Defining the Magnitude of Ocular Complications from Leprosy: Problems of Methodology[1]

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Ocular complications from leprosy were first documented in Norwegian patients by Bull and Hansen in 1873 ([6]). Dozens of surveys from leprosy-endemic and nonendemic regions have subsequently been published. Unfortunately, these surveys, whether evaluated individually or as a group, do not provide adequate information for defining the incidence or prevalence of ocular involvement, nor the level of disability and blindness from leprosy. This deficiency was highlighted recently in "Prevention of Blindness in Leprosy:" "Data on blindness in leprosy is incomplete and often unreliable because of the problems in obtaining representative population-based estimates. From existing surveys it is estimated that up to one-quarter million leprosy patients are blind (vision < 3/60). This figure rises further if a visual acuity of less than 6/60 is considered. The visual disability in these patients is further compounded by other disabilities, particularly sensory impairment and deformity of the extremities" ([10]).

Two major shortcomings are readily apparent if one reviews existing data. These are a) methodological problems in the published surveys and b) lack of information about epidemiologic patterns and features of (systemic) leprosy. This paper focuses exclusively on the former, since an excellent discussion of the limitations inherent in our understanding of the epidemiologic patterns and features of leprosy has been published ([18]).

MATERIALS AND METHODS

All ocular surveys of leprosy patients appearing in the English-language scientific literature were reviewed. Case presentations were not reviewed nor were surveys published before 1940. Disability surveys, often different in scope, purpose and methodology, are also excluded from this discussion. Methodological problems limiting the interpretation of published results were tabulated for each survey. The methodological problems, as reflected in The Table, are: a) lack of survey sampling techniques; b) institution-based or clinic-based populations as the study population; c) inadequate instruments for the detection of clinical signs; d) non-ophthalmically trained individual as the examiner; e) definition of "ocular" disease that included non-ocular conditions; f) failure to analyze by clinical type; and g) failure to analyze by duration of disease or therapy. All of the studies tabulated are complicated by one or more of these methodological problems which are addressed separately in the Discussion section.

RESULTS

Methodological problems in published surveys. All published studies assess the magnitude of ocular complications from leprosy through cross-sectional methodology. A review of the 40 published studies listed in The Table reveals a range of ocular involvement. Several papers ([1, 14, 16, 19, 41]) refer to incidence rates, but careful analysis suggests that these are prevalence rates. The absence of longitudinal information makes it impossible to determine the incidence of, and risk factors for, specific ocular complications.

Authors have occasionally constructed summary measures of ocular involvement from previously published surveys and compared these results to those collected from their sampled population. However, it is inappropriate to pool data from studies with methodological flaws ([46, 50]). In addition, it is unclear from most of these surveys whether the investigators have made the distinction between blindness due to lep-

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THE TABLE. *Review of ocular surveys in leprosy.*

Year	Site	No.	Ocular leprosy		Methodologic problems[b]	Reference citation
			Complications (%)	Blind[a] (%)		
			Africa			
1961	Tanzania	1,212	8	?[c]	2a, 3?, 6	34
1964	Ghana	250	13	3	1, 2a, 2b, 3, 5, 7	7
1970	Malawi	8,325	6	<1	3, 4	51
1970	Uganda	890	21	<1	1?, 2a, 3, 5	16
1971	Egypt	98	94	22	1, 2b, 5, 6, 7	53
1983	Kenya	199	51	3	1, 2b, 5	26
1984	Egypt	133	?	17‡	2a, 5, 7	47
			Americas			
1940	U.S.A.	350	91	6	2a, 2b, 5, 6, 7	38
1946	Panama	150	90	41≠	2a, 6, 7	20
1974	Brazil	100	72	22†	2a, 5, 6, 7	49
1977	Canal Zone	48	96	50≠	2a, 2b, 3?, 5, 6, 7	21
1985	U.S.A.	55	75	0	1, 2b, 5, 6, 7	50
			Europe			
1983	Netherlands	121	20	0	1, 2b, 3?, 5, 6, 7	23
			Oceania			
1950	Australia	55	64	?	1?, 2a, 3?, 5, 6, 7	
1980	Papua New Guinea	234	23	?	1, 2b, 3, 4	
1981	Papua New Guinea	121	20	0	1, 2b, 5, 7	
			Asia			
1955	Israel	59	90	3	1, 2a, 3?, 5, 6, 7	31
1961	Singapore	625	15	1	1, 2a, 2b, 3?, 7	27
1966	India	385	46	?	1, 2b, 7	2
1969	Sri Lanka	630	47	5	2a, 3?, 6, 7	54
1971	India	60	70	0	1, 2b, 3?, 5, 6, 7	46
1972	Malaysia	444	52	2	1, 2a, 3?, 5, 6, 7	55
1973	Nepal	57	49	0	1, 2a, 2b, 4, 6, 7	15
1973	South Vietnam	51	76	?	1, 2b, 3?, 5, 6, 7	24
1973	India	654	26	?	2a, 2b, 4, 5	25
1976	India	430	25	?	1, 2b, 5, 7	48
1976	Malaysia	239	?	8	1, 2a, 3, 4, 5, 6, 7	14
1978	India	2,731	11	<1	1, 2a, 2b, 3?, 5, 7	1
1978	Iran	100	?	?	1, 2a, 2b, 3, 4, 6, 7	40
1980	India	150	100[d]	9	1, 2a, 3?, 5, 6, 7	11
1980	India	320	?	5‡	1?, 2a, 3, 6, 7	39
1981	India	8,803	1	0	3, 4, 7	43
1981	Nepal	116	70	9‡	1, 2a, 5, 7	5
1981	Nepal	466	74	13≠	1?, 2a, 3, 5	32
1983	India	435	35[e]	3–10	1, 2a, 2b, 3, 6, 7	30
1984	India	380	19	2	2a, 3?, 5	37
1984	India	1,800	8	?	1?, 2a, 3?, 4?, 5, 6, 7	41
1984	India	11,697	10	2	1, 3, 5, 6, 7	42
1984	Korea	2,925	40	11†	3, 4, 6, 7	9
1985	India	143	64	9	1, 2b, 3, 5, 6, 7	52

