■ *Review article*

Ocular tuberculosis: an update

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Abstract

Tuberculosis (TB) is an infectious disease responsible for significant morbidity and mortality worldwide. It is a resurgent disease in the developed world. The World Health Organization estimates that one third of the world's population is currently infected, with 9 million new cases occurring annually, leading to 3 million deaths per year (WHO Report, 2007). The disease affects the ocular anterior segment, the posterior segment, and adnexa. The purpose of this review is to describe the ocular manifestations, diagnosis and treatment of tuberculosis and to emphasize the fact that ocular tuberculosis may occur in the absence of systemic clinical activity and may mimic several clinical entities. Various studies have shown a clinical significance of purified protein derivative test results and computerized tomography of the chest while, molecular diagnostic procedures have provided a new approach to establishing the diagnosis of ocular tuberculosis. The current review focuses on the diagnostic modalities, various clinical features, and treatments for management of intraocular tuberculosis recommended in recent publications. It is an update on the manifestations and management of ocular tuberculosis.

Keywords: tuberculosis, uveitis, choroiditis, granuloma, Mantoux Skin Test, Interferon-g release assays, anti tubercular treatment

Introduction

The World Health Organization (WHO) has declared tuberculosis to be a global emergency, as it remains the most common single cause of morbidity and mortality worldwide (Centers for Disease Control and Prevention, 1994 & 2004; Duke-Elder S & Perkin, 2004). It has estimated 9 million cases and 2 million deaths from TB for 2005. In Africa, TB incidence has tripled in association with high levels of HIV. Similarly, increasing rates of TB is seen in certain regions of Eastern Europe and Southeast Asia. Likewise, multiple drug resistant tuberculosis (MDR-TB) is on the rise. 60% of patients with extra-pulmonary manifestations of TB have no evidence of pulmonary infection on chest roentgenogram or sputum culture. However, it is estimated that only 10% of patients infected with Mycobacterium tuberculosis develop active disease (WHO Report, 2007; Tabbara, 2007). The proportion of cases with extrapulmonary tuberculosis has increased in recent years in immune-compromised individuals. It is seen in more than 50% of the patients who have both AIDS and tuberculosis (Golden & Vikram, 2005). Jones et al (1993) showed that the risk of extra-pulmonary tuberculosis was higher in patients with low CD4 þ counts: 70% of the patients with CD4þ counts of less than 100 developed extra-pulmonary diseases compared to 28% with CD4þ counts of more than 300. Ocular TB can especially be difficult to identify for both its mimicry and its lack of accessible sampling. A high index of suspicion, therefore, is required. In patients with confirmed active pulmonary or active non-ocular extra-pulmonary TB. Ocular TB incidence ranges from 1.4-5.74%.In HIV patients, the incidence may be higher, reported from 2.8-11.4%. In some African

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countries, the high incidence of HIV infection has increased the incidence of tuberculosis and it may have exceeded 50% (WHO Report, 2007; Kestelyn PG; Cunningham ET, 2001). It is now estimated that 1.86 billion people or one-third of the world's population are currently infected by M. tuberculosis. A study done in Chicago, more than 15% of persons with newly diagnosed TB were found to be HIV positive, suggesting the association between TB and HIV (Centers for Disease Control and Prevention, 1995). Because of the lack of uniformity in the diagnostic criteria for intraocular tuberculosis, and the difficulty of confirming the diagnosis by laboratory methods, there are no reliable data to indicate its true prevalence. (Cunningham & Rathinam, 2001) Over the last 50 years, anti-TB antibiotics have been developed, resulting in successful therapies for TB. Poor compliance with these therapies has promoted multiple drug resistant (MDR) strains of M tuberculosis, resulting in difficulties in controlling the disease, Patients in Southeast Asia and Western Pacific regions combined account for approximately 60% of the newly occurring multidrug-resistant tuberculosis (MDR-TB)cases in the world (Mori, 2007). Drug and alcohol use, incarceration, poor socioeconomic status, general ethnic disparities in health status, differential access to care, unequal treatment, and structural impediment to the health care system have been postulated to be the possible causes of this disparity (Center for Disease Control and Prevention, 2004)

Pathophysiology

Tuberculosis is caused by M. tuberculosis, which is an obligate aerobic slow growing, nonspore forming, nonmotile bacterium. Humans are the only natural host. It is primarily spread as an airborne aerosol which gains access to susceptible hosts through the lung and results in a latent or dormant infection in hosts with normally functioning immune systems. Mycobacterium avium-intracellulare complex (MAC) should be considered in AIDS patients, in addition to M tuberculosis. In about 5% of patients, the infection causes disease within the first few years after exposure. In another 5% the disease may develop several years later as a result of altered host immunity. This late-developing disease is known as reactivation of latent infection (Dannenberg, 1991; Dannenberg, 1999). The onset of symptoms can occur after a breakdown of the patient's immune system associated with age, disease, or the use of immunosuppressive therapy for other conditions.The organism can invade any tissue or organ in the body (Rathinam et al 2000, Bouza et al 1997). Usually, between 5 and 200 inhaled bacilli are needed to cause infection in humans (Dannenberg, 1999). Rapid progression of the disorder may occur in immunocompromised individuals. It sometimes invades the local lymph nodes and spreads to extrapulmonary sites, usually via haematogenous routes (Sheu et al 2001). Infected end organs typically have high regional oxygen tension (apices of the lungs, kidneys, bones, meninges, eye, and choroid). M. tuberculosis tends to grow successfully in the choroid and ciliary body where the oxygen tension is high compared with other ocular structures (Sheu et al 2001). The organism preferentially infects macrophages and other reticuloendothelial cells and recently, TNF inhibitors have been seen to be associated with tuberculosis. Genetic susceptibility may play a role in the dissemination of tuberculosis. Th1 cell response is associated with protection and control of tuberculosis, whereas Th2 responses predominate in patients who are unable to contain infection and develop active disease (Khalid, 2007).

