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SEEK WISDOM, ELEVATE YOUR INTELLECT AND SERVE HUMANITY !

FIVE YEARS RETROSPECTIVE STUDY ON THE MAGNITUDE AND TREND OF LEPROSY REACTIONS IN ALL AFRICA LEPROSY AND TUBERCULOSIS RESEARCH AND REHABILITATION CENTER ADDIS ABABA, ETHIOPIA.

By

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A Thesis Submitted to School of Graduate Studies of Addis Ababa University in Partial Fulfillment of the Requirements in dermatovenerology specialty

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Table of contents

List of Table

List of Figures

Acronyms

AAU:	Addis Ababa University
ALERT:	All African Leprosy Rehabilitation Training Center
BB:	Borderline-Borderline
BI:	Bacterial Index
BL:	Borderline Leprosy
BT:	Borderline Tuberculoid
ENL:	Erythema Nodusom Leprosum
GC:	Gregorian calendar
LL:	Lepromatous Leprosy
MBL:	Multi bacillary Leprosy
MDT:	Multi Drug Therapy
MDTL:	Multi Drug Therapy for Leprosy
MI:	Microbial Index
MRN-	Medical Record number
NTD:	Neglected Tropical Diseases
NFI:	Nerve Function Impairment
PBL:	Pauci bacillary Leprosy
RR:	Reversal Reaction
SPSS :	Statistical Package For Social Science
TT:	Tuberculoid Leprosy
WHO:	***World Health Organization***

Abstract

Background: Leprosy reactions are immunologically mediated conditions that cause disability and can occur before, during or after completion of multidrug therapy. Little data is available on the magnitude and trends of leprosy reactions in Ethiopia**.**

Objective: To describe the magnitude and trend of leprosy reactions over a five-year period

Methods: Descriptive retrospective cross-sectional institutional based study carried out in ALERT Comprehensives Socialized Referral Hospital from medical records of leprosy reaction cases registered from January 1, 2018, to December 30, 2022. G.C

Result: A total of 234 registered cases were eligible for the study. Of them, 162(69.2%) were male; the remaining 72(38.2%) were females. The male to female ratio was 2.25:1. The mean age for the group was 33±12.1 year.

Among the reactions, 221 (94.4%) cases were MBL while 13(5.6%) were PBL. 164 (70.1%) cases were BI positive at initial leprosy diagnosis. Of all reactions, 121 (51.7%) were ENL and 113 (48.3%) RR cases.

As to the time of diagnosis, 136 (58.1%) cases diagnosed after MDT completion, 74 (31.6%) while on MDT and 24(10.3%) at the start of MDT.160 (68.4. %) cases had more than one episode of reactions. The magnitude and trend of reactions were fluctuant over five study periods.

The majority of 77 (30.9%) cases were treated with prednisolone within 24 -48 weeks and 72 (30.8%) cases were on treatment for more than 96 weeks. The mean treatment period was 79.4±65.1 weeks.

In a multivariate analysis, the MB type of leprosy, positive bacterial index and reactions developed during MDT and after MDT completed were statistically significant association with ENL.

Conclusion:

In this study, the occurrence of ENL and RR reactions were comparable in magnitude. Most Leprosy reaction cases were multi-bacillary leprosy and Patients with MB leprosy and positive bacillary index were more likely to develop ENL reaction as compared to RR, which is statistically significant in multivariate analysis. The overall trend of reaction was inconsistence in magnitude and severity.

Key word: MB, PB Reaction, RR, ENL

1. Introduction

1.1. Background

Leprosy is a contagious disease caused by Mycobacterium leprae. It is a chronic contagious disease mainly spreading through droplets from nose and mouth. Its transmission is higher during close and repeated contacts with untreated infected individuals. It is the major infectious cause of disability. Its prevalence has fallen to a large extent in the past 50 years but new infection continues and leprosy still remains one of the public health problems in developing countries in particular. It also negatively affects the socioeconomic status of affected individuals [1].

There are various clinical and histopathologic manifestations showing the broad range of cellular immune response to the M. leprae complex. The Ridley-Jopling classification gives the optimal classification of leprosy as it reflects the entire spectrum of these clinical and pathologic features [2].

The Leprosy spectrum ranges from a robust immune response with very few organisms (tuberculoid or paucibacillary) to a form of weaker immune response with a higher burden of organisms (lepromatous or multibacillary). The classification is based on the cutaneous, neurologic and histological findings, all of which correlate with immunological capability of the individual [3].

The World Health Organization (WHO) classification system was designed for use in situations where little or no clinical expertise or laboratory supports. It is based upon the number of skin lesions; peripheral nerve involvement and microscopic detection of bacilli in a slit-skin smear [4].

