SCIENTIFIC REPORT

Iris atrophy in patients with newly diagnosed multibacillary leprosy: at diagnosis, during and after completion of multidrug treatment

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Aim: To describe the prevalence and incidence of iris atrophy in patients with multibacillary (MB) leprosy.

Methods and patients: Prospective longitudinal cohort study. 301 newly diagnosed patients with MB leprosy were followed up during the 2 years of treatment with multidrug therapy (MDT) and for a further 5 years with biannual ocular examinations. Incidence of iris atrophy was calculated as the number of patients with iris atrophy per person-year (PY) of follow-up among those who did not have iris atrophy at baseline. Stepwise multiple regression confirmed the presence of specific associations of demographic and clinical characteristics ($p < 0.05$) with iris atrophy, detected by univariate analysis.

Results: Iris atrophy was present in 6 (2%) patients at enrolment. During MDT, with 445 PYs of follow-up, 9 patients developed iris atrophy (IR 0.02, 95% CI 0.01 to 0.04) that was associated with cataract (HR 15.13, 95% CI 3.71 to 61.79, $p < 0.001$) and corneal opacities (HR 6.83, 95% CI 1.62 to 28.8, $p = 0.009$). After MDT, with 2005 PYs of follow-up, 60 patients developed iris atrophy (IR 0.03, 95% CI 0.023 to 0.039) that was associated with age (per decade; HR 1.40, 95% CI 1.10 to 1.78, $p = 0.006$), skin smear positivity (HR 3.50, 95% CI 1.33 to 9.24, $p = 0.011$), cataract (HR 3.66, 95% CI 1.85 to 7.25, $p < 0.001$), keratic precipitates (HR 2.76, 95% CI 1.02 to 7.47, $p = 0.046$) and corneal opacity (HR 3.95, 95% CI 1.86 to 8.38, $p < 0.001$).

Conclusions: Iris atrophy continues to develop in 3% of patients with MB leprosy every year after they complete a 2-year course of MDT, and is associated with age, increasing loads of mycobacteria, subclinical inflammation, cataract and corneal opacity.

Leprosy is a chronic granulomatous disease caused by *Mycobacterium leprae*. The disease is broadly classified into paucibacillary and multibacillary (MB) leprosy. Patients with MB leprosy are selectively immunologically unresponsive to *M leprae*, usually have a higher bacterial content and manifest the more severe form of the disease. Although the disease primarily affects the skin and nerves, ocular complications are frequently observed in patients with MB leprosy, and their occurrence during and after completion of multidrug therapy (MDT) has been described.^{1,2} An estimated 500 000 new patients with leprosy are being diagnosed annually, and approximately 14 million patients with leprosy would have completed treatment with MDT by the end of 2006.³

Among the ocular tissues, the uvea and, in particular, the iris are vulnerable to host reactions that follow invasion by *M leprae*. Inflammatory conditions that involve the uveal tissue are an

important cause of ocular morbidity and blindness among patients with MB leprosy. Atrophy of the iris has long been recognised to occur in patients with MB leprosy. It usually occurs in patients with lepromatous leprosy with a prolonged duration and chronic inflammation of the iris and ciliary body. Severe forms of iris atrophy can sometimes result in polycoria, affecting vision.

Knowledge of the incidence of iris atrophy and the factors associated with its manifestation is essential in outlining measures needed either to prevent or to delay damage to the tissue and, subsequently, reduce its contribution to ocular morbidity in leprosy. Iris atrophy was prospectively documented during treatment with MDT and for 5 years after completion of MDT in a cohort of Indians with MB leprosy.

