Leprosy Reactions: Experience in the Puerto Rico Hansen's Disease Population

Diana V. Rodriguez-Rivera, MD*; Natalia M. Pelet-del Toro, MD*†;
Aida L. Quintero-Noriega, MD*

Objective: Hansen's disease (HD) is a chronic granulomatous infection endemic in the tropics. Its main clinical manifestations involve the cutaneous, nervous, and musculoskeletal systems. Leprosy reactions (LR) are systemic inflammatory and immune-mediated complications of HD. These include reversal reactions (RR), erythema nodosum leprosum (ENL), and Lucio phenomenon. These reactions significantly increase disease-related morbidity and disability. We aimed to determine the number and type of LR, their association to hosts' immune responses (Ridley Jopling classification), timing of development, and treatment of HD patients in Puerto Rico.

Methods: A retrospective medical record review was performed on 291 HD patients containing LR status data available from the Dermatology Service at the Hispanic Alliance for Clinical & Translational Research.

Results: Our data revealed that 83 (29%) patients developed LR, of which 31% had RR and 69% had ENL. Most LR were observed in patients in the lepromatous border (97%): Borderline lepromatous leprosy (BL) and Lepromatous Leprosy (LL). Most patients with RR and ENL had a single episode (83% and 62%, respectively), and those that received multi-drug therapy (MDT) had a reaction onset occurring most frequently within the first year of MDT and after the first year of MDT, respectively. Prednisone was the first line treatment used to manage both types of LR.

Conclusion: Most lepromatous reactions occur within the lepromatous border. ENL was the most common LR. Prompt recognition and management of these immunologic reactions is essential to prevent long term nerve function impairment. [*P R Health Sci J 2023;42(3):197-202*]

Key words: Leprosy, Leprosy Reactions, Erythema Nodosum Leprosum, Reversal reaction, Tropical Dermatology

Hansen's disease (HD) is a chronic granulomatous infection caused by the *Mycobacterium leprae* complex, composed of *M leprae* and *M lepromatosis* (1). The main clinical manifestations of this infection involve the cutaneous, nervous, and musculoskeletal systems. Its transmission is not completely understood, but respiratory droplets are the most likely mechanism of transmission (2). In the general population, following exposure, only 3-5% of people will express a clinically detectable infection (3). The reported incidence of leprosy in Puerto Rico from 2000 to 2011 was 4.2 cases per year (4). Despite widespread treatment with multidrug therapy (MDT) regimen as detailed in Table 1, its incidence in endemic countries, including Puerto Rico, has remained stable.

Leprosy is defined within a spectrum by the Ridley-Jopling classification system, based on clinical features, histopathologic findings, and immunologic response (1,2,5). This classification scheme includes the polar tuberculoid leprosy (TT), borderline tuberculoid leprosy (BT), mid-borderline leprosy (BB), borderline lepromatous leprosy (BL), and polar lepromatous leprosy (LL). The number of lesions and bacilli increase moving from the tuberculoid to lepromatous subtypes. The immune response in the tuberculoid border is primarily a robust cellular Th1 (T Helper Type 1) response, whereas the lepromatous border is characterized by ineffective humoral and Th2 (T Helper Type 2) response.

Hansen's disease patients, most commonly those from the Lepromatous and Borderline subtypes, may develop immunologic reactions or leprosy reactions as part of their disease course (6). These inflammatory and immunologically mediated complications may occur before, during, or after MDT. Leprosy reactions consist of reversal reaction (RR) or

*Department of Dermatology, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico; †Transitional-Year Program, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico

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Address correspondence to: Aida L. Quintero-Noriega, MD, Department of Dermatology, University of Puerto Rico School of Medicine, Medical Sciences Campus, PO BOX 365067, San Juan, Puerto Rico 00936-5067. Email: aquinteronoriega@hotmail.com

type I reaction, erythema nodosum leprosum (ENL) or type II reaction, and Lucio phenomenon (type III reaction). RR most commonly present as abrupt erythematous, edematous skin changes in existing lesions or neuritis, or both (6). Type I reaction is the main cause of nerve damage leading to nerve function impairment (7). ENL is characterized by the presence of new painful, erythematous subcutaneous nodules that may ulcerate. Lucio phenomenon, a rare leprosy reaction, primarily occurs as painful, nontender violaceous macules or plaques with surrounding erythema that may progress to necrotic ulcers. Systemic and organ involvement may be present in all leprosy reactions.

