Diagnostic Testing in Uveitis

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ABSTRACT

Uveitis is the inflammation of uveal tissue which includes a multitude of ocular and systemic disorders. Diagnostic tests are of crucial importance to define both infectious and non-infectious etiologies in uveitis. In this measure, an armamentarium of laboratory tests including blood and fluid serologies, ocular fluid/tissue sampling and imaging modalities are available for clinical diagnosis of uveitis. However, the predictive values of these tests are highly dependent to the patients' clinical findings and epidemiological factors. Therefore, clinical data acquired from patient history and examination should provide a reference for choosing diagnostic tests in order to prevent misinterpreting test results that would lead to wrong diagnosis and treatment decisions. In this review, we will discuss the diagnostic tests that are frequently used in uveitis practice and their power to predict true diagnosis on a statistical perspective.

Keywords: Uveitis; diagnostic tests; serology, Bayesian statistics; likelihood ratio, Positive predictive value.

BACKGROUND

Diagnosis of uveitic entities constitutes clinical challenges in ophthalmology practice. Multiple etiological factors and systemic diseases are associated with various forms of uveitis, which in turn requires a multitude of diagnostic tests for analysis of the present clinical setting. However, lack of standardized protocols leads to substantial variations in evaluating patients among uveitis specialists. As the examination is highly dependent on laboratory tests, performing ''unnecessary'' diagnostic tests might increase false positive results and mislead diagnosis, which therefore result in wrong treatment, loss of patient compliance, consumption of time, resources and funding.

A web-based survey consisting of 13 patient scenarios that was performed among Executive Committee and Trustees of the American Uveitis Society demonstrated a substantial variability in the evaluations and a low-level agreement on specific testing plans[1]. Furthermore, there also was limited consensus among providers in test selection, with most tests in each scenario ordered by fewer than half of the providers suggesting the need for evidence-based practice guidelines for the evaluation of uveitis patients. On the other hand, it is also better to keep in mind that according to a study by Rodriguez et al. out of 1273 uveitis patients only among 16 percent a definite diagnosis could be made at first visit[2]. Goal in uveitis diagnosis process should be to choose most appropriate, low cost tests with the highest possible sensitivity and specificity, while keeping the number of tests at minimum.

PATHWAY TO DIAGNOSIS

The classical method to diagnose uveitic diseases, similar to all other ocular and systemic diseases, requires a combination of detailed patient history and rigorous ophthalmologic examination in order to recognize ''patterns'' that indicate particular conditions (''pattern recognition''). When these patterns remain insufficient in clarifying the investigated ocular state, differential diagnosis should be performed, which requires to establish a list of possible diagnoses (''probabilistic method'') through indirect or intuitive approaches that are guided by clinical experience and consultation. Both pattern recognition and probabilistic methods should be supported with diagnostic tests that include serologic tests, imaging modalities and tissue sampling.

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BAYESIAN STATISTICS AND ITS IMPLICATIONS

Bayesian statistics are based on Bayes' theorem, which describes the probability of an event based on previously known conditions that are related to occurring event. The theorem is stated by following equation:

$$P(A|B) = \frac{P(B|A)P(A)}{P(B)}$$

In this setting, Bayes' theorem could be adapted to the probability of diagnostic test results as P(A) giving the prevalence of the ocular condition in the general population (**pre-test probability**) and P(B) giving the total rate of individuals that were tested positive among the whole population (calculated as follows: P(B) = sensitivity × P(A) + (1-sensitivity) × (1-P(A)). Subsequently, P(A|B) gives the positive predictive value of the test (**post-test probability**), and P(B|A) gives the true positive rate of the test. The ratio between post-test probability and pre-test probability is defined as the **likelihood ratio (LR)**, which gives the diagnostic value of the performed test. Positive (LR+) and negative (LR-) ratios can be calculated from sensitivity and specificity values accordingly:

$$LR+ = \frac{sensitivity}{1 - specificity}$$

$$LR- = \frac{1 - sensitivity}{specificity}$$

The greater value of LR+/LR- test, the more likely a positive/negative test result indicates a true positive/ negative case, respectively.