WHO defines Paucibacillary (PB) leprosy as five or fewer skin lesions without detectable bacilli on skin smears examination. Patients with only one skin lesion can be classified separately as PB.

The definition of Multibacillary (MB) leprosy is that a patient has six or more skin lesions and may have a positive skin smear exam. Only counting skin lesions alone may lead to mis-classification of

many patients with PB leprosy rather than MB leprosy, which leads to under treatment in some cases [3].

Leprosy reactions are immunological processes occurring over the course of the disease which affect skin, nerves and other body organs, resulting in physical and social disability in leprosy patients. Leprosy reactions may occur before, during or after successful completion of multi-drug therapy (MDT). Reaction can be precipitated by varying conditions such as stress, infection and physiological changes like pregnancy [9].

The two common forms of leprosy reactions are type-I or Reversal Reaction (RR) and type –II or Erythema Nodusom leprosum (ENL).

Reversal Reaction is the development of acute Eythema and swelling of existing skin lesions due to cell-mediate immunity. It is a type-IV hypersensitivity reaction where there is partial shift of cell mediated immunity most frequently observed in borderline categories i.e., BT, BB and BL with a frequency of 30% of patients or in Multibacillary (MB) cases. It represents the acute immune episodes of TH1 response to Mycobacterium leprae antigen that occurs in the skin and nerves, which is responsible for nerve function impairment. The skin lesions become acutely inflamed and edematous while the nerves become enlarged and tender. It can occur at any time but more frequently occur after starting MDT or during the puerperium [7].

Type - II reaction (Eythema Nodosumleprosum, ENL) is the appearance of skin nodules due to the formation of immune complexes in the humoral immunity. It is a type-III hypersensitivity reaction caused by extra vascular deposition of immune complexes resulting in neutrophil infiltration and complement activation. Type - II reaction has a prevalence of 24% in leprosy patients [up to 50% in Lepromatous Leprosy (LL) and 9% in Borderline Lepromatous (BL)]. A great infiltration of the skin and a higher bacterial index are two relevant risks for developing ENL [7].

ENL affects many organs including uveitis, neuritis, arthritis, dactylitis, lymphadenitis and orchitis, with an acute onset, but evolves into a chronic phase and can be recurrent [8]. Systemic symptoms are more prominent, like fever and painful tender red papules or nodules, and can occur in a single anatomical site or distributed throughout different body parts, often affecting the face and extensor surfaces of the limbs.

Early recognition and prompt corticosteroid therapy is important to minimize nerve damage due to reactions. Corticosteroids are the mainstay of treatment for leprosy reactions and work by controlling acute inflammation. Adjunctive therapies to control Type-II reactions, such as thalidomide or clofazimine, are often needed [15]

1.2. Statement of the problem

Annually, over 200,000 new Leprosy cases have been recorded globally. Ethiopia is one of the Leprosy high burden countries.

In 2018/19, there were 3,426 leprosy cases notified to the national program, of which 96.2% were newly diagnosed [10].

Leprosy reactions are common problems that could lead to physical and psychological disability and even deaths due to steroid treatment complications.

A Retrospective Hospital-Based Study done in ALERT showed that there were 10 reaction cases (8 ENL & 2 RR) who died of largely due to complications related to administration of oral corticosteroid [11].

1.3. Significance of the study

This study could help to assess the magnitude and pattern of leprosy reactions recorded over five years period in the facility

It also evaluates the management and care procedures implemented on leprosy reaction cases in the leprosy treatment center

The study finding could also be a source of information for further study as there is limited data in this area

1.4. Objectives

1.4.1 General Objective

To describe the magnitude and trends of leprosy reactions among leprosy cases recorded over five years at ALERT Comprehensive Specialized Hospital Leprosy Treatment Center.

1.4.2. Specific Objectives

- To describe the distribution of leprosy reaction in the treatment cent over a five year period.
- To observe the pattern of leprosy reactions in magnitude and severity in a five year study period

2. Literature Review

Hansen's disease is considered as one of the oldest infectious diseases ever known in human history. It is a neglected tropical disease (NTD) which still occurs in more than 120 countries and affects more than 200,000 new cases every year globally. Elimination of leprosy as a public health problem worldwide is defined as the prevalence of less than 1 per 10,000 population, which was achieved in 2000 (as per World Health Assembly resolution 44.9) and in most countries by 2010. The reduction in the number of new cases has been gradual globally.[18].

There were 140, 594 new leprosy cases reported globally during 2021 and made a case detection rate of 17.83 per million populations.

