WORLD VIEW

Incidence of ocular complications in patients with multibacillary leprosy after completion of a 2 year course of multidrug therapy

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Aim: To evaluate the incidence of and risk factors for ocular complications in multibacillary (MB) leprosy patients following completion of 2 year, fixed duration, multidrug therapy (MDT).

Methods: Biannual eye examinations were conducted prospectively on a cohort of MB patients who had completed MDT and followed up for 5 years. The incidence of ocular pathology was calculated as the number of events per person year of event free follow up of patients who did not have the specific finding before completion of MDT.

Results: 278 patients had one or more follow up visits after completion of MDT. The incidence of lagophthalmos was 0.24%/patient year (95% CI 0.10% to 0.37%); corneal opacity, 5.35%/patient year (95% CI 4.27% to 6.70%); uveal involvement, 3.78%/patient year (95% CI 2.96% to 4.83%); and cataract that reduced vision to 6/18 or less, 2.4%/patient year (95% CI 1.77% to 3.26%). Overall, 5.65%/patient year (95% CI 4.51% to 7.09%) developed leprosy related ocular disease and 3.86%/patient year (95% CI 3.00% to 4.95%) developed leprosy related, potentially blinding ocular pathology during the period following MDT. Age and other disability also predicted incident eye disease.

Conclusions: Every year, approximately 5.6% of patients with MB who have completed MDT can be expected to develop new ocular complications of leprosy, which often (3.9%) are potentially vision threatening. Because many of these complications cannot be detected without slit lamp examination, periodic monitoring, particularly of older patients and those with other disability, is recommended, in order to detect and treat ocular complications satisfactorily.

It is estimated that by the end of the year 2005, more than 14 million leprosy patients will have completed a standard course of anti-leprosy multidrug therapy (MDT).[1] Although the incidence of leprosy is declining in some areas, approximately half a million new patients are diagnosed with leprosy each year. Recent changes in the epidemiology of leprosy include a gradual shift in the proportion of the type of leprosy from the paucibacillary to the multibacillary (MB) form, as well as a shift to an older age at diagnosis of disease.[2] Improving health care and socioeconomic conditions predict increasing survival, with the fortunate result that there will be an ever increasing number of antimicrobially "cured" leprosy patients than ever existed in history.

There is evidence that even after adequate treatment with MDT, a sizeable proportion of cured leprosy patients continue to manifest progressive impairment of nerve function.[3 4] Although the pathophysiology of this process is not fully understood, it is thought to be related to continuing immunological reactions and slow evolution of pre-existing nerve damage.[5 6] Ocular complications are frequently observed in newly diagnosed leprosy patients and in patients who are undergoing MDT.[7–9]

However, little information exists on the incidence of ocular complications after completion of MDT in MB patients who have completed the recommended course of MDT. Knowledge of the risk and nature of ocular morbidity in leprosy patients after treatment with MDT is needed to prevent and/or manage such complications promptly and effectively in programmes worldwide. Such information potentially could identify risk factors that may be amenable to intervention and help prioritise groups for more active follow up.

In our previous reports, we have described a cohort of newly diagnosed MB leprosy patients who were followed for ocular complications during 2 year fixed MDT.[8 10] These patients were followed up for a further 5 years. In this paper, we report information on ocular complications that were incident during the post-MDT period.

MATERIAL AND METHODS

All new clinically diagnosed MB patients starting on a 2 year MDT and living within the leprosy control area of the Schieffelin Leprosy Research and Training Centre in southern India were invited to participate. Recruitment began in 1991 and was completed in 1997. Consenting patients received a baseline ocular examination followed by biannual examinations during MDT and for a period of at least 5 years after completion of MDT. Based on sample size calculations taking into account possible losses to follow up resulting from migration and mortality, 301 MB leprosy patients were enrolled over a period of 6 years. Research methods and protocols were approved by the institutional review board of the Schieffelin Leprosy Research and Training Centre. All patients were examined and given 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 Jopling[11]; deformity grading of hands and legs, based on the WHO classification[12]; the bacterial index, calculated from the results of the acid fast staining of smears from specific skin sites[13]; presence or