This theorem implies that the positive predictive value of each diagnostic test is strongly related to the prevalence of the investigated ocular disease in the general population. Given below is the example of a disease, which has a 1:1000 prevalence rate in the population and has a given diagnostic test with 99% sensitivity and 95% specificity. Any patient with no previously known ocular or systemic finding would therefore have 0.1% pre-test probability of having the disease. When the positive predictive value (PPV) is calculated:

$$PPV = \frac{0.99 \times 0.001}{0.95 \times 0.001 + 0.05 \times 0.999} = 0.019$$

Result indicates that only 1.9% of cases that were tested positive might actually have that disease. According to Bayes' theorem, narrowing the general prevalence by performing the diagnostic test to cases with specific clinical findings would be the only way to increase the post-test probability.

LABORATORY TESTS

Serological tests are essential diagnostic tools in detecting both infectious and non-infectious etiologies of ocular inflammatory diseases. The most common serological tests aim to detect infectious diseases including tuberculosis, syphilis, toxoplasmosis, cat-scratch disease, Lyme etc. and non-infectious diseases including HLA-B27 related diseases, sarcoidosis, juvenile inflammatory arthritis etc.

Tuberculosis

Purified protein derivatives (PPD) test is performed to detect latent *M. tuberculosis* infection[3]. The intracutaneous application of 5 tuberculin units of PPD is expected to provoke an induration of the skin in 48-72 hours. The diameter of induration that is accepted for a positive result depends on the immune response capacity of the individual, which is affected by multiple factors including the state of BCG vaccination, the presence of accompanying diseases (i.e. viral infection, chronic diseases, malignancy, sarcoidosis). Detection of IFN-γ expression following antigen stimulation (Quantiferon®-TB Gold) is a more rapid diagnostic test which shows less cross-reaction with BCG[4]. Both tests, if all patients would have been screened hypothetically, could reach 1 to 11% positive predictive values; narrowing the tested subjects to an endemic area or to cases with clinical findings (serpiginous choroiditis, granulomata, etc.) would increase PPVs of PPD and Quantiferon® tests up to 82 and 96%, respectively[4].

Syphilis

Syphilis is a spirochetal infection caused by *T. pallidum* and could be detected by two groups of serological tests: Non-treponemal VDRL (Venereal Disease Research Laboratories), RPR (rapid plasma reagin) and cardiolipin antigen tests are used to screen active disease, and treponemal FTA-ABS, MHA-TP, TPHA, EIA and syphilis IgG tests that recognize *T. pallidum* specific antibodies and demonstrate previous syphilitic exposure. It should be noted that false positive results for non-treponemal tests might occur in various conditions such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Lyme disease, tuberculosis, malaria, pregnancy, HIV infection, advanced stage malignancy, intravenous drug addiction, hepatitis and biliary cirrhosis. In addition, 30% of RPR and VDRL tests might give false negative results for latent disease and neurosyphilis.[5] In tertiary referral clinics, in order not to avoid false negative results a specific test are such as Syphilis IgG is recommended. (Figure 1)

