ORIGINAL ARTICLE

Role of Antitubercular therapy in Eales' Disease

Yog Raj Sharma, Kumar Ram Krishna, Hem Kumar Tewari, Ashok Rattan, Deependra Vikram Singh

Abstract

Eales' disease is most frequently found linked with tuberculosis. Hence, the present prospective randomized study was conducted to evaluate the role of anti-tuberculosis therapy in Eales'disease, by carrying out physical, neurological, ophthalmological examination and laboratory tests. The results of present study reveals that there is no rationale for prescribing anti-tuberculosis treatment with active Eales' disease with no systemic tuberculosis

Key Words

Eales' diseases, Anti-tubercular therapy, Vitreal hemorrhages

Introduction

Eale's disease initially described as abnormal retinal veins in healthy young men with recurrent vitreal hemorrhages by Henry Eale's in 1880 but did not include vascular inflammation or neovascularization as part of disease spectrum (1). Most investigators now believe that Eale's disease is a distinct entity characterized by idiopathic retinal perivasculitis and peripheral nonperfusion along with development of neovascularization, recurrent vitreous hemorrhages and tractional retinal detachment. The disease is still a diagnosis of exclusion.

Eale's disease appears most commonly to affect healthy young adults in the third and fourth decades of life (2). The disease is prevalent in India, Pakistan, and Afghanistan (2). Although active vasculitis has been a well established clinical entity for more than a century, the etiology and treatment are still elusive. The disease most frequently linked to Eale's disease is tuberculosis. Hypersensitivity to tuberculoprotein has been suggested by many studies. Some patients diagnosed with Eale's disease have had concurrent active pulmonary tuberculosis (3-6). Recently, *Mycobacterium tuberculosis* complex DNA was detected in vitreous fluid samples of Eale's' disease patients using polymerase chain reaction (7). The presence of *Mycobacterium tuberculosis* DNA by nested polymerase chain reaction technique in epiretinal membrane specimens from patients with Eale's disease was demonstrated by another study (8). Bacteriological examination of vitreous fluid samples did not reveal the presence of acid fast bacilli (7). In addition, Biswas *et al* (9) found statistically significant higher phenotype frequencies of HLA B5 (B51), DR1, and DR4 in patients with Eale's disease compared with healthy people. It is hypothesized that individuals with the HLA predisposition may develop retinal vasculitis as a result of a cell mediated immunological tissue damage triggered by a sequestered *Mycobacterium tuberculosis* antigen in an inactive form and clinically present as Eale's disease (8). Although steroids for active vasculitis and scatter photocoagulation of ischemic retina for retinal neovascularization have been the main stay antitubercular

From Vitreo-Retina Services, Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS, Ansari Nagar, New Delhi-110029, India.
Correspondence to: Dr. Deependra V. Singh, R. No. 493, Dr Rajendra Prasad Centre for Ophthalmic Sciences AIIMS, Ansari Nagar, New Delhi.

chemotherapy (ATT) has also been used with some success in past. We conducted this randomized masked trial to evaluate the role of ATT in management of Eale's disease which if found effective would also help in establishing the etiological role of mycobacterium.

Material and Methods

Sixty eyes with idiopathic active retinal vasculitis defined as presence of perivascular cuffing, retinal edema, preretinal exudates and leaking retinal vessels on fluorescein angiography were randomly assigned to one of the six different groups; **A** – receiving ATT (standard doses of isoniazid and rifampicin adjusted to weight of the patient) only, **B –** receiving systemic steroids (prednisolone 1mg/kg/day) only, **C –** receiving periocular steroids (Methyl prednisolone ½ cc/20mg 3 injections repeated every three weeks) only, **D** – receiving both ATT and systemic steroids, **E** – receiving ATT and periocular steroids, **F** – control group: no treatment. At presentation, all the patients had full medical and ophthalmological examinations. This included complete history and a physical, neurological, and ophthalmological examination and laboratory tests (Table 1).