Globally, the registered prevalence of leprosy (number of cases on treatment at the end of 2021) was 133 802, and the prevalence rate was 16.9 per million population. The number of registered cases at the end of the year in Africa was 20,960 (prevalence rate 18.0) [9].

In Ethiopia, leprosy cases were 2,589 in 2021. Data from the National Leprosy mapping shows an annual case load above 1 per 10,000 populations in some districts.

The distribution of Leprosy varies significantly by region, ranging from 2.4 per 10,000 in Gambella to as low as 0.1 per 10,000 population in the Somali region [10].

Leprosy reactions are considered the leading causes of disability if left untreated or improperly managed that may lead to irreversible damage causing physical deformities or grade II disability. Reactions can occur up to 30% of patients diagnosed with multi-bacillary (MB) leprosy.

Type-I Reaction is a major cause of NFI in leprosy patients and affects up to 30% of susceptible individuals. It occurs due to sudden alteration in cell-mediated immunity result in delayed type

hypersensitivity. Type-I reactions may be presenting feature of leprosy or occur during treatment with multidrug therapy (MDT) or even after treatment completed.

Erythema nodosum leprosum is a multisystem, relapsing and remitting disorder occurring in patients with lepromatous leprosy and borderline lepromatous. The incidence varied between countries ranging from 5% in Ethiopia and 37% in Brazil. Bacillary index over 4.3 is a common risk in EN [12].

Varies factors could also precipitate leprosy reactions. A cross-sectional study in Brazil found out that among 225 leprosy cases, 54.2% of them had leprosy reactions and co-infections, of which 63.9% of them presented with ENL and 36.1% exhibited RRs [13].

Another retrospective study in Indonesia also found out that there are certain risk factors for Type-I Leprosy reaction. Among 75 patients with Type-I reaction, analysis showed that age, leprosy type, and treatment regimen were significantly associated with the incidence of Type-I reaction ($p = 0.023$; 0.003 and 0.004, respectively), of which, the leprosy type was the most dominant risk factor. Age 15–34 years old; leprosy types BB, BL, and BT; and the MB MDTL therapeutic regimen are risk factors for the occurrence of Type- I- leprosy reaction [14].

In relation to the time of leprosy reaction in the course of leprosy treatment, the Canadian dermatologic association documented that 26% of leprosy reactions were seen during treatment (20% with Type-II and 6% with Type-II, and 11% had reactions after treatment completion (10% with Type-I and 1% with Type-II[15].

In another cross-sectional retrospective study in Brazil, Rio de Janeiro, from a total of 440 leprosy patients evaluated, they found out that 57% of them had leprosy reactions and the majority or 80.5% developed multibacillary leprosy. MB patients had an increased probability of having a leprosy reaction compared with all non-MB patients (CI = 3.59-9.82, $p < 0.001$). Immunologically, there was a predominance of borderline-tuberculoid (BT) patients, about 33.9%, followed by lepromatous (LL)

patients, 24.3%. As to the time of reaction, 73.5% developed reactions during the first three months of MDT and 92.8% developed reactions up to nine months after the initiation of treatment [16].

In a Bangladesh observational study, among 722 leprosy cases, 10.5% of them had leprosy reaction, of which 7.6% were type-I and 2.9% were type-II reaction. Of which 7.1% presented reaction at diagnosis and 3.4% during or after completion of treatment. Only 2.3% of patients with PB leprosy had reaction, all of which were type-I. On the other hand, 39.4% of MB patients had reaction (26.3% type-I and 13.1% type-II). Type-II reaction exclusively included LL and BL patients (19/21 and 2/21) respectively, while type-I reaction was mostly confined to borderline cases (48/55) but also involved a few cases of TT and LL (7/55).

The Lepromatous end of the spectrum had higher frequency of reaction (71% in LL and 64.0% in BL in comparison to 6.0%, 5.3% and 23.1% in TT, BT and BB patients respectively)[17].

A retrospective Hospital-Based Study conducted in Ethiopia by ALERT Hospital Leprosy Treatment Center demonstrated that among 312 patients admitted to leprosy wards, 99 patients were diagnosed with ENL with 147 Type-I reaction.

The time occurrence of those about thirty-four percent (34.7%) diagnosed with EN were presented at the time of their leprosy diagnosis whereas 39 (39.8%) developed during treatment with MDT and 25 (25.5%) after having successfully completed a 12-month course of MDT. In this study two patients with Type -I reaction and eight patients with ENL were died). The cause of death was considered to be prolonged use of oral corticosteroid therapy with statistically significant $p = 0.0168$, (Fisher's Exact Test) as a definite and possibly contributory factor [11].