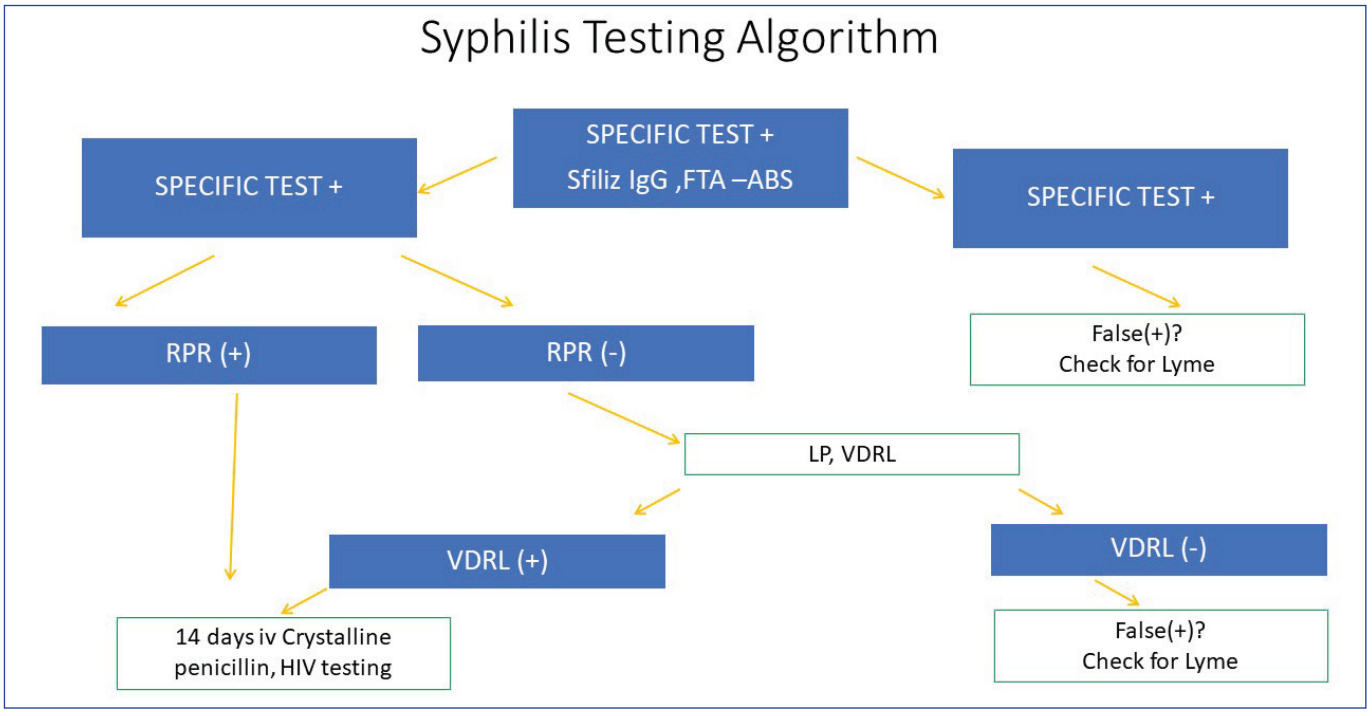

Figure 1. *Syphilis testing algorithm.*

HLA-B27

Human Leukocyte Antigen B27 (HLA-B27) is the most frequently found leukocyte surface antigen in patients with acute anterior uveitis (AAU). With 5% prevalence in normal population, the expressivity of HLA-B27 increases from 50 to 80% in cases with unilateral AAU[6], it might also be found positive in cases with chronic, bilateral anterior uveitis and vitritis. PPV of the test varies depending on the anatomic location of uveitis with anterior uveitis being highest.

ANA

Antinuclear antibody (ANA) test is commonly used to define autoimmune connective tissue disorders including SLE, rheumatoid arthritis, scleroderma, Sjögren's syndrome and polymyositis/dermatomyositis. With a positive predictive value of 1%, it has very limited use in diagnosis of uveitic syndromes which only encompasses juvenile inflammatory arthritis (JIA)[7], scleritis, peripheral ulcerative keratitis and vasculitis. In chronic anterior uveitis of childhood positive predictive value of ANA positivity increases in favor of juvenile rheumatoid arthritis.

ANCA

Antineutrophil cytoplasmic antibody (ANCA) is an antibody, which is expressed against enzymatic granules of neutrophils and monocytes. Cytoplasmic (c-ANCA) and perinuclear (p-ANCA) patterns are expressed in Granulomatosis with polyangiitis and microscopic polyangiitis respectively. ANCA auto-antibodies are used for differential diagnosis of necrotizing scleritis, peripheral ulcerative keratitis and retinal vasculitis.[8]

Sarcoidosis

Sarcoidosis is a systemic inflammatory disease that features granuloma formation in various organs including the eye and orbital tissue. The elevation of serum angiotensin converting enzyme (ACE) and lysozyme levels are used to indicate the presence of sarcoidosis. With sensitivity and specificity of 60-90% and 83-95% respectively, the increase in ACE level has a PPV of 47% in diagnosing sarcoidosis-associated uveitis, which increases to 72% when combined with increased serum lysozyme levels.[9] ACE presents higher levels in the pediatric population and might show false positive results in several conditions including tuberculosis, leprosy, silicosis, primary biliary cirrhosis, hyperthyroidism, diabetes, asbestosis and histoplasmosis. On the other hand, false negative results with occur in patients with cystic fibrosis, lung cancer and use of several medications including ACE inhibitors and systemic corticosteroids.

Urinary β_2-microglobulin

Urinary β_2-microglobulin is a useful marker to screen tubulointerstitial nephritis and uveitis syndrome (TINU) in bilateral AAU patients[10]. It is found positive over 87% of TINU cases[11], which should be confirmed by renal biopsy for definitive diagnosis.

