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ANTI-TUBERCULOSIS TREATMENT IN PRESUMED OCULAR TUBERCULOSIS PATIENTS WITH GRANULOMATOSIS OCULAR PATHOLOGIES: SINGLE CENTER EXPERIENCE FROM TURKIYE

GRANÜLOMATOZ GÖZ PATOLOJİSİ SAPTANARAK GÖZ TÜBERKÜLOZU KABUL EDİLEN HASTALARDA ANTİTÜBERKÜLOZ TEDAVİ: TÜRKİYE TEK MERKEZ DENEYİMİ

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ABSTRACT

Objective: Ocular tuberculosis is still considered to be a controversial issue in terms of both terminology and diagnostic criteria and treatment options. There is no common diagnostic/treatment algorithm even though new approaches exist.In this study, the results of the treatment of "presumed ocular tuberculosis patients" are evaluated.

Materials and Methods: Anti-tuberculosis treatment was given to cases who had latent tuberculosis infection, had no other diagnosis and who did not respond to steroid treatment. These cases were considered to have presumed ocular tuberculosis.

Results: Sixty four cases who were considered to have "presumed ocular tuberculosis" received anti-tuberculosis treatment for a minimum of three months and were followed up regularly. The 64 cases were made up of 32 women and 32 men, with a mean age of 42.1±12.09 years. Mean antituberculosis treatment duration was 8.18±2.17 months (3-15 month). After the treatment, 47 (73.4%) of 64 patients reported improvement in vision. Only 36 of these 64 cases (31 bilateral, 5 unilateral, 67 eyes in total) were evaluated with objective vision test before and after the treatment. Disease involvement was uveitis (anterior, intermediate, posterior, panuveitis) in 61 eyes (91%), and retinal vasculitis in 6 eyes (9%). According to the vision analysis among 67 eyes, 42 (62.7%), visual acuities were detected to be improved

ÖZET

Amaç: Göz tüberkülozu hem terminoloji, hem tanı kriterleri hem de tedavi seçenekleri açısından halen tartışmalı bir konu olarak kabul edilmektedir. Yeni yaklaşımlar olmasına rağmen ortak bir tanı/tedavi algoritması bulunmamaktadır. Bu çalışmada "Göz tüberkülozu hastalarının" tedavi sonuçları değerlendirilmiştir.

Gereç ve Yöntem: Latent tüberküloz enfeksiyonu olan, başka tanısı olmayan, steroid tedavisine yanıt vermeyen ve göz tüberkülozu düşünülen olgulara antitüberküloz tedavisi verildi.

Bulgular: Göz tüberkülozu düşünülen ve en az üç ay süreyle antitüberküloz tedavisi gören ve düzenli takipleri yapılan 64 olgu (32 kadın, 32 erkek, ortalama 42,1±12,09 yıl) değerlendirildi. Ortalama antitüberküloz tedavi süresi 8,18±2,17 ay (3-15 ay) idi. Tedaviden sonra 64 hastanın toplam 47'si (%73,4) görmesinde iyileşme bildirdi. Bu hastaların sadece 36'sında (31 bilateral, 5 tek taraflı, toplam 67 göz) tedavi öncesi ve sonrası objektif görme değerlendirmesi yapılabildi. Bu hastalarda hastalık tutulumu 61 gözde (%91) üveit (ön, orta, arka, panüveit), 6 gözde (%9) retinal vaskülitti. Altmış yedi gözde yapılan görme analizine göre, 42 (%62,7)'sinin görme keskinliklerinde değişken düzeylerde iyileşme tespit edildi. Ortalama sağ göz görme keskinliği tedavi öncesi 0,56±0,049, tedavi sonrası 0,71±0,047 idi (p<0,001). Ortalama sol göz görme keskinliği tedavi öncesi 0,60±0,51, tedavi sonrası 0,73±0,043 idi (p<0,004).

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at variable levels. Mean right eye visual acuity was 0.56±0.049 before treatment, and 0.71±0.047 after treatment (p<0.001). Mean left eye visual acuity was 0.60±0.51 before treatment, and 0.73±0.043 after treatment (p<0.004).

