

LONGITUDINAL OCULAR SURVEY OF 202 FILIPINO PATIENTS WITH MULTI-BACILLARY (MB) LEPROSY TREATED WITH 2 YEAR WHO-MULTIPLE DRUG THERAPY

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Abstract. The aim of this study was to describe the ocular conditions in multi-bacillary (MB) leprosy patients treated with 2 year WHO multiple drug therapy (MDT), consisting of dapsone, clofazimine and rifampin, a regimen expected to reduce ocular complications of leprosy. We conducted comprehensive eye examinations in 202 Filipino MB leprosy patients before, during, and after WHO 2 year MDT. Assessments were carried out for at least 5 years. Inflammatory "lepra" reactions occurred in 62% (reversal reaction, 52%; erythema nodosum leprosum, 10%); most were mild. Eye abnormalities consisted mostly of diminished corneal sensitivity before MDT (6%) and lagophthalmos ($n = 7$, 3.4%). Six of 7 lagophthalmos cases occurred in a subset of 132 patients with facial patches (5%). Visual acuity scores, intra-ocular pressures and pupil cycle times were unremarkable. Bacillary invasion, keratitis, episcleritis, iridocyclitis, ectropion, synechiae, glaucoma and cataract formation were not detected. Scleral clofazimine pigmentation was frequent, resolving in most within 3 years of treatment cessation. Facial patches at presentation may denote a higher risk for lagophthalmos. We propose the generally low rates of ocular problems reflected mild lepra reactions, due to anti-inflammatory properties of clofazimine, a relatively young cohort, and a readily accessible community-based clinic permitting earlier diagnosis and prompt treatment.

Keywords: leprosy, lepra reactions, ocular disease, WHO multi-drug therapy (MDT)

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INTRODUCTION

Leprosy, caused by *Mycobacterium leprae*, usually presents with skin lesions and enlarged nerves (Sehgal, 1994). Patients with multi-bacillary (MB) or disseminated leprosy, often consisting of lepromatous (LL) and borderline lepromatous (BL) leprosy, are at high risk for ocular lesions, either from inflammatory episodes called

“lepra” reactions or, less commonly, “by direct invasion with *M. leprae* (Schwab, 1992; Chacko *et al*, 1997; Ffytche, 1998). Two kinds of lepra reactions, reversal reaction (RR) and erythema nodosum leprosum (ENL), may cause nerve damage, leading to eye complications, that in many leprosy endemic communities, is a leading cause of visual impairment (Courtright, 1988; Ffytche, 1989; 1998; Schwab, 1992; Sundar Rao *et al*, 1998). Facial leprosy lesions, also called face patches, may increase the risk for ocular complications. However, the frequency of ocular morbidity varies greatly by region, and is attributed to genetic, immunologic and environmental factors, and differences in diagnostic and treatment resources (Courtright, 1988, 1998; Courtright *et al*, 1997).

In 1982, the World Health Organization (WHO) recommended two year multiple drug therapy (MDT), consisting of dapsone, rifampin, and clofazimine, for all patients with MB leprosy (Sehgal, 1994). Clofazimine, a drug with anti-bacterial and strong anti-inflammatory properties, is expected to reduce the incidence and severity of leprosy disabilities, including ocular complications, partly by reducing lepra reactions (Fajardo *et al*, 1999). Clofazimine darkens skin and sclera (Moore, 1983).

Between 1991 and 1998, a “Longitudinal Ocular Study of Leprosy” (LOSOL) was undertaken in several countries to describe ocular complications where prompt, supervised MDT is routine, with a goal of providing information to address ocular morbidity in other leprosy endemic regions (Courtright *et al*, 2002; Daniel *et al*, 2006a, b). This report describes data from Cebu, an urban setting which enrolled a relatively young cohort with ready access to a well known community-based clinic,

Table 1
Annual enrollment of 202 patients assessed per protocol.

Year	Number enrolled
1989	12
1990	33
1991	50
1992	36
1993	19
1994	3
1995	0
1996	14
1997	30
1998	5
Total	202

permitting earlier diagnosis, prompt treatment monitoring and regular follow-up visits.

MATERIALS AND METHODS

Study design

This was a prospective, longitudinal survey of newly diagnosed MB leprosy patients conducted at the Leonard Wood Memorial (LWM) Center for Leprosy Research. The study was approved by the LWM institutional review board. Enrolment occurred from 1989 to 1998, with study follow-up visits through 2003 (Table 1).

