The Collaborative Ocular Tuberculosis Study (COTS)-1: A Multinational Descriptive Review of Tubercular Uveitis in Paediatric Population

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Abstract

Purpose To examine disease profile of tubercular uveitis (TBU) in paediatric population.

Methods Among 945 patients of the retrospective multinational study by the Collaborative Ocular Tuberculosis Study (COTS)-1, 29 paediatric patients diagnosed with TBU were analysed.

Results Mean age of disease presentation was 12.8 (range 4-18 years), with predominance of males (n=14/20;70.0%) and Asian ethnicity (n=25/29;86.2%). Posterior uveitis (n=14/28;50%) was the most frequent uveitis phenotype, with choroidal involvement occurring in 64.7% (n=11/17). Incidence of optic disc oedema and macular oedema was higher in children (n=8/18;44.4% and n=5/18;27.8%, respectively) than in adults (n=160/942;16.9% and n=135/942;14.3%, respectively). Comparison of optic disc oedema between subgroups showed a significant difference (*P=.006*). All patients received oral corticosteroids, most of them with antitubercular therapy. Treatment failure developed in 4.8% (n=1/21).

Conclusions Children have a more severe inflammatory response to the disease, and an intensive anti-inflammatory therapeutic regimen is required to achieve a positive treatment outcome.

Keywords Ocular tuberculosis, tubercular uveitis, paediatric population, children, Collaborative Ocular Tuberculosis Study (COTS)

Ocular tuberculosis (OTB) is a rare form of uveitis, with prevalence ranging from 0.2% to 10.5% across different regions of the world.[1-4] As in adults, paediatric uveitis incidence, prevalence and aetiology are affected by geographical variations and ethnicity .[5,6] Higher incidence of the disease has been reported amongst children coming from tuberculosis (TB) endemic areas, such as India, where the figures related to OTB account for 4.9-7.4% of all paediatric cases.[7-9] A lower incidence in non-endemic countries, together with heterogeneous clinical manifestations and lack of agreement on diagnostic investigations, has led to a paucity of data in the paediatric population.[1-3,10-12] The availability of data is further affected by concurrent reporting with adult case series, without a separate analysis for the paediatric subset.

This review by the Collaborative Ocular Tuberculosis Study (COTS)-1 was conducted with the aim of highlighting clinical findings and disease profile of tubercular uveitis (TBU) in a paediatric population, by analysing the data from the largest collaborative multicentre dataset on TBU from 25 international eye care centres located in both endemic and non-endemic countries.[13-18]

Methods

The COTS-1 retrospectively reviewed demographics, clinical features, investigations, treatment regimen and outcome of patients diagnosed with TBU from January 2004 to December 2014 across 25 multinational centres. The study obtained the ethical approval by each local institutional ethics committee. **Appendix 1** lists all participating centres. Patients included in the study satisfied the diagnostic criteria for TBU (**Appendix 2**), other diagnosis excluded by ancillary and laboratory investigations. Patients had a minimum follow up of 12 months with availability of baseline and follow-up reviews detailed medical records. In the present report, the subset of paediatric patients from COTS-1 was analysed. The age for inclusion in paediatric population was defined as individual under 18 years old.

Data collection A novel data entry platform (Cognito Form, Columbia, South Carolina, USA) was created to collect COTS-1 patients' data. The platform was programmed to address the heterogeneous manifestations of TBU and incorporate the multiple variables associated with the disease. The platform consisted of a web-based smart form providing users with explanations and prompts for questions, reinforcing information to be used in the study, such as diagnostic and inclusion criteria or treatment failure definitions. Confidential patients' information was not recorded in data collection. Variables for which data was not entered were treated as missing values with pairwise deletion for statistical analysis.

For the detailed methodology of the study and data collection please refer to methods section from 'Clinical features and outcomes of patients with tubercular uveitis treated with antitubercular therapy in the Collaborative Ocular Tuberculosis Study (COTS)-1'.[14]

Results

Among 945 patients diagnosed with TBU in COTS-1, 29 paediatric patients were included in the analysis.

Mean age of disease presentation in paediatric population was 12.8 (range 4-18 years), with predominance of males (70.0%, n = 14/20), and Asian ethnicity (86.2%, n = 25/29). Among the patients in whom information related to systemic disease and OTB was available, 85.2% (n = 23/27) had no known history of systemic TB, and only 9.5% (n = 2/21) had clinical features of systemic disease, including chronic cough, night sweats and weigh loss. Demographics and systemic findings of COTS-1 paediatric population are described in **Table 1**.