[a] Vision less than 3/60 in better eye unless otherwise noted: † = Vision less than 6/60 in the better eye; ‡ = Vision less than 3/60 in the worst eye; ≠ = Vision less than 6/60 in the worst eye.

[b] Methodologic problems include: 1) Lack of survey sampling techniques; 2a) Institution-based sample; 2b) Clinic-based sample; 3) Inadequate instruments for the detection of clinical signs; 4) Non-ophthalmically trained individual as examiner; 5) Definition of "ocular" disease that includes non-ocular conditions; 6) Failure to analyze by clinical type; 7) Failure to analyze by duration of disease or therapy.

[c] ? = Information not available/unclear.

[d] Only patients with ocular complications examined.

[e] Potentially sight-threatening lesions only.

rosy and blindness from other causes. Prevalence surveys have failed to analyze the level of background eye disease in the population to accurately reflect the contribution of *Mycobacterium leprae* to ocular morbidity and blindness. Furthermore, the role of other blinding conditions endemic to the region (e.g., trachoma, onchocerciasis) is rarely considered. Cataract, secondary to chronic uveitis, is a leading cause of blindness in leprosy patients; however, in only one study is the contribution of cataract to blindness in leprosy investigated ([4]).

DISCUSSION

Lack of survey sampling techniques

The lack of adequate sampling techniques and application is one of the most common characteristics of published ocular leprosy surveys. Without exception, sampling procedures were never utilized to select a study population. In one third of the surveys, study populations consist exclusively of leprosaria residents ([20, 21, 34, 37, 38, 47, 49, 54]) or leprosy clinic outpatients ([25]), usually sequentially sampled. It is important to note, however, that leprosy patients tend to visit clinics when prompted by symptoms of particular conditions (e.g., the onset of acute iridocyclitis which is characterized by severe pain, photophobia, excessive lacrimation and pericorneal injection). However, many other ocular complications from leprosy are asymptomatic. For example, involvement of the 5th facial nerve can result in corneal hypesthesia, decreasing the ability of this organ to alert the patient to epithelial injury ([29]). Thus, self-selection among clinic populations can be expected to result in the overestimation of acute symptomatic conditions, whereas asymptomatic conditions, if not associated with acute signs, are likely to be underrepresented.

Potentially confounding factors, such as clinical type, age and duration of disease, are likely to be influential in self-selection. Consequently, when the allocation of patients for survey purposes is not random, the prevalence of ocular involvement and blindness due to leprosy will tend to be an overestimation. In some settings, randomization of patients is impractical. Registered domiciliary patients in societies where leprosy has stigmatizing characteristics often have minimal contact with the health care system. Therefore, local conditions, natural and artificial clustering of patients, and sociocultural factors surrounding leprosy in the community must be carefully considered prior to sampling.