Conclusion: In the presence of latent tuberculosis infection, successful results can be obtained with antituberculosis treatment for cases diagnosed as presumed ocular tuberculosis.

Keywords: Extra-pulmonary tuberculosis, granulomatosis ocular pathologies, ocular tuberculosis

Sonuç: Latent tüberküloz enfeksiyonu varlığında göz tüberkülozu düşünülen olgularda antitüberküloz tedavisi ile başarılı sonuçlar alınabilir.

Anahtar Kelimeler: Ekstrapulmoner tüberküloz, granülomatöz göz patolojileri, göz tüberkülozu

INTRODUCTION

Tuberculosis is one of the top 10 causes of death worldwide. In 2020, 9.9 million people had tuberculosis, and 1,3 million died from the disease. Globally calculated tuberculosis incidence is 127 per 100.000. According to WHO's data, in 2020, 15% of 6.624.523 tuberculosis cases reported worldwide had extra-pulmonary tuberculosis (1). Turkiye is among the countries with medium tuberculosis incidence. According to the data of the Turkish Ministry of Health, tuberculosis incidence was 10.6 per 100.000 in 2020 in Turkiye. Of these patients, 34.3% were reported to have extra-pulmonary tuberculosis (2). Among the patients with tuberculosis, there are studies reporting eye involvement ranging from 1.4% to 18% (3-5). The reason of these differences is that there is no standardized diagnostic criteria. Furthermore, tuberculosis incidence of the country or the region is important for the cross-sectional studies searching the tuberculosis frequency among all uveitis cases. The ratio varies between 1-4% in the countries with low tuberculosis incidence, while it is between 10-26% in the countries with high tuberculosis incidence (6). In a study conducted in our country, this rate was 1.3% (7).

Clinically, intraocular tuberculosis may be due to direct infection or indirect immune-mediated hypersensitivity response to mycobacterial antigens when there is no defined active systemic lesion elsewhere or the lesion is thought to be inactive. Choroidal tubercles and tuberculomas are reported to be the most common intraocular manifestations of tuberculosis (8). However, tuberculous uveitis is a hardly diagnosed disease since its symptoms imitate uveitis of different etiology, and since it is hard to obtain materials for microbiologic and pathologic examination. Tuberculous uveitis is a vision-threatening disease that inevitably leads to blindness if not properly diagnosed and treated (9).

On the other hand, ocular tuberculosis is still considered to be a controversial issue in terms of both terminology and diagnostic criteria and treatment options (8, 10). There is no common diagnostic/treatment algorithm even though new approaches exist (11). In this study, the clinical approach that we used for defining presumed ocular tuberculosis and the treatment results of the cases with ocular tuberculosis were evaluated.

MATERIALS AND METHODS

All patients with suspicion of ocular tuberculosis who were referred from the Istanbul Medical Faculty Ophthalmology Department of Istanbul University to the Pulmonology Department of Istanbul University between 2008-2016 were evaluated. All the subjects voluntarily signed their informed consent. The study was carried out according to the principles of the Helsinki Declaration. It was approved by Istanbul Medical Faculty Ethical Committee of Istanbul University (Date: 11.06.2018, No: 738).

All patients were asked whether they previously had active tuberculosis or not, and had close contact history with a tuberculosis patient. Tuberculin skin test (TST) and/or Quantiferon test, chest X-ray and if needed computerized thorax tomography were performed in all patients. Non - tuberculosis infections (HIV, fungal infections etc., sarcoidosis, connective tissue diseases, and vasculitis were investigated, and such patients were excluded. Surgical biopsy, bronchoscopic transbronchial lung biopsy and/or transtracheal/transbronchial lymph node aspiration were performed in patients in which sarcoidosis and tuberculosis cannot be differentiated.

Patients with sarcoidosis, active tuberculosis of any organ other than the eye or patients who did not have tuberculosis infection were excluded. Patients with latent tuberculosis infection who did not have any other pathology explaining the ocular involvement and who did not respond to previously given prednisolone and/or other immunosuppressive therapies were given 9-month anti-tuberculosis treatment (ATT). Of these patients, the ones who received treatment for at least three months were evaluated.

