Vol. 35 / No. 3 / December 2023
Sinta 2 (Decree No: 200/M/KPT/2020)
Online ISSN : 2549-4082 ; Print ISSN : 1978-4279
Available online at https://e-journal.unair.ac.id/BIKK

Berkala Ilmu Kesehatan Kulit dan Kelamin

Original Article
Periodical of Dermatology and Venereology

The Burden of Leprosy Reaction in the Post-Elimination Era: A Study from Gresik City, Indonesia

Hapsari Kinanti[1], Kurniati[2], Wind Faidati[2]

[1]*General Practitioner, Ibnu Sina General Hospital, Gresik - Indonesia*

[2]*Deparment of Dermatology and Venereology, Ibnu Sina General Academic Hospital, Gresik – Indonesia*

ABSTRACT

Background: The attention of leprosy management has shifted to reduce the burden of leprosy complications, including leprosy reactions. Leprosy reaction is the predominant cause of nerve impairment that leads to disability and lowers the quality of life of the affected. **Purpose:** The aim of this study was to provide primary data about leprosy reaction epidemiology, risk factor, and outcomes in the post-elimination era. **Methods:** A cross-sectional study was held in a general hospital in Gresik City, Indonesia, to give clinical demography, risk factors, and outcomes of leprosy reaction. **Result:** New leprosy reaction cases remain detected each year. There were 57 (58.8%) out of 97 leprosy patients who had a reactional episode. The incidence of leprosy reactions has been increasing in the last three years. The multibacillary (MB) group and type 2 reactions dominated leprosy reactions, which mostly occurred in the young adult population. Some of the leprosy reaction patients had developed a complication due to prolonged steroid usage. **Conclusion:** Leprosy cases in a young population with a high risk of developing reaction episodes need collaboration in the management to prevent deformity in youth.

Keywords: leprosy reaction, leprosy, neglected tropical disease, erythematous nodosum leprosum, reversal reaction.

Correspondence: Hapsari Kinanti, Ibnu Sina General Hospital, Dr. Wahidin Sudiro Husodo No. 234B, Krembangan, Klangonan, Kebomas, Gresik, East Java, Indonesia,Telephone: +6281246504384, e - email: hapsari_kinanti@yahoo.co.id.

| Article info |
Submited: 14-03-2023, Accepted: 28-08-2023, Published: 31-03-2024

BACKGROUND

Morbus Hansen, also known as Leprosy is a chronic neglected tropical disease (NTD) caused by *Mycobacterium lepra*.[1–5] This disease primarily affects the skin and peripheral nervous system, upper respiratory tract mucosa, and eye.[1–4] This disease remains a crucial public health problem.[6,7] Indonesia is one of the endemic countries with the most leprosy cases following India and Brazil.[2,3,6,8,9] Based on World Health Organization (WHO) data, the number of new leprosy cases detected in 2021 was 10,976. East Java province is one of the provinces with the highest prevalence of leprosy in Indonesia.[9] Therefore, intensive efforts are still needed to eliminate leprosy in Indonesia. WHO has recommended multidrug therapy (MDT) since 1982, which successfully reduces leprosy incidence.[1,3] Therefore, attention has shifted to reducing the disease burden in advance, significantly eliminating leprosy, and diminishing its complications.[10] One of the leprosy complications is the leprosy reaction.[1–3] Leprosy reaction is an immune-mediated episode in leprosy that plays a significant role in the disease's morbidity.[2,7,11,12] There are two types of leprosy reactions. They are type-1 reaction (T1R), known as reversal reaction, and type-2 reaction (T2R), or erythematous nodosum leprosy (ENL).[2,7,11,13] Both types could cause severe and irreversible nerve damage, which contributes to disability.[2,12,13] It also caused pain and neurological impairment that depressed the quality of life and often required long-term immunosuppressive therapy.[1,2,7,11]

Leprosy reactions are problematic because they are perceived as an indication of ineffective leprosy antimicrobial treatment with MDT. People affected by leprosy could lose faith that leprosy can be

