ROLE OF ANTITUBERCULOUS THERAPY IN INTERMEDIATE UVEITIS

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ABSTRACT

BACKGROUND

Intermediate uveitis is a form of uveitis localised to the vitreous and peripheral retina. Primary sites of inflammation include the vitreous of which other such entities as pars planitis, posterior cyclitis and hyalitis are encompassed.

The aim of this study was to describe the demographic features and clinical outcomes in patients with intermediate uveitis.

MATERIALS AND METHODS

39 patients were included in our study for the institution of antituberculous therapy. After obtaining informed consent, they underwent a complete ophthalmological examination. All patients of presumed tuberculous aetiology underwent Mantoux skin testing, ESR, chest x-ray and QuantiFERON gold TB testing when necessary. All patients were started on antituberculous therapy along with oral prednisolone. Reduction in vitritis by two grades or improvement in BCVA by two lines was considered as response to therapy along with reduction in recurrence of inflammation. Patients were reviewed periodically.

RESULTS

The mean age of the study population was 35.4 years. The patients presented with symptoms like defective vision and the commonest sign was vitritis. The commonest complication encountered in our study was cystoid macular oedema. The recurrences were found to be lower when compared to the episodes before the institution of antituberculous therapy and was found to be statistically significant ($p<0.05$).

CONCLUSION

In patients with intermediate uveitis, detailed evaluation should be carried out to rule out tuberculous aetiology. Prompt institution of antituberculous therapy may reduce complications and improve the visual outcome.

KEYWORDS

Intermediate Uveitis, Intraocular Tuberculosis, Antituberculous Therapy.

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BACKGROUND

Intraocular inflammation may predominantly involve any ocular structure and maybe associated with systemic features and they pose a diagnostic conundrum to ophthalmologists. In order to simplify and streamline the process of diagnosis and treatment, uveitis has been classified into many subtypes by the International Uveitis Study Group[1] (IUSG). It is also of immense help to prognosticate the patient's condition. The IUSG suggested the term Intermediate Uveitis (IU) to denote an idiopathic inflammatory syndrome mainly involving the anterior vitreous, peripheral retina and the ciliary body with minimal or no anterior segment or chorioretinal signs. Pars planitis, chronic cyclitis, peripheral uveitis, vitritis, cyclochorioretinitis, chronic posterior cyclitis and peripheral uveoretinitis are the other names that have been used to describe this condition.[2] In the Standardisation of Uveitis Nomenclature (SUN), working groups international workshop for reporting clinical data, the consensus reached was that the term IU should be used for that subset of uveitis where the vitreous is the major site of the inflammation and if there is an associated infection (for example, Lyme's disease) or systemic disease (for example, sarcoidosis).[3]Though the major cause of intermediate uveitis in developed countries is of autoimmune aetiology, infectious causes predominate in majority of the developing nations. Among the infectious causes, tuberculosis seems to be the most common aetiology in Indian population.

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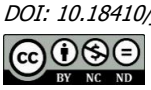

Purpose

The purpose of this study is to define the epidemiological features, clinical features, course and visual outcome in patients with suspected tubercular intermediate uveitis. This

study also aims to evaluate the purpose of antituberculous therapy in patients with recurrent episodes of intermediate uveitis and in patients not responding to conventional steroid therapy.

Subject selection

This study was conducted in Uvea and Retina Services of Regional Institute of Ophthalmology and Government Ophthalmic Hospital, Egmore, Chennai, from January 2012 to October 2017. A total of 86 patients diagnosed as intermediate uveitis attended our clinic in this time period. After thorough investigations, patients were initially treated with injection PST and topical steroids. Among them, 39 patients responded well and showed good resolution of symptoms and signs. The remaining 57 patients were instituted on additional systemic steroid therapy. Twelve patients responded well to oral steroids. The remaining subset of 45 patients who had repeated episodes of vitiritis or poor response to steroid therapy were subjected to the following inclusion and exclusion criteria.

