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## Retrospective study of the morbidity associated with Erythema Nodosum Leprosum in Brazilian leprosy patients

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### *Summary*

*Introduction:* Leprosy patients may develop immune-mediated inflammatory reactions, which are the main cause of nerve function impairment and disability. Among them, Erythema Nodosum Leprosum (ENL) is a potentially life-threatening systemic condition. There are few data on ENL-associated morbidity and mortality, and the need of hospitalisation due to its complications.

*Material and methods:* We conducted a retrospective cohort study including patients diagnosed at the Souza Araújo Outpatient Clinic, Rio de Janeiro. All patients had a first ENL episode at the clinic or were admitted to the Evandro Chagas Hospital, between 2005–2010. In 2014, we obtained the required data from the patients' files to describe ENL morbidity and mortality, including treatment-related adverse events.

*Results:* A total of 112 patients (72% male, median age at diagnosis 35 years, 83% had lepromatous leprosy) developed ENL, among the 676 patients diagnosed with leprosy during the study period. Most of the episodes were chronic and severe. Patients were treated with thalidomide and corticosteroids. Half of the patients receiving corticosteroids had adverse events. 14 patients were hospitalised, ten due to ENL complications. Six patients died, four during the ENL episode. None of these deaths could be considered directly caused by ENL or its treatment.

*Conclusion:* In the group of patients studied, although a high morbidity due to the reaction itself and to the adverse effects of its prolonged treatment was observed, mortality due to ENL was not registered. Prospective studies are required in order to recognise leprosy complications, such as ENL, as consequential causes of death.

## Introduction

Brazil reported 26,875 cases of leprosy to the World Health Organization (WHO) in 2017 of which 73.8% were multibacillary (MB) cases.<sup>1</sup> The latter are patients with low cell-mediated immunity to *Mycobacterium leprae* and have high bacterial loads with widespread dissemination of organisms to tissues other than skin and peripheral nerves.

Leprosy can be complicated by inflammatory episodes called reactions, which are the leading cause of nerve function impairment (NFI), the hallmark of the disease.<sup>2</sup> Reversal reactions and erythema nodosum leprosum (ENL) can occur before, during or after successful completion of multi-drug therapy (MDT).<sup>3,4</sup> ENL is a life-threatening, painful, systemic disorder due to an inflammatory immune response to *M. leprae* antigen.<sup>5,6</sup> It occurs in patients with borderline lepromatous (BL) leprosy and lepromatous leprosy (LL). A bacterial index greater than or equal to four is also a risk factor for ENL.<sup>7</sup> ENL is characterised by the development of crops of erythematous tender skin nodules, fever and inflammation in other organs such as peripheral nerves, joints, bones, eyes, lymph nodes and testes.<sup>6</sup>

Although the first line therapy for ENL in most leprosy endemic countries is oral corticosteroids,<sup>8</sup> in Brazil, the Ministry of Health recommends the use of thalidomide. It has a rapid onset of action for ameliorating ENL symptoms. Its use reduces the need for chronic oral corticosteroids that produce important adverse effects. There is evidence to support the use of thalidomide as a first line treatment for moderately severe and severe ENL.<sup>9</sup> Thalidomide is prescribed in accordance with strict guidelines, which include a pregnancy prevention plan for women with reproductive capacity.<sup>10</sup> However, in some countries its use is banned because of the risk of teratogenicity whilst in others it is only available at certified centres (where its use may be further restricted to male patients or in-patients).<sup>11</sup>

A study of patients with ENL in Ethiopia, where thalidomide is not available, found morbidity and mortality associated with corticosteroids treatment.<sup>12</sup> There are few data on the long-term outcomes for people treated for ENL. Patients treated with thalidomide or other immunomodulating drugs might have different outcomes to those who receive corticosteroids. A study at The Hospital for Tropical Diseases, London, in a cohort of 30 patients diagnosed with ENL between 1996 and 2013, four had ENL for over 10 and up to 16 years.<sup>13</sup>

Patients at Souza Araujo Outpatient Clinic, a national referral centre, are treated with either corticosteroids and/or thalidomide or with other drugs such as pentoxifylline, minocycline or non-steroidal anti-inflammatory drugs. We studied the morbidity and mortality associated with ENL in a retrospective study of patients with clinically diagnosed ENL, between 2005 and 2014.