DOI : 10.20473/bikk.V36.1.2024.41-46

cured and that leprosy reactions can be controlled.[2] Leprosy reactions are distressing events that adversely affect the physical, psychological, and social spheres, which reinforce each other.[2] Periodic epidemiological evaluation is an essential public health activity that helps the researcher acknowledge disease status.[12] There was very little data regarding the burden of leprosy reactions in Indonesia, especially in Gresik City. Therefore, this research was done to provide primary data about leprosy reaction epidemiology, risk factors, and outcomes in the post-elimination era to improve the strategy for managing leprosy reactions in Indonesia.

METHODS

This study was a retrospective analytic study conducted at the Department of Dermatology and Venereology in a general hospital in Gresik City. We reviewed the medical records of outpatient and inpatient leprosy reactions from January 2019 until September 2022. Ethical approval was granted by the ethical review committees of Ibnu Sina General Hospital No. 071/074/437.76.57/2022.

We used total data sampling and excluded incomplete medical records. Clinico-demographic data were collected from the medical record and evaluated by simple descriptive analysis. Descriptive analysis was used for the baseline characteristics, and IBM SPSS Statistics was used for statistical analysis. A *p*-value less than 0.05 was considered statistically significant. The Chi-square test was used to examine the differences between the nominal variables. When the data does not fulfil the prerequisite for the chi-square, we use Fisher's exact test. Categorical data were analyzed using the Mann-Whitney test. The diagnosis was based on the clinical ground of the cardinal sign of leprosy. Leprosy cases were classified based on WHO criteria. If the number of skin lesions is less than five, it is included in the paucibacillary (PB) type. Meanwhile, if the number of skin lesions is more than five, it is included in the multibacillary (MB) type. The type I reaction was diagnosed when the skin lesions were raised, warm, and erythematous with an enlarged, tender peripheral nerve adjacent to the lesion. In contrast, multiple tender subcutaneous nodules were diagnosed as type II reaction with systemic features such as fever.[11,14,15]

In this study, co-infection and co-morbidities factors were examined generally based on the clinical manifestations. Co-infections were confirmed based on the clinical manifestations, and only the inpatient cases would undergo laboratory examinations. Dental infection suspicions were referred to dentists for confirmation. Co-morbidities were confirmed through the clinical manifestations and laboratory examinations conducted by other specialists, such as internists or ENT (Ear-Nose-Throat) specialists.

RESULT

In this study, there were a total of 98 leprosy patients from 2019 until September 2022 treated in the Department of Dermatology and Venereology of a general hospital in Gresik City, both outpatients and inpatients. Out of the 98 leprosy patients, 57 (58.8%) underwent leprosy reactions. In the last three years, there have been an increasing number of leprosy reactions. The characteristics of the leprosy reaction in our study are shown in Table 1. Most leprosy reactions occurred in the group aged of 35-55 (50.9%), followed by the age group of 15-34 years old (33.3%). Leprosy reactions were dominated by the male group (57.9%). All leprosy patients who developed reaction episodes were classified as a MB group (100%), and most leprosy reaction episodes occurred during MDT treatment (49.1%).

T2R was the most frequent type of leprosy reaction present in this study (54.5%). Some of the leprosy patients (29.1%) underwent both type 1 and type 2 leprosy reactions. Recurrent reaction episodes were found in this study (54.4%), and some leprosy reactions need inpatient management (29.8%). Recurrence episodes of leprosy reaction frequently arise during MDT treatment (Figure 1). T2R was the type of leprosy reaction that mostly had recurrence episodes (Figure 2) and deformities (Figure 3), rather than T1R. There was a statistically significant difference in the risk factor for leprosy reactions (Table 2). Whereas leprosy patients with comorbidities and co-infections had a higher risk of developing leprosy reactions. Neither group's age nor gender had statistical value.