Inclusion Criteria

1. Patients above the age of 18 years.
2. Patients with a history of contact with tuberculosis patients.
3. Patients with previous history of pulmonary or extrapulmonary tuberculosis.
4. Patients with a positive Mantoux test (>10 mm) with or without an elevated erythrocyte sedimentation rate.
5. Patients with a positive QuantiFERON gold TB test.
6. Patients with a minimum of 9 months of follow up after completion of ATT.

Exclusion Criteria

1. Patients with an evidence of an active chorioretinal patch or an old scar or patients with a prominent anterior chamber granulomatous inflammation.
2. History of any intraocular surgery in the recent past.
3. Patients with elevated angiotensin converting enzyme levels.
4. Patients with features suggestive of demyelination or evidence of demyelinating plaques in T1 weighted MRI.
5. Presence of peripheral periphlebitis or vascular sheathing.

39 patients satisfied our inclusion and exclusion criteria and were included in our study for the institution of antituberculous therapy. The remaining six patients were thoroughly investigated to rule out pars planitis or multiple sclerosis and were proceeded to be treated with immunosuppressive therapy.

Methodology

After obtaining informed consent from all patients included in our study, they underwent a complete ophthalmological examination- uncorrected and best spectacle corrected visual acuity, intraocular pressure measurement with Goldmann applanation tonometry and a detailed anterior segment examination with a slit lamp. All patients of presumed tuberculous aetiology underwent Mantoux skin testing, complete blood count with erythrocyte sedimentation rate, chest x-ray and QuantiFERON gold TB testing when necessary. Fundus evaluation was done by slit-lamp biomicroscopy with a +90D lens and indirect ophthalmoscopy. Fundus fluorescein angiography and optical coherence tomography were performed when necessary to rule out any evidence of cystoid macular oedema and presence of epiretinal membrane respectively. B scan ultrasound was also done in patients when required. Monitoring and follow up of patients was documented by taking serial fundus photographs of patients using Kowa VX 10 along with routine fundus examination to document the resolution of vitritis and vitreous exudates. A pulmonologist opinion was obtained for all patients with chest x-ray and tuberculin skin testing to rule out any evidence of pulmonary or extrapulmonary tuberculosis. QuantiFERON gold Tb testing was done when required. Presence of vitreous cells with predominance in the anterior vitreous phase with vitreous condensation with snowball and snow banking was considered as evidence of active vitritis. The grading of vitritis was done as shown in Table 1.

Haze Severity	Grading
Good view of Nerve Fibre Layer (NFL)	0
Clear disc and vessels, but hazy NFL	+1
Disc and vessels hazy	+2
Only disc visible	+3
Disc not visible	+4

Table 1. Grading of Vitreous Haze

All patients were started on category-1 antituberculous therapy, which consisted of four drugs - isoniazid, ethambutol, pyrazinamide and rifampicin for first two months followed by isoniazid and rifampicin for the next four months. Patients were also started on oral prednisolone of 1 mg/kg body weight, which was tapered and stopped over duration of six weeks. Reduction in vitritis by two grades or improvement in best corrected visual acuity by two lines was considered as response to therapy. Recurrence of inflammation after six months of completion of therapy was also considered. All quantitative variables were estimated using measures of central location (mean, median) and measures of dispersion (standard deviation).

Follow Up

The best spectacle corrected visual acuity and the presence and absence of inflammation were assessed while starting ATT and at the completion of the regimen. Patients were reviewed every month while on ATT and every two months after completion of ATT for a period of 9 months to one year. Detailed anterior segment examination with a slit lamp and fundus examination with slit-lamp biomicroscopy with 90D and indirect ophthalmoscopy was done during each visit.