Ocular involvement occurs in about 1%to 2% of patients with TB (Donahue, 1967). It usually masquerades as other infectious and disease processes .The hallmark of extra-pulmonary TB is caseating granuloma and necrosis.Extrapulmonary TB occurs either in association with clinically apparent pulmonary tuberculosis or in isolation, with no clinical or laboratory evidence of pulmonary infection (Glassroth et al 1980).

Clinical presentation

Patients with systemic tuberculosis develop fatigue, weight loss, night sweats, cough and fever. Majority of children have no symptoms and may present with postauricular lymphadenopathy or other systemic manifestations. The disease is usually chronic and insidious. In the eye, it can affect any structures. It may be unilateral or bilateral which can result from haematogenous spread, from direct local extension from the skin, mucous membranes, and sinuses or, as hypersensitivity response to distant infection. The most common clinical presentation appears to be posterior uveitis followed by anterior uveitis,

panuveitis, and intermediate uveitis It typically presents as a granulomatous uveitis while, sometimes may be nongranulomatous so should also be suspected in cases of intense nongranulomatous anterior uveitis of short duration, mild relapsing uveitis or chronic smouldering inflammatory disease (Coles, 1963) . Other ophthalmologic findings include interstitial keratitis, retinitis, scleritis, orbital abscess ,optic neuropathy and cranial nerve palsies (Smith & Blasi, 2009). Since the last major review (Helm & Holland, 1993) over a decade ago, several new manifestations of intraocular tuberculosis have been reported and the pathogenesis and molecular diagnosis of ''tuberculous retinal vasculitis'' and Eales disease clarified.

· **Eye lid**

The eyelid manifestations may appear as a small nodule that mimics a chalazion. The primary conjunctival and eyelid tuberculous granuloma may occur rarely (Zaborowski et al 2006, Biswas et al 2002).

· **Orbit**

Proptosis, intermittent diplopia and headaches or extra-ocular muscle motility restriction may be the presenting complaint secondary to intracranial inflammation. Orbital granuloma as well as lacrimal gland and lacrimal sac granuloma may occur secondary to infection with M tuberculosis (Bansal et al 2006, Raina et al 2004). Orbital disease may be associated with preauricular lymphadenopathy**.** Children may present with preseptal cellulitis with a spontaneously draining fistula. Tuberculosis is a mediating factor for abducens nerve palsy in children (Smith & Blasi, 2009).

· **Conjunctiva, cornea and sclera**

Interstitial Keratitis and phlyctenular keratoconjunctivitis are common findings which represent an immunologic response to the mycobacteria (Scott, 2004). Phlyctenulosis is due to delayed hypersensitivity reaction to mycobacterial antigens and limbal phlyctenulosis occurs more commonly in children. It may present with photophobia, tearing and blepharospasm (Tabbara, 2007). Eruptions may also occur on the conjunctiva which may sometimes be associated with cervical lymph nodes enlargement and responds promptly to topical application of corticosteroids. Tuberculous scleritis presents with localized focal elevated nodules of the sclera. This may undergo necrosis and may lead to scleromalacia (Pecorella, 2006; Tabbara, 2005). Mostly it presents as is anterior scleritis while posterior scleritis is rare. It does not respond to topical steroids and requires antituberculous therapy.