## Methods and definitions

The Souza Araújo Outpatient Clinic is a reference centre for leprosy in Rio de Janeiro, Brazil. All patients diagnosed for the first time with leprosy at the clinic or admitted to the Evandro

Chagas Hospital, National Institute of Infectiology, Oswaldo Cruz Foundation, between 1st January 2005 and 31st December 2010, were identified from the electronic database. Only individuals who presented with or developed their first episode of ENL during the study period and had complete medical records were included. Data were collected on demographic and clinical characteristics; ENL clinical features, treatment and its adverse effects. The cause of death was obtained from the medical records, from either the social worker (as referred by the patient's family) or the attending physician annotations.

MB Leprosy was diagnosed by the presence of acid fast bacilli in at least one of four/six slit skin smear samples and skin lesion histopathology.<sup>10</sup>

ENL was defined as crops of erythematous, tender cutaneous or subcutaneous nodules, plaques and/or papules in a patient with MB leprosy.<sup>6,14</sup> Once the patients were diagnosed with ENL, they started treatment with thalidomide, prednisone and/or pentoxifylline.<sup>8</sup>

An ENL episode was defined by the period of ENL treatment and the subsequent treatment-free period for up to 89 days. Additional episode(s) occurring 90 days or more after stopping treatment for a previous episode was defined as recurrent ENL. ENL duration could be acute if it required treatment for less than 24 weeks, or chronic, if treated for 24 weeks or longer (or where any interruption of treatment was for 89 days or less during this period).<sup>6</sup>

The episodes were classified into mild (less than 10 skin lesions), moderate (more than 10 skin lesions and no systemic symptoms), and severe (skin lesions with at least one other organ system or neurological involvement).<sup>6</sup>

Fever was defined as a documented axillary temperature greater than 37.5°C.

Neuritis was defined as tenderness, inflammation and enlargement of the peripheral nerve trunks with or without NFI.<sup>2</sup>

A drug-related adverse event was present if a noxious and unintended response occurred "at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function."<sup>15</sup>

Anonymised data were extracted from the patients' files in June 2014 using a standard data collection template and entered into Excel™. The data were analysed using Stata 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP). Descriptive statistics were performed for sociodemographic and clinical variables. The Chi-squared test ( $\chi^2$ ) was used to compare differences between groups.

Ethical approval was obtained from the Oswaldo Cruz Institute (CAAE 32884814.3.0000.5248), Evandro Chagas National Institute of Infectology (CAAE 32884814.3.3001.5262) and the London School of Hygiene and Tropical Medicine Research Ethics Review Boards.

## Results

During the study period, 676 patients were diagnosed with leprosy at Souza Araújo Outpatient clinic; 300 (44.4%) were classified as MB. A total of 112 (37.3%) patients ( $n = 81$ , 72% male) had a first ENL episode between 2005–2010 (Table 1). Most of them ( $n = 93$ , 83%) were diagnosed with LL and treated with standard MDT for MB leprosy ( $n = 91$ , 81.3%). However, 21 (19%) patients received alternative MDT due to contraindications for the use of dapson. Only 24 (21%) patients had their HIV status recorded, and two (2%) patients were HIV-positive. The median age at onset of ENL was 34.8 years (Range = 13.4–79.6). 19 women (61%) were of childbearing age, under 40 years old,

**Table 1.** The demographics, leprosy classification and treatment status of 112 patients diagnosed with ENL at the Outpatient Clinic during 2005–2010

	Characteristics	Number of patients (%) or mean $\pm$ sd	
Gender	Male	81 (72.3)	
	Female	31 (27.7)	
Age (years)	Leprosy diagnosis	Male	<b>37.3 <math>\pm</math> 14.6</b>
		Female	<b>37.2 <math>\pm</math> 16.8</b>
	ENL diagnosis	Male	<b>37.9 <math>\pm</math> 14.5</b>
		Female	<b>38.0 <math>\pm</math> 16.8</b>
Ridley-Jopling classification	BL	19 (17.0)	
	LL	93 (83.0)	
Leprosy treatment	WHO MB MDT	91 (81.3)	
	Rifampicin and clofazimine	5 (4.5)	
	Rifampicin, clofazimine and ofloxacin	15 (13.4)	
	Rifampicin, clofazimine and minocycline	1 (0.8)	
Timing of ENL Diagnosis	Before MDT	28 (25.0)	
	During MDT	53 (47.3)	
	After MDT	31 (27.7)	

ENL = Erythema nodosum leprosum, BL = borderline leprosy, LL = lepromatous leprosy, WHO = World Health Organization, MB = multibacillary, MDT = multidrug therapy.

at the time of their first ENL diagnosis. The first episode was most frequently diagnosed during leprosy treatment (47% of the patients), mainly during the first 6 months of MDT ( $n = 36$ , 67.9%).