Bartonellosis

Ocular findings of bartonellosis (cat-scratch disease) are neuroretinitis, macular star, focal retinochoroiditis/ retinal infiltrates and retinal vascular abnormalities. Serological tests are based on IgM and IgG detection, with indirect fluorescent antibody (IFA) and enzyme-linked immunoassays (EIA) being the most reliable and frequently used tests[12]. PCR analysis from lymph node samples are also recently used for diagnosis.

Ocular toxoplasmosis

Ocular toxoplasmosis is the major cause of uveitis-associated visual impairment in developed countries which accounts for up to 85% of posterior uveitis[13]. The main ocular finding is focal necrotizing retinitis that is usually associated with vitritis, anterior chamber reaction and papillitis. The seropositivity for *T. gondii* is high worldwide due to frequent exposure from domestic animals. Therefore, detecting *T. gondii* antibodies or DNA in aqueous and vitreous tap are used to better confirm diagnosis[14].

IMAGING MODALITIES

Chest radiography

Posteroanterior chest radiography is an effective imaging modality to evaluate lung involvement in uveitic cases with suspected tuberculosis and sarcoidosis. Multinodular infiltrates and cavitations in the upper lobes as well as pleural effusion are not uncommon in tuberculosis, whereas hilar lymphadenopathy, ground glass appearance, fine reticular miliary lesions, contracted and distorted lungs due to pulmonary fibrosis could be detected in sarcoidosis[15].

High resolution CT

High resolution computerized tomography (HRCT) chest scan is a sensitive method to visualize parenchymal, mediastinal and hilar structures. Its diagnostic value increases for cases in inactive sarcoidosis with uveitic findings[15].

MRI

Cranial MRI is essential for detection of multiple sclerosis-associated white matter plaques in patients with intermediate uveitis[16]. It is also commonly used to evaluate orbital involvement in various inflammatory diseases including thyroid orbitopathy, ocular myositis, sarcoidosis, orbital cellulitis and idiopathic orbital inflammatory disease[17].

TISSUE SAMPLING

Sampling material from aqueous humor, vitreous and periocular tissues should be evaluated when clinical findings, serological tests and imaging modalities fail to reveal the diagnosis. Tissue sampling could be an essential method for differential diagnosis of granulomatous inflammations (sarcoidosis, tuberculosis etc.), retinal/ choroidal infections, intraocular tumors and lymphoma. Gram staining and culture, PCR, cytology, flow cytometry, gene sequencing and histological methods are commonly used to analyze aqueous, vitreous and tissue biopsy material. In particular, PCR analysis of aqueous and vitreous tap could reveal presence of virtually all bacterial and fungal infections, viral infections including HSV (herpes simplex virus), VZV (varicella zoster virus), EBV (Epstein-Barr virus), CMV (cytomegalovirus), HIV (human immunodeficiency virus), HTLV-1 (human T-lymphotrophic virus 1), HHV-6 and HHV-8 (human herpesvirus 6 and 8), rubella, and protozoal infections including toxoplasmosis and oncocercosis[18 19]. (Table 1)

CLINICAL BASED APPROACH

Anterior uveitis

Anterior uveitis is the most frequent uveitic inflammation. Around 50% of cases with anterior uveitis are associated with non-granulomatous HLA-B27 positive inflammatory

Table 1. *Tissue sampling in uveitis.*

Infection	Test	Rationale	Aqueous / vitreous	Comments
Bacterial	Culture	Multiple organism	Both	Medium dependent
Fungal	Culture	Ineffective if local	Vitreous	Vitrectomy more efficient
Spirochetae	Antibody	Local immune reaction	Aqueous	Mostly serum antibody
Toxoplasma, small lesion	Antibody	Local immune reaction	Aqueous	Usually not needed
Toxoplasma, large lesion	PCR	Tachyzoites in ocular fluids	Both	Above 4-5 mm, elderly immunocompromised patient
Viral	PCR	Detects capsid DNA		

diseases. Anterior uveitis may require further investigation with FTA-ABS/VDRL/syphilis serology, chest radiography, serum ACE/lysozyme and PPD/Quantiferon® tests for evaluation of syphilis, sarcoidosis and tuberculosis. Urinary β_2-microglobulin is also helpful to assess TINU in the pediatric population, and CMV PCR test from aqueous tap should also be considered[20]. Autoimmune markers such as RF, ANA and ANCA are unlikely to be related to uveitis in the adult population unless specific findings including PUK and scleritis are present. Similarly, there is no indication for toxoplasma screening as it usually presents as posterior uveitis.