Abbreviations: LROP, leprosy related ocular pathology; MB, multibacillary; MDT, multidrug therapy; PBLROP, potentially blinding leprosy related ocular pathology

Table 1 Incidence of ocular morbidity after completion of 2 year fixed MDT, by patient

Ocular conditions	Person time at risk (years)	Number of patients at risk*	Number of cases	Incidence rate per 100 person years	95% CI
Lid conditions					
Orbicularis weakness	2033	256	11	0.54	(0.30 to 0.98)
Lagophthalmos	2106	262	5	0.24	(0.10 to 0.57)
Ectropion	2186	271	4	0.18	(0.07 to 0.49)
Trichiasis	2163	272	14	0.65	(0.38 to 1.09)
Conjunctival conditions					
B663 crystals†	2203	273	2	0.09	(0.02 to 0.36)
NLD‡	2139	270	12	0.56	(0.32 to 0.99)
Pterygium	1839	231	13	0.71	(0.41 to 1.22)
Corneal conditions					
Corneal opacity	1420	221	76	5.35	(4.27 to 6.70)
Punctate keratitis¶	2057	267	21	1.02	(0.66 to 1.57)
Corneal ulcer	2229	278	3	0.13	(0.04 to 0.42)
Corneal nerve beading	2006	260	19	0.95	(0.60 to 1.48)
Uveal conditions					
Keratic precipitates	1886	249	20	1.06	(0.68 to 1.64)
Flare and/or cells	2198	274	5	0.23	(0.09 to 0.55)
Iris atrophy	2005	263	60	2.99	(2.32 to 3.85)
Uveal involvement, total§	1692	236	64	3.78	(2.96 to 4.83)
Episcleritis	2224	277	4	0.18	(0.07 to 0.48)
Cataract					
Cataract	1293	179	54	4.18	(3.20 to 5.45)
Cataract and visual acuity $\leqslant$6/18	1706	229	41	2.40	(1.77 to 3.26)
Grouped					
LROP	1326	202	75	5.65	(4.51 to 7.09)
PBLROP 1608	225	62	3.86		(3.01 to 4.95)

MDT, multidrug therapy; LROP, leprosy related ocular pathology includes muscle weakness, lagophthalmos, ectropion, entropion, trichiasis, episcleritis, scleritis, corneal nerve beading, punctate keratitis and uveal involvement. PBLROP, potentially blinding leprosy related ocular pathology includes lagophthalmos and/or uveal involvement.
*The number of patients at risk for each event is based on the number of patients who were event free at the completion of MDT and who had at least one follow up examination visit thereafter. †B663 crystals, clofazamine crystals in cornea or conjuctiva; ‡Nasolacrimal duct patency; ¶Neurotrophic or exposure related. §Any uveal involvement includes flare and cell, keratic precipitates, and/or iris atrophy. Corneal opacities were not included, because none of them was vision threatening.

history of type 1 (reversal reaction) or type 2 (erythema nodosum leprosum) reactions; and 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; clofazamine crystals in the cornea or conjunctiva; anterior chamber flare and/or cells; posterior synechiae; small pupil size; pupillary reaction to light; iris atrophy; and cataract. When synechiae or cataracts were suspected, mydriatic drops were instilled and the patient was re-examined to confirm the diagnosis. For purposes of the analyses reported here, cataract was defined as the presence of lens opacity observed by slit lamp examination consistent with a measured corrected visual acuity of 6/18 or worse. Patients free of cataract at enrolment who underwent cataract surgery during follow up also were considered to have developed cataract, as of the midpoint between visits before and after cataract surgery was performed.