The objective response to the treatment of tuberculosis was evaluated by testing visual acuity before and after the ATT. The visual acuity was compared separately for both eyes. Patients who underwent treatment and had follow-up data of pre-treatment and post-treatment were analyzed.

Statistical analysis

Statistical evaluations were performed using SPSS (Statistical Package Social Science 21.0 package program). Descriptive values were given as mean, standard deviation, median and minimum-maximum. Categorical variables were expressed as number of cases and percentage value. Whether continuous variables were appropriate to normal distribution or not were analyzed using Shapiro–Wilktests. Wilcoxon test was used to compare the changes in right and left visual acuity before and after the ATT. A p value <0.05 was considered as statistically significant.

RESULTS

We evaluated 104 patients who were referred to our Outpatient Clinic of Pulmonary Diseases with the diagnosis of presumed ocular tuberculosis. Of the 104 patients evaluated, 40 were excluded because of sarcoidosis, presence of active tuberculosis in lung or extrapulmonary involvement than the eye. The remaining 64 (61.5%) cases were given ATT with the clinical diagnosis of presumed ocular tuberculosis.

Clinical parameters and treatment response of these patients who received ATT and underwent regular follow-up were evaluated. Demographic and clinical characteristics of 64 cases were given in Table 1. Of those 64 patients, 32 (50%) were female and 32 (50%) were male, and the mean age was 42.1±12.09 years (18-69 years). The mean disease duration was 8.64±6.99 months (1-31 months). Nonspecific minimal sequel changes in chest X-ray and/or thoracic computed tomography (CT) were present in most of the cases (60.9%, n=39). There were no radiological clinical signs of active tuberculosis.

Table 1: Demographics and clinical findings of the patients

	n=64
Age (year) Mean±SD	42.19±12.09
Gender (Female/male) (n)	32/32
Disease duration (month) Mean±SD	8.64±6.99
TST (mm) Mean±SD	19.28±4.58
ATT duration (month) Mean±SD	8.18±2.17
Quantiferon positivity (n, %)	64 (100%)
Bilateral disease/unilateral (n, %)	33/31 (51%/48.4%)
Sequel lesion in chest X-ray and/or Thoracic CT (n, %)	39 (60.9%)
Tuberculosis contact (n, %)	18 (28.1%)
Tuberculosis history (n, %)	7 (10.9%)
Immunosuppressive treatment history (n, %)	62 (96%)
Hepatotoxicity (n, %)	2 (3.1%)
Patient subjective treatment response (n, %)	47 (73.4%)

TST: tuberculin skin test, ATT: anti-tuberculosis treatment, CT: Computed tomography

Approximately one third (28%, n=18) had contact with active tuberculosis, and 7 (10.9%) had a history of tuberculosis. TST values of all patients were ≥10 mm, and the mean TST values were 19.28±4.58 mm (10-32mm). Quantiferon TB test was performed in 64 (100%) cases, and all were positive. In all of the nine cases in which interferon-gamma release assay (IGRA) test could not be performed, TST was ≥10mm, and in 7 of them it was ≥15mm (77%).

Sixty two cases (96.8%) were previously treated with corticosteroids (local and/or systemic) and other immunosuppressive therapies (azathioprine, methotrexate, etc.) before the treatment of tuberculosis, and there was no response to these treatments. Two patients received concomitant steroid and ATT. Treatment decision was based on the presence of typical findings of tuberculosis such as choroidal tubercles, exclusion of other diseases and the presence of latent tuberculosis infection. Duration of ATT was 8.18±2.17 month (3-15 month). Treatment was stopped in 3 and 5 months due to the hepatotoxicity in 2 cases (3.1%). ATT was given at least for 6 months in other cases.

After treatment, 47 of 64 patients (73.4%) reported improvement in vision. Objective visual evaluation was performed in 36 of 64 patients (31 bilateral, 5 unilateral, a total of 67 eyes) before and after treatment.

