

Current capabilities and limitations for the diagnosis of etiology of ocular tuberculosis: a review

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Сучасні можливості та обмеження етіологічної діагностики офтальмотуберкульозу: огляд літератури

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Abstract

Ocular tuberculosis (OTB) remains one of the most diagnostically challenging extrapulmonary forms of tuberculosis in terms of determining the etiology. The paucibacillary nature of the disease, small quantity of intraocular samples, and pathogenetic heterogeneity significantly complicate the direct confirmation of *Mycobacterium tuberculosis* (MBT) in ocular tissue and fluid samples. This paper reviewed current capabilities and limitations for the diagnosis of etiology of OTB. Molecular gene methods for direct detection of MBT, including polymerase chain reaction (PCR), automated molecular platforms and studies on cell-free DNA analysis, were considered. Despite advances in these methods, they still do not have enough sensitivity for negative results to rule out OTB. Special attention was given to the methods allowing indirect confirmation of MBT infection, tuberculin skin test (TST) and interferon-gamma release analysis (IGRA), particularly, QuantiFERON. A positive IGRA result indicates the presence of a specific immune response to MBT, but does

not localize the infectious process or independently confirm a causal relationship between MBT infection and intraocular inflammation. The absence of an independent and sufficiently sensitive reference standard for OTB detection is a major issue in the assessment of diagnostic accuracy of current OTB detection methods. Future research should be aimed not only at increasing the sensitivity of direct diagnostic methods, but also focused on the search for, and independent validation of markers that will allow differentiation between etiologically MBT-related intraocular inflammation from concomitant latent infection.

Keywords: ocular tuberculosis, uveitis, *Mycobacterium tuberculosis*, PCR, interferon-gamma release assays, tuberculin test.

Резюме

Офтальмотуберкульоз залишається однією з діагностично складних форм позалегенового туберкульозу для визначення етіології. Пауцибацилярний характер захворювання, обмежена кількість внутрішньоочного матеріалу та патогенетична гетерогенність значно ускладнюють безпосереднє підтвердження *Mycobacterium tuberculosis* (МБТ) у тканинах і рідинах ока. У цьому огляді проаналізовано сучасні можливості та обмеження етіологічної діагностики офтальмотуберкульозу. Розглянуто молекулярно-генетичні методи прямого виявлення МБТ, включаючи ПЛР, автоматизовані молекулярні платформи та дослідження позаклітинної ДНК. Незважаючи на розвиток цих методів, їх чутливість залишається варіабельною, тому негативний результат не дозволяє надійно виключити туберкульозну етіологію внутрішньоочного запалення. Окрему увагу приділено непрямым методам підтвердження МБТ-інфікування – туберкуліновій шкірній пробі та тестам вивільнення

DOI: <https://doi.org/10.31288/Ukr.j.ophthalmol.202656976>

UDC: 617.7:616-002.5-07

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Received 2026-09-01

Accepted 2026-10-04

Cite this article as: Kolesnichenko VV, Dorokhova OE, Zborovska OV. Current capabilities and limitations for the diagnosis of etiology of ocular tuberculosis: a review. Ukr. j. ophthalmol. 2026;5:69-76.



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інтерферону-γ (interferon-gamma release assays, IGRA), зокрема QuantiFERON (QFT). Позитивний результат IGRA свідчить про наявність специфічної імунної відповіді на МБТ, однак не визначає локалізацію інфекційного процесу та самостійно не підтверджує причинний зв'язок між МБТ-інфікуванням і внутрішньоочним запаленням. Однією з основних проблем оцінки діагностичної точності сучасних методів залишається відсутність незалежного та достатньо чутливого референтного стандарту для офтальмотуберкульозу. Подальші дослі-

дження мають бути спрямовані не тільки на підвищення чутливості методів прямої діагностики, а й на пошук та незалежну перевірку маркерів, які дозволять відрізнити етіологічно пов'язане з МБТ внутрішньоочне запалення від супутнього латентного інфікування.

Ключові слова: офтальмотуберкульоз, увеїт, *Mycobacterium tuberculosis*, полімеразна ланцюгова реакція, тести вивільнення інтерферону-γ, туберкулінова проба.

