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Clinical profile of uveitis in Hansen's disease after completion of treatment – A study of 50 cases using Polymerase Chain Reaction (PCR) on aqueous humour

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ABSTRACT:

Chronic low grade anterior uveitis is the commonest cause of blindness in leprosy. It is usually asymptomatic until the late stages and patients seek help only after irreversible visual loss. We analysed patients who had a recurrence of uveitis after completion of treatment with anti-leprosy drugs and had been proven as histopathologically negative. The presence of chronic uveitis, complications and the extent of ocular damage it may cause, can continue even after treatment, emphasising the importance of follow-up, early detection and treatment. This is a prospective cohort study. Ophthalmic evaluation was performed using slit lamp examination, biomicroscopy, indirect ophthalmoscopy, applanation tonometry, corneal sensation and Schirmer's test. Split skin microscopy was done to confirm the activity of leprosy. In patients with recalcitrant iridocyclitis, anterior chamber paracentesis was performed. The sample was analysed both by smear and polymerase chain reaction. The sequences that were targeted using PCR included genes encoding the DNA of 36-kDa antigen, 18-kDa antigen, 65-kDa antigen and the repetitive sequences among other M. leprae genes. Aqueous aspirate showed copies of mycobacterium leprae DNA in five out of twelve patients with recalcitrant anterior uveitis. Direct smear and staining with Ziehl- Neelson staining for mycobacteria was positive showing both live and dead bacilli. Live bacilli can persist in the aqueous humour even after completion of treatment. In our study this was more frequently observed in tuberculoid leprosy. This is possibly due to an immune mediated response combined with inadequate treatment dose in these patients.

Key words: Hansen's disease, uveitis, polymerase chain reaction, aqueous humour, split skin microscopy

INTRODUCTION

Leprosy also called Hansen's disease is one of the systemic diseases which can give rise to a plethora of features in the eye. Ocular involvement in leprosy is estimated to be 70-75%. Of this about 10-50% of leprosy patients suffer from severe ocular symptoms and blindness occurs in about 5% of patients[1].Leprosy causes ocular damage in several ways.One mechanism is through paralysis of trigeminal and facial nerve leading to lid abnormalities and corneal anaesthesia. Decreased corneal sensation can result in corneal ulceration, opacification and blindness.It can affect the eye through direct corneal invasion resulting in keratitis, scleritis and iridocyclitis[2].Another mechanism is by destruction of the fibres from the autonomic nervous system resulting in pinpoint pupil and chronic low grade iridocyclitis. Acute anterior iridocyclitis is uncommon and bilateral but can occur due to lepra reaction more commonly than due to active disease. It develops during the reactional state, with erythema nodosumleprosum and is related to T cell suppression and an immune complex deposition[3]. The commonest form of uveitis in leprosy is a chronic, low grade, bilateral uveitis which produces minimal or no symptoms until late in the disease process[4]. Cataracts, synechiae, pinpoint pupils, glaucoma, iris atrophy, and ciliary body damage occur insidiously, resulting in ocular morbidity[5].It has been postulated that this form of uveitis is neuroparalytic in origin[6].Chronic low grade anterior uveitis is the commonest cause of blindness in leprosy. It is usually asymptomatic until the late stages, and

often patients seek help only after irreversible visual impairment has occurred. We present here an analysis of 50 cases of uveitis in patients with leprosy. All of them had completed treatment with anti- leprosy drugs in doses as recommended by the world health organisation. They had been proven as histopathologically negative by slit skin microscopy. This study reinforces the effects on inflammation which occurred several years after treatment. The need for early detection, treatment, and frequent monitoring of the eye problem after resolution of the systemic disease is important to prevent late visual loss.

