ABSTRACT

Nature and significance of the study: from a universal outlook to that in India and Chennai

An elusive aetiology of serpiginous choroiditis makes the diagnosis and management of this condition a challenge. It causes painless progressive loss of vision, acute vision-threatening choroiditis needs timely institution of appropriate treatment to salvage vision. Serpiginous choroiditis in the Indian population differs from other studies in the Caucasian population which report a later onset of the disease and unilateral presentation. Preponderance of the disease in the younger age groups of life has been noted in the Indian population. Bilateral involvement of eyes is more common in our patients with many having macular involvement at initial presentation, necessitating early diagnosis and institution of therapy. The visual loss itself is a consequence of complications such as active choroiditis involving the macula during the acute phase and choroidal neovascular membranes or scarring at the macula in the healed stages. Although considered idiopathic, the resemblance of the lesions to tubercular multifocal choroiditis needs to be explored and the possibility of mycobacterium tuberculosis (MTB) as the underlying cause has to be investigated. The purpose of this study is to detect underlying
tuberculosis if it does exist and to supplement treatment with antitubercular treatment (ATT) to hasten resolution of the disease and prevent the ocular morbidity associated with it.

**Aim**

The primary aim of the study is to study serpiginous choroiditis and its aetiology with emphasis on tubercle bacilli and to analyse the utility of aqueous humour analysis in comparison with conventional investigations in the recognition of choroiditis due to tubercular aetiology.

**Secondary objectives:**

1. Determine the usefulness of real time polymerase chain reaction (RT-PCR) in serpiginous choroiditis.

2. Determine the clinical features of posterior uveitis in serpiginous choroiditis due to autoimmune or non-tubercular aetiology and in tubercular multifocal choroiditis.

3. Identify the investigations to be employed to confirm diagnosis when all other tests are negative but clinical suspicion remains high.

**Materials and Methods**
The study was approved by the Institutional Ethics committee in Sri Ramachandra University and in SankaraNethralaya. Study population comprised of 126 patients and 27 control subjects attending a tertiary eye care institute in Chennai, South India over a period of four years. RT- PCR was done on 28 eyes and nested PCR performed on 3 eyes. It is a prospective study conducted on a cohort of patients who presented with symptoms and signs of posterior uveitis. Inclusion criteria were defined as active serpiginous choroiditis and multifocal choroiditis with or without anterior uveitis. Exclusion criteria were all patients in whom diagnosis was unequivocal and the aetiology established. During the first visit a structured questionnaire was provided to all patients. The questionnaire had queries related to clinical findings and the family history. The time for answering the questionnaire and completing examination required approximately forty five minutes time. Both blood samples and aqueous humour samples were collected from each patient. There are almost NO risks to the patient. However on rare occasions complications during anterior chamber tap have been reported. They are

- Wound leak
- Hyphaema
- Iritis
• Lens injury

To prevent these complications and infections precautions were adopted such as creation of a corneal valve to prevent wound leak, a careful tap in a constricted or normal pupil to prevent lens injury and antibiotics administered after the procedure.

Possible benefits to the participant: Usefulness of the project/study.

In India, where tuberculosis is endemic this study could demonstrate an aetiology of tuberculosis for a disease considered idiopathic as of now. Detection of an aetiology of tuberculosis could change the management. The current management is oral corticosteroids or immunosuppressive agents which when given to the patient halts the progression of the disease temporarily but does not prevent recurrence. Knowledge of origin and risk factors along with initiation of oral corticosteroids in concurrence with anti-tuberculosis treatment (ATT) could address this recurrence and prevent complications like choroidal neovascular membranes and subretinal scarring which are the main causes of visual loss in these patients.

Statistical analysis
SPSS 11.0 statistical software (Chicago IL, United States of America) was used for all statistical analyses, K-related samples and Kendall’s (coefficient of concordance) non parametric tests were selected for comparison of the various investigative procedures. The true and false, positive and negative cases were recorded. Calculations were performed to determine the sensitivity and specificity of selected tests.

The proposed project involved the following stages

STAGE 1: Establishing the existence and type of serpiginous choroiditis.

STAGE 2: After diagnosis the patients were subjected to ancillary investigations such as fundus fluorescein angiography, indocyanine green angiography, fundus autofluorescence and optical coherence tomography. Complete blood counts, Purified protein derivative tests, X ray chest, high resolution chest tomography and QuantiFERON- TB Gold were performed in all patients.