RESULTS

89 patients were diagnosed as intermediate uveitis in the study period from 2012 to 2017. Of this, 39 patients fit into our inclusion and exclusion criteria and diagnosed as intermediate uveitis of presumed tubercular aetiology were considered for our study. There were 18 men and 21 females with a male-to-female ratio of 1:1.6. Mean age of the study population was 35.4 years (median = 32 years, IQR = 33). The uveitis was bilateral in 74.48% of the patients. The demographic details of the patients are depicted in Table 1.

Factors	Tuberculous IU (n=39 Patients)	Overall (N=86 Patients)
Age	35.4 ± 15.3	38.5 ± 11.4
Sex (M/F)	1:1.6	1:1.2
Bilateral	31 (74.48%)	69 (80.23%)

Table 1. Demographic Details of Study Population

The patients presented with symptoms like defective vision, which was present in 89.74%, floaters in 69.23%, pain in the eye with headache in 25.6% and redness in 20.5% of the patients. The commonest sign was vitritis, which was present in all the patients. Spillover anterior segment reaction was found in 43.5% of the patients. The symptoms and signs of patients are depicted in Table 2.

Factors	Tuberculous Intermediate Uveitis	Overall
Defective vision	35 (89.74%)	74 (86.04%)
Floaters	27 (69.23%)	62 (72.09%)
Pain and headache	10 (25.6%)	23 (26.74%)
Redness	8 (20.5%)	38 (44.18%)
Vitritis	39 (100%)	86 (100%)
AC reaction	17 (43.58%)	56 (65.11%)

Table 2. Clinical Features of Our Study Population

Among our study subjects, 74.35% of the patients were Mantoux test positive, 28.2% of the patients had history of contact with tuberculosis. 46.15% of the patients had a previous history of pulmonary or extrapulmonary tuberculosis. Among the Mantoux test, negative population 6 patients were positive for QuantiFERON gold TB. Based on these criteria, the patients were grouped under the diagnosis of presumed ocular tuberculosis was made. These are the patients who did not respond to initial conventional steroid therapy.

Factor	No. of Patients
Mantoux test positive	29 (74.35%)
Contact with TB	11 (28.2%)
History of pulmonary or extrapulmonary TB	18 (46.15%)
Interferon gamma release assay +	6 (15.38%)

Table 3. Diagnostic Features of Study Population

All patients were started on antituberculous therapy for 9 months with tapering dose of oral steroids.

The most common complication seen over the followup was complicated cataract, which was seen in 25.6% of the patients. Other complications were Cystoid Macular Oedema (CME) in 17.9%, glaucoma in 7.7% and Epiretinal Membrane (ERM) in 2.6% (Table 4).

Complications	Tuberculous Intermediate Uveitis (n=39)
CME	7 (17.9%)
Complicated cataract	10 (25.6%)
Glaucoma	3 (7.7%)
Epiretinal membrane	1 (2.6%)

Table 4. Complications We Encountered in Patients with Tuberculous Intermediate Uveitis

The patients who were diagnosed as intermediate uveitis due to tubercular aetiology were started on antituberculous therapy. The recurrences were found to be lower when compared to the episodes before the institution of antituberculous therapy. The analysis was done using Statistical Package for Social Sciences (SPSS Inc., Chicago, IL,) software. It was found to be statistically significant ($p<0.05$).

Response			
	Observed N	**Expected N**	**Residual**
0.00	12	7.5	4.5
1.00	3	7.5	-4.5
Total	**15**		

Test Statistics	
	Response
Chi-square	5.400[a]
Df	1
Asymp. Sig.	.0020

a. 0 cells (0.0%) have expected frequencies less than 5. The minimum expected cell frequency is 7.5

Table 5, 6. Demonstrating Chi-Square Test. The Response to ATT was Found to be Statistically Significant with a p=0.02.