Eye involvement type of 36 patients (31 bilateral, 5 unilateral total 67 eyes) who had complete visual acuity evaluation before and after treatment was uveitis (anterior, intermediate, posterior, panuveitis) in 61 eyes (91%), and retinal vasculitis in 6 eyes (9%) (Table 2). Mean visual acuity of the right eyes was 0.56±0.049 before the treatment, and 0.71±0.047 after the treatment (p<0.001). Mean visual acuity of the left eyes was 0.60±0.51 before treatment, and 0.73±0.043 after treatment (p=0.004) (Table 3). Visual acuity was improved in 42 (62.7%) of 67 eyes at any level. There was no significant difference between the types of ocular involvement in terms of treatment response.

Table 2: Ophthalmologic findings of the eyes with possible ocular tuberculosis

Ophthalmologic findings of 67 eyes	n, (%)
Anterior uveitis	5 (7.5%)
Intermediate uveitis	5 (7.5%)
Posterior uveitis	23 (34%)
Panuveitis	28 (42%)
Vasculitis	6 (9%)

Table 3: Pre-treatment and post-treatment visual acuities

	Right eye (n=33) Mean±SD; Median (Min-Max)	Left eye (n=34) Mean±SD; Median (Min-Max)
Pre-treatment	0.54±0.34; 0.50 (0.05-1.0)	0.60±0.35; 0.75 (0.05-1.0)
Post-treatment	0.67±0.34; 0.80 (0.05-1.0)	0.70±0.31; 0.85 (0.10-1.0)
p value	0.002	0.02

DISCUSSION

This study reveals that anti-tuberculosis treatment may be successful in presumed ocular tuberculosis cases where active clinical tuberculosis is not detected and the presence of latent tuberculosis infection is shown.

Because of epidemiological differences and the differences in definition, the rate of detection of ocular tuberculosis within tuberculosis cases and in cases with uveitis shows great differences among countries. Ocular tuberculosis was reported to be between 1% and 85%, and tuberculosis uveitis was between 1% and 26% in cases with tuberculosis (10, 12). In different endemic regions in Europe, eye involvement in case of tuberculosis changes from 10% to 85%, and this data indicates the absence of standardization in the definition (13).

For the diagnosis of uveitis, the identification of clinical signs such as broad-based synechiae, retinal vasculitis, multifocal choroiditis, and serpiginoid choroiditis may be suggested in some endemic regions (8, 14, 15). Retinal perivasculitis and multifocal serpiginoid choroiditis, in particular, have been reported to have positive predictive values of ≥90% (8, 14). Nevertheless, in non-tuberculosis-endemic areas, broad or extensive posterior synechiae occur much more frequently in eyes with HLA-B27 or sarcoid associated uveitis than intraocular tuberculosis, and so this particular sign may be less predictive in such settings (16, 17). In our study, most cases were defined as granulomatous uveitis, but no significant difference was found between the groups in terms of treatment response.

In the study of Lou et al., which was performed in United States and Europe, it was found that the diagnosis and treatment of tuberculosis uveitis were not found to be compatible (18, 19). Although most clinicians are questioned in countries with a low incidence of tuberculosis, most clinicians routinely perform TST, IGRA, chest X-ray and chest CT similar to our approach in countries with a high incidence of tuberculosis.