· **Uvea**

Tuberculosis is a well-known cause of acute or chronic granulomatous anterior uveitis that may be associated with iris or angle granulomas with mutton-fat keratic precipitates, and posterior synechiae (Asensi et al 1991, Biswas et al 1999). Duke-Elder & Perkin (1966) suggested that the disease (iritis and cyclitis) begins as a nodule in the pars plana from where the infection travels either into the anterior chamber, resulting in granulomatous uveitis or posteriorly into the vitreous and perivascular spaces along the retinal veins. Ohmart induced optic neuritis in an animal model by inoculating Tubercle bacilli into the ciliary body, (Ortega-Larrocea et al 2003) suggesting the posterior dissemination of the organisms. Current evidence, however, suggests haematogenous dissemination of the mycobacteria (Rathinam & Rao, 2004; Biswas et al 1995). Such dissemination occurs when a caseous pulmonary lesion erodes into the blood vessels or the lymphatic channels (Olazabal, 1967), uveitis in ocular tuberculosis presents with a smouldering, insidious, progressive form (Tabbara, 2005). Clinically, these nodules first appear as small gray elevations that, if left untreated, grow up to 3 mm in size (Duke-Elder & Perkin, 1966). Overtime, the colour changes from gray to yellow, and the nodules become vascularized.t may be seen as granulomatous anterior uveitis, where the surface of iris may show multiple nodules, especially near the pupillary border or the iris root (Finnoff, 1931). Essential iris atrophy also has been reported (Paez, 1952). Although granulomas are absent in these eyes, small translucent nodules may be seen at the pupillary margin (Koeppe nodules). Inferior corneal edema secondary to the mutton-fat keratic precipitates may occur (Smith & Coster, 1998). Cyclitis is frequently seen and may cause caseating granuloma (Tabbara, 2005). During relapses, mutton-fat keratic precipitates may develop, along with extensive posterior synechiae, complicated cataract, and vitritis (Duke-Elder & Perkin, 1966). Recent studies have retreated the previous findings that the iris or angle granulomas usually associated with muttonfat keratic precipitates and posterior

synechiae constitute the main features of tubercular iridocyclitis (Tabbara KF 2005). Tubercular granuloma in the anterior chamber angle may have minimal anterior segment inflammation (Saricaog¡lu et al 2004). Pigmented hypopyon may be a presenting feature (Rathinam & Rao, 2004). Patients on retroviral therapy can show an immune recovery uveitis. In children, diffuse endophthalmitis may lead to leukocoria mimicking retinoblastoma (Centers for Disease Control and Prevention 2002 & 2004). Intraocular tuberculosis can present with features of intermediate uveitis simulating pars planitis. Patients generally present with a low-grade, smoldering, chronic uveitis, vitritis, snowball opacities, snow banking, peripheral vascular sheathing and peripheral retinochoroidal granuloma. (Ness & Virchow, 2001). Fluorescein gonioangiography has been reported to show small, discrete, white lesions in the ciliary body band near the iris root that demonstrate early hyperfluorescence. (Kimura, 1982) Posterior segment involvement is common in some patients. The most frequently encountered sign of tuberculous involvement of the posterior segment is multifocal choroiditis (Tabbara, 2002). The ocular changes can be divided into four groups: **choroidal tubercles, choroidal tuberculoma, serpiginous-like choroiditis and subretinal abscess.**

1. Choroidal Tuberculoma

Less commonly, intraocular tuberculosis may present as a large tuberculoma (Cangemi et al 1980; Mansour & Haymond, 1990). These tuberculomas may be located anywhere may mimic a tumor may measure from 4 to 14 mm in size and generally present as a yellowish, subretinal mass with surrounding exudative retinal detachment. M. tuberculosis is an aerobic bacillus and starts infection in the choroid leading to multifocal or diffuse choroiditis. Solitary choroidal tuberculoma may occur in immunocompetent patients (Levecq & Potter, 2005) and in patients with disseminated tuberculosis (Ohta et al 2003, Sharma et al 2003). Sometimes choroidal tubercles may be seen in patients with central nervous system tuberculosis (Mehta et al 2006, Tooke, 1936) studies have reiterated that the tubercles result from hematogenous spread (Pe´rez et al 2003). Their association with meningitis has also been affirmed (Tejada et al 1994). Clinically, the tubercles appear as small nodules. They may be uni- or bilateral, found mostly in the posterior pole Small multiple tubercles are seen in miliary tuberculosis (Darrell, 1986). Active choroidal tubercles usually respond well to ATT and generally take up to 3 to 4 months to heal. The healed lesions show atrophic areas with variable pigmentation.

2. Serpiginous choroiditis

It is a chronic, recurrent inflammation that primarily involves the choroid and choriocapillaris and progresses to involve the retina secondarily (Gass, 1997). The lesions are slowly progressive, multifocal and may lead to relentless destruction of the retina, retinal pigment epithelium and choroid adjacent to the optic nerve (Rao et al 2006). The healing of such lesions may lead to peripapillary retinochoroiditsi scar. Choroiditis simulating serpiginous lesions maybe seen in intraocular tuberculous infection (Gupta et al 2003). The exact mechanism of serpiginous-like choroiditis presentation in tuberculosisis is unknown. It may represent an immune-mediated hypersensitivity reaction with relentless progression despite administration of systemic corticosteroids and immunosuppressive agents. Because serpiginous choroiditis of presumed tubercular origin has been reported primarily in patients of Indian origin so it is better to investigate all patients of Asian Indian origin with serpiginous choroiditis to rule out possible tubercular etiology (Gupta et al 2003). The retinochoroiditis may become extensive and may involve the ciliary body causing cyclitis with hypotony and phthisis bulbi.

3. Sub-retinal abscesses

Multiplication of the bacilli in the caseous material of the granulomas can lead to liquefaction necrosis and abscess formation. Patients with disseminated tuberculosis may present with sub-retinal abscess with little overlying vitreous inflammation (Demirci et al 2004), usually heal with ATT and healed lesions may show pigmentation and atrophy with chances of good visual recovery (Mason, 2000; Wang et al 2001). Sub-retinal neo-vascularization may develop within the scar (Chung et al 1989).