Introduction

Despite the advent of new laboratory and molecular gene diagnosis techniques, the diagnosis of ocular tuberculosis (OTB) remains a challenge. One of the main reasons is the difficulty in directly confirming the presence of *Mycobacterium tuberculosis* (Mtb) in intraocular specimens. The paucibacillary nature of the disease, small quantity of specimens available for microbiological study, and the possibility of an immune-mediated inflammatory response limit direct etiological verification [1, 2]. Hence, a large proportion of cases with OTB remain diagnostically uncertain, and the diagnosis is often made clinically supported by direct and indirect evidence of the disease [3].

Molecular gene methods enable direct detection of Mtb genetic material in intraocular specimens, but they do not have enough sensitivity for negative results to rule out OTB. Indirect methods, tuberculin skin test (TST) and interferon-gamma release analysis (IGRA), are also widely used to confirm Mtb infection. IGRA has higher specificity than TST, especially in BCG-vaccinated populations, but does not allow localization of the infectious process or establishing its direct connection with intraocular inflammation [1, 4].

The purpose of this paper was to review current capabilities for the etiological diagnosis of OTB, and their diagnostic value and major limitations. The majority of attention was focused on (1) methods for direct detection of Mtb in intraocular specimens and (2) TST та IGRA for indirect confirmation of the infection. The diagnostic value of QuantiFERON was discussed separately. This paper provides no detailed review of the clinical criteria for OTB, multimodal imaging techniques and selection algorithms for antitubercular therapy (ATT). Clinical and diagnostic characteristics were considered only if they are relevant to interpreting the results of laboratory tests. First, we considered current understanding of OTB and major difficulties in confirmation of its etiology. Second, we reviewed the capabilities and limitations of molecular gene methods. Third, we reviewed the methods for indirect confirmation of Mtb infection with a major focus on IGRA and QuantiFERON. The Discussion summarized major limitations of current methods for, and unresolved issues in, the etiological diagnosis of OTB.

Major part of the paper

Current understanding of OTB

OTB is an extrapulmonary Mtb infection. According to a 2025 review by Konana and Babu, OTB is as an extrapulmonary manifestation of tuberculosis caused by Mtb which can affect various ocular structures and is characterized by various clinical presentations [2]. More recently, Alabed and Finkel [3] noted that, in the majority of real-world clinical situations, OTB is determined not by a single diagnostic criterion, but by a constellation of signs and symptoms that establish relative confidence in the diagnosis. This resulted in the wide use of the terms “confirmed ocular TB” and “presumed ocular TB” [3]. The term “confirmed ocular TB” is used when referring to ocular inflammation on ophthalmic examination with microbiological, molecular or histopathological evidence of Mtb from an intraocular tissue or fluid specimen. On the other hand, “presumed ocular TB” is used in reference to cases of uveitis in the setting of TB infection evidence via IGRA, TST, and/or supportive systemic evaluation with no better alternative etiological explanation. Alabed and Finkel [3] believe that comparison across settings is difficult, partly because published studies use heterogeneous definitions, workups, and treatment thresholds, which makes comparisons across settings difficult.

OTB can manifest as anterior, intermediate, posterior or panuveitis, choroidal granuloma, retinal vasculitis, and other forms of intraocular inflammation. Additionally, certain types of inflammation differ in their diagnostic value. OTB is usually diagnosed through a comprehensive assessment of ocular phenotype, epidemiologic risk, systemic evaluation, TB immunologic testing, and mimic exclusion. Higher-suspicion phenotypes include serpiginous-like choroiditis, occlusive retinal vasculitis, choroidal tuberculoma, anterior uveitis with iris nodules, and chronic granulomatous anterior uveitis in the appropriate clinical context [3]. Therefore, the term “OTB” encompasses conditions that differ in specificity of their ocular manifestations and evidence of their relationship with Mtb. The absence of active systemic tuberculosis does not exclude OTB. In some patients, ocular inflammation can be the only manifestation of an Mtb-associated process [3]. Environmental factors of MTB strains have a potential influence on (1) the rate at which patients exhibit evidence

of direct MTB infection and (2) characteristics of patients diagnosed with OTB. This was well demonstrated by Putera and colleagues [5] who conducted a medical chart review of 339 OTB patients from the Netherlands and Indonesia and found that Indonesian OTB patients displayed a higher prevalence of chest radiograph findings indicative of TB infection and concurrent active systemic TB and had a more severe initial clinical presentation [5].