Material and Methods: This is a prospective study performed in a tertiary referral hospital in India. It was performed after institutional ethics committee approval and an informed consent was obtained from all patients. Inclusion criteria comprised of all patients with Hansen's disease who had completed treatment for either paucibacillary, multibacillary or indeterminate type of leprosy. Patients who had not completed treatment and those with other forms of systemic infections such as tuberculosis, toxocariasis, candida retinochoroiditis were excluded from the study. All cases were referred from a leprosy rehabilitation centre in Chennai, Tamilnadu and the study was conducted in concurrence with the department of dermatology. Other criteria for enrolment in the study were, adequate follow-up for at least one year from the onset of uveitis and completeness of the medical and ocular records. The ocular examination included a visual acuity examination, slit-lamp examination, applanation tonometry, corneal sensation and Schirmer's tests. The treatment for multibacillary leprosy was a standard regimen for 12 months consisting of rifampicin 600mg once a month, dapsone 100mg daily and clofazamine300mg once a month. Those with paucibacillary leprosy had completed a regimen of 6 months durationwhich included rifampicin 600mg once a month and dapsone 100mg daily. Management of uveitis was done using topical cycloplegics and corticosteroid eye drops to manage inflammation. A split skin microscopy was performed in each patient to confirm the activity of the disease, the extent of systemic disease and the response to treatment. The smear estimated the number of acid-fast bacilli that were detected and this was reported as the bacterial Index. Skin smears were taken from earlobes, elbows and knees as well as from lesions in the patient. AC paracentesis was performed under aseptic precautions using povidone iodine and a 26 gauge needle mounted on a tuberculin syringe. 0.1ml of aqueous humour sample was obtained. Ziehl Neelson Carbol Fuchsin stain was used for the diagnosis after the slide was prepared. In those with recalcitrant uveitis, a polymerase chain reaction (PCR) was performed on the aqueous humor sample. The sequences that were targeted using PCR included genes encoding the DNA of 36-kDa antigen, 18-kDa antigen, 65-kDa antigen and the repetitive sequences among other M. leprae genes. Apart from genetic sequencing, complete blood counts, purified protein tests and chest x rays were done for all patients. Follow up was done for 5 years and during each visit a complete ophthalmic evaluation was performed.

RESULTS

This study was performed on 50 eyes of 50 patients with uveitis over a five year period. Ages ranged from 25 to 60 years. 63% were tuberculoid leprosy, 25% were lepromatous leprosy and 12% were indeterminate type. 38% showed acute anterior uveitis and 62% showed chronic anterior uveitis. It was granulomatous in 63% with the predominant clinical feature being iris sphincter atrophy and dilated pupil with large mutton keratic precipitates (Figure 1) and anterior chamber cells and flare. 27 % of patients presented with a non- granulomatous iridocyclitis although that is not a usual presentation in uveitis. Cataract was noted in 33% of patients (Figure 2). On morphological evaluation, posterior subcapsular cataract was the most common feature and both senile and complicated cataract were seen. Several of our patients had dilated pupil due to iris sphincter atrophy (Figure 3). Vitritis was present in 3% of patients and was seen as grade 2 cells with vitreous haze. Fundus examination was normal in all patients. 12% of patients had scleritis of the nodular type. Those with scleritis showed resolution with topical steroids with no recurrence and a scraping was not performed on them. Treatment for iridocyclitis was 1% atropine eye drops,1% prednisolone acetate eye drops and oral steroids in the dose of 1mg per kg bodyweight was added in a few. In those with no resolution to this treatment for more than 3 weeks, an anterior chamber paracentesis was performed. PCR performed on the aqueous humour of12 patients with recalcitrant uveitis showed detection of DNA of M. leprae in 5 of them (Figure 4). A smear in these patients showed the presence of live and dead bacilli. Microscopy showed the typical morphology of fully formed live bacillus and beaded dead bacilli both existing in the same sample (Figure 5). After completion of treatment, the onset of uveitis in the paucibacillary type occurred within 1 year in 9% of patients, 2 years in 33% and within 3 years in 11% and within 5 years in 2% of patients. Those with multibacillary leprosy had recurrence of uveitis after 3 years of completion of treatment. No patients had uveitis before that time period.

DISCUSSION

India is endemic for leprosy. Poor nutrition, immunity, unhygienic living atmosphere and overcrowding have been identified as the cause for higher prevalence of leprosy in our population. Ocular manifestations in leprosy can involve the eyelids, cornea, lacrimal sac, cornea, uvea and sclera. Commonly reported clinical features are madarosis, ectropion, entropion, trichiasis, lagophthalmos, dacryocystitis, conjunctivitis, scleritis or episcleritis.

Corneal involvement occurs in the form of loss of corneal sensation, superficial keratitis, corneal opacities, interstitial keratitis, adherent leucoma, corneal ulcer or pannus and secondary to uveal involvement. Uveal involvement may be seen as any one of three types. An acute granulomatous iridocyclitis with mutton fat keratic precipitates, posterior synechiae and anterior chamber cells and flare. The second type described is a neuroparalytic uveitis with dilator muscle atrophy. A third type with iris pearls and complicated cataract has been reported. Leprosy control programmes are aimed at reducing the burden of cataract in these patients [7]. A rare case of hypopyon[8]in leprosy uveitisand recurrent scleritis[9]have been reported.

The prevalence of ocular lesions was found to be higher in those with longer duration of the disease and in leprosy rehabilitation centres[10]. Anterior chamber paracentesis has been used to confirm the aetiology of uveitis in patients with Hansen's disease when there was atypical presentation[11]by Ziehl-Nielsen staining method.Among other systemic diseases leprosy is known to cause ocular complications more frequently[12].The presence of uveitis during the long course of leprosy has been reported even in countries non- endemic for tuberculosis[13]. In a rural community endemic for Hansen's disease, significant ocular morbidity has been reported among those who have completed treatment for multibacillary leprosy [14].

