Visual morbidity in Ocular Tuberculosis – Collaborative Ocular Tuberculosis Study (COTS)-1: Report #6

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ABSTRACT:

Objective: Aim of the study was to examine extent, natural history and clinical features associated with visual impairment (VI) in patients diagnosed with ocular tuberculosis (OTB) by the Collaborative Ocular Tuberculosis Study (COTS)-1.

Methods: Multi-center retrospective cohort study. Main outcomes were VI.

Results: A total of 302 patients were included in the study, including 175 patients whose data related to BCVA were available throughout the 2 years of follow up. Mean BCVA grossly improved at 12, 18 and 24 months of follow-up (p<0.001). Mean BCVA was worse at 12-18th month follow-up for patients treated with ATT versus patients who were not treated with ATT, but patients treated with ATT had a statistically significant improvement in BCVA at the 24-month endpoint.

Conclusions: OTB is associated with significant visual morbidity, future well designed prospective studies are warranted to establish the causal association between OTB and visual loss.

Key words:
Tuberculosis; Uveitis;   Visual morbidity; Visual impairment; Blindness

INTRODUCTION

Ocular tuberculosis (OTB) manifests with heterogenous clinical findings that can involve various ocular structures.[1] Diagnosis of OTB is often delayed due to its protean ocular manifestations that can mimic other uveitis entities. The lack of standardized diagnostic criteria and the absence of best practice treatment guidelines have further contributed to the existing uncertainties regarding the management of the disease.[1-5]

All these factors contribute to the significant visual morbidity associated with the disease. Significant visual morbidity associated with OTB has already been reported in a few cohort studies with limitations such as short duration of follow-up, lack of standardized diagnostic criteria as well as non-endemic and single-center origin of the study populations.[7-10] The present study has addressed these limitations analyzing the visual outcome of patients coming from a multinational cohort with 2 years of follow-up, using strict inclusion criteria. The study aims to describe the extent and causes of visual impairment (VI) in patients affected by OTB, examining clinical factors associated with poor visual prognosis. To our knowledge, this study presents the largest dataset on visual outcomes of patients with OTB originating from both endemic and non-endemic countries.

METHODOLOGY

This retrospective, multinational cohort study included data from 25 leading eye-care centers participating in the Collaborative Ocular Tuberculosis Study (COTS)-1 group through an online web-based secure and encrypted platform. In the current study, a total of 302 out of the 945 patients diagnosed with OTB between January 2004 and December 2014 were included. Inclusion criteria for this investigation were a minimum follow-up of 2 years, and documented best corrected visual acuity (BCVA) at baseline or during follow-up and at 2-year endpoint. Ethical approval was sought by individual participating centres and granted from their local institutional ethics committee. Diagnostic criteria for OTB used for the COTS-1 study are detailed in the first report of COTS group (Appendix 1).[2]

Ethics approval was obtained from all the centres. The study followed guidelines laid down by Declaration of Helsinki. As this was a retrospective data collection, individual patient consent was not obtained prior to collecting deidentified data and the same was approved by ethics committee. Study data were entered into a novel, web-based, secure and encrypted data collection platform (Cognito Form, Columbia, South Carolina, USA). BCVA at baseline and follow-up were noted. Worse affected eye was selected for analysis in patients with bilateral ocular involvement. BCVA was analyzed categorically based on World Health Organization (WHO) definitions for VI, whereby a BCVA equal or better than 6/18 was considered mild or no VI, BCVA between 6/18 and 6/60 was moderate VI, BCVA between 3/60 and 6/60 was severe VI, and BCVA less than 3/60 was blindness.[11]

Statistical analysis was conducted using SPSS statistical software, version 20 (IBM Corp). Variables for which data was not entered were treated as missing values and deleted pairwise for statistical analysis. The demographic and clinical features of TB uveitis patients were summarized according to scale of measurement. The categorical features were expressed as frequency and percentage, while continuous features were expressed in terms of mean, standard deviation and range. Snellen BCVA was approximated to logMAR values for statistical analysis, wherever required. The primary outcome measure was VI, defined as movement between a clinical category of VI (example mild to severe) during the follow up. Secondary

analyses include the association between usage of anti-tubercular therapy (ATT) and BCVA as well as factors affecting BCVA. The patient data was segregated based on ATT administered or not, and accordingly the effect of each clinical sign on the average gain in BCVA with time was studied using linear mixed effect model. The average gain in VA was defined as the average of slopes of VA taken across time for patients with a particular clinical condition. The dependent variable in the model was VA across time for each patient, which was the repeated measure on the same individual. The independent variable was the presence/absence of clinical sign. For analysis purpose, the anatomical distribution was split into anterior uveitis, intermediate uveitis, posterior uveitis, and panuveitis. The coefficient values, along with 95% CI, standard error and p-value were obtained for each clinical sign and in treatment category. The unadjusted coefficients were obtained through univariate approach with single variable included in the model. The average gain in VA corresponding to presence of clinical condition as compared to absence was obtained as indicated by the coefficient value. The coefficients for the interaction term between time and the clinical sign were reported indicating the difference in slopes for a present condition as compared to absent condition of the sign. For laterality and anatomical distribution, unilateral and anterior uveitis were regarded as reference levels and the coefficients for other levels were obtained.