Immunologic leprosy reactions occur in approximately 30 to 50% of HD patients, significantly impacting the course of disease and disability associated with leprosy (6,8). These reactions increase disease-related morbidity and should be treated as medical emergencies (6,8). In this study, we determined the number and type of immunologic reactions, their association to a hosts' immune response determined by the Hansen's disease subtypes, timing of development in relation to MDT, and subsequent treatment in Hansen's disease participants from Puerto Rico.

Materials and Methods

We conducted an IRB-approved single-center retrospective medical record review of Hansen's Disease patients seen in the University of Puerto Rico Tropical Dermatology Clinic prior to 2006, and participants in the ongoing study *Clofazimine (Lamprene) Use in the Long-Term Treatment of Leprosy, Phase III* (Protocol A2450111) at the Hispanic Alliance for Clinical & Translational Research from 2007 to 2021. Patients with a Hansen's disease diagnosis and recorded leprosy reactions were included in this study. The clinicopathologic diagnosis of Hansen's Disease was based on the presence of two criteria established by the National Hansen's Disease Program (NHDP): cardinal signs and skin biopsy findings. Cardinal signs are defined as localized skin lesions (raised or flat, light or pigmented, and sensory loss in lesion) and/or thickened peripheral nerves. Skin biopsy results consistent with the inclusion criteria was those showing acid-fast bacilli or changes consistent with Hansen's Disease (Leprosy). However, immunologic leprosy reactions are a clinical diagnosis based on dermatological, neurological, or systemic findings as described previously.

The following variables were obtained: age at HD diagnosis, sex, Ridley-Jopling classification, treatment for Hansen's Disease and its duration, immunologic reaction type, duration, and timing in relation to MDT, and treatments. Patients within both BL and LL were referred to and grouped into the lepromatous border, those within the BT and TT were in the tuberculoid border, and BT, BB, and BL were referred as being in the borderline zone.

Participants with immunologic reactions were further stratified into four groups: reversal reaction (RR), erythema nodosum leprosum (ENL), Lucio phenomenon, and the fourth group presented with both RR and ENL. The ENL type was further classified into acute, recurrent, or chronic, as described by Walker et al (9). Acute ENL was defined as a single ENL episode lasting less than 24 weeks. Recurrent ENL was defined as repeated episodes of ENL after 28 days after stopping treatment for ENL. Lastly, chronic ENL was defined as: ENL occurring for 24 weeks or more, where a patient required continuous treatment or any treatment-free period has been 27 days or less (9), and patients with mixed recurrent reactions. Patient exclusion was based on the following criteria: patients with an HD subtype based on a classification system other than Ridley-Jopling, absence of immunologic reaction data, those only presenting neuritic disease, or those with an incomplete medical record. Descriptive statistics were used in the data analysis for this study.

Results

Our clinics' HD database (unpublished) consisted of 376 patients, characterized in Table 1 according to the Ridley Jopling classification, where 57% were males and 43% were females. Of these patients, 291 had sufficient information to define their leprosy reaction status (Table 2). This cohort showed a similar gender distribution as those in the PR HD database, for 54% were males and 46% were females, and the mean age at the time of HD diagnosis was 37 years of age. Over half of the patients in both the Puerto Rico Hansen's Disease database (60%) and the patients included in our cohort with complete leprosy reactions data (58%) were classified into the lepromatous border subtypes (LL and BL).

