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Ocular tuberculosis epidemiology, clinic features and diagnosis: A brief review

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ABSTRACT

The spread of tuberculosis is directly related to the processes of globalization and migration. Tuberculosis has also been the main cause of fatality associated with antimicrobial resistance and also the main cause of death in people who have HIV infection. Additionally, tuberculosis smites the lungs in 80% of patients, and in the remaining 20% of patients the tuberculosis may smites other organs, such as the vision/eye. Ocular tuberculosis is a specific infectious disease of bacterial etiology with a chronic and persistent course, the prognosis of which is extremely doubtful. Even effective chemotherapy can be accompanied by a decrease in visual acuity, and clinical recovery is not always persistent. Ocular tuberculosis often leads to permanent disability and, as a result, the quality of life of patients decreases. A statistical reporting of this disease does not always reflect the true picture, since ocular tuberculosis sometimes develops against the background of an existing specific lesion in the lung tissue. Currently, ocular tuberculosis remains substantially a conjectural clinical diagnosis. This review paper presents an analytical review of the literature on the epidemiology, clinical features, and diagnosis methods of ocular tuberculosis. The results of recent studies that focused on the modern clinical manifestations of this pathology, its diagnosis, and complex therapy are systematized. The development of new rational regimens and pathogenetic treatment methods are also highlighted in this review.

1. Introduction

Tuberculosis (TB) as one of the infectious disease has existed since ancient times. Tuberculosis, as a systemic infectious disease, is caused by *Mycobacterium tuberculosis* (MBT). TB infection is one of the main causes of sickness and mortality rate worldwide.

According to the statistics of the World Health Organization (WHO), tentatively one-third of the world's populations, which is more than two billion people, have been suffering with this disease. Based on the recent reports, 10% of infected people have symptoms of the disease, and 90% of people have latent tuberculosis [1–3].

People with latent *Mycobacterium tuberculosis* infection are not infective and basically, do not show symptoms of active tuberculosis, but the disease may be developed by them at any time during the lifetime.

More than 95% of new tuberculosis infections occur in developing or in indigent countries located in South Asia and Africa. However, the number of tuberculosis case is growing in both developed and developing countries because of the global migration, human immunodeficiency virus (HIV) and multidrug-resistant tuberculosis [4–6].

Regardless of ethnic origin, general weakness, poor socioeconomic conditions, and immunosuppression are considered as substantial presumptive factors [7].

Tuberculosis primarily affects the lungs and it can also affect other organs, such as the vision/eye. Ocular tuberculosis is a serious disease with a long recurrent course, often leading to a significant decrease in the visual functions and quality of life of patients. Extrapulmonary localization of tuberculosis reaches 20%, and ocular tuberculosis ranges from 3.5 to 5.1% mainly with the generalization of a specific process in HIV infected patients [8–10]. The incidence and prevalence of TB among HIV-infected people is 12.8 and 8.5 times higher and mortality from tuberculosis of HIV-infected people exceeds the same indicator of the entire population by 13.4 times [11,12]. Disseminated and miliary tuberculosis of the lungs and other organs are most often detected in the structure of clinical forms with a combined infection [13,14]. Eye

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Table 1
The prevalence of suspected ocular TB countries [25].

Country	Population[a]	TB Prevalence
India	1,352,642,280	0.4–9.8%
China	1,427,647,786	4,0%
Japan	126,150,000	7,0%
Thailand	69,428,453	2,2%
Philippines	100,981,437	6,8%

[a] World Population Prospects: The 2019 Revision" (xslx). UN Department of Economic and Social Affairs.

damage by a specific pathogen is often the first diagnosed pathology in an immunodeficiency state; therefore examination by an ophthalmologist is mandatory in HIV-infected individuals [15]. The classification of ocular tuberculosis depends on the localization of the process. Tuberculosis of additional structures includes tuberculosis of the eyelids skin, tuberculous dacryocystitis, tuberculous dacryoadenitis and tuberculous osteomyelitis of bone formations around the orbit [16,17]. Also, tuberculosis is divided into anterior (conjunctivitis, episiscleritis, scleritis, blepharoconjunctivitis, iridocyclitis, and keratitis) and posterior (chorioretinitis and choroiditis) parts of the eye [18,19]. Uveitis, peripheralitis, and tuberculous thrombosis are released if the retina and its vessels are involved in the process, and neuritis and papillitis are relased if the optic nerve is damaged [20,21]. Uveitis is a serious problem in ophthalmology due to the characteristics of the disease - an inconspicuous onset, chronic course and a high incidence of disabling complications. As well as, it is still indeterminate whether TB uveitis is the result of a hypersensitivity reaction or direct infection of mycobacteria, and this is certainly reflected in its treatment process.

