

Clinical description and treatment of patients with presumed ocular tuberculosis in São Paulo, Brazil. Retrospective study

Aspectos clínicos e tratamento de pacientes com tuberculose ocular presumida em centro de referência de São Paulo, Brasil. Estudo retrospectivo

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ABSTRACT

Purpose: To analyze and describe the therapy used in presumed ocular tuberculosis in a referral center in São Paulo, Brazil. **Methods:** Retrospective, descriptive study. Fisher's exact test was performed when appropriate. **Results:** The most common complaint was low visual acuity (83.1%), followed by generalized ocular pain (25.3%) and blurred vision (22.8%). Posterior uveitis was the most common presentation (35.7%). Treatment consisted of the currently recommended association of rifampin, isoniazid, pyrazinamide, ethambutol (RHZE) regimen. Oral prednisone was included in the treatment of 37 patients for acute inflammation, although it did not significantly decrease the prevalence of chronic complications compared to full recovery ($p = 0,1$). Early diagnosis (< 70 days) was associated with higher rates of full recovery ($p = 0.005$). No statistical significance was observed when comparing 6 to 9-month therapy ($p = 0.7$). **Conclusion:** Tuberculous uveitis can be treated with a 6-month duration RHZE therapy. A brief course of steroids may improve acute symptoms, although it did not reduce long-term disabilities.

Keywords: Ocular tuberculosis/drug therapy; Uveitis/drug therapy; Tuberculin; Steroids/therapeutic use

RESUMO

Objetivo: Descrever aspectos clínicos e esquema terapêutico dos pacientes com tuberculose ocular presumida tratados em um centro de referência em tuberculose de São Paulo. **Métodos:** Estudo retrospectivo descritivo. O teste exato de Fisher foi realizado quando apropriado. **Resultados:** A queixa mais comum foi baixa acuidade visual (83,1%), seguida por dor ocular generalizada (25,3%) e visão turva (22,8%). A uveíte posterior foi a apresentação mais comum (35,7%). O tratamento consistiu no esquema atualmente recomendado de rifampicina, isoniazida, pirazinamida e etambutol (RHZE). A prednisona oral foi incluída no tratamento de 37 pacientes, para tratamento da inflamação aguda, embora não tenha diminuído a prevalência de complicações crônicas, em comparação com a recuperação completa ($p = 0,1$). O diagnóstico precoce (< 70 dias) foi associado a maiores taxas de recuperação total ($p = 0,005$). Não houve significância estatística quando se comparou a terapia de 6 a 9 meses ($p = 0,7$). **Conclusão:** A uveíte tuberculosa pode ser tratada por uma terapia com duração de seis meses. Um breve curso de esteroides melhora os sintomas agudos, embora não reduza as complicações a longo prazo.

Descritores: Tuberculose ocular/tratamento farmacológico; Uveíte/tratamento farmacológico; Tuberculina; Esteroides/uso terapêutico

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INTRODUCTION

Mycobacterium tuberculosis infection is still a notable concern in developing countries, representing a major cause of uveitis in Brazil.^(1,2) This mycobacterium mainly invades the lungs, but it can affect any organ usually through hematogenous spread or hypersensitivity reactions.

Extrapulmonary tuberculosis (EPTB) is defined by any evidence of tuberculosis without pulmonary radiographic abnormalities.⁽³⁾ Ocular tuberculosis (OT) manifests as primary disease (when the eye is the initial focus of infection) or secondary disease (when the ocular involvement occurs via hematogenous route - cases in which there may be concomitance of other sites of involvement).^(4,5) The eye is a rare extrapulmonary localization of tuberculosis (TB): it occurs in 1 to 2% of systemic tuberculosis cases.⁽⁶⁾ Lee⁽⁷⁾ described EPTB patterns seen in Korea, although there was no ocular manifestations. When considering the eye, mycobacterium seems to affect the most vascularized areas of the eye such as the uvea due to its vascular content and oxygen supply.⁽⁸⁾

When infection affects the anterior uvea, patients may also have concomitant signs of conjunctivitis, keratitis, and scleritis.^(9,10) When it affects the posterior uvea, patients may often have choroiditis, retinal vasculitis, and optic nerve damage.⁽¹¹⁻¹³⁾ Studies have shown that choroidal tubercles are the most common pattern of ocular inflammation in this infection,^(14,15) besides presenting a positive correlation in patients with HIV, as has been proposed in the past.⁽¹⁶⁾

Diagnosis can be very difficult, and is often established by the absence of other alterations⁽¹⁷⁾ or presumably.⁽¹⁸⁾ When associated, clinical history of prior contact, positive skin test for tuberculosis (PPD), and eye lesion with presence of mycobacterial infection anywhere in the body indicate the need for immediate treatment as specific therapy with antituberculosis and corticosteroid medications take time to work. Common infections that can induce visual dysfunction and are often associated with TB such as cytomegalovirus, toxoplasmosis and syphilis should also be evaluated, and treatment should be appropriate for each case.