Uveitis was bilateral in 62.1% of paediatric patients (n = 18/29). Posterior uveitis was the most common phenotype (50%, n = 14/28), followed by panuveitis (21.4%, n = 6/28), anterior uveitis (14.3%, n = 4/28) and intermediate uveitis (10.7%, n = 3/28). Regarding clinical features, choroidal involvement was found to be the most common clinical finding (64.7%, n = 11/17), followed by disc oedema (44.4%, n = 8/18), macular oedema (27.8%, n = 5/18) and retinal vasculitis (21.1%, n = 4/19). Among the 11 patients with choroiditis, serpiginous-like phenotype was the most common one, manifesting in 63.6% (n = 7/11). Different forms of choroidal involvement included acute posterior multifocal placoid pigment

epitheliopathy (APMPPE) (9.1%, n = 1/11), ampiginous choroiditis (9.1%, n = 1/11), and tuberculoma (9.1%, n = 1/11). Clinical features of COTS-1 paediatric population are detailed in **Table 2.**

A comparative analysis between the paediatric and adult subgroups is provided in **table 3**. From the analysis it emerged that the number of cases with bilateral disease, disc oedema and macular oedema was higher in children than in adults, but only disc oedema showed significant difference between the two subgroups (44.4%, n = 8/18 in children vs 16.9%, n = 160/942 in adults; *P = .006*). Retinal vasculitis was less common in paediatric population than in adults, but the comparison between the two subgroups was not significant (21.1%, n = 4/19 in children vs 26.4%, n = 249/942 in adults; *P = .792).*

Around 63% (n = 17/27) of the patients underwent radiological investigations, and among those with documented results, 33.3% (n = 4/12) had features consistent with inactive or healed pulmonary TB. The most performed test in children was tuberculin skin test (TST), performed in 65.5% (n = 19/29), compared to Interferon-Gamma Release Assays (IGRAs), performed in 46.4% (n = 13/28). TST was positive in 68.4% (n = 13/19). Among 13 patients who underwent IGRAs, QuantiFERON TB-Gold was performed in 92.3% (n = 12/13) and was positive in 85.7% (n = 6/7), whereas T-SPOT.TB was performed in 7.7% (n = 1/13), and was positive in all cases. Results of investigations in COTS-1 paediatric population are detailed in **Table 4**.

In COTS-1 patients were treated with antitubercular therapy (ATT) and/or corticosteroids and immunosuppressive agents as decided by the attending physician in collaboration with respiratory or infectious disease specialists. Decisions were based on local institutional protocols, depending on phenotype and severity of TBU, and patients' comorbidities. In paediatric subset analysis, 21 patients (72.4%, n = 21/29) received ATT, 22 patients (75.9%, n = 22/29) corticosteroids, and 3 patients (12.0%, n = 3/25) corticosteroid-sparing immunosuppressive agents. A total of 19 patients (86.4%, n = 19/22) received both ATT and corticosteroids, 2 (9.1%, n = 2/22) received ATT, corticosteroids and immunosuppressive agents, and 1 (4.5%, n = 1/22) received corticosteroids and immunosuppressive agents. Treatment regimen is further described in **Table 5**.

In our study, treatment failure was assessed at standardized 6 month intervals from initial diagnosis up

to 24 months, and defined as persistence or recurrence of inflammation within 6 months of completing ATT, or inability to taper oral corticosteroids to <10 mg/day or topical steroid <twice a day, or recalcitrant inflammation necessitating steroid-sparing immunosuppressive agents. Among 21 patients receiving ATT, 20 (95.2%, n = 20/21) were successfully treated. Treatment failure occurred at the six-months' follow-up only in 1 patient (4.8%, n = 1/21). The patient was affected by posterior uveitis with choroidal involvement and vitritis, treated with ATT plus oral corticosteroids with no immunosuppressive agent. The patient receiving corticosteroids and immunosuppressive agents alone (azathioprine) without ATT was a 9 years old Asian female diagnosed with unilateral posterior uveitis with choroidal involvement, vitritis and disc oedema. The patient did not develop any recurrence of uveitis up to 24 months of follow up. Among the other 7 patients not treated with ATT, 3 had anterior uveitis, 3 had posterior uveitis with choroidal involvement, including 2 serpiginous-like, and 1 had clinical features not recorded. Nobody of them developed recurrences of uveitis during the follow up.