The purpose of this review is to show the different manifestations of ocular TB, as well as the main attention is paid to diagnostic criteria and to the significance of a tuberculin skin test.

2. Epidemiology

One-third of the world's population or almost two billion people infected with *Mycobacterium tuberculosis*, and 10% of them can lapse into illness during their lifetime [22]. A geographic distribution of TB is surprisingly diverse. Nevertheless, 22 countries (Afghanistan, Bangladesh, Brazil, China, Cambodia, Democratic Republic of Congo, Ethiopia, India, Indonesia, Kenya, Myanmar, Nigeria, Pakistan, Peru, Philippines, Russian Federation, South Africa, Tanzania, Thailand, Uganda, Vietnam, and Zimbabwe) have been identified as contributing 80% of the world's total burden of tuberculosis [23,24]. Table 1 shows five most densely populated Asian Pacific countries where prevalence of suspected ocular tuberculosis exists.

WHO reported 3.7 million TB cases in 2000: 38% in Southeast Asia, 20% in Africa, 10% in Europe, 6% in America, 4% in the eastern Mediterranean, and 22% in the western Pacific [24,26,27]. The epidemiological study which was conducted in 2004 by the Centers for Disease Control and Prevention (CDC) in the USA revealed 14,511 confirmed cases of tuberculosis (4.9 cases per 100,000 populations) [28]. More than 50% were immigrants of foreign origin among these confirmed cases. 20% tuberculosis occurred in Asians, African Americans, and Hispanics, which are respectively 8.3 and 7.5% times higher than that of the local population [28]. Recently, over the past 10 years, the CDC reported TB incidence in the USA. It was found that the rate of incidence among non-Hispanic indigenous people was very low, while Indians and Hispanics (Alaska) were all significantly higher in the Asia-Pacific region. Further examination showed the comparative number of tuberculosis cases in the USA with people of foreign nationals/origin. The number of tuberculosis cases among US-born persons decreased by 64% between 1992 and 2003 but amplified 8% among people foreign nationals/origin. The percentage of tuberculosis cases in the USA that occurred among foreign nationals/origin increased from 27% in 1992 to 53.3% in 2003. Nevertheless, the ratio amplified to 8.4% in 2002, which indicates a smaller decrease in the number and speed of cases in non-US born people [29,30]. Poor socioeconomic status, the use of alcohol and drugs, imprisonment, differentiated access to medical care, structural barriers and unequal treatment to the health care system and general ethnic differences in health status is determined to be an expected reason for this mismatch [31]. In addition, in the USA, extrapulmonary TB is basically observed in Native Americans and Asians, children, and women [32]. The TB incidence in the USA is still at historically very low levels (e.g. 14,874 cases in 2003 and 14,511 in 2004) [23,28,29]. Even though the number of reported cases of pulmonary TB is noticeably reduced each year, a reduction rate of this disease was less than 1% per year at the same time period [32]. HIV epidemic has had a considerable impact on the global TB epidemiology. TB infection can easily be spread and acquired among patients infected with HIV [33].

TB is the most common opportunistic infection in HIV-infected patients in many developing countries, mainly in the result of poor unsanitary conditions, hygiene, drug resistance, and poverty. In a recent study conducted from January 2004 to February 2005 in Cambodia, tuberculosis was diagnosed in 24% of patients out of 450 HIV-infected people who were screened [34]. In a Chicago study, more than 15% of people newly diagnosed with tuberculosis have HIV-positive tests, suggesting a link between TB and HIV [35]. WHO calls to look at these two diseases as "Two diseases - one patient" and comprehensively help against HIV infection and tuberculosis.