Intermediate uveitis

Various ocular and systemic disorders should be considered on the differential diagnosis of intermediate uveitis including multiple sclerosis, sarcoidosis, syphilis, Lyme disease, tuberculosis and pars planitis. Therefore, investigations including FTA-ABS/VDRL/syphilis serology, chest radiography, serum ACE/lysozyme, Lyme serology, cranial MRI and PPD/Quantiferon® are needed. HLA-B27, RF, ANCA and ANA tests are unnecessary and should be omitted in intermediate uveitis.

Posterior / panuveitis

Differential diagnosis of infectious etiologies are crucial in posterior and panuveitis. In addition to tests of sarcoidosis, tuberculosis and syphilis, other bacterial (cat-scratch disease), viral (HSV, VZV, CMV) and parasitic (toxoplasmosis, toxocariasis, oncocercosis) infections should be investigated. Hematuria and proteinuria should also be assessed for systemic involvement in retinal vasculitis, scleritis and PUK. There is no need to perform RF, ANA, ANCA and HLA-B27 tests if no vasculitis or related systemic involvement is suspected.

PUK / scleritis

Peripheral ulcerative keratitis (PUK) and scleritis are likely associated with systemic autoimmune connective tissue disorders including rheumatoid arthritis, SLE and Wegener's necrotizing vasculitis. Therefore, serological tests that include RF, anti-cyclic citrullinated peptide (anti-CCP), ANCA, renal function tests and urine markers should be assessed accordingly[21].

SPECIAL CONSIDERATIONS

Pediatric uveitis

Juvenile inflammatory arthritis (JIA) is the most common identifiable etiology in pediatric patients with anterior uveitis. Following the age of onset and disease duration, ANA screening emerges as the essential test for diagnosis and detection of disease type and progression. Juvenile spondyloarthropathies should also be investigated with HLA-B27 for anterior uveitis. In childhood anterior uveitis, urinary β_2-microglobulin levels are important to to rule out TINU. Intermediate uveitis accounts for 12-28% of pediatric cases[22,23], which requires assessment of sarcoidosis, syphilis, Lyme disease, tuberculosis and multiple sclerosis. Posterior uveitis might occur due to parasitic infections, especially toxoplasmosis and toxocariasis. Masquerade syndromes such as retinoblastoma, lymphoma and retinitis pigmentosa can simulate both anterior and posterior uveitis, which require specific attention[24].

Bilateral non-granulomatous uveitis

Unlike unilateral acute anterior uveitis, bilateral non-granulomatous uveitis is a rare and unique condition that may be related to post-infection and drug use. Systemic medications including rifabutin, bisphosphonates, cidofovir, fluoroquinolones, anti-CTLA drugs[25] (ipilimumab) and MEK inhibitors[26] should be suspected. Systemic disorders like TINU, HLA-B27 associated inflammation and Kawasaki[27] disease might be present.

Uveitic glaucoma

Identifying glaucomatous findings in uveitis is substantial, as the main treatment should address underlying etiologies rather than empirical corticosteroid use. Viral uveitis is usually associated with increased intraocular pressure, therefore viral serology tests including HSV, VZV and CMV should be considered[28]. Masquerade syndromes like intraocular tumors[29] and non-malignant entities including ocular ischemic syndrome, Schwartz syndrome, pigment dispersion and acute angle closure can present with intraocular inflammatory findings. Anti-glaucomatous medications that include metipranolol, prostaglandins and brimonidine can exacerbate or trigger inflammation, which in case may need further attention.

A FUTURE DIRECTION FOR DIAGNOSIS: BAYESIAN BELIEF NETWORK ALGORITHM

Bayesian belief network algorithms assess conditional dependencies of variables in probabilistic relationships. Bayesian network algorithms have a wide range of applications that are extended to natural and social sciences, information technologies and disease diagnosis in medicine. Bayesian belief network algorithm for differential diagnosis of uveitis disease is a promising tool for establishing a standardized protocol that would increase the likelihood ratios of diagnostic tests when applied, thus resulting in easier and more reliable outcomes[30].