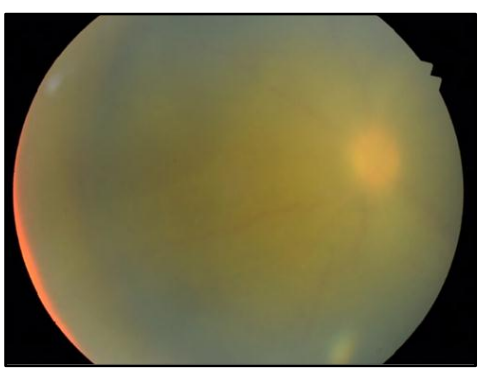

Image 1. Tuberculous Intermediate Uveitis of Vitritis Grade 2

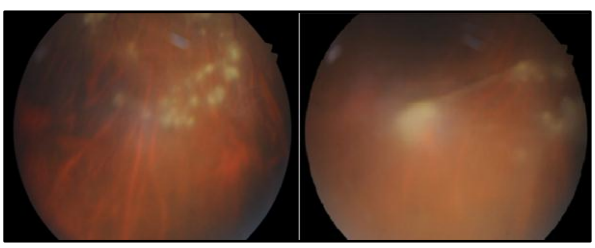

Image 2. Snowballs in the Periphery of a 35-Year-Old Patient, which were Present Bilaterally

DISCUSSION

Intermediate uveitis is characterised by inflammation, which predominates in the vitreous cavity. Though the main aetiology of vitritis is thought to be due to immune mediated mechanisms in developed nations, in countries like India infectious causes predominate. Among many infectious causes like Lyme's disease, tuberculosis tends to predominate in our country.[4] A study conducted in the North eastern population, put forward tuberculosis and sarcoidosis as the main aetiologies of intermediate uveitis.[5] In our study, the patients underwent testing for angiotensin-converting enzyme levels and were safely excluded from our study population.

The epidemiological characteristics of our study population were similar to the previous studies conducted in the same region.[4-7] The commonest feature was vitreous reaction without any evidence of focus in the retina. This suggests that any patient who presents with vitritis without prominent snow banking should be thoroughly investigated and tuberculous aetiology should be ruled out.

In our study, patients were considered for the diagnosis of intermediated uveitis with tuberculous aetiology when vitritis without snowballs or snow banking was present along with either one of the following- a) Positive Mantoux reaction >10 mm; b) History of contact with tuberculosis; c) Previous history of pulmonary or extrapulmonary tuberculosis even in the absence of microbiological evidence of Mycobacterium tuberculosis or positive PCR. Recurrent flare up of vitritis even though the patients are under strict steroid cover should also raise the suspicion of tuberculosis as it is the commonest aetiology in our region.[4] These patients when instituted with antituberculous therapy showed a statistically significant response to treatment as evidenced by reduction in the number of recurrences. Therefore, we suggest that the criteria for attributing the aetiology tuberculosis could be made less stringent in the absence of microbiological or PCR evidence, but with suggestive clinical features. This also reduces the number of patients being considered for the more aggressive immunosuppressive therapy.

The visual prognosis was good in present series as patients could achieve a final visual acuity of 6/12 or better. Presence of various complications like cystoid macular oedema and complicated cataract were associated with poor visual outcome. Such complications were addressed accordingly.

Therefore, in any patient with features of vitritis in whom other infectious aetiologies and noninfectious causes have been ruled out, but have a history of contact with tuberculosis, elevated erythrocyte sedimentation rate, positive tuberculin skin testing or with a previous history of pulmonary or extrapulmonary tuberculosis should be considered for antituberculous therapy before labelling the patients of pars planitis or proceeding with immunosuppressive therapy. Such patients show a good response to antituberculous therapy with a reduction in recurrence of intraocular inflammation.

CONCLUSION

In patients with intermediate uveitis who do not respond well to steroids and in patients with recurrences after cessation of steroid therapy detailed evaluation should be carried out to rule out tuberculous aetiology. Prompt institution of antituberculous therapy may reduce complications in patients with intermediate uveitis and improve the visual outcome as these patients respond well to ATT. We also recommend following less stringent but appropriate criteria for the diagnosis of tuberculous intermediate uveitis.

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