Institution-based and clinic-based populations

In most communities, sociocultural factors involving leprosy beliefs and attitudes have tended to segregate patients from the general population. This has led to secondary (artificial) clustering of leprosy patients. For example, leprosaria tend to house patients with deformities. Those who do not reside in leprosaria, but who are also unwelcome in their home communities, may resettle in leprosy villages. In general, three discrete subgroups of patients may be discerned:

Patients who remain in the community (domiciliary patients). These patients generally have few visible disabilities. To date, only two ocular surveys of domiciliary patients have been conducted. In both, all registered patients in the region were examined—8325 patients in southern Malawi ([51]) and 8803 patients in southeastern India ([43]).

Patients in leprosaria. Throughout the world, leprosaria have been established to provide for leprosy patients who are unable to care for themselves, to segregate these individuals from society, or to house those rejected by their family or community. This has meant that leprosaria patients generally exhibit one or more of the following characteristics: old age, disease of long duration, increased prevalence of physical deformities, increased access to medical care, and reduced work exposure. Two thirds of the published surveys utilize leprosaria samples. In most of these cases, the results from these surveys can be expected to overestimate ocular disability when compared to population-based surveys.

Patients in leprosy resettlement villages. Resettlement villages are not common to all leprosy-endemic regions. Much of the impetus for their establishment was to initiate de-institutionalization of patients in societies where leprosy carries a stigma. There is only one ocular survey of resettlement village patients in the literature ([9]). The results from this survey may reflect

ocular disability at a level consistent with the degree of ostracism in the society and ocular complications in the overall leprosy population.

There is considerable regional variation in the proportion of registered leprosy patients in leprosaria, resettlement villages, and the general community. An accurate measurement of the occurrence of ocular complications and blindness in a region necessitates the inclusion of all resident types (domiciliary, village and leprosaria) in the sample.

Inadequate instruments for detection of clinical signs

The slit lamp (biomicroscope), loupe, and penlight are the tools for detecting ocular pathology in the anterior segment of the eye. The magnifying qualities of the slit lamp and loupe increase the ability of the examiner to detect subtle changes in ocular physiology that are not detectable by simple illumination. Recognition of chronic and acute uveal inflammation, including detection of cells, flare, and keratic precipitates, often is not discernable by loupe or simple illumination and, therefore, necessitates the utilization of a slit lamp ([22]). Intraocular damage resulting from long-standing chronic uveal inflammation can be detected by illumination as a pinpoint non-reacting pupil. Thus, investigators utilizing a loupe or penlight will tend to underestimate the occurrence of chronic iritis, especially in patients with limited disease duration. Detection of early cataract will also be underestimated by these techniques.

In 34% of the surveys investigators did not describe the instruments they utilized. In an additional 32% of the surveys, a loupe or penlight was utilized instead of a slit lamp.

Non-ophthalmically trained individual as examiner

In most (74%) of the surveys, ophthalmologists performed the clinical examination. In the remainder, ophthalmic assistants and other health care workers conducted the ocular examinations. Due to the anterior segment nature of the blinding complications of leprosy, ophthalmic assistants and similarly trained personnel can accurately identify these conditions.

Unlike eye diseases such as trachoma and xerophthalmia, the criteria for detection of the full range of clinical conditions of ocular leprosy has not been standardized. A format for the recording of clinical signs was suggested in the literature in 1983 ([17]) and recently two pro formas—for ophthalmologists and for paramedical workers—have been recommended ([10]). To date, observer variation has not been assessed. Thus, it is impossible to determine if observer variation and variation in recording procedures among ophthalmologists account for underestimation or overestimation in reported prevalence.

The interpretation of surveys conducted by non-ophthalmically trained individuals is additionally complicated by the utilization of instruments that are inadequate to detect many ocular complications. In the surveys in southern Malawi ([51]) and India ([43]), domiciliary patients were screened by paramedical workers utilizing penlights followed by slit-lamp examination on referred patients.

Definition of ocular disease that includes non-ocular conditions

Non-ocular conditions, primarily madarosis, are included by two thirds of the investigators when they construct a measure of ocular complication. Madarosis, the loss of eyebrows, has no associated impact upon vision or any ocular structures. This sign is recognized by the community as an indication of leprosy. Madarosis is tabulated as the single leading "ocular" condition from leprosy in almost all of these surveys, suggesting that the prevalence of ocular complications in these surveys is overestimated.