RESULTS

A total of 302 patients diagnosed with OTB were included in the study. The mean age of presentation was 42.6+14.8 years, with a slight predominance of female gender (50.3%, n=152/302). Out of a total of 302 patients, 72.8% belonged to Asian ethnicity (n=206/302) and 56% to East-Asian geographical origin (n=169/302). At the time of presentation, bilateral involvement was seen in 62.9% (n=190/302). Panuveitis was the most frequent clinical presentation (36.5%, n=108/296), followed by posterior uveitis (33.8%, n=100/296), anterior uveitis (17.6%, n=52/296) and intermediate uveitis (12.2%, n=36/296). 35.5% of patients (n=65/183) had features consistent with retinal vasculitis (occlusive in 20.8% and non-occlusive in 14.4%). Choroidal involvement was present in 86 patients (64.6%, n=86/133), with serpiginous-like choroiditis (31.6%, n=42/133) being the most common phenotype. The majority of the patients received treatment with ATT (84.8%, n=256/302). Forty-six patients were not treated with ATT but received other treatments. 43.5% (n=20/46) was treated with systemic corticosteroids only, 2.2% (n=1/46) received immunosuppressive treatment only, 6.5% (n=3/46) was treated with both corticosteroids and immunosuppressants, and 47.8% (n=22/46) did not receive any therapy. Demographics and clinical phenotypes are further detailed in **Table 1**. In patients with bilateral disease, the worst affected eye was considered for further analysis.

Distribution of final VI based on individual clinical features and usage of ATT is detailed in **Table 2**. The comparison of visual impairment referring to WHO criteria was performed between baseline and different time points (**Table 3**), and included 175 out of 302 patients whose data were available throughout the 2 years of follow up. At 12 months, there was significant change in marginal distributions as observed using marginal homogeneity test (p < 0.001) irrespective of the treatment category. The number of mild VI cases increased significantly as compared to baseline. Similar was the observation at 18 months and 24 months. This is also indicated by line graphs in Figure 1A and 1B. During follow-up, the mean BCVA improved from 0.49 to 0.67 in the first three months and subsequently remained relatively stable (**Figure 1A**). The mean BCVA was worse at 12-18th month follow-up for patients treated with ATT versus patients who were not treated with ATT, but was better in patients treated with ATT at 24 months of follow-up (**Figure 1B**).

As regards the secondary analysis, **Table 4** provides the relationship between clinical phenotypes and average gain in VA in two treatment groups. In the no ATT treatment category [ATT not given], bilateral involvement showed significant worsening of vision as indicated by negative coefficient of -0.043 (95% CI: -0.083, -0.004; p=0.031) as compared to unilateral involvement. Further, presence of snowbank and disc edema were also associated with significant worsening of vision with coefficients -0.138 (95% CI: -0.276, -0.001; p=0.048) and -0.082 (95% CI: -0.158, -0.006; p=0.033) respectively. These variables were included in the multivariate model to obtain the adjusted estimates of the variables. The analysis revealed that only disc edema showed significant worsening of vision with coefficient -0.112 (95% CI: -0.199, -0.025; p=0.012), while other variables, although indicated worsening, the effect was statistically insignificant.

On similar lines, the analysis was performed in the treatment category [ATT given]. In the univariate analysis, the presence of intermediate or posterior uveitis showed significant average gain in vision [0.044 (95% CI: 0.022, 0.067; p=0.001)] as compared to anterior uveitis, unlike that of without ATT group. Further, the average gain in vision was significantly higher in patients with vitreous haze [0.027 (95% CI: 0.012, 0.044; p=0.001)] as compared to absence of haze. Similar was the observation with presence of snowball and snowbank with coefficients 0.039 (95% CI: 0.016, 0.062; p=0.001) and 0.057 (95% CI: 0.019, 0.094; p=0.003) respectively. Presence of macular edema also indicated significant average gain in vision as compared to absence of edema in the treatment group [0.03 (95% CI: 0.011, 0.050; p=0.003)]. The multivariate analysis with these variables revealed that intermediate or posterior uveitis category still showed significant gain in vision as compared to anterior [0.028 (95% CI: 0.004, 0.053; p=0.024)]. Even with the presence of snowbank and macular edema, there was significant gain in VA as compared to their respective reference levels. The analysis reveals that the treatment was effective even with adverse clinical conditions as regards to average gain in vision.

DISCUSSION

OTB has been associated with significant VI.[1,7-10] However, there is a lack of multicenter data spanning endemic and non-endemic geographies that have described the association of VI associated with OTB and investigated risk factors for VI in these patients. The current study presents the largest multinational dataset on VI in OTB, to date. This study describes in detail the temporal profile of mean BCVA in patients with OTB over a follow-up of 24 months.