· **Retinitis and retinal vasculitis**

Retinal vasculitis in patients with tuberculosis may involve the veins or, rarely, the arteries (Chan & Pang, 1990). The diagnosis is often presumptive as there is no confirmatory evidence (Gupta et al 2007). The characteristic features include vitreous infiltrates (vitritis), retinal haemorrhages, neo-vascularization,

and neuro-retinitis. Treatment comprises administration of oral corticosteroids and laser photocoagulation of the ischemic non-perfused retina with concomitant ATT. In cases of no resolving vitreous haemorrhage, pars plana vitrectomy may be required (Gupta et al 2001). It is believed that the organism may persist in the ocular tissue and initiate an immune-mediated hypersensitivity response manifesting clinically as vasculitis (Biswas et al 2002).

· **Eales disease**

Eales disease was first described by Henry Eales as recurrent vitreous haemorrhages associated with headache, peripheral circulation disorders, constipation, and epistaxsis (Eales, 1882). The disease is known affects healthy adults, mostly men, in their third to fourth decade of life and is characterized by peri-phlebitis, capillary non-perfusion, neo-vascularization, recurrent vitreous haemorrhages, and fibro-vascular proliferation in a quiet eye (Elliot, 1954). A number of theories have been postulated regarding the pathogenesis of Eales disease. The most widely accepted theory is either tuberculosis or a hypersensitivity reaction to tuberculoproteins (Wagener, 1958; Bonnet, 1959). Recent reports of the detection of M. tuberculosis DNA by PCR in a vitreous fluid specimens shows the association of M. tuberculosis with Eales disease (Biswas et al 1999, Madhavan et al 2002).

Neuro-retinitis and optic neuropathy

Tuberculous optic neuropathy and neuro-retinitis could result from contiguous spread from the choroid or from disseminated haematogenous spread of the tuberculous organisms from the pulmonary or other primary infectious focus and should be considered as a differential diagnosis while evaluating a patient of neuro-retinitis (Ray & Gragoudas, 2001; Reed et al 1998). The optic neuropathy develops either from direct infection induced by the mycobacteria or from a hypersensitivity to the infectious agent. The involvement may manifest as an optic nerve tubercle (Mansour, 1998) papillitis, papilledema, optic neuritis, retrobulbar neuritis, neuroretinitis, (Minton, 1956; Biswas et al 1999; Madhavan et al 2002), or opticochiasmatic arachnoiditis (Lamba et al 1986). Endophthalmitis and Panophthalmitis-generally has an acute onset and rapid progression with destruction of the intraocular tissues. Formation of choroidal and subretinal abscesses when left untreated, can undergo liquefaction necrosis with rapid multiplication of acid-fast bacilli and can eventually burst into the vitreous cavity (Dvorak-Theobald, 1958; Manthey et al 1982; Raina et al 2000). In panophthalmitis, however, the sclera is also involved, which may result in globe perforation. In advanced cases, scleral calcification may occur (Raina et al 2000).

Intraocular tuberculosis in the immune-compromised patient

Both M tuberculosis and atypical mycobacteria cause systemic and ocular morbidity, including massive choroidal infiltrates (Blodi et al 1989), choroidal nodules,vitritis (Desimone et al 2003) endophthalmitis, nonreactive choroidal tuberculoma (DiLoreto & Rao, 2001), choroiditis, (Zamir et al 2002), multifocal choroiditis (Lai et al 2002) and chorioretinitis (Recillas-Gispert et al 1997).

Diagnosis

Both diagnosis and treatment of active ocular tuberculosis are important in the prevention of blindness (Thompson & Albert, 2005). Diagnostic criteria for ocular tuberculosis encompass clinical findings, supportive systemic investigations, tuberculin skintest, positive response to empiric anti-tuberculosis treatment ,evidence of Mycobacterium tuberculosis or its DNA in ocular fluids/tissues and imaging. PCR has been shown to be a sensitive and highly specific technique (Bodaghi & LeHoang, 2000). Recent advances in diagnostic tools for tuberculous infection, including molecular biology techniques for detection of M tuberculosis DNA and interferon-gamma release assays, have improved the specificity of the diagnosis and the ability to ascertain exposure to the infectious agent (Bansal et al 2008) . Imaging of the posterior segment by fluorescein angiography, optical coherence tomography indocyanine green angiography and ultrasonography can help in outlining the lesions and their complications (Salman et al 2006). Endoretinal biopsy specimens may help in some cases (Cassoux et al 2005). However, the definition of what constitutes a case of tuberculosis may vary in different countries or in different regions of one country (Blumberg et al 2003). The large variations in clinical presentation and the lack of uniformity in diagnostic criteria make the diagnosis of intraocular tuberculosis difficult (Cunningham & Rathinam, 2001). Moreover, most of the investigations

are invasive, costly, and inaccessible to most patients. While the diagnosis of intraocular tuberculosis could pose a challenge in patients with HIV in the absence of molecular or other diagnostic tests as PPD test may be negative due to energy. These patients benefit from concomitant management by an infectious disease expert, and should not be managed by ophthalmologists alone.