Table 1. Diagnostic studies performed on patients with Eales' disease

Routine tests	Other tests (whenever required)
Complete blood count	Infectious diseases
Erythrocyte sedimentation rate (increased if >15mm/hr for male and > 20mm/hr for female)	VDRL
Blood Sugar	FTA-ABS
Chest Radiograph	PPD
Mantoux test (positive if induration >10mm at 72 hrs)	Systemic autoimmune disorders
ELISA for Mycobacterium	Antinuclear antibody, Anti-double stranded DNA antibodies, ANCA

Ophthalmological evaluation included determination of visual acuity, applanation tonometry, slit lamp examination of the anterior segment, and direct and indirect ophthalmoscopy, including examination of the posterior and peripheral retina with a Goldmann three mirror contact lens after pupillary dilatation, fundus photographs, and intravenous fluorescein angiography (FA) in eyes with clear media. Only one eye of a patient was included and eyes, which have received photocoagulation or have undergone vitrectomy were excluded. Patients having pulmonary or extra pulmonary tuberculosis were also excluded. Envelope method was used for randomization.

All patients were followed up for at least 12 weeks with FA, scatter photocoagulation and vitrectomy done whenever required. Final BCVA and presence/absence of active vasculitis were final outcome measures at 12 weeks. Absence of ophthalmocsopic and angiographic signs of activity as defined earlier with or without sclerosed vessels or chorioretinal scars was considered healed vasculitis. Eyes showing substantial improvement but not complete absence of perivascular cuffing or leaks on FA were considered as partly improving.

Wilcoxon signed-rank test was used to find any significant difference in incidence of increased ESR and positive Mantoux test between the 6 groups. All patients receiving ATT were observed for development of ocular or systemic adverse effects by repeated liver function tests, visual evoked responses and color vision. Mantoux positive patients receiving systemic steroids alone were also observed for reactivation of pulmonary tuberculosis.

Results

This prospective randomized trial enrolled 60 male patients whose age ranged from 16 to 45 years with a mean of 27.40 years. Nineteen patients were found to be Mantoux positive (Table 2). Only 4 patients had increased erythrocyte sedimentation rate. The difference in incidence of Mantoux positive rate and ESR between the 6 groups was not found to be statistically different on Wilcoxon signed-rank test.

The final healing responses of six regimens given to six different groups are shown in (Table 3). The response of eyes treated with ATT alone (Group A) was comparable to eyes receiving no treatment (control Group F) with less than 30% of eyes in each group showing partial or complete response. Although difference in healing response between none of the groups was found to be statistically significant, there was better response to combination of ATT with periocular steroids (Group

Table 2. Results of Mantoux test

Groups	Positive Mantoux test (No of eyes)	Negative Mantoux test (No of eyes)
A	2	8
B	3	7
C	5	5
D	3	7
E	3	7
F	3	7
Mantoux test positive if induration > 10mm at 72 hrs		

Table 3. Response of 60 eyes (10 each group) to six different regimen at 12 weeks.

Groups	Healed	Partial improvement	No improvement/ worsening
A (ATT)	1	1	8
B (SS)	2	4	4
C (PS)	5	0	5
D (ATT,SS)	2	3	5
E (ATT, PS)	5	2	3
F (Control)	1	2	7
ATT-Antitubercular chemotherapy, SS-Systemic steroids, PS-Periocular steroids			

Table 4. Pretreatment and post treatment BCVA for six treatment groups.

E) as compared to combination of ATT with systemic steroids (Group D) or steroids alone (Group B & C).

Final visual acuity at six months is depicted in (Table 4). There was no statistically significant difference in pre and post treatment BCVA in all the groups.

No eye developed tractional retinal detachment. Two eyes one each in group A and F required pars plana vitrectomy along with endo-photocoagulation for nonclearing vitreous hemorrhage. Five eyes, 2 in group F and 1 each in groups A, B and C required scatter photocoagulation for retinal neovascularization. None of the patients receiving ATT developed any adverse effects. No Mantoux positive patient receiving systemic steroids alone showed any sign of reactivation of pulmonary tuberculosis.