Taken together, this data indicate that OTB is not a homogeneous clinical- pathological entity with a single set of diagnostic traits, but comprises a spectrum of Mtb-associated intraocular inflammatory conditions with diverse clinical phenotypes, potential pathogenetic mechanisms and levels of evidence of tuberculous etiology. It is this heterogeneity that explains the difficulty of formulating universal diagnostic criteria and makes the comparison of the results of different studies challenging. Therefore, in the current diagnostics of OTB, it is of primary importance not only to detect signs of Mtb infection, but also to determine the likelihood that the infection is the cause of a particular intraocular inflammation.

Problem of the etiological confirmation of OTB

Etiological confirmation of OTB remains one of the most difficult problems in the diagnosis of the disease. The gold standard for the diagnosis of OTB is the direct demonstration of the MTB in ocular tissues or ocular fluids either by Ziehl–Neelsen Stain, culture or molecular diagnostic techniques such as polymerase chain reaction (PCR) [2]. This is onerous owing to the paucibacillary nature of the disease, small quantity of specimens, and low sensitivity and specificity of molecular diagnostic tests. Hence, most often, the diagnosis of OTB is presumed based on indirect clinical, laboratory and radiological evidences suggestive of TB [2].

A multifactorial pathogenesis of the disease contributes to the difficulty of diagnosis. Broadly there are two fundamental mechanisms that may underlie the development of MTB-associated ocular inflammation: (a) inflammatory response to live (replicating) MTB in the eye, and (b) immune mediated ocular inflammation induced by non-viable MTB or its components in the eye [6]. Basu and colleagues [6] do not state that one mechanism is more important than another and do not juxtapose them to each other, but state that both may coexist and one mechanism may prevail over the other in a particular case [6].

The immune mediated mechanism of ocular inflammation has been mentioned also in a 2023 review by Ludi and colleagues [1]. They pointed that OTB could be (a) a manifestation of a hypersensitivity response to MTB antigens in the setting of local ocular infection, or (b) an autoimmune reaction to ocular antigens that results from antigenic mimicry between MTB and ocular antigens [1]. A 2020 study by Agrawal and colleagues [7] also noted the possibility of (a) persistence of MTB, particularly in retinal pigment epithelial (RPE) cells and (b) the role of systemic immune sensitization and autoimmune response in the development of inflammation in the eye [7]. There-

fore, the pathogenesis of OTB should be considered while taking into account the immune-mediated mechanisms.

Such multifactorial nature of the disease is of direct diagnostic value. Identifying the presence of OTB or its genetic material in intraocular specimens is a valid reason for the confirmation of OTB. However, given indirect immune mechanisms, a negative result does not necessary rule out tuberculosis-associated inflammation. The same can be said about classifying intraocular inflammation as a tuberculous inflammation based solely on the presence of systemic sensitization to Mtb. Therefore, the pathogenetic features of OTB form a peculiar diagnostic paradox: the absence of direct evidence of Mtb does not exclude a tuberculous etiology of intraocular inflammation, whereas the presence of signs of systemic Mtb infection by itself does not prove a tuberculous etiology [1, 6].

It is also important to note about harvesting specimen for direct examination. Intraocular sampling is invasive, the amount of available material is small, and mycobacteria may localize in ocular tissue structures and not shed into the aqueous humor or vitreous. Thus, in the Collaborative Ocular Tuberculosis Study (COTS-1), only 59 of 962 patients with OTB (6.1%) underwent PCR analysis. Ludia and colleagues [1] reported that PCR has been not commonly used for detecting MTB in the aqueous specimen [1, 8].

The major problem of the confirmation of the etiology of OTB is that an individual laboratory test has a low informative value in the diagnosis. Given the paucibacillary nature of the disease, limited availability of intraocular material and varying contribution of infectious and immune-mediated mechanisms, standardizing OTB diagnosis is a challenging endeavor. Even in a recent 2026 review on ocular TB as the only manifestation of TB, it was underscored that the diagnosis is often made clinically supported by indirect evidence of Mtb infection, a compatible ocular phenotype and the results of systemic evaluation [3].