3. Methodology

3.1. **Study area**: All leprosy reaction cases in all African Leprosy Rehabilitation Training Center (ALERT) that registered from January 1, 2018, to December 30, 2022, G. C, were included in this study.

3.2. **Study design:** An institutional based retrospective descriptive cross-sectional study was employed to assess the magnitude and the trend of leprosy reaction over five - years study period.

3.3. **Study population and sampling method:** All leprosy reactions registered in the treatment center were collected based on medical record number, and their medical records were retrieved from hospital archives using a non - probability convenient sampling method and the required data were collected from selected eligible medical records.

3.4. **Inclusion and exclusion criteria:** While all leprosy reaction cases registered in the five-year period were included, lost medical records, and inappropriate records were discarded.

3.5. **Data collection process:** After a brief orientation given to professional nurses assigned to the leprosy treatment center, data was filled using data extraction sheets that contained study variables.

The principal investigator was actively engaged and supervised the data collection process to insure completeness, clarity and consistency of the data according to study variables.

3.6. **Data entry and analysis**: Data was entered and analyzed using the SPSS Version 25.0 software package. The percentage, Mean and Standard Deviation (SD) were calculated using the software. Data was presented using text, tables and graphs. The Chi Square test (X2) and multi-variant analyses were used to compute the data.

The P – Value <0.05, was considered as a value point for statistically significant association among variables.

3.7. **Study variables**: The variables included in this study were demographic (sex, age and address), background of leprosy (leprosy type, BI status) and leprosy reactions (type of reaction, on set of reaction in relation to MDT, number of reaction episodes and treatment period for the reaction.

3.8. **Ethical clearance:** Prior to the data collection, ethical clearance was obtained from the research committee of Addis Ababa University Dermatology and venereology Department and from ALERT Academic and Research Directorate Office to retrieve patient medical records from the hospital archives.

3.9. Operational Definitions:

Magnitude of leprosy reaction: number of patients registered for leprosy reactions in five year study periods.

Trend of leprosy reaction: change in the infrequency and severity of leprosy reaction over a five-year period.

Mild RR: cases with inflammation of skin lesion and managed with NSAIDs and prednisolone for less than 12 weeks

Sever RR: reaction to neuritis, limb and facial swelling which can be managed with prednisolone treatment for 6 months

Mild ENL: ENL reaction with subcutaneous nodules and other constitutional symptoms with ENLIST severity scale less than 8.

Sever ENL: reactions with diffused painful subcutaneous nodules in different body areas, with other organs involved and ENLIST severity scale more 8..

4. Results

4.1. Socio Demographic Character and Leprosy Types In Reactions cases.

A total of 415 reaction cases were selected in the leprosy treatment registration center log book in the five years of the study, of which 234 (56.4%) were eligible for this study but 181 (43.6%) were excluded due to incomplete information recorded and lost medical records.

Out of the 234 reactions, 162(69.2%) were males and 72(38.2%) were females with a male to female ratio of 2.25:1. The mean age of the group was 33 + 12.1 years old with the range between 10 and 75 years and the majority of cases,25 (53.4%) belonged to the age group of 16–30 years old.

Most of the cases came from the Oromia region, which accounts for 95(40.6%), followed by Addis Ababa city administration 87(37.2%). According to the WHO leprosy classification, the majority of the cases, 221 (94.4%), belonged to the multibacillary group and the few, 13(5.6%) were the paucibacillary group (Table -1).

Table- 1- Frequency distribution of study variables of Leprosy reaction case in Alert specialized hospitals, Addis Ababa, 2023 Ethiopia

Variables	Category	Frequency	Percent (%)
Sex	Male	162	69.2
	Female	72	30.8
Age group	<15	6	2.6
	16-30	125	53.4
	31-45	65	27.8
	46-60	30	12.8
	>60	08	3.4
Address in Region	Oromia	95	40.6
	Addis Ababa	87	37.2
	Amhara	40	17.1
	Others	12	5.1
Leprosy type	MB	221	94.4
	PB	13	5.6
Bacterial index	Positive	164	70.1
	Negative	70	29.9
Reaction type	ENL	121	51.7
	RR	113	48.3
Year of Reaction diagnosis	2018	39	16.7
	2019	59	25.2
	2020	35	15.0
	2021	56	23.9
	2022	45	19.2
Time of reaction diagnosis	At start of MDT	24	10.3
	During MDT	74	31.6
	After MDT	136	58.1
Number of reaction episodes	1	74	31.6
	2	89	38.0
	≥3	71	30.4
Period of treatment (weeks)	<24	28	12.0
	24-48	77	32.9
	49-72	38	16.2
	73-96	19	8.1
	>96	72	30.8

4.2. Characteristic of Bacterial Index and Leprosy Reaction Types

At the initial leprosy diagnosis, bacillary index (BI) was positive for 70.1% of cases and negative for 29.9%. Among those BI positive cases, the majority, 68.9% developed ENL and 31.1% were RR cases.