STAGE 3

Anterior chamber tap was performed under topical anaesthesia and the specimen was sent for analysis. PCR was done on all patients. Real time PCR was performed on a subset of 28 eyes as economic constraints did not permit this test for all patients. Nested PCR was performed on 3 eyes in whom PCR results were negative although clinical suspicion was very high.
Results

The results were calculated based on two groups, those with evidence of tuberculosis on investigations belonged to the TB group and those without evidence of TB the non-tubercular (non TB) group.

Background characteristics

- Age group was segregated decade wise. Serpiginous choroiditis was seen predominantly in the 3rd decade of life.
- In both the TB and non TB group defective vision was the presenting symptom and was seen in 71.2% of patients. Floaters were seen more commonly in the TB group.
- There was no significant difference noted in gender distribution. A slight female preponderance over males was noted in both TB and non-TB groups.

Results of clinical presentation

- An aetiology of tuberculosis was seen in 70.7% and an autoimmune or non-tubercular aetiology in 29.3% of patients.
- Among all patients studied, involvement of the right eye was seen in 59 patients, the left eye in 25 patients and both eyes in 39 patients. In the TB group, unilateral involvement with right eye was seen in 93.2% and
involvement of left eye was seen in 91.7%. In the non-tubercular group, unilateral involvement with right eye was seen in 6.8% and left eye was seen in 8.3%.

- Grading of anterior chamber cells was done using Standardised Uveitis Nomenclature (SUN) classification and was found to be more common in the TB group, percentage being 87.2%. However, anterior chamber cells were observed in a small proportion of patients even in the non TB group (12.8%).

- The difference in the presence of vitreous cells was statistically significant (p=0.002). In patients with tubercular serpiginous choroiditis, vitreous cells and haze were present in 94.7% and absent in 5.3%. In the group of patients with serpiginous choroiditis due to non-tubercular aetiology, vitreous cells were present in 7% and absent in 93%.

- Among patients who presented with various morphological features, in tubercular aetiology, the presentations were ampiginous choroiditis in 71 patients, macular serpiginous choroiditis in 11 patients and peripapillary serpiginous choroiditis in 7 patients. The presentation in the non- tubercular group was peripapillary serpiginous choroiditis in 24 patients, macular
serpiginous choroiditis in 5 patients and ampiginous choroiditis in 8 patients. The varied presentation in those with tubercular and non-tubercular aetiology was found to be highly statistically significant (p < 0.001).

**Results of Systemic Investigations**

- Among all patients with serpiginous choroiditis, in those with evidence of TB, Mantoux test was positive in 60 (84%) and in those with no evidence of TB, positive reaction was still seen in 18 (15.6%) of cases. However even among those with a negative Mantoux reaction, evidence of TB was seen in 19 (41.7%) of patients.

- ESR was found to be raised in 51 patients of whom 38(74.5%) had evidence of TB. However even in patients with normal ESR 23 (33%), evidence of TB was present in 14 (60.9%). In those with TB and raised ESR, 11 patients were found to have active TB and 27 patients had latent TB.

- QuantiFERON-TB Gold (QFT Gold) Test: Among those who were QFT Gold positive, 92 % had evidence of TB. In 16.7% of patients who were
QFT Gold negative other investigations still suggested evidence of TB. This difference was highly statistically significant (p=.000/p<0.001).

- HRCT provided evidence of tuberculosis in 81 (91 %) patients with positive findings. This was statistically significant (p=0.002). HRCT was negative in 8 patients (9%). However other investigations still revealed tuberculosis in 4 (50%) patients with negative HRCT.

**Results of Investigations on Aqueous Humour**

Polymerase chain reaction (PCR): Analysis of aqueous humour by PCR and nested PCR showed that 71% were positive in those with evidence of TB and 10% were positive in those with no evidence of TB. This was statistically significant (p=0.001). The 10% indicate false positivity.

