WORLD VIEW

Evolution of vision reducing cataract in skin smear positive lepromatous patients: does it have an inflammatory basis?

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Aim: To describe the incidence and risk factors of vision reducing cataract in skin smear positive lepromatous patients.

Methods: Prospective longitudinal cohort study: 212 newly diagnosed lepromatous patients were followed during the two years of treatment with multidrug therapy and for a further five years, with biannual ocular examinations. Incidence of vision reducing ($\leq 6/18$) cataract was calculated as the number of patients with cataract per person year of cataract-free follow up among those who did not have cataract at baseline.

Results: Cataract was present in 27 (11%) of lepromatous patients at diagnosis. Forty nine patients (2.87%/person year (95% confidence interval (CI), 2.17% to 3.80%)) developed cataract during a total follow up period of 1704 person years; 45 of these were ≥ 41 years old and were followed for a total of 638 person years with an incident rate of 0.070 (95% CI, 0.0523 to 0.094). Stepwise multiple regression confirmed the association of age (per decade) (hazard ratio (HR) = 2.50 (95% CI, 1.82 to 2.78), $p < 0.001$), clofazimine crystals on the cornea (HR = 49.92 (5.48 to 454.82), $p = 0.001$), grade 2 deformity in all limbs (HR = 3.17 (1.12 to 8.97), $p = 0.029$), and uveal inflammation (HR = 3.52 (1.42 to 8.67), $p = 0.006$). No significant association was found with oral steroids.

Conclusions: Cataract develops at the rate of 7%/person year in lepromatous patients over 40 years of age. It is associated with increasing age, subclinical intraocular inflammation, and grade 2 deformity.

Cataract is recognised to be the leading cause of blindness in the world. As the world's population ages, cataract induced visual dysfunction and blindness is on the increase.

The cure for cataract has been almost entirely through surgical methods, but this is not equally available to all, and the surgery which is available does not produce equal outcomes.¹ The challenge is to prevent or delay cataract formation, and ongoing efforts are increasingly focused on factors that initiate and sustain the development of cataract. For reasons that are still largely elusive, populations from the Indian subcontinent have a very high incidence of cataract.²

The Indian subcontinent is also home to more than half the world's leprosy population. Although recent estimates of new cases show a gradually declining trend, in early 2006 around 220 000 new cases of leprosy were diagnosed worldwide.³ Largely because of the extensive coverage of multidrug therapy (MDT) and improved socioeconomic conditions in endemic nations, there were an estimated 14 million cured leprosy patients worldwide by the end of 2006.⁴ A significant number of these will continue to bear the consequences of disability and disfigurement, and ocular complications would occur during their MDT as well as during periods after completion of therapy.^{5,6}

Cataract, a major cause of visual impairment among leprosy patients, may not merely be related to aging but linked in some way to the disease process. Factors that could influence its evolution in leprosy patients include steroid treatment and intraocular inflammation. Knowledge of possible associated risk factors would help in formulating measures to prevent or delay the onset of cataract in patients affected with leprosy.

METHODS

All newly diagnosed multibacillary (MB) leprosy patients resident within the leprosy control area of the Schieffelin Leprosy Research and Training Centre in the Vellore District of

South India were invited to participate in a longitudinal ocular study. Patient recruitment started in 1991 and was completed in 1997. Consenting study patients received a baseline ocular examination followed by prospective biannual examinations during the two year period they were on MDT and for five years thereafter. Patients were actively followed up in the field by public health workers belonging to their own community and encouraged to come for regular biannual check up examinations. Research methods and protocols were approved by the institutional review board of the Schieffelin Leprosy Research and Training Centre, and were conducted in accordance with the principles of the Declaration of Helsinki. All patients were provided with examinations and treatment free of charge.

At enrolment, the following leprosy characteristics were recorded: the type of MB leprosy based on the clinical classification of Ridley and Jopling⁷; deformity grading of hands and legs based on the World Health Organisation (WHO) classification⁸; the bacterial index calculated from the results of the acid-fast staining of smears from specific skin sites⁹; the presence of type 1 (reversal reaction) or type 2 (erythema nodosum leprosum) reactions; and a history of hypopigmented or erythematous patches on the face.