Best corrected visual acuity was measured by a trained examiner using a Snellen chart. After examination of the ocular adnexae, slit lamp biomicroscopy was carried out on all patients. Goldmann applanation tension was recorded in the upright position. Direct ophthalmoscopy without dilatation was performed in all cases during each visit; patients with decreased vision or with intraocular complications underwent pupil dilatation and indirect ophthalmoscopy.

Among patients free of each condition studied upon completion of MDT, the incidence of ocular complications of leprosy was calculated as the number of each kind of event observed per person year at risk during follow up after MDT. In addition, compound outcomes to describe the incidence of complications were created, as follows. Leprosy related ocular pathology (LROP) was defined as the presence of one or more of the following: lagophthalmos, corneal nerve beading, corneal opacity, punctate keratitis, and observations indicative of uveal involvement (flare and cells, keratic precipitates, and/or iris atrophy). This grouping was created to encompass all leprosy related ocular conditions. Potentially blinding leprosy related ocular pathology (PBLROP) was defined as the presence of lagophthalmos and/or uveal involvement—constituting those leprosy related conditions associated with substantial risk of vision loss. Corneal opacity was not included under PBLROP as no cases were associated with a drop in visual acuity. Cataract was not included in this group on the conservative assumption that cataract is not a uniquely leprosy induced condition.

Statistical analysis was conducted with the unit of observation being the individual rather than the eye. Univariate and multivariate Cox proportional hazards regression models were used to analyse the incidence of specific findings, and evaluate their relation to demographic and clinical characteristics. p Values, hazard ratios (HR), and 95% confidence intervals (CI) were generated.

RESULTS

Among all newly diagnosed MB patients eligible for the study, 15 (13 males and two females) opted not to participate and a total of 301 patients were enrolled. The characteristics of this cohort have previously been reported.[10] During the 2 year MDT treatment period there were 14 deaths and nine migrations; thus, the analysis after completion of MDT is based on 278 patients (92%), who were followed until their last examination visit in 2004 or until death or migration, whichever occurred earliest. Between completion of MDT and the last examination visit in June 2004, a further 28 (9.3%) patients died and 30 (10%) migrated to distant places. These

Table 2 Risk factors for corneal opacity

	Hazard ratio	95% CI	p Value
Patient characteristics			
Age (per decade)	1.02	(0.87 to 1.19)	0.729
Sex (female *v* male)	0.52	(0.30 to 0.90)	0.020
Leprosy characteristics (baseline)			
Classification			
(LL *v* BL)	0.70	(0.32 to 1.53)	0.373
Duration of disease			
⩾1 year *v* <1 year	1.37	(0.86 to 2.16)	0.182
Reactions			
History of face patch	1.18	(0.75 to 1.85)	0.477
History of reactions	1.37	(0.78 to 2.41)	0.275
Face patch	1.24	(0.97 to 1.58)	0.091
Type 1 reaction	1.01	(0.59 to 1.72)	0.966
Type 2 reaction	1.95	(0.48 to 8.01)	0.354
Smear			
Bacterial index	0.96	(0.82 to 1.13)	0.637
Smear positivity	0.75	(0.42 to 1.32)	0.316
Deformity			
Grade 1 deformity	1.80	(0.85 to 3.81)	0.126
Grade 2 deformity	3.54	(1.21 to 10.36)	0.021

patients contributed follow up time to the analysis until they were lost. Thus, from the time of enrolment to the last visit in 2004, a total of 42 patients died and 39 migrated and were lost to follow up. During 2004, additional efforts were made to contact and examine all patients from the original cohort, and 41 patients were seen in 2004 who had not been seen for 3 years or more before the final visit.