PATIENTS AND METHODS

A total of 301 newly diagnosed patients with MB leprosy were enrolled over a period of 6 years (1991–7), from a population living within the geographically defined leprosy control programme area of the Schieffelin Leprosy Research and Training Centre (Karigiri, South India). The patients with MB leprosy were followed up during the period of their 2-year course of MDT and for 5 years after completion of MDT, with biannual ophthalmic examinations. Research methods and protocols, described previously,^{1,2} were approved by the institutional review board of the Schieffelin Leprosy Research and Training Centre. All patients were given an examination and treatment free of charge, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

At enrolment, the following leprosy characteristics were recorded: the type of MB leprosy based on the clinical classification of Ridley and Jopling⁴; World Health Organization deformity grading of hands and feet⁵; the bacterial index calculated from the results of the acid-fast staining of smears from specific skin sites⁶; type 1 (reversal reaction) or type 2 (erythema nodosum leprosum) reactions; history of hypopigmented or erythematous patches on the face; history of type 1 reactions; presenting leprosy reactions; presenting face patches; and duration of leprosy. The following ophthalmic characteristics were recorded at baseline and at every follow-up visit: visual acuity with correction; presence of orbicularis oculi weakness, lagophthalmos, ectropion, entropion, trichiasis, corneal opacity, corneal ulcer, punctate keratitis, episcleritis, scleritis, clofazamine crystals on the cornea or conjunctiva, corneal nerve beading, keratic precipitates, flare and cells, iris atrophy and cataract.

Iris atrophy was defined as the occurrence of any one of the following: depigmentation or hypopigmentation on the surface

Abbreviations: MB, multibacillary; MDT, multidrug therapy; PY, person-year

Table 1 Risk factors for iris atrophy incident during multidrug therapy

	Hazard ratio (95% CI)	p Value
Patient characteristics		
Age (per decade)	1.460 (0.905 to 2.356)	0.121
Sex	0.694 (0.144 to 3.339)	0.648
Leprosy characteristics		
Duration of leprosy ≥ 1 year vs < 1 year	1.003 (0.267 to 3.768)	0.996
Reaction		
History of face patch	1.688 (0.453 to 6.288)	0.435
History of reactions	0.787 (0.097 to 6.399)	0.823
Face patch	1.585 (0.756 to 3.325)	0.222
Smear		
Smear at enrolment	1.970 (0.245 to 15.818)	0.524
Deformity		
Grade 1 deformity in all limbs	2.368 (0.315 to 17.793)	0.402
Grade 2 deformity in all limbs	9.373 (0.828 to 106.102)	0.071
Ocular characteristics		
Trichiasis	17.069 (2.072 to 140.618)	0.008
Pterygium	3.032 (0.718 to 12.797)	0.131
Corneal opacity	3.975 (0.962 to 16.420)	0.057
Keratic precipitates	3.156 (0.388 to 25.653)	0.282
Cataract	11.635 (3.091 to 43.794)	< 0.001

of the iris that was localised or diffused, gaps in the posterior pigmented layer manifesting as transillumination defects, excavation of the iris tissue revealing the stromal layer or muscle fibres and polycoria. When synechia or cataracts were suspected, mydriatic drops were instilled and the patient was re-examined to confirm the diagnosis. Best-corrected visual acuity was measured using 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 performed in all cases; in patients with decreased vision or with intraocular complications, the pupils were dilated and indirect ophthalmoscopy was carried out.

Statistical analysis was conducted with the unit of observation as the individual rather than the eye. Stepwise multiple regression was used to confirm the presence of specific associations of demographic and clinical characteristics ($p < 0.05$) with pathology, detected by univariate analysis. Hazard ratios (HRs), 95% CIs and p values were generated. Incidence of iris atrophy during MDT was calculated as the number of patients with iris atrophy while taking MDT observed per person-year (PY) of follow-up among patients who did not have iris atrophy at baseline. Patients were censored after the last visit prior to discontinuation of MDT, or on loss to follow-up.

The incidence of iris atrophy was calculated as the number of patients with iris atrophy per PY of follow-up among those who did not have iris atrophy at baseline.