METHODS

Retrospective descriptive study in which data was collected from eighty-three (83) medical records (166 eyes) of patients treated at Instituto Clemente Ferreira (tertiary tuberculosis referral center in the city of São Paulo, Brazil), and at the Department of Ophthalmology, Universidade Federal de São Paulo from 2010 to 2013. Data was collected and analyzed to describe the clinical features observed at the ophthalmic examination, which included corrected visual acuity, applanation tonometry, biomicroscopy (cells, flare, pKs), and retinal mapping. Data regarding the description of lesions (when present), therapeutic options, and resolution of ocular tuberculosis were also considered.

Inclusion criteria were based on the presence of eye lesions suggestive of TB, and confirmed by ophthalmic examination, PPD greater than 10 mm, alterations in chest X-ray and high-resolution computed tomography, considering the presence of immunosuppression or previous history of contact with TB. PPD results greater than 15 mm were considered positive for all cases.

Patients diagnosed with another infectious disease (proven by serology) and those with negative PPD or incomplete medical records were excluded. Frequency comparison and Fisher's exact test were carried out when appropriate.

The present study adheres to the principles of the Declaration of Helsinki, and was approved by the ethics committee of Instituto Clemente Ferreira, which waived the consent form as it was a retrospective study.

RESULTS

The most common complaint was low visual acuity (LVA), present in 69 patients (83.1%), followed by generalized eye pain (25.3% - 21), and blurred vision (22.8% - 16). Other symptoms were also described in 34 patients, and are presented in table 1.

Table 1
Signs and symptoms

Signs and symptoms	% and No.
Ocular hyperemia	14 (37.8)
Photophobia	9 (24.3)
Burning eyes	3 (8.1)
Eyelid nodule	2 (5.4)
Ptosis and eyelid edema	2 (5.4)
Itching	2 (5.4)
Diplopia	2 (5.4)
Floaters	2 (5.4)
Excessive tearing	1 (2.7)
Ocular foreign body sensation	1 (2.7)
Total	34 (100)

Patients were evaluated according to history of exposure to Mycobacterium tuberculosis, and only 12% reported a source of infection, whereas 59% reported no apparent exposure, and 28.9% provided no information. The age distribution is shown in table 2.

Table 2
Age distribution

Age (years)	% and No.
≤ 20	4 (4.81)
21- 40	31(37.3)
41- 60	34 (40.9)
61- 80	3 (14.4)
≥ 81	2 (2.4)
Total	84 (100)

The average age (and standard deviation) of the affected patients was 46 ± 14.4 years (range: 16 to 82 years), and the average area of PPD induration was 25.2 ± 6.58 (range 10 to 39 mm).

Forty-six (55%) patients had bilateral ocular lesions in the initial assessment or during the course of active infection, while 37 (45%) patients had unilateral lesions.

Almost all patients (82 patients comprising 98.7% of all patients) were treated with the currently prescribed antituberculous therapy, i.e., the fourfold regimen of rifampicin, isoniazid, pyrazinamide and ethambutol. Only one patient (1.2% of total) received another unspecified treatment. Treatment

duration was 6 months for 11 patients (13.2%), 9 months for 46 patients (55.4%), and 12 months for 21 patients (25.3%). Five patients (6%) were not included due to loss of follow-up. In addition to the currently indicated antituberculous therapy, patients were also evaluated for concomitant use of oral prednisone in decreasing doses over 6 weeks from 60 mg per day. This same oral corticosteroid therapy scheme was repeated with new evidence of ocular inflammation, along with the investigation of another possible alternative diagnosis. Only 37 patients (44.5%) were thus prescribed in writing, whereas 43 patients (51.8%) were advised to attend the clinic where they were medicated by trained staff. No information on the form of prescription was available for three patients (3.6%).