At each visit, the following ophthalmic characteristics were recorded: visual acuity (with and without correction); presence of orbicularis oculi weakness, lagophthalmos, ectropion, entropion, trichiasis, corneal opacity, corneal ulcer, episcleritis, scleritis, clofazimine crystals on the cornea, flare and cells, posterior synechia, iris atrophy, and cataract. Best corrected visual acuity was measured with Snellen's chart by a trained examiner. After examination of the adnexae, slit lamp biomicroscopy was done on all patients. Applanation tension was recorded in the upright position. Direct ophthalmoscopy without dilatation was carried out in all patients during each visit, and those with decreased vision or intraocular

Abbreviations: MB, multibacillary; MDT, multidrug therapy

Table 1 Risk factors for developing cataract in smear positive lepromatous patients

Factor	Hazard ratio (95% CI)	p Value
Demographic		
Age (per decade)	2.315 (1.890 to 2.836)	<0.001
Sex (female v male)	1.053 (0.566 to 1.958)	0.870
Leprosy		
Classification (LL v BL)	1.178 (0.552 to 2.515)	0.671
Duration of leprosy (>1 v ≤1 year)	1.840 (1.001 to 3.381)	0.049
History of face patch	0.888 (0.496 to 1.588)	0.688
Face patch	0.938 (0.696 to 1.263)	0.674
History of reactions	0.632 (0.250 to 1.598)	0.332
No reaction v type 1 reaction	0.971 (0.505 to 1.866)	0.929
No reaction v type 2 reaction	1.845 (0.252 to 13.481)	0.546
Skin smear (≥3.00 v <3.00)	0.748 (0.363 to 1.543)	0.432
Grade 1 or 2 in any limb v no deformity	1.701 (3.341 to 0.123)	0.866
Grade 1 or 2 in all limbs v no deformity	3.528 (1.607 to 7.747)	0.002
Grade 2 deformity in all limbs	1.874 (1.253 to 2.804)	0.002
Ocular		
Lagophthalmos	0.638 (0.088 to 4.623)	0.656
Impaired corneal sensation	1.896 (0.918 to 3.913)	0.084
Peripheral corneal opacity	0.901 (0.324 to 2.508)	0.842
Punctate keratitis	0.904 (0.125 to 6.550)	0.920
Flare and/or cells	29.297 (3.604 to 238.125)	0.002
Keratic precipitates	4.691 (1.680 to 13.097)	0.003
Iris atrophy	11.699 (3.483 to 39.289)	<0.001
Uveal inflammation*	5.814 (2.453 to 13.777)	<0.001
Naso-lacrimal duct patency	6.256 (2.237 to 17.493)	<0.001
Pterygium	2.715 (1.384 to 5.327)	0.004
Intraocular pressure†	1.741 (0.903 to 3.358)	0.098
Drugs		
Oral steroids		
Cumulative dose <2000 mg v no steroids	0.789 (0.593 to 0.332)	1.880
Cumulative dose >2000 mg v no steroids	0.805 (0.547 to 0.397)	1.632
Corneal B663 crystals	51.847 (5.795 to 463.876)	<0.001

*Uveal inflammation includes flare and cells and/or keratic precipitates and/or iris atrophy.

†Pressure ≤10 mm Hg v pressure between 10 and 20 mm Hg.

BL, borderline lepromatous leprosy; LL, lepromatous leprosy.

complications underwent pupil dilatation and were examined with an indirect ophthalmoscope.

Cataract was defined as the presence of any lens opacity observed during slit lamp examination and confirmed by distant direct ophthalmoscopy after dilatation, and consistent with a corrected visual acuity of 6/18 or worse. For analytical purposes, patients free of cataract at enrolment who underwent cataract surgery during follow up also were also considered to have developed cataract.

The incidence of cataract was calculated as the number of patients with cataract observed per person year of cataract-free follow up while taking MDT and for a period of five years after completion of therapy, among patients who did not have cataract at baseline. Patients were followed either until completion of the study in June 2004 or until death or migration, whichever occurred earlier. Statistical analysis was conducted, with the unit of observation being the individual rather than the eye. Cox proportional hazards regression was used to analyse the occurrence of cataract according to demographic and clinical characteristics associated ($p < 0.05$) with pathology by univariate analysis. Probability (p) values, hazard ratios (HR), and 95% confidence intervals (CI) were generated. Patients who did not have positive skin smears for *M leprae* at enrolment and those who had no follow up visits were excluded from analysis.

RESULTS

In all, 301 MB patients were enrolled. Fifty five of them were negative for *M leprae* at enrolment. Of the remaining 246 patients, 27 presented with cataracts and seven did not have any follow up visits after enrolment. Thus the analysis was on 212 smear positive lepromatous patients who had no cataracts at diagnosis. None of the patients had central corneal opacities or significant peripheral corneal opacities that compromised vision.

There were 154 male and 58 female patients. Age ranged from 7 years to 74 years with a mean (SD) of 39.3 (13.4) years; 33 had lepromatous leprosy and 179 had borderline lepromatous leprosy. Eighty one had no deformity of the limbs, 101 had either grade 1 or grade 2 deformity in one or more limbs, and 30 had grade 1 or grade 2 deformity in all limbs.