Suggested guidelines for diagnosis of intraocular tuberculosis

Although several attempts have been made in the past to recommend guidelines for diagnosis of intraocular tuberculosis, these attempts could not provide well-defined criteria (Ustinova, 2001). Based on such laboratory investigations and clinical parameters, follow-up examinations and therapeutic response to ATT, there are few guidelines for the diagnosis of intraocular tuberculosis (Gupta & Gupta, 2005).

I. Clinical signs

Presence of features of any one of the following: uveitis, cyclitis , choroiditis retinitis ,retinal vasculitis, neuro-retinitis ,optic neuropathy, endophthalmitis and pan-ophthalmitis (Gupta et al 2007) . An intractable disease course with multiple recurrences on nonspecific treatment (corticosteroids) is a clue suggesting a possible tubercular etiology.

II. Ocular investigations

a. Demonstration of AFB by microscope or culture of M tuberculosis from the intraocular fluid/tissue-media-Although gold standard, process is prolonged and cumbersome, and it may not provide positive results because of the low yield of organisms

b. Positive polymerase chain reaction from intraocular fluids for IS 6110 or other conserved sequences in M. tuberculosis genome.

PCR is a sensitive and highly specific technique that can amplify mycobacteial DNA several-fold for easy detection. This is especially useful for intraocular fluids, as it can be performed with very small sample sizes, either aqueous (Gupta & Gupta, 2005), vitreous humor, subretinal fluid, or chorioretinal biopsy. It is extremely useful for the early diagnosis of intraocular tuberculosis (Arora et al 1999; Van Gelder, 2001). However, and major concerns exist with regard to false positivity and are thus not routinely recommended. Real-time PCR technology can differentiate commensals and contaminants from infecting microbes (Van Gelder, 2001). Patients diagnosed as tubercular uveitis, based on a positive PCR showed reduction in the number of recurrences on receiving anti tuberculosis treatment (ATT) (Gupta et al 1998). However, PCR analyses of ocular samples have poor sensitivities and require long processing time (Dinnes et al 2007).

III. Systemic investigations

a. Positive Mantoux reaction

Purified Protein Derivative/Mantoux Skin Test is the primary screening and diagnostic test and the only rapid diagnostic tool available since 1912 to aid the decision on whether to institute ATT. Abrahams & Schlaegel (1983) found this test significant for diagnosing tubercular uveitis and ocular hypersensitivity has been found to be directly related to cutaneous hypersensitivity (Woods et al 1938). Intracutaneous injection of purified protein derivative (PPD) or intermediate strength purified protein derivative (IPPD) is injected and delayed-type hypersensitivity is read within 48-72 hours. Infection by M.Tuberculosis is reflected by the positive PPD reaction (Sakai et al 2001). Any palpable induration measuring 10 mm or more is considered positive; 5-9 mm is doubtful which might also be due to cross-reactions caused by previous BCG vaccination in a person with normal immune responses leading to false-positive results. Lesion measuring less than 5 mm means a negative response in immunologically intact individuals. Repeat testing may also cause a booster effect and false-positive results. Hence, it is subjective and requires multiple visits, with many false-positive results and has a low specificity and sensitivity (Gupta et al 2007). Sub-conjunctival injection of PPD has been tried in past but is not in use currently (Tuovinen et al 1966).

b. Evidence of healed or active tubercular lesion on radiography of the chest

Chest radiography and computerized tomography

Although ocular tuberculosis may occur without evidence of pulmonary disease (Smith, 2003), the chest radiograph may provide evidence of active or

healed/primary or reactivated tuberculosis with consolidation, increased hilar densities, cavitation, fibrosis, and calcification (inactive disease) or rarely lymph node enlargement (Regillo et al 1991). A traditional lateral and PA view should be ordered in addition to the more sensitive apical lordotic view, which permits better visualization of the hyper oxygenated apices and increases the sensitivity of the chest X-ray for indolent or dormant disease. However, majority of chest radiographs are normal in TB uveitis (WHO Report, 2007; Tabbara, 2007). Computerized tomography of the chest and skeleton and cerebral MRI may be undertaken if there is a high index of clinical suspicion as these are more sensitive than radiograph. It scans to identify active lesions or lymph nodes in the body.

c. Evidence of confirmed active extrapulmonary tuberculosis (either by microscopic examination or by culture of the affected tissue for M tuberculosis).

Examination of Smear and Staining for Acid-Fast Organisms but at least 106 organisms/ml of sputum is required for detection on a smear (Biswas et al 1995).

IV. Exclusion of other uveitis entities

In the geographic regions where tuberculosis is low in incidence, other causes of uveitis must be excluded by various laboratory investigations including serology for syphilis, toxoplasmosis and others. Serodiagnosis has been used for detection of antibodies or antigens for both pulmonary and ocular tuberculosis (Sakai et al 2001) However, these tests are currently not preferred because of their low sensitivity and the high number of false-positive test results (Gupta et al 2006).