In this cohort, a total of 83 patients (83/291; 29%) presented with leprosy reactions (Table 3). There were 90 recorded

Table 1. Multidrug therapy used for HD as per NHDP

	Multidrug therapy NHDP 1982	
	Medications	**Duration**
Paucibacillary	Dapsone and rifampin daily	12 months
Multibacillary	Dapsone, rifampin and clofazimine daily	24 months

Table 2. Ridley-Jopling classification of Hansen disease patients with Leprosy reactions

Ridley-Jopling classification	PR Hansen disease database N = 376	Patients with LR status data N = 291
LL	171 (45)	122 (42)
BL	56 (15)	47 (16)
BB	6 (2)	6 (2)
BT	59 (16)	49 (17)
TT	63 (17)	49 (17)
Indeterminate	21 (5)	18 (6)

PR, Puerto Rico; LR, leprosy reaction; LL, lepromatous leprosy; BL, borderline lepromatous leprosy; BB, mid-borderline leprosy; BT, borderline tuberculoid leprosy; TT, tuberculoid leprosy

leprosy reactions in our population, where seven patients presented with both RR and ENL. These seven patients were registered as 3 BL and 4 LL, under the Ridley-Jopling classification. Concerning the lepromatous border (BL and LL), 47% of patients (80/169) presented with leprosy reactions, and it is important to highlight, that most of the patients who developed leprosy reactions (80/83) were within this border as well.

Moreover, our cohort revealed that there were 28/90 (31%) reversal reactions (RR) and 62/90 (69%) erythema nodosum leprosum (ENL) reactions. No patients presented with Lucio phenomenon.

Reversal Reaction or Type 1 Reaction (see Table 3)

There were 19 of 28 (68%) patients who developed RR that were classified within the borderline zone (BT, BB, BL) and 27/28 (96%) were in the lepromatous border. Information on the number of leprosy reaction episodes and treatment with MDT was available for 23 of 28 patients with recorded reversal reactions. Of those 23, 19 (83%) had a single episode and 4 (17%) had two episodes. Multi-drug therapy was prescribed to 19 (83%) of the patients with RR. The onset of the RR in relation to MDT occurred in 32% (6/19) at the initiation of treatment, 42% (8/19) within the first year of MDT, and 26% (5/19) after the first year of treatment. Signs and symptoms of neuritis were recorded in 39% (9/23) of patients with RR.

Specific treatment data for RR was available for 23 of 28 patients. Six patients (6/23, 26%) were managed with supportive treatment with either NSAIDS or no treatment and continued with MDT as required. Two patients (2/23, 9%) were treated with clofazimine alone. Fifteen patients (15/23, 65%) received prednisone for RR therapy, and 73% of patients were treated for over 20 weeks. One patient was treated with prednisone monotherapy, and fourteen patients received it in conjunction with clofazimine: 36% (5/14) as part of MDT and 64% (9/14) at an increased dose. One patient also received MTX as a steroid-sparing treatment.

Erythema Nodosum Leprosum or Type 2 Reaction (see Table 3)

Of the 62 patients who developed ENL, 51 (51/62, 82%) patients had LL and 9 (15%) had BL. There were 48 of 62 (77%) available patient medical records with complete MDT treatment status data, of which 60% (29/48) received MDT. ENL onset in relation to MDT was reported in 28 of these patients as follows: 14% (4/28) at treatment initiation, 29% (8/28) within the first year, and 57% (16/28) after the first year of MDT. Of the forty-three patients with sufficient data on the type of ENL, 37 (86%) had chronic ENL and 6 (14%) had acute ENL. Information regarding ENL episode frequency was available for 42 patients: 26 (62%) had a single episode, 11 (26%) developed 2 episodes, 3 (7%) had three episodes, and 2 (5%) had four episodes.

In addition, four out of six patients with acute ENL received supportive treatment consisting of NSAIDs, MDT or no treatment. One acute ENL patient was treated with clofazimine alone, while another was managed with a combination of prednisone and clofazimine.

Chronic ENL treatment data was available for 36 of 37 patients. Prednisone was the primary treatment agent in 29 of 36 (81%) patients, alone or in combination with another medication. Of the patients receiving prednisone for chronic ENL, 10 received prednisone and clofazimine, 8 received prednisone, clofazimine and thalidomide, 7 received prednisone and thalidomide, and, lastly, 4 patients received prednisone monotherapy. Methotrexate was used as a steroid-sparing agent in four patients receiving prednisone, of which all but one was tapered off both medications. Six patients with chronic ENL were managed with clofazimine alone, and one patient received thalidomide monotherapy.

