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Original Article

Ocular hypotension and hypotony in multibacillary leprosy patients; at diagnosis, during and after completion of multidrug therapy

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The prevalence and incidence of ocular hypotony (IOP<7 mm Hg) and hypotension (IOP<10 mm Hg) and factors associated with them were determined in a Leprosy Referral Centre at Tamilnadu, India. Applanation intraocular pressures were measured every six months in a cohort of newly diagnosed multibacillary (MB) leprosy patients who were followed-up during the two year period of multidrug therapy (MDT) and for five years thereafter. Transient hypotony was present in two patients at the time of diagnosis, in 3 patients during MDT and in 9 patients after MDT with a cumulative prevalence of 4.65%. Transient ocular hypotension was present in 24 patients (8%) at disease diagnosis. 25 patients developed hypotension during MDT that was associated with trichiasis (HR 8.83 95% CI 2.06, 37.78 p=0.003) and flare or/and cells (HR 4.60 95% CI 1.08, 19.64 p=0.039). 29 patients developed ocular hypotension after MDT that was associated with punctate keratitis and uveal involvement. In general, MB leprosy patients with hypotension had a mean IOP of 12.60 mm Hg which differed significantly (p<0.0001) from the mean IOP of 14.9 mm Hg in those who did not have hypotension. Transient hypotension and hypotony in MB leprosy patients are associated with signs of intraocular inflammation.

Key words: Multibacillary leprosy, Ocular hypotony, Ocular hypotension

Introduction

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae.* Ocular manifestations of the disease are common and largely confined to the anterior segment of the eye. The presence of *Mycobacterium leprae* in the uveal tissues of multibacillary (MB) patients and the subsequent damage, it produces by stimulating host reactions have been well documented. (Daniel et al 1997, Job et al 1998, Ebenezer and Daniel 2000). These inflammatory reactions, if not treated early and adequately, can produce peripheral iris adhesions that impede aqueous flow and raise intraocular pressures to levels that damage the optic nerve head giving rise to

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irreversible blindness. However, such secondary glaucoma in MB patients have been reported to be relatively rare (Thomas et al 2003).

Long standing inflammatory reactions could also damage the ciliary body and impair its ability to produce adequate amounts of aqueous humor and as a consequence affect the firmness of the globe and possibly decrease nutrient supply to the avascular lens and cornea. The decrease in aqueous production is manifested clinically by recorded reductions in intraocular pressure (IOP). Compared to raised IOP that has a well known association with irreversible damage to the optic nerve, little interest has been focused on decreased intraocular pressure other than in therapeutic investigations that sought to reduce high IOP. Decreased IOP, unless of a very extreme degree that is associated with visible changes in the cornea and globe is an innocuous entity. Its occurrence, however, has been specifically noted in leprosy patients (Brandt et al 1981, Hussein et al 1989, Lewallen et al 1990, Karaçorlu et al 1991, Daniel et al 1994).

The extent to which low IOP is prevalent in newly diagnosed MB patients is not known. Its incidence in MB patients during the standard two year multidrug therapy (MDT) and after completion of MDT is also not known. This is primarily because IOP measurements in existing studies had been done on patients whose disease classification, duration and treatment varied widely and because none of them were followed-up for any reasonable length of time. Since, low IOP has the potential to adversely affect the tissues of the eye and possibly contribute to adverse outcomes in surgical interventions such as cataract surgery; it is important to understand its characteristics and factors that may influence its incidence. We therefore, undertook to study the prevalence of low IOP in a cohort of newly diagnosed MB leprosy patients. The incidence of low IOP during MDT and after completion of MDT was assessed according to leprosy and ocular characteristics associated with its occurrence.

Patients and Methods

Methods undertaken in this study have been described previously (Courtright et al 2002, Daniel et al 2006). Briefly, all new, clinically diagnosed MB patients starting on a two-year anti-leprosy MDT and living within the leprosy control area of the Schieffelin Leprosy Research & Training Center, Karigiri were invited to participate. Recruitment of patients started in 1991 and was completed in 1997. Consenting patients received a baseline ocular examination followed by prospective biannual examinations during MDT. Patients not returning for examination were contacted by public health workers in their own community to encourage follow-up. Research methods and protocols were approved by the Institutional Review Board of the Schieffelin Leprosy Research & Training Center, Karigiri and were conducted in accordance with the principles of the Declaration of Helsinki. Based on sample size calculations taking into account possible losses to follow-up resulting from migration and mortality, 301 patients were enrolled over a period of 6 years. All patients were provided examination and treatment free of charge and were followed-up until completion of the study in 2004.