Table 2 shows the clinical features of the first ENL episode. Most patients ( $n = 94$ , 84%) experienced ENL as a multisystem disorder, mainly due to oedema ( $n = 63$ , 56%), fever ( $n = 52$ , 46%) and arthritis ( $n = 46$ , 41%). According to skin lesion morphology, most patients had nodules ( $n = 106$ , 95%). Complications of skin lesions during the first ENL episode were observed in only six (5.4%) of the patients, five (83%) with ulceration and one (17%) with necrosis. Five (4.5%) patients had mild, 13 (11.6%) moderate and 94 (84%) severe ENL. Most of the patients ( $n = 71$ , 63.4%) had only one ENL episode during the study period. The two HIV-positive patients had their first episode during MDT, were treated with thalidomide and prednisone, and had no complications due to ENL.

The median interval between starting treatment for ENL and no longer requiring treatment was 35 months. However, one person required treatment for a period of almost 9 years. There was no significant difference between men and women concerning first ENL treatment duration.

Regarding the treatment used during the first episode, 98 (88%) patients received thalidomide (between 100 mg and 300 mg daily), either alone or in combination with corticosteroids and other drugs (Table 3). Most of the women ( $n = 23$ , 74%) received corticosteroids. However, most of them in combination with thalidomide ( $n = 15$ , 65%). Four (13%) other women were treated with pentoxifylline monotherapy and two (6%) with minocycline alone.

Adverse drug reactions (ADR) were registered for 36 (32%) patients, 22 (61%) of them males. Thirty (46.9%) of the 64 individuals who received corticosteroids had ADR (Figure 1), mainly glucose intolerance ( $n = 15$ , 50%) and hypertension ( $n = 10$ , 33.3%). Thalidomide

**Table 2.** Characteristics of first ENL episode observed in 112 patients

	Characteristics	Number (%) or median [range]
ENL duration	Acute	21 (18.8)
	Chronic	91 (81.2)
Interval between first ENL treatment and last (months)	All	35 [0.2–108.5]
	Male	31.7 [0.2–108.5]
	Female	39.2 [2.9–77.5]
Number of ENL recurrences	1	35 (85)
	2	5 (12)
	3	1 (2)
Clinical features of first ENL episode	Skin lesions only	18 (16.1)
	Oedema	63 (56.3)
	Fever	52 (46.4)
	Arthritis	46 (41.1)
	Neuritis	34 (30.4)
	Lymphadenopathy	31 (27.7)
	Iritis	22 (19.6)
	Orchitis	9 (11 of men)
Type of skin lesion on first ENL episode onset	Nodules	106 (94.6)
	Plaques	22 (19.6)
	Papules	8 (7.1)
Skin lesion complications on first ENL episode	Ulceration	5 (83)
	Necrosis	1 (17)

was recorded as responsible for ADR in only six (0.6%) of the 98 individuals who received the drug; constipation being their main complaint ( $n = 5$ , 83%). Pentoxifylline, minocycline and NSAIDs produced higher proportion of ADRs than thalidomide. Out of the 50 patients that received pentoxifylline, only two (4%) had ADR, of the 29 patients that were treated with minocycline, two women (7%) complained of ADR, and out of the 24 patients that received NSAIDs, two (17%) patients had ADR.