Table 3. Leprosy reactions patient characteristics

Ridley-Jopling classification	RR (n, %)	ENL (n, %)
LL	9 (32)	51 (82)
BL	18 (64)	9 (15)
BB	0 (0)	0 (0)
BT	1 (4)	1 (2)
TT	0 (0)	1 (2)
	28/90 reactions	62/90 reactions
Patients treated with MDT	n = 23	n = 48*
Yes	19 (83)	29 (60)
No	4 (17)	19 (40)
Onset of first LR in relation to MDT	n = 19¶	n = 28†
At treatment initiation	6 (32)	4 (14)
Within the 1st year	8 (42)	8 (29)
After the 1st year	5 (26)	16 (57)
LR episodes	n = 23	n = 42‡
single episode	19 (83)	26 (62)
two episodes	4 (17)	11 (26)
three episodes	-	3 (7)
four episodes	-	2 (5)
Length of prednisone treatment in RR	n = 15 λ	
< 12 weeks	2 (1)	-
12 – 20 weeks	2 (1)	-
> 20 weeks	11 (73)	-
Neuritis in RR	n = 23	
Yes	9 (39)	-
No	14 (61)	-
Type of ENL		n = 43 §
Acute	-	6 (14)
Chronic	-	37 (86)

RR, reversal reaction; ENL, erythema nodosum leprosum; LL, lepromatous leprosy; BL, borderline lepromatous leprosy; BB, mid-borderline leprosy; BT, borderline tuberculoid leprosy; TT, tuberculoid leprosy; MDT, multi-drug therapy; LR, leprosy reaction. *Treatment information with MDT was available for 48 of 62 patients with ENL. ¶Onset of LR in relation to MDT was available in 19 patients with RR; 4 patients had insufficient data. †Onset of LR in relation to MDT was available in 28 patients with ENL; 1 patient had insufficient data. ‡Information on the number of LR episodes was available for 42 patients with ENL; 6 patients had insufficient data. λLength of treatment with prednisone in RR was available for 15 of 23 patients with RR; 8 patients had insufficient data. §Information on the type of ENL was available for 43 patients; 5 patients had insufficient data.

Table 4. Comparison of Erythema Nodosum Leprosum onset

ENL onset	Puerto Rico	India[13]	Ethiopia[15]	Nepal[22]
At treatment initiation	14%	23%	23%	34%
During 1st year of therapy	29%	19%	35%	46%
After 1st year of therapy	57%	58%	43%	20%

ENL, erythema nodosum leprosum

Table 5. Comparison of Erythema Nodosum Leprosum episode frequency

Number of ENL episodes	Puerto Rico	Nepal[22]	India[12]
1	62%	45%	36%
2	26%	25%	64%*
3	7%	12%	-
4	5%	5%	24%*
>4	-	7%	-

ENL, erythema nodosum leprosum; *64% had more than one episode, while 24% had 4 or more.

Discussion

Hansen's disease is a chronic granulomatous infection that affects multiple organ systems and may have complications such as immunologic leprosy reactions. These reactions are considered medical emergencies due to the associated disease morbidity and disability. In our PR Hansen's Disease population, 60% of the patients were classified in the lepromatous border (BL, LL); data analogous to that observed in the US where 54% (10) of the patients are reported in this same border. Both in PR (32%) and the US (34%) (10), about one-third of the patients were in the Borderline Zone (BT, BB, BL). Forty-seven percent of the patients in the lepromatous border developed leprosy reactions and 97% (87/90) of the leprosy reactions reported occurred in this border in our population. Since the lepromatous border represented more than 50% of the cases in PR and the US, and it is within this border where most of the leprosy reactions occur, it is imperative to remain vigilant, with a high index of suspicion to recognize these reactions promptly.

Previous studies report that 30-50% of patients develop a leprosy reaction at some point during the disease course (6, 11). Our study revealed that 29% (83 patients) had leprosy reactions compared to 45% in Thailand (12) and 46% in India (13). The lower percentage in our population may be due to the availability, access, and use of clofazimine, as part of multidrug therapy for Hansen's disease (14), as this medication has an anti-inflammatory effect (15). Leprosy reactions were seen more often in males, similar to our HD patient distribution. Scollard et al. reported that ENL occurs in equal frequency in both sexes from a population in Thailand (12). However, they reported RR as more prevalent in women, despite the general population being predominantly male (12). Interestingly, Kumar et al. report the female gender as a risk factor for developing RR and ENL in a North Indian population (13).