CONCLUSION

In summary, the guidance of clinical knowledge and experience is essential for choosing diagnostic tests adequately in assessment of uveitic diseases. In this context, assembling clinical experience, statistical algorithms and incidence databases would provide an effective synthesis to improve the reliability of diagnostic tests that are currently being used in clinical practice.

REFERENCES

1. Lee CS, Randhawa S, Lee AY, et al. Patterns of Laboratory Testing Utilization Among Uveitis Specialists. *Am J Ophthalmol* 2016;170:161-67. doi: 10.1016/j.ajo.2016.08.004 [published Online First: 2016/08/16]
2. Rodriguez A, Calonge M, Pedroza-Seres M, et al. Referral patterns of uveitis in a tertiary eye care center. *Arch Ophthalmol* 1996;114:593-9. doi: 10.1001/archopht.1996.01100130585016 [published Online First: 1996/05/01]
3. Klausen J, Magnusson M, Andersen AB, et al. Characterization of purified protein derivative of tuberculin by use of monoclonal antibodies: isolation of a delayed-type hypersensitivity reactive component from M. tuberculosis culture filtrate. *Scand J Immunol* 1994;40:345-9. doi: 10.1111/j.1365-3083.1994.tb03471.x [published Online First: 1994/09/01]
4. Chen G, Wang H, Wang Y. Clinical application of QuantiFERON-TB Gold in-tube in the diagnosis and treatment of tuberculosis. *Eur J Clin Microbiol Infect Dis* 2020;39:607-12. doi: 10.1007/s10096-019-03768-9 [published Online First: 2019/12/02]
5. Marra CM, Tantalo LC, Maxwell CL, et al. The rapid plasma reagin test cannot replace the venereal disease research laboratory test for neurosyphilis diagnosis. *Sex Transm Dis* 2012;39:453-7. doi: 10.1097/OLQ.0b013e31824b1cde [published Online First: 2012/05/18]
6. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. *Surv Ophthalmol* 2005;50:364-88. doi: 10.1016/j.survophthal.2005.04.003 [published Online First: 2005/06/22]
7. Campanilho-Marques R, Bogas M, Ramos F, et al. Prognostic value of antinuclear antibodies in juvenile idiopathic arthritis and anterior uveitis. Results from a systematic literature review. *Acta Reumatol Port* 2014;39:116-22. [published Online First: 2014/06/01]
8. Espinoza GM, Desai A, Akduman L. Ocular vasculitis. *Curr Rheumatol Rep* 2013;15:355. doi: 10.1007/s11926-013-0355-x [published Online First: 2013/07/28]
9. Baarsma GS, La Hey E, Glasius E, et al. The predictive value of serum angiotensin converting enzyme and lysozyme levels in the diagnosis of ocular sarcoidosis. *Am J Ophthalmol* 1987;104:211-7. doi: 10.1016/0002-9394(87)90406-5 [published Online First: 1987/09/15]
10. Pakzad-Vaezi K, Pepple KL. Tubulointerstitial nephritis and uveitis. *Curr Opin Ophthalmol* 2017;28:629-35. doi: 10.1097/ICU.0000000000000421 [published Online First: 2017/08/15]
11. Mackensen F, Billing H. Tubulointerstitial nephritis and uveitis syndrome. *Curr Opin Ophthalmol* 2009;20:525-31. doi: 10.1097/ICU.0b013e3283318f9a [published Online First: 2009/09/16]
12. Litwin CM, Martins TB, Hill HR. Immunologic response to Bartonella henselae as determined by enzyme immunoassay and Western blot analysis. *Am J Clin Pathol* 1997;108:202-9. doi: 10.1093/ajcp/108.2.202 [published Online First: 1997/08/01]
13. Maenz M, Schluter D, Liesenfeld O, et al. Ocular toxoplasmosis past, present and new aspects of an old disease. *Prog Retin Eye Res* 2014;39:77-106. doi: 10.1016/j.preteyeres.2013.12.005 [published Online First: 2014/01/15]
14. Ozgonul C, Besirli CG. Recent Developments in the Diagnosis and Treatment of Ocular Toxoplasmosis. *Ophthalmic Res* 2017;57:1-12. doi: 10.1159/000449169 [published Online First: 2016/10/11]
15. Weclawek M, Ziora D, Jastrzebski D. Imaging methods for pulmonary sarcoidosis. *Adv Respir Med* 2020;88:18-26. doi: 10.5603/ARM.2020.0074 [published Online First: 2020/03/11]
16. Petrushkin H, Kidd D, Pavesio C. Intermediate uveitis and multiple sclerosis: to scan or not to scan. *Br J Ophthalmol* 2015;99:1591-3. doi: 10.1136/bjophthalmol-2015-307269 [published Online First: 2015/09/05]
17. Cunnane MB, Curtin HD. Imaging of orbital disorders. *Handb Clin Neurol* 2016;135:659-72. doi: 10.1016/B978-0-444-53485-9.00031-3 [published Online First: 2016/07/20]
18. Choi W, Kang HG, Choi EY, et al. Clinical utility of aqueous humor polymerase chain reaction and serologic testing for suspected infectious uveitis: a single-center retrospective study in South Korea. *BMC Ophthalmol* 2020;20:242. doi: 10.1186/s12886-020-01513-x [published Online First: 2020/06/21]
19. Mochizuki M, Sugita S, Kamoi K, et al. A new era of uveitis: impact of polymerase chain reaction in intraocular inflammatory diseases. *Jpn J Ophthalmol* 2017;61:1-20. doi: 10.1007/s10384-016-0474-9 [published Online First: 2016/10/28]
20. Pohlmann D, Pahlitzsch M, Schlickeiser S, et al. Virus-associated anterior uveitis and secondary glaucoma: Diagnostics, clinical characteristics, and surgical options. *PLoS One* 2020;15:e0229260. doi: 10.1371/journal.pone.0229260 [published Online First: 2020/02/25]
21. Artifoni M, Rothschild PR, Brezin A, et al. Ocular inflammatory diseases associated with rheumatoid arthritis. *Nat Rev*