At enrollment, the following leprosy characteristics were recorded; the type of multibacillary leprosy based on the clinical classification of Ridley and Jopling (1966); deformity grading of hands and legs based on the WHO classification (WHO 1988); the bacterial index calculated from the results of the acid-fast staining of smears from specific skin sites (Abraham and Cariappa 1991); presence of type 1 (reversal reaction) or type 2 (erythema nodosum leprosum) reactions, 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 on

the cornea or conjunctiva, flare and cells, posterior synechia, small pupil, sluggish pupillary reaction to light, iris atrophy and cataract. 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 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 at every six-monthly visit by an ophthalmologist using a Goldman applanation tonometer mounted on a Haag-Striet slit-lamp. Direct ophthalmoscopy without dilatation was performed in all cases during each visit; patients with decreased vision or with intraocular complications had dilatation and indirect ophthalmoscopy.

We defined intraocular pressures below 10 mm Hg as ocular hypotension and pressures below 7 mm Hg as ocular hypotony. Sustained ocular hypotension and ocular hypotony were identified by the presence of persistent hypotention or hypotony during at least three consecutive visits. Ocular hypotension included patients with ocular hypotony. Incidence of both ocular hypotension and ocular hypotony were calculated as the number of each kind of event observed per person-year of event-free follow-up while taking MDT among patients who did not have these events at baseline; as the number of each kind of event observed per person-year of event-free follow-up after taking treatment with MDT among patients who did not have these events at the time of completion of MDT. Statistical analysis was conducted with the unit of observation being the individual rather than the eye.

In addition, we created a number of grouped characteristics to describe ocular complications. Uveal involvement was defined as flare and cells and/or keratic precipitates and/or iris atrophy; leprosy related ocular pathology (LROP) was defined as presence of any of the following: lagophthalmos, corneal nerve beading, corneal opacity, punctate keratitis and uveal involvement. LROP was created to define all leprosy-related ocular conditions regardless of their contribution to disability or vision loss. Potentially blinding leprosy related ocular pathology (PBLROP) was defined as presence of any of the following-lagophthalmos and/or uveal involvement (flare and cells and/or keratic precipitates, and/or iris atrophy)-constituting those leprosy-related conditions known to be associated with disability or vision loss.

Cox proportional hazards regression was used to analyse the occurrence of specific findings according to demographic and clinical characteristics associated ($p<0.05$) with pathology by univariate analysis, generating p-values, hazard ratios (HR) and 95% confidence intervals (CI). Step-wise multiple regression analysis was done to confirm significant values obtained earlier. Analysis was done using STATA software package version 9.0.

Results

There were 213 males (71%) and 88 females (29%) among the 301 MB patients that were enrolled. Age of patients ranged from 7 to 78 years with a mean (SD) of 41.6 (14.3) years. Ocular hypotony and hypotension detected in our study were not consistently present during every follow-up period. Ocular hypotony (IOP < 7 mm Hg) was present in two patients (0.66%) at the time of diagnosis. During MDT, out of 288 patients at risk (465 patient years), 3 patients developed hypotony giving an incidence rate of 0.006/PY (95% CI 0.002-0.020). After completion of MDT, 273 patients were followed-up for a total of 2203 patient years. 9 patients developed hypotony giving an incidence rate of 0.004/PY (95% CI 0.002-0.008).

Ocular hypotension (IOP < 10 mm Hg) was present in 24 patients (8%) at the time of diagnosis. During MDT, out of 269 patients at risk (417 patient years), 25 patients developed hypotony giving an incidence rate of 0.060/PY (95% CI 0.041-0.089). Risk factors for ocular hypotension included the

presence of other deformities, uveal conditions and trichiasis (Table 1). Independent associations were detected between ocular hypotension and trichiasis (HR 8.83 95% CI 2.06, 37.78 p=0.003) and flare or/and cells (HR 4.60 95% CI 1.08, 19.64 p=0.039) at the time of diagnosis.

Patients with hypotony and hypotension had a mean IOP of 12.60 mm Hg (SE 0.07 95% CI 12.45 - 12.74). This differed significantly (p<0.0001) from the mean IOP (14.9 mm Hg SE 0.04 95% CI 14.8 - 15.03) of those who did not have hypotony or hypotension.