Table 2.Characteristics of reaction type in relation to Bacterial Index status Alert specialized hospitals, Addis Ababa, 2023 Ethiopia

	Reaction Type	
Lab result	ENL	RR
BI Negative	8	62
BI Positive	113	51

4.3. WHO Operational Classification of Leprosy and Reaction Types

Great majority of reaction cases were multibacillary type of leprosy accounted 221 (94.4%) and the few, 13(5.6%) were pausi bacillary leprosy types.

Among the MB patients, more than half of the cases were ENL 117(52.9%) and 104 (47.1%) were RR, (Table -3).

Table -3.Types of Leprosy reaction in relation to WHO leprosy classification Alert specialized hospitals, Addis Ababa, 2023 Ethiopia

Leprosy Type	Reaction type		
	ENL	RR	Total
MB	117	104	221
PB	4	9	13
Total	121	113	234

4.4. Severity of Leprosy Reaction among Cases of Leprosy Reaction.

Of the total reactions, the majority, 152 (65%) were mild types of reactions whereas 82(35%) were severe reactions. In both RR and ENL reactions types, the mild form of reactions were higher than their severe counter parts with frequencies of 67(55.4%) and 85 (70.2%) respectively, (Table-4).

Table- 4- Severity of leprosy reaction in ALERT specialized hospitals, Addis Ababa, 2023 Ethiopia

Study periods	Reaction type				
	RR		ENL		total
	mild	Sever	mild	Sever	
2018	7	12	6	14	39
2019	15	12	18	14	59
2020	11	9	10	5	35
2021	19	8	27	1	56
2022	15	5	24	2	45
Total	67	46	85	36	234

4.5. Trends of Leprosy Reaction in Five Years Period

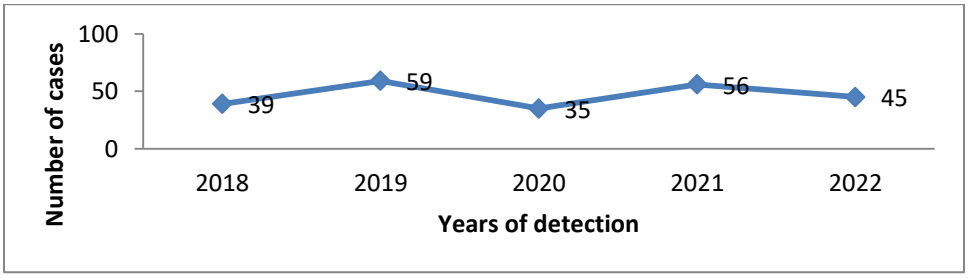

Figure 1 -Trends of Leprosy reaction from 2018-2022, ALERT specialized hospitals, Addis Ababa, 2023 Ethiopia

4.6. Time of Reaction Developed in the Course of Leprosy Treatment.

In relation to onset of reaction with regard to MDT, the majority, 136 (58.1%) cases developed reaction after the completion of MDT.

In respective reaction types, among 121 ENL reactions, the majority of 84, (69.4%) were diagnosed after MDT was completed, and a similar trend was observed in RR where 52(46%) were developed after MDT was completed, (Table-5).

Table- 5 -Onset of leprosy reaction regarding to MDT ALERT specialized hospitals, Addis Ababa, 2023 Ethiopia

Type of reaction	Time of reaction diagnosis		
	At leprosy diagnosis	During MDT	After MDT
RR	20	41	52
ENL	4	33	84
Total	24	74	136

4.7. Number of Reaction Episodes Occurred among Reaction Cases

Of the total 234 reactions, 160 (68.4%) cases exhibited more than one reaction episode, of which 91(56.9 %) were ENL and 69 (43.1%) cases were RRs. Among all reaction cases, 89 (38.0%) had two episodes.

Of the reversal reactions, most of them had one episode, 44(38.9%). Whereas in the case of ENL, the majority, 48(39.7%) had two episodes,(Table-6).

Table -6 -Number of reaction Episodes among leprosy reaction case in five years, ALERT specialized hospitals, Addis Ababa, 2023 Ethiopia

Reaction type	Number of reaction episodes		
	1	2	≥3
RR	44	41	28
ENL	30	48	43
Total	**74**	**89**	**71**

4.8. Duration of Treatment Period to Reaction Cases during their Follow up

The mean treatment period for all reaction cases was 79.4±65weeks with the range of minimum 3 and maximum 263 weeks.