After completion of MDT, among 225 patients (1631 patient years) who had visual acuity better than 6/18 at the time of completion of their MDT, 49 (3%/patient year, 95% CI 2.27% to 3.97%) developed reduction of visual acuity to 6/18 or worse. Among these, 20 patients (1%/patient year, 95% CI 0.6% to 1.5%) became severely visually impaired (less than 6/60 vision in one or both eyes). Age at enrolment (HR = 1.08 95% CI 1.03 to 1.13 p = 0.003) and grade 2 deformity in all limbs (HR = 5.91 95% CI 0.97 to 36.23 p = 0.05) were associated with severe visual impairment. Vision was reduced to less than 3/60 in 21 eyes (0.5%/patient year, 95% CI 0.3% to 0.7%). Five patients became blind (vision <3/60 in both eyes) during this period (0.2%/patient year, 95% CI 0.1% to 0.5%) and cataract was the cause of blindness in all of these patients.

Table 1 summarises the incidence of various ocular morbidity that occurred after completion of MDT. Lagophthalmos developed in only five patients (0.0024/patient year). Except for grade 2 deformity (HR = 10.2, 95% CI: 1.1 to 92.5, p = 0.039) none of the demographic or leprosy related characteristics were significantly associated with incident lagophthalmos. Corneal opacity occurred in 76 patients (0.0535/patient year; see table 2). Multiple regression confirmed corneal opacity to be significantly associated with grade 2 deformity (HR = 1.86, 95% CI: 1.15 to 3.00), sex (female *v* male) (HR = 0.50, 95% CI: 0.29 to 0.87), and PBLROP (HR = 2.55 SE 0.87 95% CI 1.30 to 4.99 p = 0.007). Table 3 summarises the risk factors associated with incident uveal involvement. Multiple regression confirmed a higher risk of uveal involvement with increasing age (HR (for each decade) = 1.57, 95% CI: 1.32 to 1.86) and grade 2 deformity (HR = 3.03, 95% CI: 1.08 to 8.53). Smear positivity at enrolment had a borderline association (HR = 2.32, 95% CI: 0.99 to 5.44).

Table 4 summarises risk factors associated with LROP. Multiple regression revealed that only higher age for each decade (HR1.20 95% CI 1.03 to 1.41, p = 0.021) was

Table 3 Risk factors for uveal involvement

	Hazard ratio	95% CI	p Value
Patient characteristics			
Age (per decade)	1.61	(1.36 to 1.90)	<0.001
Sex (female *v* male)	1.01	(0.59 to 1.71)	0.985
Leprosy characteristics			
Classification			
LL *v* BL	1.30	(0.66 to 2.55)	0.452
Duration of disease			
Duration ⩾1 year *v* <1 year	1.17	(0.70 to 1.94)	0.547
Reaction			
History of face patch	0.69	(0.41 to 1.16)	0.164
History of reactions	0.92	(0.45 to 1.87)	0.817
Face patch	0.96	(0.74 to 1.26)	0.777
Type 1 reactions	1.25	(0.71 to 2.21)	0.444
Type 2 reactions	1.33	(0.18 to 9.68)	0.777
Smear			
Bacterial index	1.00	(0.84 to 1.20)	0.976
Smear positivity	2.38	(1.02 to 5.52)	0.044
Deformity			
Grade 1	1.37	(0.77 to 2.44)	0.284
Grade 2	3.08	(1.54 to 6.16)	0.001

Table 4 Risk factors for leprosy related ocular pathology

	Hazard ratio	95% CI	p Value
Patient characteristics			
Age (per decade)	1.21	(1.04 to 1.42)	0.016
Sex (female *v* male)	0.96	(0.59 to 1.57)	0.882
Leprosy characteristics (baseline)			
Classification			
LL *v* BL	1.42	(0.72 to 2.77)	0.310
Duration of the disease			
Duration ⩾1 year *v* <1 year	1.20	(0.76 to 1.91)	0.438
Reaction			
History of face patch	0.96	(0.60 to 1.51)	0.845
History of reactions	1.55	(0.86 to 2.77)	0.142
Face patch	0.97	(0.76 to 1.24)	0.801
Type 1 reaction	0.99	(0.56 to 1.75)	0.981
Type 2 reaction	0.80	(0.11 to 5.77)	0.823
Smear			
Bacterial index	0.99	(0.84 to 1.18)	0.940
Smear positivity	1.90	(0.97 to 3.71)	0.062
Deformity			
Grade 1	1.26	(0.76 to 2.10)	0.363
Grade 2	2.17	(1.11 to 4.23)	0.023