Capabilities and limitations of molecular genetics methods

Today a variety of molecular gene methods are available for direct detection of Mtb in intraocular specimen, but the issue of confirmation of OTB etiology has not been solved yet. Inconsistency in the results of different studies is partly due to the selection of gene targets. Balne et al [9] evaluated factors affecting PCR outcomes in patients with clinically suspected OTB. The rate of positive PCR testing depended on the sequencing target. MPB64 was positive in 70.2% of tested specimen, protein b in 40.0%, and IS6110 in only 9.1%. Some controls (patients with culture proven or culture-negative non-tuberculous endophthalmitis), however, also tested positive for PCR. The authors concluded that careful selection of gene targets can yield high PCR positivity in clinically suspected ocular TB but false-positive results may be seen in ocular inflammation unrelated to OTB [9].

Other researchers used quantitative PCR assays and multitarget PCR assays in an attempt to improve the informative value of PCR in the diagnosis of OTB. In a study by Barik et al [10], mycobacterial copy numbers (mbp64 gene) were normalized to host genome copy numbers in ocular fluid specimen from patients with tubercular uveitis and controls. Normalized quantitative PCR had specificity, sensitivity and diagnostic accuracy of 85.0%, специфічність 94.4% and 89.4%, respectively, whereas the above values for conventional PCR were 61.1%, 90.0% and 74.3%, respectively [10].

In a comparative study by Sharma et al [11], Xpert MTB/RIF Ultra (Ultra) was evaluated on OTB specimen and compared with Xpert. Seventy-five vitreous fluid specimens (3 confirmed OTB, 47 clinically suspected OTB, and 25 controls) were subjected to Ultra, Xpert and Multiplex PCR (MPCR) and compared against culture, composite reference standard and gene sequencing. The sensitivity of Ultra was 50% in diagnosing OTB. The overall sensitivity of Xpert and MPCR was 16% and 72%, respectively [11].

Similar results were demonstrated in a study on Truenat MTB Plus [12]. In 75 vitreous fluid specimens, the overall sensitivity of Truenat MTB Plus, MPCR and Ultra in diagnosing OTB was 66.6%, 73.3% and 55.5%, respectively [12]. An advantage of automated molecular genetics tools is that they may be simultaneously used for detecting particular gene mutations to antibacterial drugs [12]. Therefore, advances in molecular diagnostic technologies have expanded the capabilities for detecting Mtb with the additional potential benefit of obtaining data on the genotype of Mtb. Molecular genetics methods, however, still do not have enough sensitivity for negative results to rule out reliably OTB.

A 2025 study by Sharma et al [13] aimed to evaluate the utility of Cell-free DNA (CF-DNA)-based Multi-targeted real-time PCR (Mrt-PCR) for diagnosing OTB. CF-DNA-based Mrt-PCR, Truenat MTB plus and Xpert Ultra were positive in 19/25(76%), 16/25(64%), and 13/25(56%) patients of OTB, respectively, and negative in all the 25 control group subjects [13].

In the COTS-1 [14], only 59/962 patients with OTB (6.1%) underwent intraocular fluid PCR testing, and PCR was positive for MRB in 33/59 patients and negative for MRB in 26/59 patients. PCR results did not show a clear association with subsequent treatment outcomes, and at 1-year follow-up, five patients with positive PCR and three patients with negative PCR had persistence/worsening of inflammation. Data from COTS-1 suggested that PCR was not commonly done for diagnosing intraocular TB and positive/negative results may not influence management of outcomes in the real-world scenario [14].

Interpretation of measures of diagnostic accuracy for PCR for intraocular specimen is complicated by the absence of an independent reference standard. A 2021 meta-analysis [15] aimed to review the diagnostic accuracy of PRC testing in confirming OTB with responses to ATT

as reference indices. The overall sensitivity and specificity were 88% and 71%, respectively, and the area under summary receiving operating curves was 0.83 [15]. Taken together, the available data indicate that a positive PCR test result is of important diagnostic value in the appropriate clinical context, but these tests still do not have enough sensitivity for negative results to rule out OTB.