Given the retrospective methodology of the study, a proper analysis based on visual outcome was not possible. However, from the recorded data it emerged that 6 out of 29 patients (20.7%) were counting fingers at baseline. One patient had anterior uveitis, 2 had posterior uveitis, 2 had panuveitis and 1 had intermediate uveitis. In 3 patients disc oedema and macular oedema were detected, in 1 patients were absent, in 2 not recorded. Twenty-four month results were available for 4 of the 6 patients: in 3 of them counting fingers improves to 6/6, 6/12 and 6/24, respectively. The patient with no improvement of visual acuity was affected by posterior uveitis with choroidal involvement associated with vitritis and macular oedema.

Discussion

The paediatric data emerged from the study is consistent with previous reported adult case series and COTS-1 overall analysis.[3,12-14,18] OTB is known to be more common amongst males, and this trend is reflected also in paediatric population.[3,13,14,18] The bias toward the Asian ethnic population can be easily explained by the global variation and distribution of TB across the world, since six of the eight countries accounting for 2/3 of TB cases worldwide are located in the Asian continent.[19]

Diagnosis of TBU still represents a challenge, being in most cases a presumptive diagnosis, based on

epidemiological factors, suggestive clinical manifestations and corroborating immunologic evidence. Furthermore, regarding systemic involvement, it is well know that OTB is an extra pulmonary form of TB and most patients do not manifest any findings of systemic involvement in terms of both clinical features or investigation results, including chest X ray or computed tomography.[1-3,10,12,14-18] In agreement with the fact that OTB may occur without any evidence of pulmonary disease, most of our paediatric patients did not show any chest pathological findings. However, the subset analysis demonstrates that chest imaging can nevertheless be useful in the diagnostic work-up of a minority of patients, providing evidence of active, healed or reactivated TB.

Paediatric TBU clinically manifests similar to adults, with posterior uveitis and choroidal involvement being the most common clinical features.[3,10,14,15,19-21] Serpiginous-like choroiditis has been reported in a higher number of children with posterior involvement, similar to figures in adult population and consistent with data from another report on paediatric TBU in endemic area.[21] However, in our retrospective analysis we noted that the number of cases with optic disc oedema and macular oedema was higher in children compared to adults, confirming the hypothesis that children tend to have a more severe inflammatory response, eventually resulting in a higher risk of ocular complications and visual loss.[18,22]

From paediatric data it emerged that a high percentage of patients was treated with both ATT and corticosteroids, all patients received systemic steroids, none of them received ATT alone but always in association with corticosteroids, with or without immunosuppressive agents. The results can be explained by that fact that, since paediatric population may have a more severe inflammatory reaction, as shown by our subset analysis, children might require a more intensive treatment and a higher level of immune suppression. In line with our results, a retrospective study by Kaur reviewing the data related to a study population of 32 children with TBU in endemic area showed how all patients were treated from the beginning with ATT in combination with systemic corticosteroids, and among those treated with a 12 month course of ATT, 35% needed oral corticosteroids and/or immunosuppressive agents beyond 1 year after treatment.[21] The more intensive treatment received by children from the beginning including anti-inflammatory agents might explain the successful outcome reported in paediatric population.[12,14,18]

Eight patients did not receive ATT and did not develop any recurrence of inflammation. A possible explanation might include a TB related inflammatory reaction characterizing specific phenotypes of TBU, as opposed to the presence of *Mycobacterium Tuberculosis* in ocular tissue. In COTS 1 study, higher incidence of treatment failure was noted in patients with choroidal involvement and vitreous haze. Such clinical manifestations seem more likely to be related to an immunologic reaction and might require a more intensive regimen for immunosuppressive therapy. The patient in the study who developed treatment failure was affected by posterior uveitis with choroidal involvement and vitritis, and was treated with ATT and corticosteroids without immunosuppressive agent. Differentiation between autoimmune and infectious etiopathogenesis in specific TBU phenotypes will help improve our understanding of the role of ATT in the management of patients with OTB.

Conclusion

COTS-1 represents the largest collaborative multicentre dataset on ocular TBU and contained the largest dataset of paediatric TBU, including patients coming from both endemic and non-endemic countries. Limitations of the study include the retrospective method, leading to a lack of standardization in data collection and hence missing data, and the small size of the sample. However, standardized inclusion and diagnostic criteria, combined with a study population including paediatric patients from TB non-endemic areas are strengths of the study.

Demographics, systemic findings, and the use of investigations in the paediatric population diagnosed with OTB appear to be like that in adults. Children and adults have similar ocular manifestations in term of anatomical distribution of uveitis and ocular phenotype. However, the reported higher incidence of clinical findings, such as optic disc oedema and macular oedema, indicates that children tend to have a more severe inflammatory response to the disease, and that they require a more intensive therapeutic approach to achieve a successful therapeutic outcome.

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