After signed informed consent, patients received a comprehensive pre-treatment eye examination, began 2 years of MDT, and had repeat eye examinations approximately every 6 months until treatment completion. Thereafter, examinations were conducted annually, with a goal of not less than 5 years of assessments, including 2 years during MDT. Ocular assessments included general eye examinations, visual acuity, pupil cycle

times, corneal sensitivity, inflammatory conditions, lagophthalmos, scleral examination for clofazimine deposition (golden brown pigmentation), and response to treatment. During this survey, incident cases of blindness related to leprosy were not expected.

MB leprosy was diagnosed by conventional slit skin smears and skin biopsies. Patients were clinically classified according to the Ridley-Jopling scale (Ridley *et al*, 1966). In this manner, patients with MB leprosy had a BI of $\geq 2+$ from one or more of 6 standard slit skin smear sites, a logarithmic measure of the bacterial load scaled from 0 to 6 (Sehgal, 1994). A "face patch" was defined as a leprosy lesion anywhere above the neck.

All patients received a 2 year MDT regimen consisting of monthly observed rifampin and clofazimine at the clinic, and daily self-administered clofazimine and dapsone, in accordance with WHO guidelines. Treatment of all ocular conditions followed local standards of care.

To reduce loss to follow-up, field personnel assisted some patients in attending the clinic for scheduled eye examinations, and some received nominal travel costs. If a patient was diagnosed with an ocular condition requiring therapy at any time during the study, treatment was implemented in a timely fashion according to local standards of care without cost. If at any time the patient declined examination or study participation, treatment was still offered. For all nonscheduled visits with ocular complaints (self-presentation or referral), a comprehensive eye examination was conducted.

Sample size, data collection and analysis

An enrollment goal of approximately 300 patients was based on an expected complication rate of 3-10%. The expected

Table 2
Age and gender of patients at enrollment.

Age range	Boys-men (n)	Girls-women (n)
0-10	5	3
11-20	44	26
21-30	50	12
31-40 ^a	31	8
41-50	7	1
51-60	5	1
61-70	7	1
71-80	1	0
Total	150	52

^a179 (88.6%) \leq 40 years old

drop out rate, based on historical trends, was 5-10%. All data were recorded on a standardized case report form, entered into a computerized database and cross checked for completeness and accuracy. The incidence of specific ocular abnormalities was tabulated in relation to demographic and clinical characteristics. Leprea reactions and ocular findings, in relation to MDT, were recorded.

RESULTS

Among 300 patients enrolled, 202 were assessed per protocol, with examinations for at least 5 years, including the two year MDT period (Table 1). Some patients enrolled earlier in the study had assessment periods extending beyond 5 years. Ninety-eight patients (33%) were classified as lost to follow-up, most citing unwillingness to comply with rigorous study requirements over a 5 year period, and the remainder due to relocation or death. All patients lost to follow-up were excluded from analysis.

Among the 202 patients assessed per protocol, 179 (89%) were $<$ 40 years old at MB leprosy diagnosis, and the male to

Table 3
Ridley-Jopling classification and mean bacteriologic index (BI) of patients at enrollment.

Leprosy classification	Number of patients (% of total)	Mean BI
Borderline tuberculoid (BT)	3 (1.5%)	1.7
Borderline (BB)	1 (0.5%)	3.0
Borderline lepromatous (BL)	122 (60%)	3.3
Lepromatous (LL)	76 (38%)	4.4
Total	202	

Table 4
Number of lepra reactions, during or after multiple drug therapy (MDT).

Leprosy type (<i>n</i>)	Reversal reactions	ENL ^a
Borderline tuberculoid (3)	1	0
Borderline (1)	0	1
Borderline lepromatous (122)	78	5
Lepromatous (76)	27	14
Total	106 (52%)	20 (10%)

^aENL, erythema nodosum leprosum

Table 5
Summary of 7 patients developing lagophthalmos.

Patient	Face patch	Reversal reaction (with skin signs) ^a	Onset	Duration
L - 052	Yes	Yes	MDT, month 20	4 years
L - 064	No	No ^a	MDT, month 19	4 years
L - 073	Yes	No ^a	MDT, month 5	Unresolved
L - 092	Yes	No ^a	MDT, month 21	2 years
L - 189	Yes	Yes	Pre MDT	Unresolved (Fig 1)
L - 195	Yes	Yes	MDT, month 7	Unresolved (Fig 2)
L - 263	Yes	Yes	MDT, month 17	6 months
Total	6/7 (86%) ^b	4/7 (57%)	6 during MDT 1 pre MDT	4 resolved 3 unresolved

MDT, multiple drug therapy

^aLagophthalmos alone can be a sign of reversal reaction, suggesting face patches are a better determinant.