Neither TST nor IGRA tests can differentiate latent infection from active tuberculosis. On the other hand, there is a study reporting a TST sensitivity of 59% in cases of histopathologically proven eye tuberculosis (13). In recent years, IGRA tests have been used more frequently, but they cost a lot or low and medium income developing countries, and have a high risk of false positive results in countries with low incidence of tuberculosis (20). However, IGRA is preferred in high-risk cases, especially those who use anti-TNF-alpha drugs (21). The combined use of TST and IGRA tests is one of the recommendations. Anget al. reported a positive predictive value of 84.6%, and a negative predictive value of 78.9% in a group of patients with both a positive TST and Quantiferon test, analyzed for their response to ATT (21). This approach is adopted in our study. In 86% of our cases, TST and IGRA were positive. In all of the 9 cases in which IGRA test could not be performed, TST was ≥10mm and ≥ 15mm in 7 (77%). Although PCR-based diagnostic studies have high specificity in eye tuberculosis cases, sensitivity values have been reported to be low (22). However, in recent years, high positive predictive value rates of around 80% have been demonstrated in multitargeted PCR tests, and this method has been introduced in new diagnostic algorithms (23, 24). Gupta A. et al. suggested to classify tuberculosis uveitis patients as ''confirmed'', ''probable'', or ''presumed'' in their study performed in India which is a high incidence country for tuberculosis (24). Confirmed case was defined when detection of Mycobacterium tuberculosis in ocular fluid or tissue as well as clinical findings. Probable case was defined as the presence of tuberculosis in lung or extrapulmonary tuberculosis and TST or IGRA test positivity although there is no microbiological evidence of *Mycobacterium tuberculosis*. The presumed case was defined as TST/IGRA positivity with clinical eye tuberculosis findings in cases where other possibilities are excluded.

The main problem in clinical practice is that the cases as the ones in our study are defined as presumed. It is not certain whether ATT treatment should be started in these cases, whether treatment should be done with steroids or how long the duration of the treatment should be (10). Several studies have shown that tuberculosis treatment with systemic steroids leads to better response in tuberculosis cases (25). Moreover, it was reported that steroid treatment alone may cause complications in these cases. Many studies have reported that inflammation is controlled by the addition of tuberculosis therapy in patients with recurrent disease on steroid treatment (26-28). Even 60% success has been reported with tuberculosis treatment alone (28). In our study, objective improvement was

detected in 62.7% of the patients who were defined as presumed ocular tuberculosis and received ATT. In the literature, similar results to our study were reported between 60%-76.6% (5, 29, 30). In this regard, such improvement with anti-tuberculosis treatment alone is remarkable in our cases that had ongoing disease despite the long-term steroid treatment (mean 8.6 months, range: 1-31 months). However, in these cases with presumed tuberculosis uveitis, the use of corticosteroids with anti-tuberculosis treatment from the beginning may be considered to be a more appropriate option for shortening the duration of disease and preventing permanent disorders.

Although there is no generally accepted consensus, a standard treatment regimen of six months is recommended for most patients. However, there is no consensus among experts on this issue; there are nine months or longer treatment recommendations (15). Similarly, in the study conducted among eye specialists, it was found that approximately 50% of the experts recommended treatment for 9 months or longer, and in developed countries, it was seen that cases were referred to infection or tuberculosis specialists for the decision of ATT (18). Due to the possibility of eye toxicity and lack of treatment experience in these cases, ethambutol was not used, and the ATT duration was nine months in our study.

Another question is to evaluate the results of the treatment. Visual acuity is difficult to measure because it is affected by many factors. The intraocular cell count seems to be a more reliable outcome measure although it may be influenced by inter-observer variability and inaccuracy in reporting (5). On the other hand, it should be kept in mind that standard treatment may be unresponsive in delayed complicated cases (31).

A significant limitation of our study is that only 56% (36/64) of the presumed ocular tuberculosis cases suggested ATT could be evaluated objectively. The other patients were evaluated according to their self-reports about the improvement in vision.

It is important to note that in this study and many of other studies, the definition of clinical and treatment outcomes was inconsistent largely due again to the lack of an exact definition of ocular tuberculosis, variation in duration and type of ATT, and the variable use of concomitant corticosteroid therapy. Therefore, a consensus is required to guide clinicians for the treatment duration of ocular tuberculosis to avoid unnecessary treatment, over exposure to side effects, and to reduce the risk of introducing drug resistance (10).

In conclusion, this study suggests that anti-tuberculosis treatment can be successful in cases of presumed ocular tuberculosis cases where other diseases are excluded and the presence of silent tuberculosis infection is shown.

Informed Consent: Written consent was obtained from the participants.

Ethics Committee Approval: This study was approved by the Clinical Research Ethical Committee of the Istanbul University, Istanbul Faculty of Medicine (Date: 11.06.2018, No: 738).

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