponding author at: Service de Médecine Interne, Hôpital de la Croix-Rousse, 103 grande rue de la Croix-Rousse, 69318 Lyon Cedex 04, France.
E-mail address: pascal.seve@chu-lyon.fr (P. Sève).

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Contents

1. Introduction

Uveitis is defined as inflammation of the iris, ciliary body, vitreous, retina or choroid. Fundamental studies have shown genetic predispositions, T and B cell involvement, cytokines and chemokines signatures and signaling pathway as well as environmental influences in uveitis [1,2]. Its incidence is 17–52/100,000 person-years and the prevalence is 38–284/100,000 persons [3–5]. A study of medical insurance claims for 4 million individuals in the USA reported a prevalence of 133/100,000 persons, including a predominance of non-infectious uveitis (90.7%) and anterior uveitis (80%) [6].

Uveitis is the cause of 5% of cases of legal blindness (central visual acuity of 1/10 or less in the better eye), mainly due to macular edema, ocular hypertonia, or retinal ischemia [7].

Around 60 causes of uveitis have been described and these can be classified into five groups (Table 1). The casual epidemiology varies depending on genetic and ethnic factors (e.g. HLA-B27 and sarcoidosis), environmental factors (e.g. tuberculosis), the definition of the disease (e.g. sarcoidosis), the inclusion of certain ophthalmologic entities in the idiopathic uveitis group (e.g. pars planitis), the paraclinical investigations carried out (e.g. nuclear imaging) and the method of recruitment of patients (e.g. tertiary centers). This explains the great heterogeneity in studies reported in the literature. The main etiologies reported are Vogt-Koyanagi-Harada disease and sarcoidosis in Japan [8,9], herpes virus in Tunisia [8], tuberculosis in India [10], and toxoplasmosis in South America [11,12]. In Western countries, approximately one-quarter of cases are linked to ophthalmologic disease, one-quarter to systemic disease fulfilling consensual diagnostic criteria, one-quarter to presumed systemic disease, and one-quarter have an unexplained origin [13]. Uveitis of unexplained origin, also known as idiopathic uveitis, represents 23–44% of cases according to recent studies from the West and Japan [9,14–23].

Knowledge of the epidemiology of uveitis is important since the diagnostic work-up should be oriented towards investigations for common diseases or diseases whose diagnosis may have therapeutic consequences.

Since 2005, uveitis has been classified anatomically according to the part of the eye affected (Fig. 1), and the rate of onset and course of the disease [24]. Uveitis is 'limited' if it lasts for <3 months and 'persistent' if it is present for >3 months, and its onset may be sudden or insidious. The term acute uveitis is reserved for uveitis which occurs suddenly with a limited course (e.g. anterior uveitis associated with histocompatibility antigen (HLA)-B27). Recurrent uveitis is defined as episodes of uveitis separated by periods of remission of >3 months without treatment. Finally, uveitis is considered to be chronic if it persists for >-3 months or reoccurs <3 months after stopping treatment. The etiologic distribution is directly linked to these factors.

Other ophthalmologic characteristics also orient the diagnosis such as the side affected, granulomatous character, existence of ocular hypertonia, synechia, retinal vasculitis (venous and/or arterial, occlusive) [25], single or multiple retinochoroidal lesions. Table 2 shows the main etiologies according to the anatomic site and semiology.

Currently, the few studies that have evaluated the value of complementary investigations in the etiologic diagnosis of uveitis have focused on one or more investigations for a specific uveitis type. The recommendations for diagnosis are mainly derived from experience and retrospective studies. When faced with similar clinical scenarios, experts have proposed a variety of complementary investigations [26]. The ULISSE study (**U**véites: évaluation c**LI**nique et médico-économique d'une **S**tratégie **S**tandardisée pour le diagnostic **E**tiologique) is the only controlled study to compare a 'standardized' 3-step approach (oriented assessment: investigations determined according to the ophthalmologic findings, possibility of prescribing 'open' examinations) to an 'open' strategy allowing the ophthalmologist to request any type of investigation [27].

In this report, we present the recommendations for the diagnosis of uveitis proposed by a group of experts (ophthalmologists, internists, and rheumatologists) following a review of data in the literature.