Table 1 : Risk factors for ocular hypotension (IOP < 10 mm Hg) during MDT*

	Hazards ratio	95% Confidence Interval	P value
Demography			
Age (per decade)	1.170	0.889 1.539	0.236
Sex (female *vs* male)	0.934	0.390 2.235	0.878
Leprosy characteristics			
Duration (=1year *vs* < 1 year)	1.042	0.477 2.296	0.918
History of face patch	0.889	0.399 1.979	0.774
History of any leprosy reactions	1.821	0.727 4.559	0.201
Skin smear (*M.leprae* positive *vs* negative)	0.662	0.264 1.657	0.378
Grade 1 deformity *vs* no deformity	0.924	0.192 4.450	0.922
Grade 2 deformity *vs* no deformity	6.074	1.569 23.520	0.009
Face patch at enrollment	0.889	0.399 1.979	0.774
Ocular characteristics			
Orbicularis muscle weakness	1.921	0.453 8.153	0.376
Lagophthalmos	2.136	0.503 9.063	0.303
Trichiasis	8.230	1.934 35.022	0.004
Corneal opacity	0.711	0.168 3.017	0.644
Corneal nerve beading	1.991	0.269 14.725	0.500
Flare and cells	8.194	1.105 60.758	0.040
Keratic precipitates	0.888	0.120 6.565	0.907
Iris atrophy	4.249	1.001 18.033	0.050
Cataract (with VA<6/18)**	2.274	0.844 6.126	0.104
Pterygium	0.954	0.286 3.190	0.940
Grouped characteristics			
Uveal involvement***	1.272	0.299 5.396	0.744
LROP[#]	2.520	1.052 6.036	0.038
PBLROP[##]	1.810	0.621 5.274	0.277

IOP : Intraocular pressure ***MDT** : 2 year fixed multidrug therapy ****Cataract** associated with reduction of vision below 6/18. *****Uveal involvement includes flare and cell and/or keratic precipitates and/or iris atrophy. [#]**LROP** : Leprosy related ocular pathology includes orbicularis oculi 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.

After completion of MDT, 233 patients were followed-up for a total of 1731 patient years, among whom 29 developed ocular hypotension giving an incidence rate of 0.017 (95% CI 0.012-0.024). Risk factors are presented in Table 2. Multiple regression analyses revealed significant independent associations with punctate keratitis (HR 7.211 95% CI 2.121,24.519 p=0.002) and uveal involvement (HR 8.359 95% CI 1.555, 9.575 p=0.004) at the time of diagnosis.

Table 2. Risk factors for ocular hypotension (IOP < 10 mm Hg) after MDT*

	Hazards ratio	95% Confidence	Interval	P value
Demography				
Age (per decade)	1.093	0.841	1.421	0.504
Sex (female *vs* male)	0.466	0.178	1.223	0.121
Leprosy characteristics				
Duration (=1year *vs* < 1 year)	0.911	0.439	1.889	0.802
History of face patch	0.833	0.396	1.752	0.630
History of any leprosy reactions	0.673	0.204	2.228	0.517
Skin smear (*M. leprae* positive *vs* negative)	1.382	0.481	3.975	0.547
Type 1 reaction *vs* no reaction	1.369	0.603	3.109	0.453
Type 2 reaction *vs* no reaction	2.469	0.330	18.451	0.378
Grade 1 deformity *vs* no deformity	2.134	0.820	5.556	0.120
Grade 2 deformity *vs* no deformity	5.026	1.785	14.154	0.002
Face patch at enrollment	0.954	0.644	1.413	0.815
Ocular characteristics				
Orbicularis muscle weakness	4.348	1.310	14.430	0.016
Lagophthalmos	5.014	1.510	16.646	0.008
Ectropion	57.496	6.426	514.422	<0.001
Episcleritis	7.752	1.049	57.306	0.045
Corneal opacity	1.429	0.497	4.110	0.507
Punctate keratitis	7.015	2.114	23.281	0.001
Keratic precipitates	2.230	0.674	7.374	0.189
Iris atrophy	8.593	2.589	28.531	0.000
Cataract (with VA<6/18)**	2.264	0.863	5.943	0.097
Pterygium	1.973	0.750	5.191	0.168
Grouped characteristics				
Uveal involvement ***	3.783	1.576	9.518	0.003
LROP [#]	3.541	1.611	7.782	0.002
PBLROP [##]	4.372	1.935	9.878	<0.001

IOP : Intraocular pressure ***MDT** : 2 year fixed multidrug therapy ****Cataract associated with reduction of vision below 6/18. *****Uveal involvement includes flare and cell and/or keratic precipitates and/or iris atrophy. [#]**LROP** : Leprosy related ocular pathology includes orbicularis oculi 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.