Among all reactions, 77(30.9%) cases were treated for the period between 24 -48 weeks. Of which 44(57.1%) were with continuous treatment and single episode.

Similarly, among the RR case, 39 (34.5%) were treated for the period between 24-48 weeks of which the majority, 25 (64.1%) of them treated continuously. With regard to ENL, most 43 (35.5%) were treated for more than 96 weeks in variable numbers of episodes, (Table-7).

Table- 7-Duration of Treatment period in Leprosy reaction cases, ALERT specialized hospitals, Addis Ababa, 2023 Ethiopia

Type of reaction	Treatment period in weeks				
	<24	**24-48**	**49- 72**	**73-96**	**>96**
RR	17	39	22	6	29
ENL	11	38	16	13	43
total	**28**	**77**	**38**	**19**	**72**

4.9. Descriptive Analysis with Chi Square Test for Selected Study Variables.

A Chi Square model was used for descriptive analysis to assess the association between selected variables and leprosy reaction types. Gender, Age, leprosy type, bacterial index, reaction episode, reaction severity and onset of reaction were tested. Among these, Bacterial index and time of reaction diagnosis were statistically significant association with erythema nodusom leprosum in the value (X^2=64.8, P =001) and (X^2=18.8, P=0.002) respectively, (Table 8).

Table - 8 - Chi square Analysis of selected Variable, ALERT specialized hospitals, Addis Ababa, 2023 Ethiopia

Variable		Reaction type		p-value	X^2
		ENL	RR		
Sex	Female	31	41	0.339	3.11
	Male	90	72		
Leprosy type	MB	117	104	0.059	2.4
	PB	4	9		
Bacterial Index	Negative	8	62	**0.001***	64.8
	Positive	113	51		
Episode	1	30	44	0.374	6.48
	2	48	41		
	≥3	43	28		
Onset of reaction	At leprosy	4	20	**0.002***	18.8
	During MDT	33	41		
	After MDT	84	52		
Age	<15	4	2	0.374	3.44
	16-30	70	55		
	31-45	28	37		
	>46	19	19		
Severity	Mild	85	67	0.079	3.04
	sever	36	46		

4.10. Multivariate logistic regression Analysis

All candidate variables selected from chi square and bivariate analysis with p-value 0.25 were entered in multivariate logistic regression to identify the associated predictors of leprosy reaction.

In this analysis, Multibacillary leprosy patients were 4.9-fold more likely to develop ENL reaction as compared to the pausibacillary leprosy case. [AOR=4.90, 95% CI (1.01-24.03)]

The bacillary index positivity is the likelihood of developing ENL reaction 29 times in comparison to bacillary negative cases [AOR=29.8,95%CI(10.04-88.52)]

Reaction cases diagnosed while on MDT had 9 times more likelihood of developing ENL reaction as compared to those reaction cases diagnosed at the start of MDT[AOR= 9.10,95%CI((2.42-33.97)]

Those leprosy patient who developed reaction after MDT treatment had more odds of ENL reaction by 2.2-fold than those who developed reaction at the start of MDT and associated statistically. .[AOR=2.15,95(1.02-4.50)] (Table -9)

Table 9 -Multivariable Logistic Regression Analysis, ALERT specialized hospitals, Addis Ababa, 2023 Ethiopia

Variable		Reaction type		AOR	95%CI	P-value
		ENL	RR			
Sex	Male	90	72	1.299	0.620-2.722	0.488
	Female	31	41	1	-	-
Age	<15	4	2	1	-	-
	16-30	70	55	4.295	(0. 467-39.51)	0.198
	31-45	28	37	6.510	(0.681-62.215	0.104
	>46	19	19	4.972	(0.465-53.118)	0.184
Leprosy type	**MB**	**117**	**10**	**4.90**	**(1.01-24.03)**	**0.043**
	PB	4	9	1	-	-
Bacterial Index	**Positive**	**113**	**51**	**29.8**	**(10.04-88.52)**	**< 0.001***
	Negative	8	62	1	-	-
Onset of reaction	At leprosy	4	20	**1**		
	During MDT	33	41	**9.10**	**(2.42-33.97)**	**0.001**
	After MDT	**84**	**52**	**2.15**	**(1.02-4.50)**	**0.043**

5. Discussion

The proportion of males among leprosy reaction was higher than females with the ratio of male to female to be 2 to 1. In a Portugal study, a higher proportion of reaction state was observed in male to female with the ratio of 1.87:1 [1]. Comparable findings were observed in a South African study with male outnumbered females with the ratio being 3 to 1 [19]. Another study conducted at ALERT Hospital Ethiopian also showed more male were reported than females [11].