Table 3
Frequency of eye lesions

Lesion described	% and No.
Posterior uveitis	28 (35.7)
1) <i>Choroid granuloma</i>	15 (19.2)
2) <i>Retinal vasculitis (± vitreous hemorrhage)</i>	10 (12.8)
3) <i>Multifocal chorioretinitis</i>	2 (2.5)
4) <i>Macular granuloma</i>	1 (1.2)
Anterior Uveitis	26 (33.2)
1) <i>Granulomatous</i>	16 (20.5)
2) <i>With iris granuloma</i>	6 (7.6)
3) <i>With posterior synechia</i>	4 (5.1)
Intermediate uveitis	7 (8.9)
1) <i>Posterior cyclitis</i>	4 (5.1)
2) <i>Non-specific</i>	3 (3.8)
Anterior scleritis	5 (6.4)
Interstitial keratitis	5 (6.4)
Granulomatous panuveitis	2 (2.5)
Undetermined uveitis	2 (2.5)
Optic neuritis	1 (1.2)
Peripheral retinal detachment	1 (1.2)
Eyelid granuloma	1 (1.2)
Total	78 (100)

The frequency of the lesions is shown in table 3 according to the ophthalmic examination.

Five patients were not included in the final total percentage due to the absence of a complete ophthalmic examination.

The therapeutic response was assessed by four parameters:

1. Improved visual acuity measured at a distance of at least 20 feet or 6 meters.

2. Improvement of ocular pain.

3. Reduction of inflammatory reaction in the anterior chamber or regression of posterior segment lesions.

4. In those individuals with pulmonary tuberculosis, by regression of chest X-ray and / or high-resolution computed tomography findings.

After follow-up, 51 patients (60.2%) had complete recovery (according to the 4 criteria above), while 27 patients (39.7%) had a chronic complication (sequela), defined as lasting for more than 6 months after termination of treatment, and summarized in table 4.

Table 4
Long term complications

Reported sequelae	% and No.
Persistent low visual acuity	
1) Irreversible Causes	10 (37)
2) Posterior subcapsular cataract	3 (14.8)
3) Nuclear cataract	2 (7.4)
4) Macular scar	2 (7.4)
Persistent itching	6 (22.2)
Chronic conjunctivitis	4 (14.8)
Eye bulb atrophy	1 (3.7)
Total	28 (100)

Persistent worsening of visual acuity was defined as worsening of visual acuity measured compared with acuity measured at initial presentation also at 6 meters away. In assessing the percentage of sequelae, patients diagnosed 70 days before onset of symptoms were less prone to have any complications described in Table 4 (44%) compared with those diagnosed later (55% - $p = 0.005$). Corticosteroids were effective in reducing symptoms of acute complaints, especially visual acuity and eye pain, although they were not significantly effective in reducing the incidence of long-term stratified sequelae ($p = 0.1$). Three patients required a new course of prednisone beyond the initial one, although no other diagnosis was found.

When comparing the treatment duration of 6 months versus 9 months, no significant difference was found ($p = 0.7$). Interestingly, the occurrence of long-term sequelae was higher in those with unilateral ocular disease compared with those with bilateral disease ($p = 0.03$).

DISCUSSION

Intraocular tuberculosis is uncommon, and its occurrence depends on the population studied.⁽¹⁹⁻²¹⁾ Primary eye infection is rare, and usually affects the anterior external segment, such as the conjunctiva, eyelid, sclera, and cornea. Posterior and internal segments of the eye such as optic nerve, retina, choroid and intraocular content were associated with secondary disease.

Although most of the lesions described in the present study suggest hematogenous dissemination, since granuloma formation points to this assumption.⁽²²⁾ Our data also describe corneal and external lesions in a few patients suggesting a possible cause of direct implant of microorganisms or possibly due to the hypersensitivity reaction triggered by a distant site,^(23,24) since vascular lesion is more associated with the latter. In addition, the frequency of injuries has been most commonly described as unilateral disease,⁽²⁵⁾ while the present study found a higher frequency of bilateral ocular injuries.

The definitive diagnosis is still quite difficult to be made as it involves delicate intraocular structures, and sometimes a direct histopathological examination is impossible.⁽²⁶⁾ Even when possible, cultures do not provide results fast enough for the immediate onset of a specific therapy.

Studies show that the lack of uniform diagnostic criteria further delays this process.^(27,28) Therefore, the diagnosis remains presumed in most cases.

Various molecular and biochemical techniques are being used for this purpose. Polymerase chain reaction of intraocular fluids was used in the past, but its sensitivity has been considered low.^(29,30) The interferon-gamma release assay (IGRA) has become increasingly used due to its satisfactory specificity and sensitivity.^(31,32)

Although these tests are not enough for a definitive diagnosis, the diagnostic accuracy increases when associated with clinical signs or positive PPD.^(33,34) No molecular tests were carried out at our service. Patients were evaluated for clinical symptoms along with positive PPD, ophthalmic examination, chest x-ray, history of close contact with an active TB patient, good response to treatment, and exclusion of other potential causes.