^b6 of 7 lagophthalmos incidents occurred in a subset of 132 patients with face patches (5%).



Fig 1—A 70 year old man with MB leprosy, presenting with trunk and face lesions, developed a reversal reaction during the 2nd month of MDT. Lagophthalmos of the right eye was noted 4 months later. This image was taken 5 years after completing MDT, underscoring the permanent nature of some ocular complications. The palpebral fissure is widened (arrow).

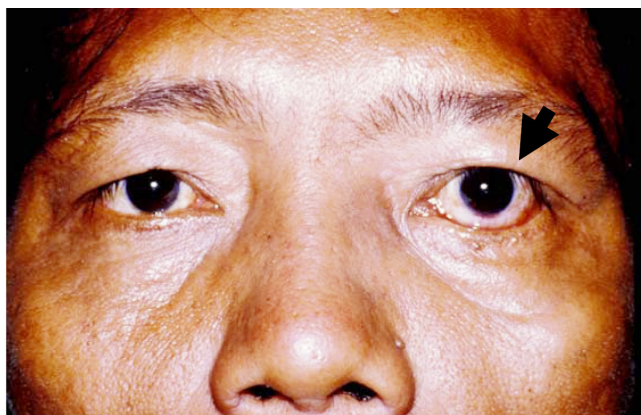


Fig 2—A 36 year old man with MB leprosy, presenting with trunk and face lesions, developed reversal reactions intermittently during MDT, then lagophthalmos of the left eye (arrow). This image was taken approximately 5 years after completing MDT.

female ratio was about 3:1 (Table 2). The average onset of clinical disease, assessed by standardized questionnaire, was approximately two years prior to diagnosis.

Nearly all 202 patients (98%) were classified as borderline lepromatous or lepromatous, the 2 most disseminated forms of leprosy (Table 3).

Table 4 shows the type and number of lepra reactions that occurred at least once in any individual patient during MDT and follow-up, with 106 (52%) developing RR and 20 (10%) developing ENL. Seventy-six patients had no reactions. All reactions were mild or moderate in severity (little or no interference with daily activities) and, for skin and nerve signs, responded to oral corticosteroids.

At enrollment, diminished corneal sensitivity was present in 6% of patients, all normalizing during MDT. Intra-ocular pressures were unremarkable, ranging from 10-18 mmHg throughout the survey (normal 10-20 mmHg). For adnexal involvement, 5 patients exhibited muscle weakness before MDT; 4 normalized after completion of MDT. For pupil cycle times (normal ≤ 2 ms), before MDT, 5 patients (2.5%) had abnormal values. After MDT completion and during follow-up, 2 of 5 remained abnormal. There were no detectable trends between abnormal pupil cycle times and age, gender, treatment status or pupil size.

As summarized in Table 5, lagophthalmos was noted in 7 patients, 1 on enrollment and 6 developing during MDT. Six lagophthalmos incidents (5%) occurred in the subset of 132 patients with face patches, *versus* 1 in 70 patients (1.5%) without face patches.