The mean age of the group in our study was 33+12.1 years old, which is lower than observed in the Nigerian study at 39.8±17.6 years old [24]. Brazil's cross-sectional study also showed the average age was higher than seen in our study population, 49.31±15.92 years [12]. The reason for the difference could be due to the demographic distribution that the younger age group presented in our population.

According to WHO, leprosy classification, the majority of 94.4% of reaction cases were MB leprosy type and only a few (5.6. %) cases were PB leprosy group. Among the MB Leprosy patients, more than half of the cases were ENL 117(52.9%). Similarly, more than half of leprosy reaction cases were from MB leprosy in other reports, South Africa 88.9% [19], Thailand 53.7% [5] Bangladesh 65.37% [18] and Brazil 64.9% [12]. A Voorend CGN a Systematic Review on the Epidemiological Data of ENL from five retrospective studies, ENL incidence among MB cases varied from 1.0% in a one year cross sectional Indonesian study to 8.9% in an Indian cohort with an average of 4.5%.

The same review in three prospective studies from the ALERT leprosy control services, the cumulative ENL incidence was 2.5% among MB cases after an average follow-up of 2.5 years, whereas after 10 years, this was doubled (26). In this study, most 70.1% of reaction cases were found to be positive for bacillary index, which is in agreement with the finding observed in Thailand of study 54.6%[5] Brazil 64.4% [3] and another study in Brazil also showed 66% of cases were positive [25].

As to the proportion of reaction types, ENL cases were slightly higher than RR at 51.7% and RR 48.3% respectively. Similarly, ENL cases were much higher than RR in other study findings, which is in Brazil ENL 63.9% versus RR 36.1% [25] and in the UK ENL 78.8% versus RR 21.2% [22].

On the contrary, in other reports, reversal reactions were found to be higher in Portugal 75% [20] Bangladesh RR 55.33 % [12], India 57.5% [21] and Ethiopia 59.4% [11].

In this study, the majority, 89.7% of the cases developed reactions after MDT and 10.3% of reactions were diagnosed at their initial visit of leprosy diagnosis. Similar result was observed in a Thailand retrospective study where 77.9% of cases developed after the start of MDT [5].

However, in the Bangladesh study, (56.33%) reactions were seen at the time of initial presentations and the rest 43.7% developed reactions after MDT started [18].

In the UK study, the majority developed reaction while on MDT (63.3%) followed by leprosy diagnosis and after MDT completion 25.8% and 10.6% respectively [22].

In this study, 160 (68.4%) exhibited more than one episode of reaction. Comparable findings were reported in an Indian retrospective study that 64.3% had recurrent episodes in ENL cases [18]. Another report from the UK's study [22] showed that 72.7% of cases had more than or equal to two reaction episodes.

Among recurrent reactions, the majority, 91(56.9%) were ENL. This is supported by Voorend CGN, et al. systemic review that ENL re-occurrence was disproportionately higher in hospital based studies with Multiple episodes found to be 39% to 77.3% of ENL patients, with an average of 2.6 episodes.[26]

Among all RR cases, the majority of 67 (59.3%) were mild and 46 (40.7%) were severe reaction. This finding was consistent with another study done in Ethiopia, ALERT Leprosy Treatment Center, where mild reaction cases were 32 % mild, 25% moderate and 28% were severe reactions [23].

In this study, among ENL cases, the majority, 85 (70.2%) had mild reaction and the rest, 36 (29.8%)) had severe reaction. This was compared with another study conducted by Lambert SM, et al. in which mild ENL was 66 (14.8%), moderate 106 (23.7%) and severe ENL 39 (8.7%) [24].

The duration of treatment for the reaction ranges from 3 to 263 weeks. Of all reaction cases, 77 (32.9%) were on prednisolone for the period between 24- 48 weeks.

The majority of RR cases, 34.5%, were also treated for the same period, of which 25 (64.1%) of them were with continuous treatment and the rest were treated for variable episodes of reactions.

Among ENL reactions, more than one third, 43 (35.5%), of reaction cases were treated for more than 96 weeks with a variable number of episodes and this could justify the recurrent and prolonged course of ENL reaction that leads to prolonged treatment of the case.