Discussion

Eale's' disease is a diagnosis of exclusion and other systemic disease such as diabetes, hypertension, blood dyscrasias, haemoglobulinopathies, sarcoidosis or systemic lupus erythematosus should be ruled out. The earliest stages of the disease are marked by low grade periphlebitis. Later the disease progresses to increasing areas of non-perfusion of the capillaries of the peripheral retina. With progression of the disease, retinal capillary closure extends contiguously in a posterior direction. With increasing retinal non-perfusion and ischemia, neovascularisation can appear, usually at the junction of perfused and non-perfused retina. The patient remains unaware of these early changes. However, when bleeding from the abnormal new blood vessels occurs, the patient can notice "floating spots" or blurred vision. Ultimately, Eale's disease can progress to functional loss of the eye through traction retinal detachment. The primary treatment of active Eale's disease has been corticosteroids. Other therapies used for controlling disease include potassium iodide orally or intravenously, thyroid extract, estrogens, vitamin C, vitamin K with most of them of very little benefit (10,11,12). Although no active bacterium has been cultured from ocular samples till date there are still a number of indirect evidences to support the role of tuberculosis in Eale's disease (2, 7, 8, 11,13). Of the several etiologies proposed, most favored is hypersensitivity to tuberculoprotein (11). Treatment of Eale's disease, without active mycobacterium infection, with ATT has been described in literature with equivocal results (12,14).

This randomized controlled trial reveals prescribing ATT alone is not significantly more effective than giving no therapy for treatment of active vasculitis (healing and or improvement at 12 weeks). The number of eyes showing healed vasculitis or improvement at 12 weeks was comparable for steroid alone and steroid with ATT groups with periocular steroid showing better response than systemic steroids.

Our data suggest the ineffectivity of ATT in controlling Eale's active vasculitis which can partly be explained by the fact that hypersenstization might have already occurred before ATT was instituted. Thus our study does not rule out the etiological role of tuberculosis in Eale's disease.

Like any other study this too has few limitations; first only 2 drugs were included in ATT, second only the

healing response of active vasculitis was studied but not the recurrence rate or rate of development of neovascularization or tractional retinal detachment. ATT might have prevented further sensitization and hence recurrent vasculitis over a longer follow up period. The study also found as many as 68% of the patients affected with Eale's disease to be Mantoux positive. This reconfirms the strong association of skin hypersensitivity to tuberculoprotein and Eale's disease as has been described earlier.

We conclude that at present there is no rationale for prescribing ATT to patients with active Eale's' disease with no systemic tuberculosis. Further studies with longer duration follow-up are warranted to totally negate the role of ATT in Eale's' disease.

References

1. Eale's H. Primary retinal hemorrhage in young men. *Ophthalmol Rev* 1882; 1: 41-6.
2. Helm CJ, Holland GN. Ocular tuberculosis. *Surv Ophthalmol* 1993; 38: 229-56.
3. Renie WA, Murphy RP, Anderson KC *et al*. The evaluation of patients with Eale's disease. *Retina* 1983; 3: 243-48.
4. Theodossiadis G. Fluorescein angiography in Eale's disease. *Am J Ophthalmol* 1970; 69: 271-77.
5. Elliot J. Thirty-year observation of patients with Eale's disease. *Am J Ophthalmol* 1975; 80: 404-48.
6. Elliot AJ. Recurrent intraocular hemorrhage in young adults (Eale's disease). A report of thirty-one cases. *Trans Am Ophthalmol Soc* 1954; 52: 811-75.
7. Biswas J, Therese L, Madhavan H. Use of polymerase chain reaction in detection of Mycobacterium tuberculosis complex DNA from vitreous sample of Eale's disease. *Br J Ophthalmol* 1999; 83: 994.
8. Madhavan HN, Therese KL, Gunisha P *et al*. Polymerase chain reaction for detection of Mycobacterium tuberculosis in Epiretinal membrane in Eale's disease. *Invest Ophthalmol Vis Sci* 2000; 41: 822-25.
9. Biswas J, Mukesh BN, Naratin S *et al*. Profiling of human leukocyte antigens in Eale's disease. *Int Ophthalmol* 1998; 21: 277-81.
10. Elliot AJ, Harris GS. The present status of the diagnosis and treatment of periphlebitis retinae (Eale's' disease). *Can J Ophthalmol* 1969; 4: 117-22.
11. Das T, Biswas J, Kumar A *et al*. Eale's disease. I*nd J Ophthalmol* 1994; 42: 3-18.
12. Mahon D. Eale's disease treated with cortisone, streptomycin and vitamin C. *J Ir Med Assoc* 1951; 28(165): 50-1.
13. Shah SM, Howard RS, Sarkies NJC *et al*. Tuberculosis presenting as retinal vasculitis. *J Roy Soc Med* 1988; 81: 232-33.
14. Sykowski P. Streptomycin in Eale's disease**.** *Am J Ophthalmol* 1951; 34(6): 889-90.