An earlier report of patients diagnosed with OTB from a non-endemic population described severe VI and blindness in 2.54% and 3.11% of patients at baseline and in 2.26% and 3.67% at follow-up, respectively.[7] The most common ocular complications were macular edema (30.5%, n=107/354) and glaucoma (28.1%, n=99/354).[7] Basu et al. reported severe VI in 19.7% (n=12/61) in an endemic setting, that was largely attributed to vitreous haemorrhage, complicated cataract and macular scarring.[8] In the current cohort, a similar incidence of severe VI-blindness (12.8%) was observed.

Closer examination of the data from this cohort reveals that the proportion of eyes developing severe VI-blindness varied with the distribution of uveitis. This was 9.6% in anterior uveitis, 2.8% in intermediate uveitis, 6.0% in posterior uveitis, and 5.6% in panuveitis. VI was significantly correlated with intermediate and posterior uveitis on univariate analysis. Their coefficients were higher and 95% CI did not include zero. Presence of snowballs was also significantly associated with severe VI on univariate analysis. In the multivariate analysis, the coefficients of intermediate and posterior uveitis got lowered (close to zero), while

that of anterior uveitis increased in magnitude compared to respective univariate coefficients. The inclusion of multiple variables in the model suppressed the effect of intermediate and posterior uveitis as well as snowball, while effect of other parameters remained the same. This alteration could be due to multicollinearity effect. However, the true effect of parameters on visual acuity was unveiled in the multivariate analysis, which was relied upon.

On the contrary, previous reports have found that poorer outcomes occurred more frequently in eyes with panuveitis or posterior uveitis in comparison with those that had anterior uveitis.[7,8] Patients with anterior uveitis phenotype could have associated pre-existing senile cataract or disease/uveitis associated complicated cataract resulting in VI, however the detailed data for this was not recorded in this retrospective cohort study. In addition, the possible reason for this discrepancy was likely due to the use of visual impairment (VI) as the primary outcome measure in this study. On the other hand, the existing reports of OTB, including those from the COTS group 2, primarily utilise the outcome of treatment failure defined as some form of persistent or recurrent inflammation. Future prospective investigations studying the various phenotypes and treatment outcomes of OTB in detail are needed to confirm these findings.

Retinal vasculitis has also been described as one of the manifestations of OTB that is associated with blindness.[7,8] In our cohort, moderate or worse VI was observed in both occlusive and non-occlusive phenotype (10.5% and 11.1%, respectively). Patients with retinal vasculitis who had vitreous haemorrhage may have a burnt out disease, and so the true incidence of blindness with occlusive vasculitis may be under-estimated in this study.

Among various types of choroiditis, multifocal choroiditis was more commonly associated with severe VI or blindness (25%). On multivariate regression analysis, disc edema and macular edema were significantly correlated with decrease in BCVA.

The study also provides a description of the mean BCVA during the course of ATT. Data suggests that, even if an improvement in BCVA in patients treated with ATT is not perceivable at 12-18 months when compared to those who are not treated, final BCVA is recorded at the 24-month endpoint. These results emphasize the need to manage patients' expectations for improvement in BCVA accordingly, and to highlight the importance of ATT to treat the underlying infectious disease. The beneficial impact of the treatment on the course of BCVA may take 18-24 months to be noted and could serve to manage patients' expectations of a rapid visual recovery and also to help encourage long-term ATT compliance.

The findings from this report suggest that clinicians may want to consider a lower threshold for aggressive investigation and/or early initiation of ATT with anti-inflammatory therapy in patients with suspected OTB that have these clinical findings to possibly prevent complications and hence VI in patients with long standing uveitis. Existing reports have already emphasized that delay in initiating antimicrobial treatment is a major factor influencing visual morbidity.[7,10] In particular, it has been described that patients with a delay in diagnosis of longer than 500 days were 20 times more likely to have irreversible vision loss and loss of the involved eye.[12] Early referral and prompt institution of appropriate therapy can be instrumental to prevent significant visual morbidity.

One of the statistical limitation in the study was the assumption of linearity of change in visual acuity with time. The complete data for all patients was not available and hence linear approximation was considered

and the models were obtained accordingly. The retrospective methods of the study led to a lack of standardization in documentation and hence, missing data. Complete information could not be obtained from medical records of all the patients included in the study, including data related to the causes of visual impairment. Future prospective studies based on a standardized protocol for acquisition of data can be useful to address potential correlations between ocular phenotype and clinical complications that might affect patients' visual acuity.

CONCLUSIONS

OTB is associated with significant visual morbidity, especially in eyes with anterior uveitis, disc edema and macular edema. The present study is the first multi-center description of the spectrum of VI in OTB over 2 years of follow-up. The study has valuable information for the development of international guidelines tailored to patient risk-profiles as well as economic modelling to determine the social impact of OTB. Future prospective study and perhaps a standardised registry will be instrumental in improving our understanding of OTB and delineating the factors contributing to poor visual outcomes in a disease where early referral and appropriate therapeutic management are mandatory to avoid severe visual loss.

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