Regarding to ocular tuberculosis, since the 19thcentury, there has been a dramatic change in the ocular TB epidemiology. Tuberculosis was considered a common cause of uveitis at that period of time. It was also considered so common, that well-known ophthalmologists of that period were able to classify tuberculosis uveitis into different types [36]. A several researchers of the time revealed tuberculosis to account approximately for up to 10% of all uveitis cases. The number of uveitis cases attributed to *Mycobacterium tuberculosis* declined over the subsequent decades. Because of the absence of precise standards and strategies for affirming the finding with other research facility techniques, there are no dependable information in the determination of intraocular tuberculosis to show its actual commonness. Eye involvement is traditionally considered as rare in patients with systemic tuberculosis. Donahue assessed case accounts of 10,524 patients with transcendently pneumonic tuberculosis who were inspected at the Sanatorium Mattapan Eye Clinic in Boston, Massachusetts [37]. He analyzed 154 (1.4%) patients with eye tuberculosis. Be that as it may, 1997 in Spain, the investigations completed by Bouza and his partners recommend a higher occurrence of eye tuberculosis; 100 arbitrarily chose patients with an affirmed culture of fundamental tuberculosis, observed in a multidisciplinary emergency clinic, 18 patients were found to have eye injuries, including choroiditis, papillitis, retinitis, vasculitis, dacryoadenitis and scleritis [38]. In the USA, until 1960, tuberculosis was the hidden etiology for granulomatous uveitis in 80% of all cases [39,40]. Be that as it may, a later report by Henderley and his partners from the tertiary connection of the uveitis administration credited the reason for granulomatous uveitis to tuberculosis in under 0.5% of cases [41]. An investigation by Wakabayashi from Japan indicated an expansion in the rate of intraocular tuberculosis [42]; from 189 instances of referenced uveitis, 6.9% had ocular tuberculosis. As indicated by the examinations directed by Abrahams and Jiang in China, 4% of all uveitis in patients recommended macular tuberculosis [43]. As indicated by Islam and Tabbar, tuberculous etiology was identified in 10.5% of cases in a review investigation of 200 patients with uveitis in Riyadh (Saudi Arabia); the second most regular frequency was herpetic uveitis (16%) [41]. Mercanti and his accomplices detailed tuberculosis contamination as the reason for front uveitis in 6.31% of patients in Italy [44]. Norn proposes that in Denmark Ocular TB is a substantial reason for visual dismalness in instances of interminable iridocyclitis, dispersed choroiditis, and fringe retinitis [45]. Lately, Ballantyne and Michaelson have revealed a pattern towards an expansion in the rate of visual tuberculosis in Russia

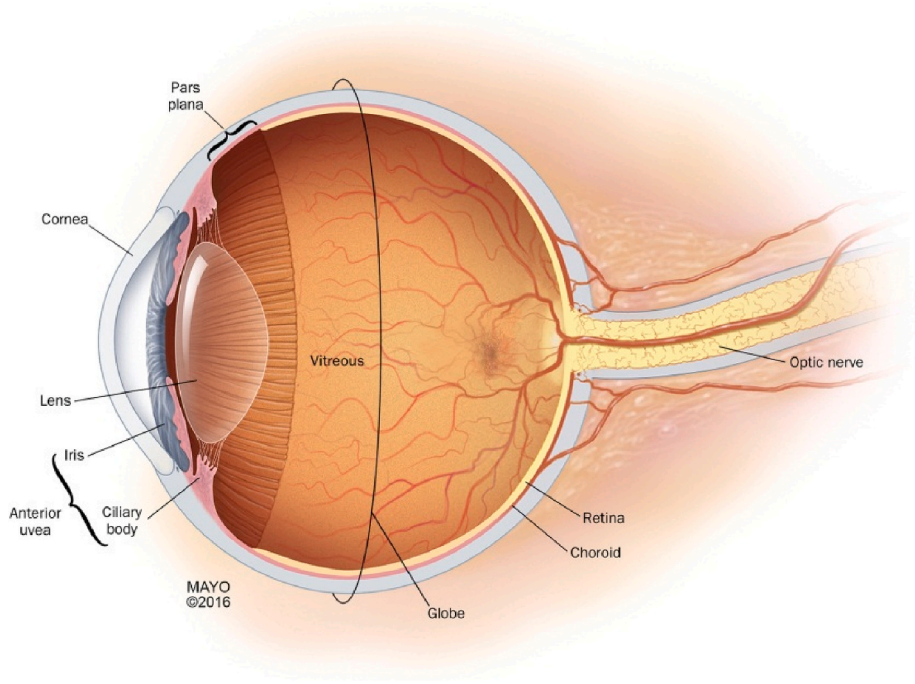

Fig. 1. The different anatomical structures of the eye that can be influenced by tuberculosis [50].