Indirect confirmation of MTB infection by TST and IGRA

Because the direct confirmation of MTB in ocular fluids or ocular tissues is obvious, indirect immunological methods play a significant role in the diagnosis of ORB. TST and IGRA actually detect a specific cellular immune response to Mtb, but not viable Mtb bacteria in the eye. A positive immunological test indicates infection or prior sensitization to Mtb, but does not independently establish the tuberculous etiology of intraocular inflammation [1, 3, 4].

TST has several limitations. The TST result depends on prior BCG vaccination, contact with non-tuberculous mycobacteria, status of an individual's cellular immunity and the correct performance and evaluation of the test. IGRA have been developed partially in order to overcome these limitations. Current commercial tests use Mtb specific antigens, particularly the region of difference (RD1) encoded early secretory antigenic target (ESAT)-6 and culture filtrate protein (CFP)-10, which are absent in many nontuberculous mycobacteria as well as in the vaccine *M. bovis* (BSG). As a result, IGRA has a higher specificity than TST for Mtb exposure, especially in BCG-vaccinated populations. QuantiFERON is based on quantitative determination of interferon-gamma (IFN- γ) released by sensitized T-cells after stimulation with specific Mtb antigens. The QuantiFERON-TB Gold Plus (QFT-Plus; Qiagen, Germantown, MD) IGRA, contrary to the previous version of the assay, the QuantiFERON-TB Gold In-Tube, has two TB antigen tubes (TB1 and TB2) [4]. Higher IGRA specificity for MTB than with TST does not mean that IGRA has higher specificity for tuberculous uveitis, because the test does not determine the location of the infection and cannot discriminate between active TB and latent TB infection [4].

The sensitivity of IGRA when compared to TST is more contentious with varying results in available reports. Ludi and colleagues (2023) [1] reviewed the studies that directly compared the two methods. In five head-to-head comparisons of IGRA and TST in TB-endemic countries, IGRA sensitivity underperformed as compared to TST. Amongst two head-to-head comparisons of IGRA and TST in non-endemic countries, only one study reported an improved IGRA sensitivity as compared to TST. Negative or indeterminate IGRA results in patients with clinical characteristics strongly suggestive of OTB should be interpreted with caution [1].

In a study by Fernández-Zamora et al [16], 191 patients with ocular inflammation were prospectively followed up to assess the performance of IGRA associated with TST

for OTB diagnosis and therapeutic decision making. Considering TST and IGRA together was more effective in assessing OTB diagnosis, with sensitivity, specificity and area under curve (AUC) of 89.6%, 99.2% and 0.98, respectively [16].

Ang et al [17] evaluated an IGRA in the diagnosis of TB-associated uveitis (TBU). Analysis included 191 patients. The TST was more sensitive (0.70 vs 0.53) but less specific (0.71 vs 0.91) than T-SOT.TB. Patients who were TST and T-SOT.TB positive were very likely to have TBU. In populations where the prevalence of TBU is high the TST should be the first-choice test; the T-SPOT.TB should be performed if the prevalence of TB is low [17].

Positive QuantiFERON as a proof of infection but not the etiology of uveitis

Xia et al (2024) performed a retrospective study [18] to evaluate the diagnostic value of QuantiFERON-Gold (QFT-G) testing for ocular inflammation in a low-prevalence TB area. Of the 338 patients that underwent QFT-G testing at the university of Colorado, 17 (4.38%) were positive. Only one patient had true TBU with anterior uveitis with iris nodules. The remaining 16 (94.1%) patients did not meet SUN criteria for TBU and were incidentally found to be QFT-G positive during laboratory work-up prior to immunosuppression. The authors concluded that, in low prevalence areas, the majority of QFT-G positive tests in uveitis patients are coincidental and unrelated to their disease process [18].

A 2025 retrospective study by Putera et al [19] compared three groups of patients (51 with uveitis and active systemic TB, 52 with undetermined cause of uveitis and positive IGRA but no active systemic uveitis, and 15 with positive MTB PCR results from ocular fluids but not active systemic TB). The study found differences in ocular manifestations between patients with active systemic TB and IGRA-positive patients without active systemic TB. It was concluded that IGRA-positive uveitis with undetermined cause is not synonymous with OTB. Additionally, the absence of active systemic TB does not exclude OTB, which was evidenced by patients with positive MTB PCR results from ocular fluids [19].