significantly associated with LROP. Multiple regression confirmed that age (for each decade) (HR1.50 95% CI 1.27 to 1.78, p = <0.001), smear positivity (HR2.37 95% CI 1.01 to 5.55, p = 0.048), and grade 2 deformity (HR3.20 95% CI 0.98 to10.42, p = 0.054) were associated significantly with PBLROP (table 5). Cataract with reduced vision and PBLROP were seen in 60 out of 194 patients at risk, occurring over 1352 patient years, giving an incidence rate of 0.44/ patient year (95% CI 0.034 to 0.057). Reactions and face patches, past and/or at enrolment, were not associated with any of the ocular complications. Cataract was not associated with the cumulative corticosteroid dose (given for neuritis). Corneal ulcers developed in three patients, which did not provide sufficient information to conduct a risk factor analysis.

DISCUSSION

This is the first systematic prospective study evaluating the incidence of ocular complications among MB patients after completion of 2 year fixed dose MDT. Findings from the study suggest that leprosy related ocular complications occur at a substantial rate, over 5% per year, in the years following completion of their MDT, with approximately 4% per year developing potentially blinding leprosy related ocular complications. In addition, cataract associated with visual impairment occurred in 2.4% per year and some of it occurred in patients with PBLROP. Thus, the overall incidence of vision threatening eye disease is 4.4% per year following presumed microbiological cure of leprosy. Comparison of results among other ocular studies in MB patients who have been released from anti-leprosy treatment are limited by the short supply of data available from population based ocular leprosy studies with extended follow up, as well as by the different classification systems and definitions used. Good participation of patients in this study for an extended period of time after completion of their therapeutic regimen adds strength to this population based study of MB patients.

Although visual acuity dropped to less than 6/60 in one or more eyes in 1% of patients per person year, only five patients (0.2%) became bilaterally blind (worse than 3/60 in both eyes) during this period. Blindness and severe loss of vision were the result of the progressive development of cataract. Results of cataract surgery in this population will be reported

Table 5 Risk factors for potentially blinding leprosy related ocular pathology

	Hazard ratio	95% CI	p Value
Patient characteristics			
Age (per decade)	1.54	(1.29 to 1.82)	<0.001
Sex	1.01	(0.59 to 1.73)	0.979
Leprosy characteristics			
Classification			
LL *v* BL	1.27	(0.64 to 2.50)	0.491
Duration of disease			
⩾1 year *v* <1 year	1.13	(0.68 to 1.90)	0.635
Reactions			
History of face patch	0.72	(0.42 to 1.21)	0.215
History of reactions	0.81	(0.39 to 1.71)	0.585
Face patch	0.96	(0.73 to 1.26)	0.782
Type 1 reaction	1.13	(0.62 to 2.06)	0.686
Type 2 reaction	1.29	(0.18 to 9.34)	0.804
Smear			
Bacterial index	1.00	(0.84 to 1.20)	0.963
Smear positivity	2.42	(1.04 to 5.63)	0.041
Deformity			
Grade 1	1.30	(0.73 to 2.33)	0.375
Grade 2	2.96	(1.46 to 6.01)	0.003

separately. Risk of cataract is likely to increase with age; access to good cataract surgical services will be important in reducing ocular morbidity in this high risk population. Uveal involvement (4%), corneal opacities (5%), and punctate keratitis (1%) were not major contributors to vision loss, perhaps because of treatment, which patients received free of charge during the study. Each of the other complications was less than 1%.