Mahendradas et al have reported that in patients with granulomatous lesions in the anterior segment, optical coherence tomography helps to identify the extent of involvement, by showing well demarcated areas with internal hyporeflectivity and after shadowing[15]. Iris biopsy has also been used in leprosy uveitis for diagnosis [16].

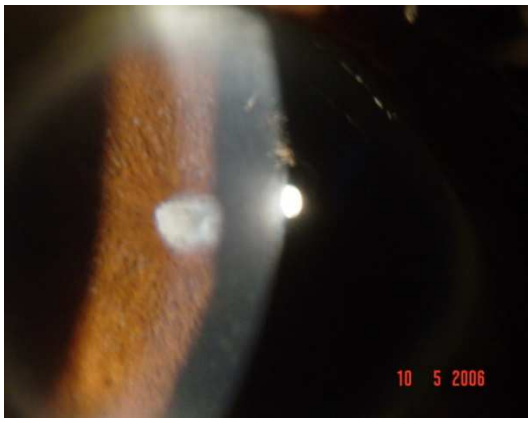

Figure 1: Mutton fat keratic precipitates and iris pearls

Figure 2: Complicated cataract in chronic uveitis

In the present study although patients with uveitis had been proven as histopathologically negative using slit skin smears, we detected the presence of leprae bacilli from aqueous humour samples. Episcleritis and scleritis was frequently observed in our patients and was more common in the tuberculoid type. Another variation that we noted in our studied was the presence of non- granulomatous iridocyclitis which is not usually seen in leprosy. Although literature reports pinpoint miotic pupil as a feature of leprosy uveitisis, dilated pupil with iris sphincter atrophy was seen in our patients. These persisting bacilli as a cause of uveitis in such patients has not been reported till now. Presence of iridocyclitis even after completion of treatment with anti-leprosy drugs meant that either paucibacillary

patients received inadequate treatment which did not permeate the anterior chamber to allow destruction of bacilli or could be due to an immune-mediated granulomatous anterior uveitis.

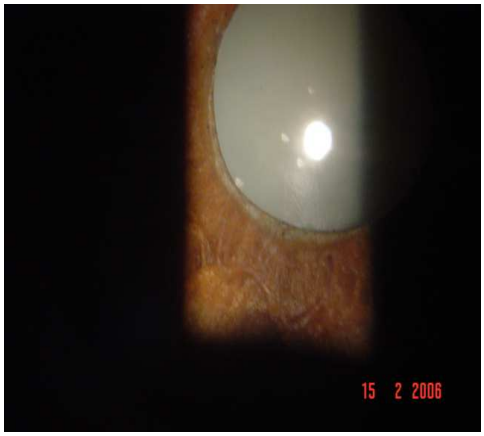

Figure 3: Iris sphincter atrophy with dilated pupil

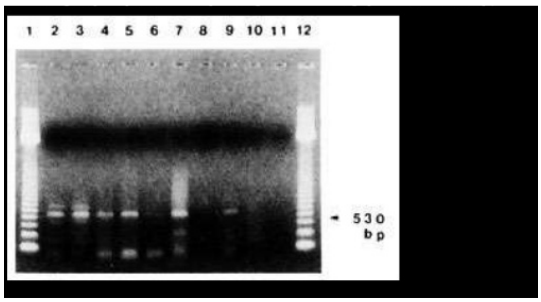

Figure 4: PCR detection of M. leprae DNA from aqueous humor samples

Figure 5: Smear made from anterior chamber aspirate shows granular beaded dead bacilli and fully formed live bacilli coexisting in the same patient. Zeihl- Neelson x 790

CONCLUSION

Evaluation and analysis of aqueous humour by PCR has shown that DNA assays can be very sensitive in identifying bacilli and their DNA. Patients who have completed treatment are more likely to have persisting M.leprae bacilli in the aqueous humour in the paucibacillary type. Also the recurrence of uveitis is earlier in these patients than the multibacillary type. We found in our study that the commonest cause of defective vision is chronic uveitis with complicated cataract which is treatable if detected early[17].It may be required to start anti leprosy treatment again when live bacilli are seen in the aqueous humour even if the systemic status has settled. PCR can certainly ascertain the diagnosis by detecting even few bacilli from a small sample. This may actually be helpful in breaking the chain of leprosy transmission. PCR of aqueous humour can be adopted as a routine in all patients who present with anterior uveitis after completion of leprosy treatment. The prevalence of uveitis and blindnessin leprosy can vary between different populations[18]. A programme for screening of leprosy should continue throughout the course of treatment and at regular intervals even after completion of treatment for both multibacillary and paucibacillary forms.

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