[46]. In India, Biswas and his accomplices conducted a total clinical visual assessment utilizing a cut light, biomicroscopy, aberrant ophthalmoscopy and fundamental assessment, X-beam assessment, Mantoux skin test, and different techniques in 1005 South Indian patients with dynamic aspiratory and extrapulmonary tuberculosis and announced rate 1,39% [47]. In another examination at a similar focus, tuberculosis was accounted for to be 0.39% in 1273 patients with uveitis [48]. Nevertheless, the examination didn't indicate the symptomatic rules for tuberculosis. Out of 602 patients with a clear analysis of uveitis, observed by Singh and partners [49], the uveitis facility uncovered an irresistible etiology in practically 30% of them. 66% of instances of irresistible uveitis were intraocular tuberculosis, while the remaining 33% had different infections. This investigation utilizes the strategy for polymerase chain response (PCR) and intraocular liquid is utilized to analyze intraocular tuberculosis. A higher occurrence is resolved in South India. This examination technique can be ascribed to delicate indicative strategies for intraocular tuberculosis. Dalvin and Smith [50] declared that paying little attention to the clinical introduction, numerous repeats of irritation in spite of treatment should build the degree of doubt for intraocular TB in a patient with TB risk factors. A number of wide variety of ways by which TB can influence the intraocular tissues are featured in Fig. 1 illustrating the pertinent structures of the eye.

3. Clinical Features

Mycobacterium TB is aerobic bacterium ordinarily found in tissues with high oxygen content. TB affects the lungs in 80% of patients and the remaining 20% can affect different organs, such as the organ of vision, where the choroid itself has high oxygen content. In addition, mycobacterium TB affects the ancillary organs of the eye and the eyeball itself. Ocular TB is generally not related with the clinical signs of pulmonary tuberculosis, since up to 60% of patients with extrapulmonary tuberculosis might not have pneumonic pulmonary tuberculosis [51].

Ocular TB is a complex clinical issue because of a wide scope of discernments and challenges in finding [52]. Tuberculosis of the organ of vision is either essential, in which the eye is the principle course of infiltration of mycobacteria into the body or the optional course of hematogenous spread from removed sores. Incipient disease is uncommon and incorporates damage to the eyelids, cornea, sclera and conjunctiva, while damage to the retina, optic nerve, and uveal tract is considered as secondary. Uveal tract inflamation is the most widely recognized tuberculous injury of the organ of vision because of its high blood supply [53,54].

TB was considered the foremost common cause of granulomatous uveitis, but in recent years the predominance of ocular TB has changed drastically, since the etiology of previously unknown infections, such as toxoplasmosis, histoplasmosis, sarcoidosis and others, are presently recognized [1].

Recently, interest in TB has renewed, caused by an increase in the spread of the HIV pandemic, the emergence of multidrug-resistant strains, and the incidence rate [52].

Tuberculosis of the organ of vision is as yet a significant reason for uveitis. The predominance of tuberculous uveitis extended from 0.5% in the US, 4% in China, 6.3% in Italy, 6.9% in Japan, 9.8% in northern India, 10.5% in Saudi Arabia, and 11.4% in Iraq, where tuberculosis is endemic [55–61].

Ocular TB has a few possible indications. It might appear on the adnexa as a sore of the eyelids or appear as incessant blepharitis or atypical exasperation of the eyelids. It can also appear as mucopurulent conjunctivitis with regional lymphadenopathy, as well as a conflict (an inflammatory nodule at the junction of sclera and cornea), infectious scleritis, inflammation in the corneal stroma (interstitial keratitis), or infectious keratitis [62].

Intraocular TB is an excellent tool for detecting different uveitis formations. It can be also considered in the differential diagnosis of any type of intraocular inflammation. Ocular inflammation can bilateral or be one-sided. Occasionally inflammation of one eye begins months or even years before the other [63]. Uveitis can manifest as posterior, panuveitis, anterior, or middle.