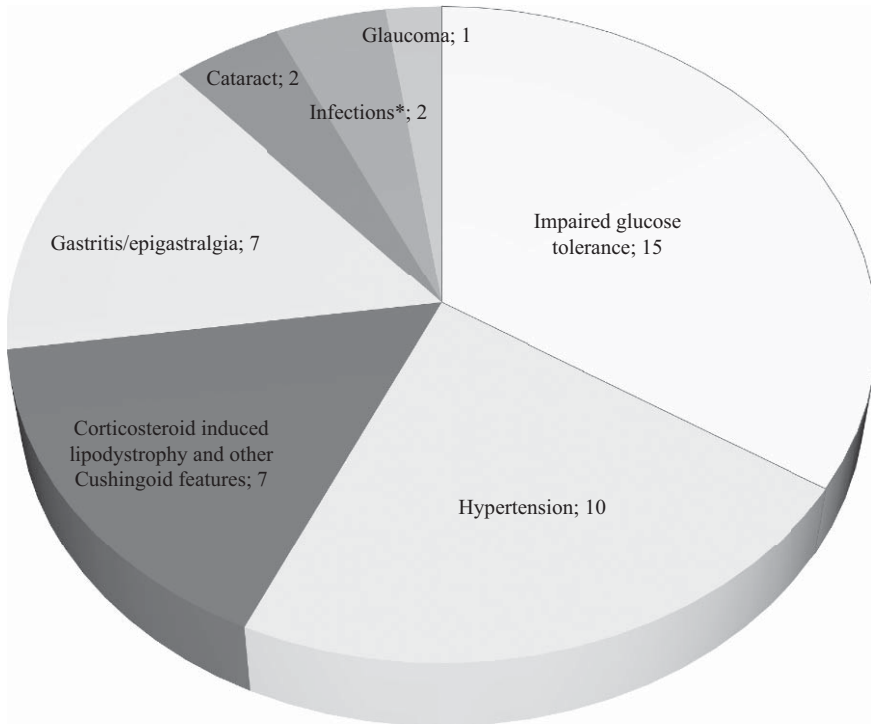
14 (12.5%) patients required inpatient treatment at the Hospital, because of complications of ENL such as secondary infection of skin lesions, lack of response to treatment or sepsis. Ten of these patients were admitted during the first ENL episode.

Six patients (5%) died during the study period (Table 4). Four deaths occurred while patients were taking treatment for ENL, all with thalidomide and corticosteroids. None of the deaths could be considered directly caused by ENL or its treatment.

**Table 3.** ENL treatment during the first episode

Gender	Treatment				Total
	Thalidomide	Corticosteroids	Thalidomide + Corticosteroids	Other drugs	
Female	2 (6.5%)	8 (25.8%)	15 (48.4%)	6 (19.4%)	31 (100%)
Male	40 (49.4%)	0 (0.0%)	41 (50.6%)	0	81 (100%)
Total	42 (37.5%)	8 (7.1%)	56 (50.0%)	6 (5.4%)	112 (100%)

Other drugs: NSAIDs = non-steroidal anti-inflammatory drugs, pentoxifylline, minocycline.



**Figure 1.** Adverse drug reactions attributed to corticosteroids in 30 patients. \*Infections: Strongyloidiasis and dermatophyte infection.

## Discussion

This retrospective study demonstrates that ENL is a complication of leprosy associated with morbidity in Brazil, but not with mortality. A much higher prevalence of ENL was observed in this study as compared to previous ones. A systematic review of the epidemiological data on ENL reported the average cumulative incidence in all MB patients of 1.2% (ranging from 0.2 in India and 4.6 in China).<sup>16</sup> As a referral center, Souza Araujo Outpatient clinic receives an elevated number of patients with late diagnosis and complications, hence the high prevalence of ENL in our sample. In general, neither sex nor age are considered risk factors for ENL.<sup>16</sup> However, there is predominance of cases in young adult males, also observed in our patients.

ENL can be considered a long lasting disease because most patients develop several episodes over many years as observed by the present and other studies.<sup>7,17</sup> A retrospective study of 481 outpatients in India over a 11-year period showed that 8% of the ENL patients had a single acute episode, a higher proportion than the 2.7% observed in our cohort. However, we observed a higher proportion of chronic cases (81.2%) than Pocaterra *et al.*<sup>7</sup> that reported between 38–63% in 88 ENL cases. Recurrence of ENL episodes are a common event as reported in the systematic review by Voorend and Post.<sup>16</sup> Recurrences vary according to the setting, in hospital-based studies, for instance, 39–77.3% of ENL patients had multiple episodes (average of 2.6 per patient). We observed a lower proportion of recurrence (36.6%) but similar mean number of episodes. Both chronicity and recurrence

**Table 4.** Demographic and clinical characteristics of six patients who died during the study period

Gender	Ridley Jopling Classification	Age at diagnosis of ENL (years)	Onset of ENL	Type of ENL (Number of recurrences)	Duration between ENL diagnosis and death (months)	Adverse Drug Reactions	Hospital admission indication	Death during ENL treatment	Reported cause of death
M	LL	67	During MDT	Acute (0)	3.5	None	NH	Yes	Myocardial infarction*
M	LL	59	At diagnosis of leprosy	Chronic (0)	35	Impaired glucose tolerance	NH	Yes	Died while sleeping*
F	BL	70	During MDT	Chronic (0)	41	Cushing syndrome	NH	Yes	Cancer*
M	LL	33	At diagnosis of leprosy	Chronic (0)	73	Headache and malaise	NH	Yes	Suicide*
F	LL	26	During MDT	Acute (1)	2.5	None	NH	No	Pneumonia
M	BL	80	During MDT	Acute (1)	4	None	ENL	No	Tuberculosis* Cerebrovascular Accident

\*Informed by family member. NH= not hospitalized.



account for worsening of leprosy morbidity, even after release from MDT. This morbidity constitutes a problem especially for young adults during their most productive period of life and imposes a considerable service load to primary and reference health centers.