Therefore, neither a systemic evaluation alone, nor an IGRA alone can clearly distinguish tuberculous from non-tuberculous intraocular inflammation. Nora et al [20] conducted a 2025 randomized clinical trial in Jakarta, Indonesia, a TB-endemic region. The study included 76 adults with newly diagnosed, active uveitis of undetermined cause and a positive IGRA who were randomized into two groups. The ATT group received systemic corticosteroids plus a six-month course of ATT, and the control group received corticosteroids only. At six months, the rate of complete uveitis resolution was higher (81.1% vs 51.3%) and uveitis relapse was less common in the ATT group than in the control group. The authors intentionally refrained from referring to all included patients as having OTB, but referred to them as “adults with newly diagnosed, active uveitis of undetermined cause and a positive IGRA”. This

terminology actually shows that a positive IGRA indicates a potential TB-associated inflammation but does not confirm the tuberculous etiology of inflammation [20].

Discussion

The review of current approaches to the diagnosis of OTB demonstrates that the main problem is not so much establishing Mtb infection, but rather determining the causal relationship between Mtb and a specific intraocular inflammation. Current laboratory methods enable direct detection of Mtb genetic material in intraocular specimen, whereas TST and IGRA determine a specific immune response to Mtb antigens [1, 2]. However, none of these approaches alone provides sufficient diagnostic accuracy in all cases. This is especially important for OTB where a large proportion of cases remain diagnostically uncertain, and diagnostic criteria vary from study to study [3]. Molecular gene methods are theoretically the closest to the etiological confirmation of OTB, but they still lack the sensitivity to be widely used in clinical settings. PCR outcomes depend on the type and amount of the material harvested from the eye, the paucibacillary nature of the process, and the selection of the gene target. Balne et al [9] demonstrated that the rate of positive PCR testing depended on the sequencing target, and later studies did not show a consistent advantage of automated platforms, Xpert MTB/RIF Ultra and Truenat, over multiplex PCR [11, 12]. In a 2025 study by Sharma et al [13], Mtb-derived CF-DNA Mrt PCR was found to be promising for diagnosing OTB, showing higher positive PCR testing rates than Truenat MTB Plus and Xpert Ultra. The study, however, included only 25 patients with OTB, and requires further external validation [13]. Therefore, positive molecular assay results have an important role in confirming the etiology of OTB, but negative results do not reliably rule out OTB.

IGRA has higher specificity than TST for detecting Mtb, especially in BCG-vaccinated populations. However, the specificity for Mtb infection is not equivalent to that for TBU [1, 4]. IGRA does not allow localization of the infectious process or establishing whether this immune sensitization is directly related to ocular inflammation. This was demonstrated in a study by Xia et al (2024) performed [18] in a low-prevalence TB area, where of the 338 patients that underwent QFT-G testing, only 17 (4.38%) were positive, including 16 patients did not meet SUN criteria for TBU. At the same time, negative IGRA cannot be considered an absolute criterion for excluding OTB. A review by Ludi and colleagues [1] reported that IGRA sensitivity for OTB varied across studies, and in five head-to-head comparisons of IGRA and TST in TB-endemic countries, IGRA sensitivity was lower than that of TST. Such findings allow comparing direct and indirect methods with regard to the strength of evidence. A positive molecular assay result is of much greater diagnostic value than a negative molecular assay result, whereas a positive IGRA result strongly indicates Mtb infection, but does not establish a causal

relationship with intraocular inflammation. Even advancements in certain laboratory methods have not yet led to the development of a test capable of independently confirming or ruling out ocular tuberculosis. Major capabilities and limitations of the discussed methods of the etiological diagnosis of OTB are briefly summarized in Table 1. The data presented demonstrate that direct and indirect methods differ in diagnostic value. None of these methods alone always enables establishing or ruling out the etiological relationship between MTB infection and intraocular inflammation in a particular patient.