Enzyme-linked immunosorbent assay (ELISA) evaluates host immunoglobulin G (IgG) and immunoglobulin M (IgM) levels and can help identify recent infection but is not a particularly sensitive test.

V. Therapeutic test

A positive response to 4-drug ATT (isoniazid, rifampicin, ethambutol, and pyrazinamide) over a period of 4 to 6 weeks can be diagnostic. Therapeutic trial with single drug isoniazid should be avoided due to risk of development of resistance.

Other imaging tests

1. Fluorescein angiography

It is also useful for confirming the diagnosis of choroidal neo-vascular membrane or retinal angiomatous proliferation that may develop in the acute phase of choroidal tubercule formation or in an inactive lesion (Gupta et al 2006). Choroidal tubercles, choroidal tuberculomas, serpiginous-like choroiditis, retinal vasculitis, It is important to obtain images so that timely laser photocoagulation can be instituted.

2. Indocyanine green angiography

Indocyanine green angiography has been used to detect subclinical choroidal lesions in cases with presumed intraocular tuberculosis.

3. Optical coherence tomography

In a relatively clear media, OCT can help detect retinal pathologies such as subretinal neovascular membrane and CME (Tranos et al 2004).

4. Ultrasonography

It is useful for cases presenting with tuberculomas mimicking intraocular malignancy. Ultrasound of these large granulomas/ abscesses shows a moderate to low internal reflectivity on A-scan but may show a solid elevated mass lesion on B-scan (Gupta et al 2006).

5. Ultrasound bio-microscopy

This helps in studying the pars plana region by detecting the presence of a granuloma in this region

New diagnostic assays

Interferon-g release assays (IGRA)

It based on the in vitro assays that measure interferon-g released by sensitized T cells after stimulation by Mycobacterium tuberculosis antigens (Pai et al 2006). The newer antigens are more specific and are not shared with BCG vaccine strains or other species of Mycobacterium.11 but are not superior to the tuberculin skin test (TST) in sensitivity as a screening test or first-line study in TB-related uveitis. Two kits are available commercially: T-SPOT.TB test (Oxford Immunotec Ltd, Oxford, UK) and the QuantiFERON —TB GOLD (QFT-G:Cellestis Ltd, Carnegie, Australia) (Pai et al 2006)

The CDC has updated its guidelines suggesting that QFT-G can be used in place of tuberculin skin test for infection control and surveillance and conversion (latent infection) (Mazurek et al 2005). The UK National Institute for Health and Clinical Excellence has recommended a two-step strategy for diagnosing latent tuberculosis, in which the tuberculin skin test is done first and those who are positive or in whom the test is unreliable, should be further considered for IGRA (Pai et al 2006). QFT is more specific than the TST in identifying infections by Mycobacterium tuberculosis. Negative QFT tests should be interpreted with caution, because they do not exclude the diagnosis. Thus, it is important to interpret the QFT together with the TST and hence, the current clinical gold standard for diagnosing a presumed TB uveitis requires a positive TST and supportive clinical ocular findings (Marcus et al 2009).

Treatment

The management of OTB is complex, requiring a stringent public health strategy and high levels of patient adherence, combined with long courses of multiple anti-tuberculous medications.

Medical

M tuberculosis requires a bacteriocidal agent and a sterilizing agent, owing to the complex lifecycle of the tubercle bacilli, including a dormant, replicating, and intracellular phase. Isoniazid initially decreases bacterial load by bacteriocidal activity, while rifampin and pyrazinamide may be used for sterilization.

Drug Regimens for Treating Intraocular Tuberculosis
Drug regimens for ocular tuberculosis are similar to those for pulmonary or extrapulmonary tuberculosis (Kuruvilla, 2003). Ocular inflammation improves with systemic treatment. For the treatment of ocular tuberculosis, few studies have described a course of chemotherapy consisting of isoniazid and rifampicin for 9 months (Morimura et al 2002; Schlaegel & Weber, 1969). The CDC recommends the use of all four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) for an initial 2-Month period followed by a choice of different Options over next 4 to 7 months for treatment of Tuberculosis (Centers for Disease Control, 2003). Fixed-dose combinations of these agents have been tried. Although these may be convenient for the patient, such combinations may reduce the bioavailability of the agents (Bodaghi & Le Hoang, 2000). In patient from those regions where the incidence of primary resistance to isoniazid is more than 4%, and in those who come from regions with higher multidrug resistant strains, the use of a four-drug regimen should be followed by consultation with an internist who has expertise in the treatment of drug-resistant tuberculosis (Vrioni et al 2004). Directly observed therapy should be used whenever possible. Schlaegel (1969) used a single drug, isoniazid (INH) (300 mg/d) as a therapeutic trial for 1 month. Resistant strains of M. tuberculosis to isoniazid have been emerging hence; because of concern for resistance this method is no longer generally acceptable. Patients with a suggestive pattern of ocular inflammation and who have a recent skin test conversion, positive sputum cultures, chest x-ray, or systemic findings consistent with TB clearly warrant treatment of pulmonary TB. The American Thoracic Society recommends a 4-drug regimen for pulmonary TB. Isoniazid, rifampin, ethambutol, and pyrazinamide are taken for 2 months (first line drugs), at which point ethambutol and pyrazinamide are discontinued. In patients who cannot take ethambutol, this can be substituted with moxifloxacin 400mg orally once daily. Ethambutol is discontinued after 2 months to prevent optic neuropathy and ganglion cell loss. Isoniazid and rifampin are continued for an additional 4-7 months for a total duration of therapy of 6-9 months depending on the response to therapy.