A large proportion of patients treated with thalidomide also required corticosteroids and other additional drugs, but few of them were women (26.8%). Thalidomide was generally well tolerated by the patients. A hospital-based study in Ethiopia, a country where thalidomide is not available, described comorbidities after ENL diagnosis in 52% of the 96 cases that could be associated with corticosteroid therapy.<sup>12</sup> Our results also show a high rate of adverse effects associated with corticosteroids particularly glucose intolerance and hypertension. It is well known the life-threatening risks long-term use of corticoids pose for patients.<sup>18</sup> It is noteworthy that 40% of this cohort did not require corticosteroids because thalidomide alone adequately controlled their symptoms. Pentoxifylline, minocycline and non-steroidal anti-inflammatory drugs, which are less effective for ENL control, also produced ADRs. Although these alternative drugs produced a much higher proportion of ADRs than thalidomide, their effects are mild.

ENL-associated mortality data are scarce. A retrospective study assessed mortality in ENL patients in Ethiopia showed that 8% of 99 ENL cases died probably due to ENL or its treatment.<sup>12</sup> We observed a lower proportion of deaths (5.4%) in our cohort. The patient that died from myocardial infarction had a medical history of diabetes, hypertension and smoking, which increase the cardiovascular risk. A systematic review and meta-analysis on venous thromboembolism in multiple myeloma patients, associated the use of thalidomide in combination with dexamethasone to a risk of thromboembolism.<sup>19</sup> Thus, the combination between these drugs could add to the cardiovascular risk of ENL patients. There is need of a prospective and systematic assessment of ADRs in patients with ENL. The development and assessment of evidence-based guidelines for thalidomide, corticosteroids and other drugs in ENL may facilitate the management of this challenging condition.

Suicide was the most common cause of death in a nation-wide leprosy mortality cross-sectional study of 584 active leprosy cases in China.<sup>20</sup> Among the 413 patients with known cause of death, 86 committed suicide, 45% of them during the first 12 months of MDT. The patient in our study committed suicide long after release from MDT. Shen *et al.*<sup>20</sup> reported four (2.8%) cases of death due to leprosy reaction, three of them occurring during the first 6 months of MDT and one after 24 months of treatment. Similarly, half of our cases died during the same period. Unfortunately, the authors do not specify the type or characteristics of the reactions, nor the source of the cause of death.

Leprosy has a low mortality rate, but in Brazil, it is more frequently registered as the cause of death than malaria, which is an important cause of death among the infectious and parasitic diseases worldwide. Between 2000–2011, 2,936 deaths were reported for leprosy whereas during the same period, only 1,288 deaths by malaria were registered.<sup>21</sup> As expected, due to natural vulnerability, the highest mortality rates are observed in older age groups,<sup>21–23</sup> as seen in our study. Interestingly, ENL occurs mainly in young adults.<sup>9</sup> In the present study, a high number of patients were women of childbearing age, which could be a problem for the use of thalidomide due to its teratogenic effects.

In our study, no direct association could be observed between mortality and ENL complications or its treatment because we had no access to the death certificates. Nevertheless, ENL is not specifically registered in the International Statistical Classification of Diseases and Related Health Problems (ICD-10). Only leprosy and its sequelae are found (ICD A30 and B92, respectively).

As a systemic disease, ENL may cause multiple organ involvement. Thus, making it difficult to determine accurately the immediate, intermediate and underlying causes of death<sup>23</sup> such as are needed to be filled in Part I of the death certificate used in Brazil.<sup>24</sup> Leprosy may also be included in Part II of the death certificate as another significant conditions contributing to death but not resulting in the underlying cause. We did not have reports of renal insufficiency or septicemia, which might have been the immediate causes of death of some of the patients, and could be associated to complications of ENL or effect of its chronic treatment. However, we did have reports of other common immediate causes of death such as Cerebrovascular Accident and myocardial infarction. Probably, ENL is an under-recognised cause of death.

## Contributors

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