Forty nine individuals (2.87%/person year (95% CI, 2.17% to 3.80%)) developed cataract during a total follow up period of 1704 person years. Forty five of these were 41 years or older and were followed up for a total of 638 person years with an incident rate of 0.070/person year (95% CI, 0.0523 to 0.094). Risk factors that were analysed for an association with vision reducing cataract are given in table 1. Although several significant associations were found on univariate analysis, stepwise multiple regression confirmed the association of only age (per decade) (HR = 2.50 (95% CI, 1.82 to 2.78), $p < 0.001$), B663 crystals on the cornea (HR = 49.92 (95% CI, 5.48 to 454.82), $p = 0.001$), grade 2 deformity in all limbs (HR = 3.17 (95% CI, 1.12 to 8.97), $p = 0.029$), and uveal involvement (HR = 3.52 (95% CI, 1.42 to 8.67), $p = 0.006$).

DISCUSSION

Multibacillary leprosy, as defined by the WHO, includes all cases with more than five hypopigmented skin patches on clinical examination. Although we followed up a cohort of newly diagnosed MB leprosy patients, our analysis was based only on patients with positive skin smears. This excluded patients belonging to the tuberculoid spectrum of the disease who are known to have fewer intraocular complications than lepromatous patients.

Our study shows that vision reducing cataract (vision ≤6/18) develops at the rate of 3% per person year among lepromatous patients. When patients 41 years or older are taken to be the population at risk, the figure goes up to 7% per person year. Comparison with other incident studies is difficult as our definition of cataract was based on vision impairment, distant direct ophthalmoscopy, and slit lamp biomicroscopy. Most studies have described only prevalence data on cataracts. Progression of cataract has been described in a population similar to the one from which our cohort was derived but the methodology used was more refined.¹⁰ A study defining cataract by using distant direct ophthalmoscopy in an Indian population had estimated that 3.8 million people go blind in India because of cataract every year.¹¹ Despite the limitation of not categorising the cataracts anatomically or grading them by severity or photographing them, the study highlights the need for continued specialised ophthalmic care, including cataract surgery, for a large microbiologically cured aging leprosy population.

Intraocular inflammation and oral steroids are two other important factors associated with the development of cataract in leprosy affected persons.¹² It is evident from our study that uveal inflammation plays a major role in the evolution of cataract in smear positive lepromatous patients. None of the patients had florid anterior uveitis during the follow up period. The subtle and low grade nature of the inflammation will not readily be apparent unless carefully screened using a slit lamp, which is not appropriate for diagnosis in a community setting. It does, however, raise the possibility of potential interventions. *M leprae* or its remnants can remain in the uveal tissue long

after completion of treatment with MDT and can stimulate inflammation.¹³ Even though increasing loads of mycobacteria in the skin were not associated with cataract formation it may be possible to destroy bacilli that are resident in the ocular tissues by using topical bactericidal drugs such as fluoroquinolones.¹⁴ Several studies have also proved that histopathology discloses many more cases of silent chronic iridocyclitis in leprosy patients than are diagnosed clinically, and it is likely that uveal inflammation plays a much greater and more significant role in the development and progression of cataract in lepromatous patients than is presented in this epidemiological study.^{13 15 16}

Lepromatous leprosy and borderline lepromatous leprosy can develop reversal reactions or erythema nodosum leprosum that necessitate treatment with oral steroids, usually for periods of three months or more.¹⁷ In our cohort even cumulative doses of more than 2000 mg of prednisone were not significantly associated with the development of cataract. Crystalline corneal deposits of clofazimine can occur in an occasional patient on MDT.¹⁸ The numbers were too small in our cohort to infer any meaningful association but their role in lenticular changes has been acknowledged.¹⁹

Persons with severe disabilities had an increased likelihood of cataract formation. Lepromatous patients with deformity are more undernourished than those without deformity,²⁰ and deficiency of factors such as essential amino acids, minerals, and vitamins in the diet can lead to cataract formation. An animal experiment has shown that a combination of vitamin E deficiency and long term prednisolone treatment can cause cataracts. Singly, however, both conditions were found to be subliminal cataractogenic risk factors.²¹

Conclusions

In summary, the risk of developing vision reducing cataract during and after MDT in skin smear positive lepromatous patients over the age of 40 years is 7%/person year and is associated with subclinical intraocular inflammation and severe forms of limb deformity, after adjusting for age. These patients are likely to be at a higher risk of further injury, and continued ophthalmic care—even after completion of MDT—is a necessary component in programmes for which prevention of disability is a major goal.

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