Therefore, current diagnostics of OTB is characterized not by the absence of informative techniques, but rather the absence of an independent criterion capable of confirming Mtb infection or proving its causative role in particular intraocular inflammation. Further enhancement of the analytical sensitivity of molecular methods remains promising, but may not completely solve the problem, given the pathologic heterogeneity of OTB and the potential role of immune-mediated mechanisms. With regard to indirect immunologic methods, it is important to look for the way to distinguish the intraocular inflammation etiologically associated with MTB from uveitis accidentally associated with latent TB infection. Promising types of biomarkers include transcriptomic, proteomic, cellular and others, but most of the proposed biomarkers have been studied in small cohorts only, and have not yet undergone sufficient external validation to be adopted [1]. Therefore, important areas of further research should include not only the search for more sensitive diagnostic tools, but also their validation in the independent cohorts of patients in conjunction with well-defined diagnostic criteria.

Author Contributions

Kolesnichenko V. V., concept, design, data collection and research, data analysis and interpretation, manuscript preparation and writing; Dorokhova O. E., concept, design, data analysis and interpretation, manuscript preparation and review; Zborovska O. V., concept, design, review of the manuscript. All authors have reviewed the final version of the manuscript, approved it and agree to be responsible for its content.

Funding

The article is part of a research project "Develop measures for early detection, immunocorrection and rehabilitation of patients with ocular tuberculosis, diabetes mellitus, ischemic neuropathy under martial law" (state registration No. 0125U002071).

Disclaimers

The views expressed in this article are solely those of the authors and do not necessarily represent the official position of their affiliated institution or any funding source.

Conflict of Interest

The authors declare that they have no conflicts of interest that could influence their opinion on the subject matter or materials described and discussed in this manuscript.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Abbreviations

ATT, antitubercular therapy; AUC, area under the curve; BCG, Bacillus Calmette-Guérin; cfDNA, cell-free DNA; CFP-10, culture filtrate protein 10 kDa; COTS-1, Collaborative Ocular Tuberculosis Study-1; ESAT-6, early secreted antigenic target 6 kDa; IFN- γ , interferon gamma; IGRA, interferon-gamma release assays; IS6110, insertion sequence 6110; Mtb, *Mycobacterium tuberculosis*; MPB64, mycobacterial protein 64; OTB, ocular tuberculosis; PCR, polymerase chain reaction; QFT, QuantiFERON; QFT-Plus, QuantiFERON-TB Gold Plus; RD1, region of difference 1; RIF, rifampicin; SROC, summary receiver operating characteristic curve; SUN — Standardization of Uveitis Nomenclature; TB, tuberculosis; TB1, tuberculosis antigen tube 1; TB2, tuberculosis antigen tube 2; T-SPOT.TB, T-SPOT.TB test; TST, tuberculin skin test.

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Table 1. Diagnostic value and major limitations of current methods of etiological diagnosis of ocular tuberculosis

Method	What the method confirms	Major limitations	Can the method confirm the tuberculous etiology of a particular case of uveitis?
PCR of intraocular specimens	Presence of the Mtb gene in an intraocular specimen	Variable sensitivity; a negative result does not rule out OTB	A positive result is an important evidence, but a negative does not rule out the tuberculous etiology
Automated molecular platforms (Xpert MTB/RIF Ultra, Truenat MTB Plus)	Mtb genetic material, information on antimicrobial resistance	Insufficient sensitivity	A positive result is suggestive of, but not diagnostic of, the tuberculous etiology A negative result does not rule out the tuberculous etiology
Mtb-derived CF-DNA Mrt PCR	Mtb-derived cf-DNA in the intraocular material	Limited evidence Small cohorts Requires external validation	May potentially confirm the tuberculous etiology, by its diagnostic value requires further external validation
TST	Specific immune response to Mtb antigens	Prior BCG vaccination Contact with non-tuberculous mycobacteria Status of an individual's cellular immunity Does not localize the infection	No
IGRA / QuantiFERON	Specific immune response to Mtb antigens	Does not localize the infection Does not confirm a causal relationship between Mtb infection and intraocular inflammation	No
TST plus IGRA	Enhances the diagnostic value with regard to the diagnosis Mtb infection	Indirect confirmation of infection. Highly dependent on the clinical and epidemiological context.	No

Note: Mtb, Mycobacterium tuberculosis OTB, ocular tuberculosis; ; cfDNA, cell-free DNA; BCG, Bacillus Calmette-GuérinCFP-10, culture filtrate protein 10 kDa; IGRA, interferon-gamma release assays; TST, tuberculin skin test.

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