The exact duration of treatment and the end point for stopping treatment for ocular tuberculosis is not known. The CDC recommends prolonged therapy for tuberculosis of any site that is slow to respond and thus the patients with intraocular TB may require prolonged therapy (Center for Disease Control, 2003). Patients with uveitis who have a suggestive pattern of ocular inflammation for TB, a positive TB skin test with no systemic associations, and negative chest x-ray and laboratory findings for TB found on extensive testing are controversial in their management. If the uveitis is severe, progressive, or difficult to manage with local immunosuppressive drugs , or in patients who have retinal vasculitis .systemic immunosuppressive drugs should be considered .Addition of anti-tubercular therapy to corticosteroids in uveitis patients with latent/manifest TB also leads to significant reduction in recurrences of uveitis (Bansal et al 2008). After the TB uveitis has clearly responded to antibiotic therapy, topical or depot corticosteroids may be considered to

decrease the local ocular inflammatory response and improve visual function. Oral corticosteroids are rarely required.

Immunosuppressive Agents Low-dose systemic corticosteroids used for 4 to 6 weeks, along with multidrug ATT may limit damage to ocular tissues caused from delayed type hypersensitivity. One should avoid using corticosteroids alone without concomitant ATT as the corticosteroids may promote multiplication of bacilli, leading to panophthalmitis (Biswas et al 1995) or they may cause a flare-up of systemic tuberculosis by activating a latent infection (Rosen et al 1990) and poor visual outcome. (Hamade & Tabbara, 2009). Topical therapy of anterior uveitis in patients with ocular tuberculosis consists of topical prednisolone acetate and cyclopentolate eye drops. For elevated intraocular pressure, topical beta blockers and carbonic anhydrase inhibitors may be given. Alpha agonists and prostaglandin analogues are avoided in uveitis patients but may be used if the intraocular pressure is not controlled by carbonic anhydrase inhibitors and betablockers. Rifabutin used for the treatment of pulmonary tuberculosis may in itself cause anterior uveitis (Skolik et al 2005).

Approach to uveitis patient with positive ppd requiring immune-modulatory agents

The anti-TNF biological treatment for uveitis or other autoimmune disorders can result in flare-ups of the latent tuberculosis infection; patients receiving anti-TNF agents should be tested with PPD. The proposed treatment regimens for latent tuberculosis (patients with positive PPD) are:

- Isoniazid 300 mg/day for 9 months,
- Isoniazid twice weekly at a dose of 15 mg/kg where daily treatment is not possible,
- Rifampicin daily for 4 months where isoniazid cannot be used, rifampicin with pyrazinamide daily for 2 months in situations where treatment period must be confined to 2 months. All these patients, irrespective of age, need treatment if the reaction to 5 tuberculin units of PPD is 10 mm or 5 mm in patients who are HIV positive, who have recent contact with an infected person, or show evidence of old tuberculosis on chest x-ray (Bates, 2004). The interaction of the human immunodeficiency virus (HIV) with TB may further complicate management (Madge & Prabhakaran, 2008).

Management of drug-resistant tuberculosis

MDR-TB is defined as tuberculosis that is resistant to isoniazid (INH) and rifampin. While, extensively drug-resistant tuberculosis (XDR-TB) is an enormous global public health problem with which tuberculosis is resistant to isoniazid, rifampin and three or more of the six second line anti-tuberculosis drugs. Recently the CDC has published that during 2000-2004, of 17,690 TB isolates, 20% were multidrug resistant and 2% were extensively drug resistant (XDR) that were resistant virtually to all second-line drugs (Centers for Disease Control and Prevention, 2006). Numerous factors, including poor compliance, improper drug regimen, and physician error in directing treatment or natural mutations, and often a combination of these factors may play a role in the development of drug-resistant tuberculosis (Harkin & Condos, 2004).

Use of multiple agents, with a minimum of three or four additional anti-tuberculosis agents for duration of 18 to 24 months, is recommended (Harkin & Condos, 2004). The additional agents include rifabutin, fluoroquinolones (Mohanty & Dhamgaye, 1993), interferon-g (Holland et al 1994) and linezolid (Harkin & Condos, 2004). In intraocular tuberculosis in the immune-compromised patient, the use of highly active anti-retroviral therapy (HAART) has been reported to show fast recovery of their CD4 counts with increased inflammatory response causing a

Dosage of anti-tubercular treatment

ATT	Adult dose	Paediatric dose
Isoniazid	5 mg/kg PO; not >300 mg/d	10-20 mg/kg/d PO; not >300 mg/d
Rifampin	600 mg PO/IV OD	10-20 mg/kg PO/IV; not >600 mg
Ethambutol	15 mg/kg PO OD	<13 years: 15-25 mg/kg/d >13 years: as in adults
Pyrazinamide	15-30 mg/kg PO OD	As in adults

Ocular side effects of anti-tubercular drugs

previously latent infection to become manifest (Zamir et al 2002). Sometimes, this immune recovery maybe directed against pathogen's residual antigens causing a severe systemic disease (Narita et al 1998). The effectiveness of retinalamine for the treatment of TB chorio-retinitis is under evaluation (Aleksandrova & Aleksandrov 2007).