This retrospective study showed a higher frequency of cases in women than in men, agreeing with previous reports⁽³⁵⁻³⁷⁾ in which the female gender is a possible risk factor for EPTB.

According to Lara et al.,⁽³⁸⁾ 5 of the 7 confirmed cases of ocular tuberculosis affected patients between 61 and 80 years. In our service, however, the majority of cases was observed in patients between 41 and 60 years (40.9%), followed by patients between 21 and 40 years (37.34%), which may indicate that ETPB is associated only with immunosenescence, as previously mentioned.⁽³⁹⁾ In contrast, young age seems to be an independent risk factor.⁽³⁶⁾

Most of the eye lesions described herein consist of focal or diffuse choroidal granulomas. Interestingly, anterior uveitis was also quite frequent, almost reaching the same ratio. Other studies^(40,41) reported panuveitis as the most common initial presentation. However, in the present study it was observed only in 2 patients (2.5%).

Possible causes of associated LVA were nuclear (7.4%) and posterior subcapsular (14.8%) cataracts, retinal vasculitis (12.8%) macular scar (7.4%), macular granuloma (1.2%), multifocal chorioretinitis (2.5%), anterior uveitis (33.2%), intermediate uveitis (8.9%), granulomatous panuveitis (2.5%), undetermined uveitis (2.5%), scleritis (6.4%), interstitial keratitis (6.4%) and optic neuritis (1.2%). Anterior uveitis, cataract, and retinal vasculitis were the most important causes of LVA, in agreement with the literature.^(8,42)

Lou et al.⁽⁴³⁾ compared the opinions of experts from developed and under development countries on the duration of ocular tuberculosis treatment, and found that 6-month and 9-month therapies were the most common treatment durations, although the latter prevailed. A retrospective study⁽³⁷⁾ compared different treatment durations, and observed a better outcome lasting at least 9 months, which leads to a lower recurrence of inflammation. In our analysis, when comparing the final outcome (full recovery versus sequelae), no significance was observed between 6-month and 9-month treatments.

Bansal et al.⁽⁴⁴⁾ proposed a typical regimen of oral corticosteroids and antituberculosis drugs for the treatment of ocular tuberculosis, although Shoughy et al.⁽⁴⁵⁾ state that the latter is sufficient for the complete resolution of sclerokeratitis.

Complete recovery seems to be associated with early diagnosis.⁽⁴²⁾ Twelve out of sixteen patients with persistent low visual acuity were diagnosed 70 days after the initial presentation.

Five patients developed cataract during or after prednisone therapy, although it was not possible to determine the true etiology since prolonged uveitis is also a cause of cataract. The standard phacoemulsification surgical procedure with

intraocular lens implantation for these patients seems safe, and can be properly performed.⁽⁴⁰⁾

Recommendations for corticosteroid therapy are still confusing. Few studies show positive results, but should not be used as a single therapy as there is a risk of recurrent inflammation.⁽⁴⁶⁻⁴⁸⁾ This is practically not the case when antituberculosis drugs are associated. The latter appear to decrease antigen loading and attenuate hypersensitivity reactions.^(49,50) The use of steroids is recommended in cases of risk to the macula, as the benefits overcome the possible adversities and reduce the risk of macular scars.⁽⁵¹⁾ Prednisone seems to decrease acute symptomatology, and no adverse events have been reported in our patients, although it has not reduced the occurrence of long-term complications.

Active ophthalmic surveillance shall be considered for high-risk patients, such as HIV-positive and EPTB patients, as it is possible for ocular inflammatory lesions without symptoms to occur, which was also observed in a cross-sectional study of HIV patients co-infected with multidrug-resistant tuberculosis when submitted to eye examination.⁽³⁸⁾ In addition, it should be noted that additional infections may commonly manifest with intraocular lesion mimicking lesions observed in ocular tuberculosis such as toxoplasmosis, syphilis and cytomegalovirus.

CONCLUSION

Due to the devastating results of untreated extrapulmonary tuberculosis and the high relative prevalence of chronic complications observed in our service, complete early ophthalmic surveillance with careful monitoring should be indicated for high-risk patients to avoid further morbidity.

Ocular tuberculosis is difficult to be diagnosed but should always be considered in cases of uveitis of unknown origin to allow treatment as soon as possible.

A brief course of oral prednisone seems to accelerate resolution and improve acute symptoms, and the minimum duration of treatment should be at least 6 months, although comparison of larger groups is required for further conclusion.

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