Recently, a more refined division of ocular lesions from leprosy into a) potentially sight-threatening lesions and b) non-sight-threatening lesions was suggested ([30]). Potentially sight-threatening lesions included: lagophthalmos, exposure keratitis and sequelae, corneal anesthesia, and iridocyclitis and its sequelae. Academic lesions included clinical findings such as beading of corneal nerves, iris pearls, and madarosis. A standardized format for the recording of clinical signs must incorporate this distinction in order to be of use in the field. Our limited understanding of the pathogenesis of ocular leprosy will prompt retooling of a recording pro forma as our knowledge increases.

Failure to analyze by clinical type

The immunologic spectrum of leprosy has been classified in clinical and histologic terms. Lepromatous leprosy is classified as bacteriologically positive, clinically malign and immunologically stable. Tuberculoid disease, occupying the opposite end of the spectrum, is also immunologically stable but with a brisk immunologic response, bacteriologically negative and clinically benign ([35]). Borderline disease covers a wide spectrum between lepromatous and tuberculoid and, thus, is immunologically unstable. Borderline patients can undergo a reversal reaction, commonly described as a delayed-hypersensitivity reaction. Erythema nodosum leprosum (ENL), an immune-complex reaction common among lepromatous and borderline patients, is a result of the deposition of immune complexes within tissues ([35]). Episodes of these reactions result in increased damage to ocular structures.

The immunologic and histologic characteristics of leprosy appear to be responsible for much of the variability in ocular involvement ([8, 45]). Ocular complications appear to be more common among lepromatous patients than among tuberculoid patients. The anterior segment of the eye provides a favorable environment for *M. leprae,* which are more numerous in lepromatous patients. Ocular involvement in lepromatous patients is not uncommon, especially among patients with long-standing disease. Investigators in the pre-sulfone era suggested that, with sufficient time, all lepromatous patients would develop eye disease ([20, 36, 38]). Survey data from this era support their view.

It has been suggested that corneal disease is the leading cause of blindness in African and Indian leprosy patients among whom tuberculoid disease is common. However, uveal changes are thought to be the leading cause of blindness in East Asian and Latin American patients where lepromatous disease predominates. A stratified analysis of clinical findings by clinical type is required to reveal type-specific ocular complications and their associated risk factors. For example, facial nerve paralysis and lagophthalmos appear to be more common in unstable borderline disease although surveys that demonstrated this did not control for the possible role of disease duration, reactions or therapeutic intervention, all of which may also be associated with the development of facial nerve involvement.

The clinical type of leprosy was correlated with eye disease in only 39% of the surveys. A dichotomous (tuberculoid versus lepromatous) analysis was most common. Without exception, stratification of clinical signs by confounding variables was not performed. Thus, it is impossible to determine the contribution of clinical type to the development of ocular complications.

Prior to introduction of multidrug therapy (MDT), tuberculoid patients were generally "healed" within several years of therapeutic intervention. Lepromatous patients, on the other hand, required therapy for many years. MDT is of much shorter duration: 6 months for paucibacillary patients and 2 years for multibacillary patients ([56]). Thus, it is not surprising that case-management procedures vary.

Case-management procedures that remove patients from leprosy registries upon completion of therapy will tend to increase the proportion of lepromatous patients among the total patient population. Removal of patients from leprosy registers after completion of MDT reflects the reduction in bacillary load of the patient. It does not reflect the presence or absence of disabilities in the population. Thus, consideration should be given to the interpretation of ocular results collected in regions with different case-management practices.

Failure to analyze by duration of disease and therapy

The incidence of ocular leprosy is associated with the duration of time since the onset of disease and the interval between onset and therapeutic intervention. Furthermore, the duration and compliance to systemic therapy would be expected to correlate with the development of ocular pathology. The progression of primary eye disease to secondary blinding conditions (e.g., corneal opacities arising from exposure keratitis, corneal hypesthesia, and lagophthalmos; phthisis bulbi as a consequence of uveal degeneration) is correlated with disease duration and systemic therapy in addition to specific ophthalmologic intervention, su-

perimposed bacterial infections, and other nonleprosy-related conditions. In all but two surveys ([2, 44]) the investigators fail to present findings stratified by duration of disease. Disease, if uninterrupted by therapy, will eventually invade the eye and cause ocular complications in the lepromatous patient ([12, 28]).

Virtually all lepromatous patients with a disease duration greater than 10 years in the pre-sulfone era had ocular leprosy. With the advent of sulfone (dapsone) therapy and, more recently, MDT, the incidence of ocular complications from leprosy has decreased from a reduction in the bacterial load. The efficacy of dapsone on ocular morbidity has been controversial. It has been suggested that dapsone therapy led to only a slight improvement in eye conditions in Sri Lanka ([54]) while across the Tamil Straits in India, dapsone was credited with averting blindness in most patients ([48]). To date there has been no objective assessment of dapsone intake in ocular survey patients. The ocular complications among patients under MDT therapy has not been systematically assessed.