Rheumatol 2014;10:108-16. doi: 10.1038/nrrheum.2013.185 [published Online First: 2013/12/11]

22. Pivetti-Pezzi P. Uveitis in children. *Eur J Ophthalmol* 1996;6(3):293-8. [published Online First: 1996/07/01]
23. Ganesh SK, Bala A, Biswas J, et al. Pattern of Pediatric Uveitis Seen at a Tertiary Referral Center from India. *Ocul Immunol Inflamm* 2016;24:402-9. doi: 10.3109/09273948.2015.1012298 [published Online First: 2015/07/15]
24. Smith JR. Management of uveitis in pediatric patients: special considerations. *Paediatr Drugs* 2002;4:183-9. doi: 10.2165/00128072-200204030-00005 [published Online First: 2002/03/23]
25. Sun Mm M.D PD, Levinson RMD, Filipowicz ADO, et al. Uveitis in Patients Treated with CTLA-4 and PD-1 Checkpoint Blockade Inhibition. *Ocul Immunol Inflamm* 2020;28:217-27. doi: 10.1080/09273948.2019.1577978 [published Online First: 2019/03/02]
26. Eikenberry J, Harris A, Torabi R, et al. Ocular side effects of target therapy and immunotherapy in patients with cutaneous malignant melanoma. *Eur J Ophthalmol* 2020:1120672120930688. doi: 10.1177/1120672120930688 [published Online First: 2020/06/02]
27. Shiari R, Jari M, Karimi S, et al. Relationship between ocular involvement and clinical manifestations, laboratory findings, and coronary artery dilatation in Kawasaki disease. *Eye (Lond)* 2020 doi: 10.1038/s41433-019-0762-y [published Online First: 2020/01/05]
28. Sherman ER, Cafiero-Chin M. Overcoming diagnostic and treatment challenges in uveitic glaucoma. *Clin Exp Optom* 2019;102:109-15. doi: 10.1111/cxo.12811 [published Online First: 2018/07/31]
29. Vempuluru VS, Jakati S, Krishnamurthy R, et al. Glaucoma as the presenting sign of intraocular tumors: beware of the masquerading sign. *Int Ophthalmol* 2020;40:1789-95. doi: 10.1007/s10792-020-01348-x [published Online First: 2020/03/22]
30. Gonzalez-Lopez JJ, Garcia-Aparicio AM, Sanchez-Ponce D, et al. Development and validation of a Bayesian network for the differential diagnosis of anterior uveitis. *Eye (Lond)* 2016;30:865-72. doi: 10.1038/eye.2016.64 [published Online First: 2016/04/09].