In this study, multibacillary leprosy cases were statistically associated with ENL (AOR: 4.90, 95%CL: 1.01-24.03,p=0.043). This finding was consistent with an investigation conducted in Thailand which resulted in higher leprosy reaction in MB leprosy patients with (AOR: 1.14.95%CI: 1.06-4.21,p=0.012)(5). Other research in Bangladesh also showed that MB leprosy is associated with ENL with (P <0.001, X2 test) (9)

Bacterial index positivity has a statistical association with ENL reaction using multivariate analysis (AOR: 29.8, 95% CI, 10.04-88.52, P<0.001). Multiple studies reported a correlation.

Between the bacteriological index (BI) and ENL up to 8.6 (CI 2.3–32) times higher risk when having a BI of six. Nepali patients with BI.4+ had a 39% higher risk of ENL (OR; 1.39 (CI 1.11–1.76) adjusted for age) and in India, BI >4 was associated with an Odds Ratio of 5.2 (2.1–12.9). An Ethiopian study found out that 9.6 times higher ENL incidence among LL patients compared to BL or BB (X2= 18.7, P=0.005) (26)

Similar findings were reported from a Thailand study with OR=1.75; 95%CI =1.19–2.56 [5] and the Brazil study also support this study with (OR=6.39; 95%CI = 4.05-10.09 and P-value =0.001) [3].

In this study, Reactions diagnosed while on MDT and after MDT completion were statistically significant association with ENL (95%Cl, 2.42-33.97, P=0.001) and (95% CI, 1.02-4.50, P=0.043) respectively. Comparative findings were found in a Brazilian study that reaction during MDT was associated with (AOR: 8.21.95% CI: 2.64-25.48,P< 0.001) and post RFT reactions were increased by 4.34-fold in ENL patients than those with other types of reactions within 95% CI:1.12-16.87, P= 0.034 [27]

6. Study Limitations and Strengths

Due to poor data recording and handling system significant numbers of reaction cases were excluded from the study.

Lost medical records not only affect the true magnitude that could be found in this study but also undermine the real performance status of the treatment center and hospital at large.

Scarcity of reaction related data in Ethiopia and other African countries limits our findings for comparison.

Limitation of related data in Ethiopia restricts our findings for comparison

With all those limitations under consideration, this study could serve as a basic input for further study to be conducted on related topics which are not covered in this retrospective study.

Meanwhile, the gap in data recording and handling systems in the treatment center and hospital at large was also an indicative of improvement.

7. Conclusion

The overall occurrence of leprosy reaction showed an inconsistent trend in the five-year study period in magnitude. Despite fluctuating, the severe form of both types of reaction showed a decline pattern in those five-year study periods. The reduction in severe reactions could be explained by either improved service quality or the early diagnosis and management of reaction cases.

The proportion of ENL and RR reactions cases were comparable in magnitude.

Leprosy reaction cases were more commonly seen in multi-bacillary leprosy patients.

MB type of leprosy and bacillary index positivity were statistically significant association with ENL in multivariate analysis. This signifies MB and BI positive cases were prone to developing leprosy reactions.

8. Recommendations.

Switch from manual data recording to an electronic data recording system for proper data handling and utilization whenever required

Update staff members assigned to the leprosy reaction treatment center on the recording and managing reaction cases as per existing national guidelines.

Developing standard operation procedure for the treatment center in line with the national one

Realizing limitations and strengths, comprehensive prospective study is recommended to fill the gaps observed in this retrospective study.

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10. ANNEX

STUDY VARIABLES TO ASSESS THE MAGNITUDE AND PATTERN OF LEPROSY REACTION FROM JANUARY 1, 2018 GC TO DECEMBER 2022 GC

Section -I - Socio demographic status

MRN : ----------

1. Age in years: ----------
2. Gender
   A) Male
   B) Female
3. Address

Section -II – leprosy status

1. Time of leprosy diagnosis in year
2. WHO classification of leprosy
   a) PB
   b) MB
3. BI status at diagnosis
   a) Positive
   b) Negative

Section -III - Status of leprosy reactions

1. Type of leprosy reaction
   a. Type- I (Reversal reaction)
      - Mild RR
      - Sever RR
   b. Type-II (ENL)
      - Mild ENL
      - Sever ENL
2. Time of leprosy reaction diagnosis
   - 2018

- 2019
- 2020
- 2021
- 2022

3. Onset of reaction in relation to MDT
    a) At diagnosis of leprosy
    b) During MDT
    c) After release from treatment
4. Episodes of leprosy reaction
    - 1 episode
    - 2 episodes
    - ≥3episodes
5. Period of treatment follow up in weeks
    i. <24 weeks
    ii. 24weeks- 48 weeks
    iii. 49-72 weeks
    iv. 73-96 weeks
    v. > 96