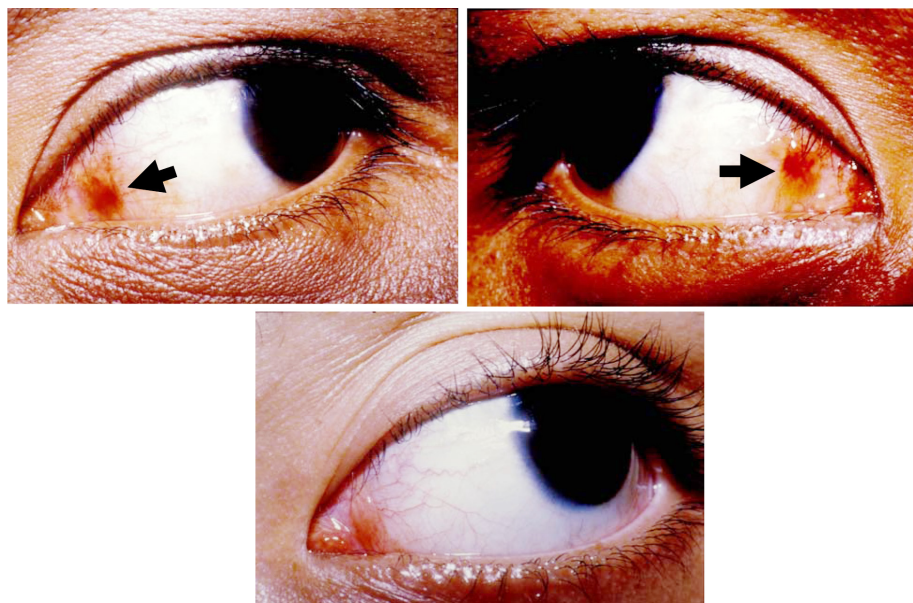


Fig 3—Top (left and right): A 20 year old woman at 1 month after completing MDT with notable bilateral scleral clofazimine deposits, near the limbus (arrows). Bottom: healthy, age matched woman, never on MDT.

More than half of the lagophthalmos incidents (4/7) occurred in patients who also developed “classic” reversal reaction at some point, to include new skin lesions, a distinction made because lagophthalmos alone, without skin lesions, can be a sign of reversal reaction. There were no incidents of lagophthalmos in any patient that developed ENL. All patients with lagophthalmos were treated with oral corticosteroids: 4 resolved fully and 3 remained unresolved at last study exam (Figs 1-2).

Approximately 70% of patients developed asymptomatic ocular clofazimine pigmentation, most within 12 months of starting MDT, primarily near the limbus (Fig 3). In most, the deposits disappeared within 3 years of treatment cessation.

Bacillary invasion with *M. leprae*, keratitis, episcleritis, iridocyclitis, ectro-

pion, synechiae, premature glaucoma and cataract formation were not detected in any patient.

DISCUSSION

As worldwide implementation of MDT for MB leprosy began in 1982, with an expected reduction in overall morbidity, including ocular complications, regional surveys like this may provide critical information. In our cohort, ocular abnormalities were relatively infrequent and mild. Lagophthalmos was the most significant problem, occurring in 3.4% of the entire cohort, and clofazimine pigmentation of the sclera, a reversible, non-pathogenic side effect, was noted in most patients. Notably, 6 of 7 lagophthalmos incidents occurred among a subset of 132 patients with face patches (about 5%), some eventually developing reversal

reaction, suggesting face patches denote a higher risk population. However, we propose the overall low rate of ocular complications reflect a low frequency of lepra reactions, likely due to the anti-inflammatory properties of clofazimine, potent anti-bacterial properties of MDT, relatively young patients, and availability of a well established, accessible clinic permitting earlier diagnosis and prompt supervised treatment.

In many communities, stigma from clofazimine pigmentation may lead to treatment default, especially if supervision is unavailable. Here, rigorous monthly observation of drug administration, per WHO guidelines, insured therapeutic levels of clofazimine (1/2 life 70 days), even if self treatment adherence was poor. MDT has greatly reduced leprosy prevalence and patients needing lifelong care now outnumber those on therapy, changing the focus of leprosy management (Lewallen, 1997; Hogeweg, 1998a, b). To maintain the risk-benefit profile of MDT, disability prevention, in including ocular complications, is important (Lewallen *et al*, 2007).

Lepra reactions, often considered the most important risk factor for ocular complications, are difficult to monitor and require prompt anti-inflammatory treatment to prevent irreversible damage (Schwab, 1992). In many regions, ocular pathology associated with reactions is poorly addressed (Chacko *et al*, 1997). In untreated leprosy patients, the natural history of ocular complications is complex and multi-factorial (Schwab, 1992; Job *et al*, 1998; Sundar Rao *et al*, 1998). In our survey, reactions were generally mild and promptly treated, factors that likely contributed to the low rate of ocular problems.

Leprosy is not distributed randomly and the clinical characteristics of disease, including ocular involvement, vary by region (Courtright *et al*, 1997). This variability generally prohibits extrapolation of data from one community to another, highlighting the importance of conducting studies in distinct geographic locations such as Cebu. Sufficient incidence, capability for long term follow-up, adequate infrastructure, ophthalmology services, and a well managed MDT program, all present in Cebu, are critical factors in accurate reporting. As eye pathology may progress after MDT completion, ocular exams should be conducted for a period of at least 5 years after diagnosis (Samanta and Das, 2007).

The data collected in Cebu underscore the value of early detection of leprosy, prompt initiation of supervised MDT per WHO guidelines, monitoring for and treatment of lepra reactions, and the important role of ophthalmology services in addressing and mitigating leprosy-related ocular morbidity.

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