RESULTS

Iris atrophy was present in six (2%) patients at the time of enrolment. During follow-up, nine patients were found to have had only one visit and two patients were seen on their second visit only after they had completed their MDT. Therefore, the analysis was conducted on 284 (94%) patients during their treatment period with MDT. The total follow-up period during MDT was 445 PYs and nine patients developed iris atrophy

(incidence ratio (IR) 0.02, 95% CI 0.01 to 0.04). Table 1 lists the association of various risk factors with iris atrophy during MDT. Backward stepwise multiple regression analysis confirmed the significant association of cataract (HR 15.13, 95% CI 3.71 to 61.79, $p < 0.001$) and corneal opacity (HR 6.83, 95% CI 1.62 to 28.8, $p = 0.009$) with iris atrophy.

Fourteen patients died and seven migrated or refused examination while they were receiving MDT, and so the analysis in the post-MDT period was done on 263 (87% of the original cohort) patients. The total follow-up period after MDT was 2005 PYs and 60 patients developed iris atrophy (IR 0.03, 95% CI 0.023 to 0.039). Table 2 gives the association of various risk factors and iris atrophy after completion of MDT. Backward stepwise multiple regression analysis confirmed the significant association of iris atrophy during the post-MDT period with age (per decade) (HR 1.40, 95% CI 1.10 to 1.78, $p = 0.006$), skin smear positivity (HR 3.50, 95% CI 1.33 to 9.24, $p = 0.011$), cataract (HR 3.66, 95% CI 1.85 to 7.25, $p < 0.001$), keratic precipitates (HR 2.76, 95% CI 1.02 to 7.47, $p = 0.046$) and corneal opacity (HR 3.95, 95% CI 1.86 to 8.38, $p < 0.001$).

Table 3 gives the association of different age groups with iris atrophy.

Cumulatively, iris atrophy occurred in 25% of the patients with MB leprosy. None of the patients with MB leprosy exhibited other iris abnormalities such as vascularisation or nodules. Patients with intraocular pressures of < 10 mm Hg during MDT had a significant association with iris atrophy at diagnosis (HR 4.23, 95% CI 0.99 to 17.96, $p = 0.05$), as had patients with pressures of < 10 mm Hg after MDT (HR 6.64, 95% CI 2.00 to 22.04, $p = 0.002$).

Table 2 Risk factors associated with incident iris atrophy after multidrug therapy

	Hazard ratio (95% CI)	p Value
Patient characteristics		
Age (per decade)	1.761 (1.466 to 2.117)	< 0.001
Sex	1.382 (0.810 to 2.358)	0.236
Leprosy characteristics		
Duration of leprosy ≥ 1 year vs < 1 year	0.912 (0.545 to 1.526)	0.726
Classification BL vs LL	0.591 (0.307 to 1.139)	0.116
Reaction		
History of face patch	0.800 (0.474 to 1.350)	0.404
History of reactions	0.736 (0.348 to 1.555)	0.422
Face patch	0.970 (0.738 to 1.274)	0.826
Reactions type 1	1.197 (0.665 to 2.156)	0.549
Reactions type 2	1.695 (0.233 to 12.348)	0.602
Smear		
Smear at enrolment	2.806 (1.118 to 7.041)	0.028
Deformity		
Grade 1 deformity in all limbs	2.079 (0.978 to 4.421)	0.057
Grade 2 deformity in all limbs	2.221 (0.511 to 9.660)	0.287
Ocular characteristics		
Lagophthalmos	1.406 (0.440 to 4.497)	0.566
NLD patency	1.901 (0.457 to 7.912)	0.377
Pterygium	1.842 (0.904 to 3.755)	0.093
Corneal opacity	2.369 (1.160 to 4.837)	0.018
Corneal nerve beading	0.793 (0.109 to 5.742)	0.818
Punctate keratitis	0.939 (0.130 to 6.789)	0.950
Keratic precipitates	3.632 (1.439 to 9.164)	0.006
Flare and/or cells	4.546 (0.625 to 33.062)	0.135
Cataract	6.284 (3.722 to 10.608)	< 0.001

BL, borderline lepromatous; LL, lepromatous leprosy; NLD, nasolachrymal duct.