The ethambutol toxicity is dose-related and is rare if the daily dose does not exceed 15 mg/kg. Ocular toxicity is experienced by less than 2% of patients receiving daily dose of 25 mg/kg or more of ethambutol (Albert et al 1999). This drug is known to cause optic neuritis, acquired red-green dyschromatopsia (Rizzo, 1993), scotomas, disk edema, disk hyperemia (Barron et al 1974), peripapillary splinter haemorrhages, optic atrophy, and rarely, retinal edema and foveal pigmentary changes. Toxicity is reported to be mediated through an excitotoxic pathway whereby the drug disturbs the mitochondrial function; and its toxicity depends on decreased ATPase activity and mitochondrial homeostasis (Heng et al 1999). The optic neuritis is abrupt in onset and is generally seen at 3—6 months of the onset of treatment. All these patients should have a baseline ophthalmic examination including visual acuity, visual field, and color vision. These patients should be examined every 2 to 4 weeks, whereas for lower doses, follow-up every 3-6 months is adequate. In case of any ocular side effect, the drug should be stopped immediately; following which the vision should improve within 10— 15 weeks. In cases where vision does not improve following discontinuation of therapy, parenteral hydroxycobalamine, 40 mg/day over a 10- to 28-week period should be considered. Majority of symptoms resolve over a period of 3—12 months, although permanent visual loss is also known to occur. Use of ethambutol in children is generally avoided. Isoniazid has only rarely been reported as a cause of optic neuritis and optic atrophy (Kass et al 1957). Rifabutin, a spiropiperidyl derivative of rifamycin, is more effective than rifampicin against slow-growing mycobacteria, including M. avium-intracellulare, and has been extensively used in HIV-infected patients. This agent, especially when combined with clarithromycin or fluconazole, can cause severe acute anterior uveitis, including hypopyon uveitis (Fineman et al 2001), corneal endothelial deposits (Golchin & McClellan, 2003) and inflammatory vitreous exudates and opacities (Khan et al 2000). However, the drug-induced intraocular inflammation responds well to topical corticosteroids.

Systemic side effects of ATT

Close follow-up and monitoring of the liver function tests and renal function are also mandatory. Pyrazinamide can lead to hepatotoxicity and increase in uric acid levels. Rifampin may interact with other drugs and may lead to acceleration of the clearance of several drugs such as warfarin, corticosteroids, estrogens, ketoconazole, cyclosporine, oral hyperglycaemic agents and protease inhibitors. Rifampin can potentiate the action of neuromuscular blocking agents. Isoniazid on the other hand, may cause hepatotoxicity and peripheral neuropathy, which can be inhibited by the intake of 50mg of pyridoxin. Pyridoxin is recommended for HIV infected patients, alcoholics and patients who have diabetes mellitus or malnutrition. Isoniazid interacts with theophyline, benzodiazepine and warfarin. When correctly identified and aggressively treated, TB uveitis can be managed successfully with elimination of inflammation and preservation of visual function.

Surgical management

Generally, surgery is not required in treating ocular TB and is usually directed to treating adverse effects of disease or treatment for the rehabilitation of vision. Cataract surgery should not be performed in a patient with tuberculous uveitis until all inflammation has been completely controlled for at least 3 months. Younger patients, noncompliant patients, and patients with severe ocular damage should be cell free for 6 months prior to elective surgery.

Standard cataract procedures should be used to maximize outcome, using modern small incision, phaco techniques and in-the-bag placement of the intraocular lens (IOL). Bio-inert materials like acrylic and hydrophilic materials are usually preferred. Concomitant pars plana vitrectomy maybe required. Vitreous gel is believed to provide capacitance for inflammatory debris, cells, and mediators. Removal of the core vitreous, therefore, may benefit patients with uveitis by reducing the need for long-term inflammatory medications. There is one report of pars plana vitrectomy with full-thickness eye wall resection for managing tuberculous granuloma (Gopal et al 2003).

Conclusion

Tuberculosis (TB) is an infectious disease responsible for significant morbidity and mortality worldwide. Ocular tuberculosis may occur in the absence of pulmonary disease. Patients present with a spectrum of clinical signs. Polymerase chain reaction is of paramount importance in diagnosing primary ocular tuberculosis. The detection of anti-cord factor antibody via enzyme-linked immunosorbent assay (ELISA) is another new diagnostic method. Drug regimens for ocular tuberculosis are similar to those for pulmonary or extra-pulmonary tuberculosis.

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