Discussion

Although several studies have investigated the presence of low intraocular pressure in leprosy patients, only a few have looked specifically at hypotony and hypotension. To our knowledge, this is the first study that has documented the prevalence of both these occurrences at the time of leprosy diagnosis and ascertained their incidence while the patients were on MDT and during the period thereafter. Several studies have estimated intraocular pressures in the general population. The objective in most of them was to screen for glaucoma and therefore, their target populace was aged 40 years or older (Jacob et al 1998, Vijaya et al 2005). A study that had measured IOP in 3834 individuals that were 10 years and above had a mean IOP of 14.5 mm Hg with a standard deviation (SD) of 2.6 mm Hg (Hashemi et al 2005). We defined hypotension to be 2SD below this mean IOP and included all patients who had pressures lower than 10 mm Hg. We defined hypotony to be 3SD below the mean IOP and included all patients who had pressures of less than 7 mm Hg.

The proportion of patients with ocular hypotony (IOP<7mm Hg) at the time of diagnosis in our study differed from two other earlier studies. Lewallen and colleagues (1990) reported that 12% of 255 foreign born US resident leprosy patients had hypotony while Hussein et al (1989) reported 15% of 72 patients in a similar population had ocular hypotony; these figures contrast with the relatively rarer occurrence (<1%) in our patients of Indian origin. Follow-up of patients during the two years they were under MDT and for five years thereafter disclosed 12 others with hypotony giving a cumulative prevalence of 4.65% (95% CI 2.56% - 7.68%). A possible explanation could be that the patients in these two earlier studies were not early diagnosed leprosy patients but were on a much later trajectory of the disease. Additionally, many of them could have had chronic iridocyclitis from a previous treatment era that had since resolved. The small number of patients with hypotony in our cohort was insufficient to deduce any meaningful associations that might exist.

Signs of uveal inflammation at diagnosis predisposes to the development of ocular hypotension during MDT and in the period following completion of MDT. Although several studies (Brandt et al 1981, Karaçorlu et al 1991) have shown an association between chronic plastic iridocyclitis that remained untreated for several years and low intraocular pressures, our study demonstrates that newly diagnosed MB patients presenting with signs of ocular inflammation in the anterior chamber are 3 to 4 times more likely to have ocular hypotension during their MDT treatment period than patients whose eyes did not have any such signs of inflammation. Patients presenting with additional uveal involvement like iris atrophy and the presence of keratic precipitates at diagnosis are 8 times more likely to develop ocular hypotension in the period after completion of their MDT than patients who did not have these conditions. There is evidence that the nerves to the ciliary body undergo destruction in MB patients (Ebenezer and Daniel 2004); this process could occur silently without accompanying clinically discernable uveal inflammatory processes and affect ciliary body function in such a way that results in hypotension. Our study also corroborates a previous finding that punctate keratitis is associated with low intraocular pressure (Lewallen et al 1990). While patients with trichiasis at the time of diagnosis were at increased risk of developing hypotension during MDT, we are unable to establish a possible explanation for this association.

Most studies investigating IOP over time have focused on increased intraocular pressure or variations in pressure than on hypotension. Therefore, our ability to compare our results with previous work is limited. We did not measure a number of factors (e.g. hypertension, obesity and other cardiac risk factors) that have been known to influence intraocular pressure (Shiose 1990, Klein et al 1992). Since all of the patients were derived from a population living within a well

defined geographical area and from similar socioeconomic groups, we assume that these factors would have been evenly distributed. Another limitation of our study is that IOP measurements were taken once and were not averages of three measurements. Corneal scarring is liable to preclude accurate measurements of IOP by applanation but in our cohort the opacities were small and peripheral and therefore unlikely to have made a significant difference.

IOP has been shown to increase with age in some population based studies (Costagliola et al 1990, Leske et al 1997). We found no correlation between age and hypotony or hypotension in our leprosy cohort. None of the patients in our study had sustained ocular hypotony or hypotension but patients who did exhibit it one time or other had a significantly lower IOP than those that did not indicating that these patients had a tendency for lowered IOP. It is not known whether this transient drop in ocular pressures contribute significantly to ocular morbidity or require remedial procedures. Studying the process, though, could contribute to our understanding of the pathogenesis of lowered intraocular pressure in systemic infectious diseases and possibly provide insights into future remedial measures in raised intraocular pressure conditions.

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