Table 3 Age group and iris atrophy

Age (years)	Total patients	Patients with iris changes	Hazard ratio (95% CI)	p Value
1-21	19	3	1.000	
22-40	127	9	0.425 (0.112 to 1.604)	0.206
41-60	107	35	2.876 (0.881 to 9.386)	0.080
>60	33	13	5.636 (1.592 to 19.955)	0.007

DISCUSSION

Iris atrophy is reported to be the most common ocular lesion occurring in patients with MB leprosy, and the role of iris changes in patients with lepromatous leprosy as a cause of ocular morbidity and vision loss has been described.⁷⁻⁸ Findings from our study show that approximately 2% of patients with newly diagnosed MB leprosy present with iris atrophy at the time of diagnosis and a further 2% develop it while undergoing treatment with MDT. The interesting finding, however, is that iris atrophy develops in 3% of patients with MB leprosy every year after they complete a 2-year course of MDT. This suggests that a process that denudes and alters the surface of the iris continues even after bacteriological cure is obtained. The process is associated with the presence of keratic precipitates, but is not significantly associated with active inflammation with cells and flare in the anterior chamber. This is probably because the 6-month period between two visits might have been too long to capture the presence of an active inflammation when it occurred. Iris atrophy is probably linked to an immune process that is for the most part a subclinical inflammation. Iridocyclitis in patients with lepromatous leprosy has been known to occur as part of the type 2 reaction. In our series of patients, however, iris atrophy was not associated with either type 1 or type 2 reactions or the presence of pathological changes in the skin of the face.

Iris atrophy is easily discernable in patients of Indian origin when compared with Caucasians as they have uniformly deeply pigmented iridis. Iris atrophy is known to occur as part of the ageing process, and this is evident from our study.⁹ Patients with MB leprosy aged ≥ 60 years are five times more likely to develop iris atrophy than patients aged ≤ 20 years. Our study also showed that patients who had cataracts and corneal opacities were more likely to have iris atrophy. It is likely that low-grade inflammation contributes to the development of both cataract and iris atrophy. It is not known at what point in time in the natural course of the disease, early iris atrophy (fig 1) would progress to a more severe form (fig 2), but severe forms of iris atrophy with transillumination defects and polycoria have generally been noted in elderly patients with lepromatous leprosy.

Atrophic areas are believed to be more permeable to aqueous humour¹⁰ and therefore the presence of iris atrophy should make acute glaucomatous attacks rare. Considering the fact that $\geq 25\%$ of patients with MB leprosy may develop iris atrophy and that patients who have iris atrophy have lower intraocular pressures, it is likely that these factors contribute significantly to the rarity of acute glaucomatous attacks in patients with MB leprosy.¹¹ Our study has also established a relationship between the presence of mycobacterium in the skin and iris atrophy in patients with MB leprosy. Iris atrophy is probably linked to a strong polyclonal antibody immune response with copious circulating antibody. There is evidence that the *M leprae* are present in the iris tissue long after patients have completed their MDT.¹² Histopathological changes occurring in the iris and destruction of the muscles of the iris have

Figure 1 Diffuse circumferential iris atrophy (black arrows) in a cohort patient with multibacillary leprosy.

Figure 2 Pronounced iris atrophy (white arrow) in a non-cohort patient with lepromatous leprosy.

been described.¹³ More than 60% of patients with leprosy who were skin smear negative after being treated with dapsone monotherapy had histopathological findings of iris atrophy.¹⁴ Hence, there is sufficient evidence that iris atrophy is widespread in leprosy and occurs particularly in patients with large numbers of *M leprae*. It is likely that the mycobacteria or its remnants residing in the uveal tissue generate an overt or subclinical inflammation, producing iris atrophic changes that manifest clinically in the years that follow MDT. Bacteriological cure does not seem to prevent this from happening, as only three patients were smear positive in our cohort at the end of 2 years of treatment with MDT. Similarly, late neuritis has been observed in patients after completion of treatment and clinical cure.¹⁵

In summary, our findings provide further evidence of *M leprae*-related intraocular damage after completion of anti-leprosy MDT. Strategies for improving follow-up of these patients need to be developed.

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