Our study revealed that 34% of our patients had RR compared to 45% in Brazil (11), 44% in Thailand (12), and 33% in India (13). On the other hand, 69% of our patients had ENL compared to 55% in Brazil (11), 56% in Thailand (12), and 23% in India (13). Similar to our population, ENL was more frequently observed than RR in Thailand (12) and Brazil (11), while RR was most commonly observed in India (13). As mentioned by Kumar et al., the use of different case definitions and diverse patient settings makes it difficult to compare RR and ENL data between studies (11, 13). The potential selection bias observed in these studies may contribute to underreporting leprosy reactions in these populations, limiting comparability and interpretations among studies.

Similar to previous studies, RR was most commonly observed during the first year after starting MDT (13, 16) and as a single episode (12, 13). Nevertheless, RR was most frequently reported in the lepromatous border (98%), which differs from the borderline zone as reported in other studies (12, 17). Nerve damage impairment, defined as spontaneous nerve palsy, tenderness, or paresthesia (6), was found in 39% of our patients compared to 52% of patients who experienced RR, as reported by Van Brakel et al. (16). Regarding the therapy for RR, prednisone was the treatment of choice (6, 18). In our cohort, most patients (69%) received over 20 weeks of prednisone. The duration of prednisone therapy has been reported to be more important than the dose (19). Nevertheless, a multi-centered randomized controlled trial reported that 20 weeks of prednisone therapy was as effective in restoring and improving nerve function impairment in leprosy patients as a 32-week regimen (20). Overall, the recommended steroid regimen for these patients has been 30-60mg of prednisone tapered over 20 weeks (19, 20).

Sixty-two patients in our study developed ENL (62/83, 75%), where 82% (51) had LL and 15% (9) had BL, compared to 66% and 34%, respectively, in Thailand (12). More than a third of our patients in the lepromatous border (60/169, 35%) developed ENL similarly Nery et al reported 37% in Brazil (11), contrasting recent studies report that close to one-fourth of patients of this subgroup develop ENL (21). Current literature suggests that the standard use of MDT in HD patients may influence the incidence of leprosy reactions due to its anti-inflammatory effects (14).

Our Leprosy Reaction status database included patients that were managed both before and after MDT was established as the standard of care for HD patients. In our cohort, only 60% of patients with ENL were treated with MDT. In contrast, a recent study reported a lower prevalence of ENL in their population, where most patients in the lepromatous border received MDT (21). The variable use of MDT may be responsible for the differences in prevalence of ENL in these populations. Similar to a study conducted in Thailand (12), 97% of ENL episodes in our study were seen in patients within the lepromatous border.

Regarding the onset of ENL in our study, 14% occurred at treatment initiation, 29% during the first year of therapy, and 57% after the first year of therapy, compared to 23%, 19%, and

58%, respectively, in India (13), 23%, 35%, and 43%, respectively, in Ethiopia (15), and 34%, 46%, and 20%, respectively, in Nepal (Table 4) (22). Similar to our population, ENL was most commonly seen after the first year of therapy in India (13) and Ethiopia (15). However, ENL was most commonly observed during the first year of therapy in Nepal (22).

The ENL episode frequency in our study was one episode in 62%, two episodes in 26%, three episodes in 7%, and four episodes in 5% compared to 45%, 25%, 12%, 5%, respectively, and 7% had over 4 episodes in Nepal (22), one episode in 36% and more than one episode in 64%, where 24% had ≥ 4 episodes, in India (Table 5) (13). The number of ENL episodes observed in our cohort was similar to previously reported data, except our patients predominantly experienced one episode and none had more than four episodes.

Similar to other studies, our population presented with an increased number of patients with chronic ENL, 86% chronic ENL vs 14% acute ENL, compared to 62.5% vs 37.5% in India (21) and 73% vs 27% in Mexico (23), respectively. Similar to previous studies (21), prednisone was used as first-line therapy for treating moderate to severe ENL. Clofazimine, our second most commonly used agent was found to be effective and reduced corticosteroid use (24). Some studies have reported thalidomide as the drug of choice (6); however, it is not always available and was even prohibited in some countries until 2002 (e.g., India) (25, 26).