**Real time Polymerase chain reaction (RT-PCR)**

Real time PCR was performed on a subset of 28 eyes and two patients in this group were positive. This may be attributed to the high bacterial load with anterior chamber spill over. In those with positive RT-PCR, HRCT was also positive in one patient.
Results of ancillary investigations

Fundus autofluorescence, fundus fluorescein angiography, indocyanine green angiography and optical coherence tomography were performed on all patients at presentation and during follow-up. Angiographic features of both typical serpiginous choroiditis and serpiginous like multifocal choroiditis associated with tuberculosis appeared similar in all 126 patients with early blockage and late staining of active lesions and central hypofluorescence of inactive lesions. Fundus autofluorescence defined the differences even better by delineating the areas of damaged retinal pigment epithelium (RPE) besides assessing focal or multifocal involvement and proximity to the fovea. Optical coherence tomography provided information on the development of cystoid macular oedema in 11 patients, epiretinal membranes in 2 patients and choroidal neovascular membranes in 5 patients during their follow-up visits.

Discussion

The most frequent age group affected was found to be patients in the 4th decade followed by those in their 3rd decade of life. No significant difference was noted in
gender distribution. Defective vision was the most common symptom in serpiginous choroiditis due to TB and non TB, however, floaters were seen predominantly in patients with TB. Anterior chamber cells were observed in few patients and most patients with cells belonged to the TB group. Their presence in a small proportion of patients even in the non TB group could be attributed to a chance variation. Vitreous cells and geographic choroiditis were a feature of tubercular multifocal choroiditis in a significant number of our study patients. In those with an aetiology of tuberculosis, the distribution of lesions was multifocal choroiditis which could be mistaken for the ampiginous type of serpiginous choroiditis. In the non-tubercular group it was predominantly peripapillary in location with or without eventual spread to the macula but primary involvement of the macula was seen only in few. Purified protein derivative test was unreliable. ESR, QFT-G test, HRCT and PCR were reliable investigations and helped in arriving at the diagnosis. Nested PCR helped in the diagnosis of tubercular aetiology in three patients in whom all other investigations were negative. Serpiginous choroiditis is believed to be an autoimmune disease. Patients particularly in tuberculosis endemic areas may have fundus changes that resemble serpiginous choroiditis but may show evidence of mycobacterial DNA in the aqueous humour. Some patients with evidence of active or latent tuberculosis
present with serpiginous like clinical features that can resemble the autoimmune type. A significant cause may be an underlying systemic or ocular infection and the likelihood of this being tuberculosis is high. Our study showed that in a country like India which is endemic for tuberculosis, the incidence of serpiginous like choroiditis and multifocal choroiditis due to tuberculosis is higher than a non-tubercular or autoimmune aetiology.

**Conclusion**

Serpiginous choroiditis is a form of ocular inflammation due to autoimmune aetiology. Multifocal choroiditis that arises due to tubercular aetiology is entirely different and does not represent a subtype of serpiginous choroiditis. In the Indian population, serpiginous choroiditis due to both tubercular and autoimmune aetiologies exist as independent diseases with a higher prevalence due to tuberculosis. The fundus appearance may be sufficient for clinical diagnosis, but laboratory investigations are recommended to rule out infectious causes before initiating treatment with immunosuppressive agents which is required in the majority of autoimmune cases. Imaging studies are required to determine activity, monitor disease progression, evaluate response to treatment and detect complications such as choroidal neovascularisation and macular oedema. However,
a difference can be observed in the pattern of presentation and following investigations. Systemic investigations in the majority of circumstances proves to be the clincher of diagnosis. Existing treatment with corticosteroids will have to be supplemented with ATT which will probably play a role in reducing complications and will prevent recurrences. A follow up for a longer period of time will help to evaluate progress and the recurrence pattern. The utility of RT-PCR to detect MTB in serpiginous choroiditis has never been reported and our results provide evidence that RT-PCR, on the aqueous humour can be applied to establish the diagnosis with certainty. It has the potential to significantly improve detection by virtue of its exquisite specificity and follow up for a longer period of time will help to evaluate progress and the recurrence pattern. In view of the ease of performing anterior chamber tap, the ability of RT-PCR to identify the presence of MTB DNA and the potential of this test to detect the response to treatment, we recommend the use of this procedure to determine whether or not TB is the aetiology and to provide quantitative assessment of the bacterial load in the eye. The presence of confirmatory MTB DNA found by RT-PCR in only two cases of 28 eyes points out to the controversy of associating serpiginous choroiditis with tuberculosis. Our study indicates that this association could not be a chance association (in an endemic country as India). Analysis of vitreous aspirate by RT-PCR may provide
conclusive evidence by detecting MTB DNA in patients with serpiginous choroiditis.