The development of corneal nerve beading after presumed microbiological cure of leprosy in 19 patients was an unexpected finding. Nerve beading is believed to be due to calcified collections of large amounts of *Mycobacterium leprae* on the fine nerves that traverse the corneal stroma. They can be missed on perfunctory biomicroscopy but when diagnosed are much more distinct entities than the nerve enlargement or thickening often reported in ocular leprosy. The strong association of corneal nerve beading with high bacillary counts both at the time of enrolment and while receiving MDT[9 10] was not seen following completion of MDT; neither was incident corneal beading following MDT associated with leprosy reactions. One potential explanation of this observation is that changes taking place in the unmyelinated corneal nerves are independent of reactions and high bacillary count.

Females were only half as likely as males to develop corneal opacities during this period. Corneal opacities were also more commonly observed among patients with severe limb deformities and those with other leprosy related ocular complications, particularly lagophthalmos; however, the corneal opacities observed were generally small, superficial, and peripheral and did not contribute to visual impairment. It could be speculated that the pathophysiology of these opacities is different from those that occur in MB patients during the time that they are taking MDT.[10] They could result from minor injuries and ocular exposure: females do less outdoor work in rural India. Patients with fewer deformities were less likely to develop these opacities, consistent with the fact that patients with more deformed extremities are more likely to injure their eyes while rubbing them. Corneal conditions such as opacities, nerve beadings, punctate keratitis and ulcers are likely to be associated with impaired corneal sensation but this correlation could not be established in our cohort as the method of estimating corneal sensation used was subjective, and not consistently reproducible.

Leprosy related uveal involvement accounts for a large proportion of the complications observed and could reflect a para-infectious mechanism of autoimmune inflammation.[14–18] For every decade increase in age, there appeared to be a 60% higher likelihood of having uveal involvement, for reasons that are unclear. Uveal involvement in this population was not related to type 2 leprosy reactions but was significantly associated with being smear positive at enrolment and having more severe limb deformities. Thus, the more severely infected MB patients and those with advanced deformity before treatment may be at a higher risk of ongoing para-infectious autoimmune disease. Previous studies have shown that patients who have nerve function impairment at the time of diagnosis have a higher risk of developing severe deformities during and after MDT.[4 19] Elderly and highly bacilliferous MB patients with more severe limb deformities constitute a risk group for developing uveal involvement during the period after completion of MDT. Further observations of the outcomes and clinical course of uveal involvement are needed to assess the contribution of leprosy related uveal involvement to ocular morbidity, but it seems likely that such disease will require ongoing management. Because detection and management of uveal involvement requires slit lamp examination and specialised training, the input of an ophthalmologist would be necessary for satisfactory follow up and management.

What are the clinical and public health implications of the findings of this study? The most important issue, from our perspective, is to make known to all those involved in the care of leprosy patients that leprosy related ocular manifestations continue to occur in MB patients after completion of MDT, at a substantial rate. Cataract, with potentially recoverable visual acuity, was the leading cause of vision loss in this period. Uveal involvement occurred in a substantial proportion of patients, and often is not detectable on penlight examinations by field workers. The long term effects of uveal disease on vision and its contribution to other ocular morbidity have not been directly studied in patients with leprosy, but are likely to be substantial in the absence of appropriate management. Lagophthalmos, neurotrophic punctate keratitis, episcleritis, and corneal ulcers appear to be infrequent in our study.

It must be emphasised that the true ''threat to sight'' pathology observed in leprosy patients living among the general population may have been obscured by the early detection and treatment facilities afforded by the study environment. This study demonstrates that after completion of MDT, vulnerable groups should continue to be screened for ocular complications of leprosy, with the involvement of an ophthalmologist, in order to satisfactorily prevent or reverse ocular morbidity caused by leprosy.

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Ethical approval: Research methods and protocols were approved by the Institutional Review Board of the Schieffelin Leprosy Research and Training Center, and were conducted in accordance with the principles of the Declaration of Helsinki.

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