Some of the limitations of our study include its retrospective design and incomplete immunologic reaction data in our Puerto Rico Hansen's Disease database. In addition, available literature often has varied classification criteria and methods for diagnosis (Ridley Jopling (12,15,21,22) vs PB/MB (13)), limited included subtypes (i.e., only BL and LL (21,22)), focused on specific medical practice locations (outpatient (13) vs inpatient setting (16)). Some studies include all immunologic reactions (15, 21), while others include only severe reactions (12), studies with self-reported (13, 15) reactions while others were diagnosed by clinicians while actively detecting (12). These variations may limit our ability to compare data directly and make generalizable conclusions. These challenges regarding the consistency and reliability of data across populations may be addressed by establishing a standard for both setting requirements and HD documentation method that takes into account classification criteria and LR data.

In summary, most HD patients in PR and US are classified within the lepromatous border (BL/LL categories). More than 25% of patients develop leprosy reactions and most occur within the lepromatous border. In Puerto Rico, ENL was the most common leprosy reaction occurring predominantly as a single chronic episode after the first year of therapy, and present in more than a third of the lepromatous border patients. Reversal reaction occurs predominantly as a single episode during the first year of therapy in patients from the lepromatous border. Prednisone was the treatment of choice for both RR and ENL, and clofazimine has been reported to have a role as an anti-inflammatory agent in HD treatment. Even though thalidomide has been considered the drug of choice for ENL in some countries, limited patients were treated with this medication in our population. In conclusion, early and prompt recognition of leprosy reactions is imperative to limit disease morbidity, especially for preventing long-term nerve function impairment. Dermatologists should be aware and remain alert, for they play an important role in diagnosing these leprosy reactions due to their prominent skin findings.

Resumen

Objetivo: La enfermedad de Hansen (EH) es una infección granulomatosa crónica, endémica en los trópicos. Las reacciones de lepra (RL) son complicaciones inflamatorias sistémicas, mediadas inmunitariamente, entre las que se encuentran la reacción de reversa (RR), el eritema nodoso leproso (ENL), y el fenómeno de Lucio. Las RL aumentan significativamente la morbilidad y la discapacidad asociadas a la enfermedad. El objetivo de nuestro estudio es determinar el número y tipo de RL, su asociación con la respuesta inmunitaria del huésped (clasificación Ridley Jopling), su punto de desarrollo y el tratamiento en pacientes con EH en Puerto Rico. Métodos: Realizamos un estudio retrospectivo de los expedientes médicos en 291 pacientes con EH e información acerca de RL del Departamento de Dermatología en La Alianza Hispana para la investigación Clínica y Traslacional. Resultados: 83 (29%) pacientes desarrollaron RL, el 31% de ellos presentó RR y 69% tuvo ENL. La mayoría de las RL fueron observadas en pacientes del borde lepromatoso (97%). La pluralidad de los pacientes con RR y ENL tuvo un episodio (83% y 62%, respectivamente), y aquellos que recibieron terapia multidroga (TMD) presentaron una reacción más frecuentemente durante el primer año de TMD y luego del primer año de TMD, respectivamente. Prednisona fue el tratamiento de primera línea utilizado en el manejo de ambas RL. Conclusiones: La mayoría de las RL ocurren dentro del borde lepromatoso. ENL fue la RL más común. El diagnóstico temprano y manejo de estas reacciones inmunitarias es esencial para prevenir daño nervioso a largo plazo.

Abbreviations

- Hansen's disease (HD)
- Leprosy reactions (LR)
- Reversal reactions (RR)
- Erythema nodosum leprosum (ENL)
- Borderline lepromatous leprosy (BL)
- Lepromatous leprosy (LL)
- Multidrug therapy (MDT)
- Tuberculoid leprosy (TT)
- Borderline tuberculoid leprosy (BT)
- Mid-borderline leprosy (BB)
- National Hansen Disease Program (NHDP)

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