Without exception, the contribution of systemic or ocular therapy, ENL, and reversal reactions is not reported. In a separate study, Brandt assessed the role of dapsone therapy in Nepalese leprosy patients ([3]). Those patients who had received therapy for the first 5 years following disease onset had a significantly lower incidence of lagophthalmos than the patients who remained untreated for longer than 5 years, regardless of clinical type. The incidence of posterior synechia (evidence of uveal involvement) did not appear to be influenced by early dapsone therapy.

The prevalence of physiologic changes in ocular structures increases with age. Many researchers present data stratified by 10-year age groups but fail to include disease duration, a significant confounding factor. The recording of disease duration and the time between onset and diagnosis is complicated and often inaccurate since it relies upon patient history rather than a clinical or immunologic marker. Duration of disease is rarely measured in these surveys, possibly due to the unreliable nature of these estimates. With the advent of testing for antibody/antigen responses to *M. leprae* and improved case-finding techniques, the accuracy of these estimates should improve ([57]).

SUMMARY

A comprehensive review of all ocular surveys (40) of leprosy patients was undertaken. These surveys do not provide adequate information for defining the incidence or prevalence of ocular disease caused by *Mycobacterium leprae*. Furthermore, the level of disability and blindness from leprosy has not been addressed. The primary methodologic problems in these surveys are: a) lack of survey sampling techniques, b) institution-based or clinic-based populations as the study population, c) inadequate instruments for the detection of clinical signs, d) non-ophthalmically trained individuals as examiners, e) definition of "ocular" disease that includes non-ocular conditions, f) failure to analyze by disease type, and g) failure to analyze by duration of disease or therapy. All of these studies were cross-sectional in nature. While this type of study is beneficial to health administrators for prioritizing eye care in health planning, a longitudinal study is required to investigate the risk factors for ocular involvement and blindness in these patients.

RESUMEN

Se hizo una revisión crítica de todos los estudios oculares (41) en pacientes con lepra. Estos estudios no proporcionan información adecuada para definir la incidencia o prevalencia de la enfermedad ocular causada por el *Mycobacterium leprae*. Además, no se ha indicado el nivel de alteración o de ceguera en los pacientes. Los problemas metodológicos primarios en estos pacientes son: a) carencia de técnicas de muestreo, b) estudios hechos indistintamente en poblaciones de instituciones y de clínicas, c) instrumentos inadecuados para la detección de signos clínicos, d) examinadores no entrenados oftalmológicamente, e) definición de enfermedad "ocular" que incluye condiciones no oculares, f) falla en el análisis por tipo de enfermedad, y g) falla en el análisis por duración de la enfermedad o por terapia. Todos estos estudios fueron de naturaleza transversal. Aunque este tipo de estudios resulta útil para los administradores de salud para priorizar el cuidado del ojo en los programas de salud, se requiere un estudio longitudinal para investigar los factores de riesgo en la afección ocular y en la ceguera de estos pacientes.

RÉSUMÉ

On a entrepris une revue exhaustive de toutes les enquêtes oculaires menées chez des malades de la lèpre. Ces enquêtes n'ont fourni aucune information valable pour définir l'incidence de la prévalence de la maladie oculaire causée par *Mycobacterium leprae*. De plus, on n'a pas envisagé les niveaux d'incapacité et de malvoyance résultant de la lèpre. Les problèmes méthodologiques qui se posent en premier lieu dans ces enquêtes sont les suivants: a) absence de techniques d'échantillonnage pour les enquêtes, b) population d'étude provenant d'institutions ou de cliniques, c) équipement inadéquat pour la détection des signes cliniques, d) examens pratiqués par des personnes qui n'avaient pas été formées au point de vue ophthalmologique, e) définition d'une maladie oculaire qui comprend également des conditions non ophthalmologiques, f) absence d'analyse du type de lèpre, g) absence d'analyse en fonction de la durée de la maladie ou du traitement administré. Toutes ces études ont été de nature transversale.

Quoique ce type d'étude puisse servir aux administrateurs de la santé pour déterminer le degré de priorité des soins oculaires dans la planification sanitaire, des études longitudinales sont nécessaires lorsqu'il s'agit d'étudier les facteurs de risque de l'atteinte oculaire de la malvoyance chez ces malades.

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