Anterior uveitis has a scheming onset and proceeds with a chronic course. Moreover, anterior uveitis is presented as a bilateral or unilateral chronic granulomatous infectious disease, which manifests itself in the form of granulomatous secretions on the corneal endothelium, sometimes associated with granulomas or iris nodes. As well as, this type of

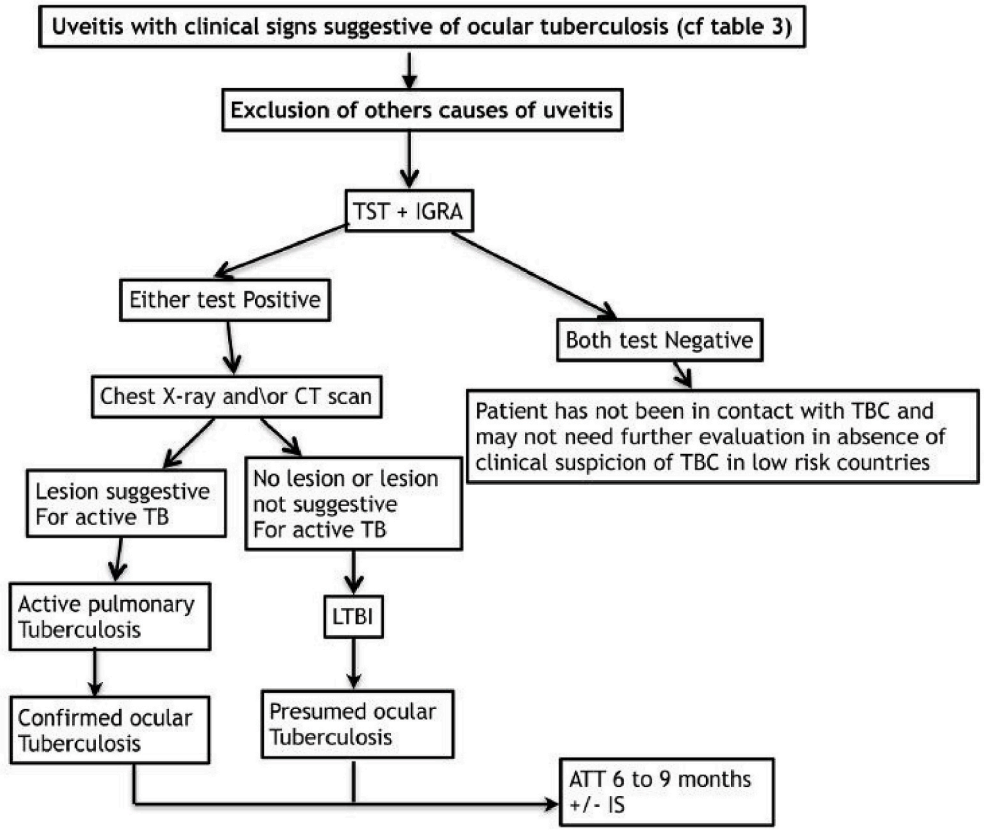

Fig. 2. Diagnostic pathways explanation for patients suspected of having TB [74].

uveitis is frequently accompanied by vitritis and is inevitably complicated by the development of cataracts and posterior synechia [1,64].

The vitreous body can be the primary focal point of inflammation and is emerged by a moderate to a serious cell response - frigid foci are noted in the vitreous. Intermediate uveitis is regularly accompanied with granulomatous deposits on the corneal endothelium. Circumferential retinal vasculitis accompanied with scars or discrete perivascular choroiditis may indicate the etiology of tuberculous. Peripheral neovascularization, cystoid macular edema, vitreous hemorrhage, and cataracts, can occur with tuberculous intermediate uveitis [64,65].

Posterior uveitis is the most widely recognized sign of intraocular tuberculosis, with lesions transcendently present in the choroid in the form of multifocal, central, or serpiginous choroiditis, numerous choroid hubs (tubercles) or single, neuroretinitis, and choroidal granuloma (tuberculosis). Endretinal abscess retinal vasculitis is frequently ischemic in nature and can prompt proliferative vascular retinopathy with repetitive vitreous hemorrhage body, neovascular glaucoma and iridescent rubeosis [63,66–71].

4. Diagnosis

Ocular TB diagnosis is frequently problematical because of the inappropriateness of taking a biopsy from the eyeball for inoculation and histopathological examination in order to provide ultimate evidence of ocular TB [54]. Ocular TB diagnosis was only a presumption in almost all reported cases.

History of pulmonary or extrapulmonary tuberculosis does not exist in most patients, who suffer with ocular TB disease [72]. Since ~60% of patients with extrapulmonary tuberculosis have no any signs of pulmonary tuberculosis, and radiography of chest is normal in cases of unmanifest tuberculosis, the absence of clinically pronounced pulmonary tuberculosis does not exclude the possibility of ocular tuberculosis [65,72,73].

In many investigations, an indicative standard for suspected tuberculous uveitis was relocation from regions endemic for tuberculosis or living arrangement, a nearness of noteworthy ophthalmological and clinical signs, and a contact history with tuberculosis patients. Moreover, other symptomatic rules are the avoidance of other known reasons for uveitis, supporting proof, for example, a positive interferon-gamma discharge test (IGRA), a positive skin tuberculin test (TST), and a positive reaction to anti-TB treatment (ATT) without recurrence. In light of the previously mentioned rules, Wellermain and his associates [74] proposed a graph clarifying the symptomatic pathways for patients associated with TB (Fig. 2). Tuberculosis of other non-visual organs likewise helps in the determination of visual tuberculosis in a patient with uveitis [54,63,65,73]. In the aftereffect of an investigation of 64 patients with suspected TB uveitis, 24 patients (37.5%) reported that they had past contact with patients with pulmonary TB, some of the time this contact was quite a while before the beginning of eye symtpoms [63].

PCR and cultures are frequently negative from intraocular fluids. Sometimes it is impossible to determine with any patient whether they are simply negative, false negative, or truly negative because the presentation is bacillary antigens' inflammation as opposed to true infectious inflammation. A biopsy is frequently impossible or extremely complicated when inflammation affects the posterior retina, optic nerve or choroid. It is of importance to receive intraocular fluids to be delivered to the culture in order to accurately confirm the diagnosis of ocular TB. Nevertheless, this is limited by the low concentration and small volume of bacteria obtained in the usual amount.

PCR was thoroughly tested on visual liquid, as limited quantities of bacilli can be enhanced, and it is also promising technique that can play a significant role in the further diagnosis of ocular TB. Nevertheless, both exactness (high explicitness but constrained sensitivity) and research clusters or laboratory technical problems remain main barriers to its broad use, although there are lacks of research reports written

about its usefulness in the case of ocular TB [75]. Additionally, a recent review proposed guidelines for the diagnosis of ocular tuberculosis, including the application of PCR. However, they have not been confirmed in the published literature [75]. Gamma-interferon tests (GIT) are in their developing stage in terms of their ability to diagnose intraocular TB [76].

These acute problems are aggravated in many countries worldwide with a great incidence of tuberculosis, where access to PCR testing, gamma interferon, biopsies, and culture is highly unavailable. Consequently, a doctor frequently has the clinical picture of "dubious ocular TB" from the chest X-ray (CXR) and skin tuberculin test (TST) results. TST is useful testing mechanism, but is also instinct with inaccuracy [77]. A positive predictive value of TST is low in order to make an active tuberculosis diagnosis. Factually, TST will be spuriously negative in 30% of patients who suffer with active tuberculosis [78]. TST with positive predictive value is further reduced in making diagnosis active tuberculosis among immunocompromised patients. If CXR shows precise data of previous or existing tuberculosis, or even if there are some other systemic manifestations of active tuberculosis, the credibility of illness after the test increases. In a number of cases where patients with suspected tuberculosis uveitis were tested, 17 of 18 cases did not show signs of inactive or active tuberculosis on CXR with therapeutic response to isoniazid [78].

In some cases, ocular diagnostic examinations such as indocyanine green angiography, fluorescein angiography, optical coherence tomography, ultrasound, and ultrasound biomicroscopy can be extremely helpful to diagnose ocular TB. Certainly, they can be applied to diagnose complications caused by tuberculous uveitis, but are seldom considered as the main or important diagnostic method in this field. Unlikely, too frequently part of the diagnostic criteria is the response of patient to anti-TB therapy process. Those patients who react with a considerable decrease in intraocular inflamation after a time of no reaction to mitigating drugs are determined to have tuberculous uveitis [77].

5. Conclusions

1. Diagnosis of ocular tuberculosis in the early stages is impossible without the alertness of ophthalmologists of the somatic network regarding the possible tuberculous etiology of eye diseases, especially in cases of their recurrent course.
2. It is important in a timely manner to refer patients to a consultation with a phthisis ophthalmologist for differential diagnosis is important.
3. The clinical picture of ocular tuberculous diseases is characterized by significant polymorphism and the absence of pathognomonic signs.
4. Differential diagnosis of inflammatory eye diseases is possible only in the conditions of a specialized phthisis ophthalmological hospital.
5. Treatment features of ocular tuberculous lesions are its duration (6–9 months), complexity, the inclusion of etiotropic and pathogenetic drugs.
6. Clinical supervision should be carried out by a phthisis ophthalmologist or alternatively by an optometrist and a phthisiologist.

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