Table 1. Characteristics of leprosy reactions: Clinical manifestation and outcome

Variable	n(%)
Year of leprosy reaction episode	
2019	30 (52.6)
2020	5 (8.9)
2021	10 (17.5)
2022	12 (21)
Type of Leprosy	
Paucibacillary	0 (0)
Multibacillary	57 (100)
Age group	
<15	4 (7)
15-34	19 (33.3)
35-55	29 (50.9)
>55	5 (8.8)
Sex	
Man	33 (57.9)
Woman	24 (42.1)
Occupation	
Unemployed	2 (3.5)
Housemaid	6 (10.5)
Student	6 (10.5)
Farmer	4 (7)
Private sector	19 (33.4)
Teacher	2 (3.5)
Type of Leprosy Reaction	
Type 1 Reaction (T1R)	9 (16.4)
Type 2 Reaction (T2R)	30 (54.5)
Both	18 (29.1)
Stage of therapy when reaction episode	
Before Treatment	11 (22.8)
During Treatment	28 (49.1)
Release from treatment	18 (28.1)
Recurrent Episode	
No	26 (45.6)
1 time	12 (21.1)
2-4 times	14 (24.6)
>4 times	5 (8.8)
Inpatient management	17 (29.8)

Table 2. Risk factors from leprosy reaction

Variable	Leprosy Reaction		*p-value*
	Yes n(%)	No n(%)	
Age Group			
<15	4 (57.1%)	3 (42.9%)	0.124
15-34	19 (70.4%)	8 (29.6%)	
35-55	29 (63%)	17 (37%)	
>55	5 (33%)	10 (66.7%)	
Sex			
Man	33 (60%)	22 (40%)	1.000
Woman	24 (60%)	16 (40%)	
Comorbidities	17 (85%)	3 (15%)	0.000*
Co-infections	17 (85%)	2 (4.3%)	0.000*

*n.b. *statistically significant*

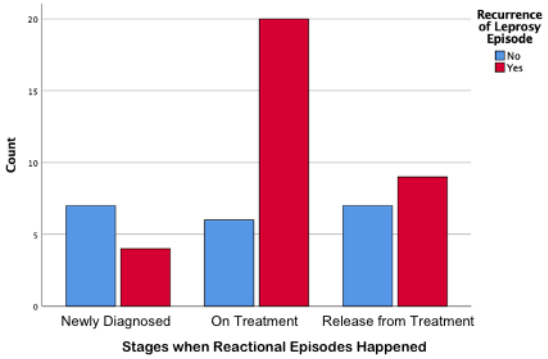
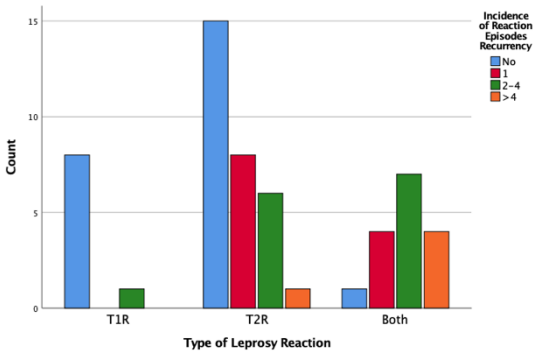
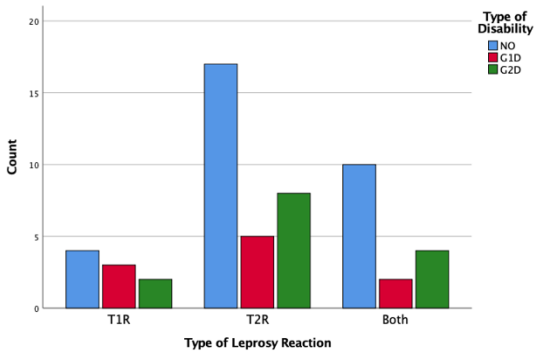


Figure 1. Distribution of therapy stages for recurrent leprosy reactions.



n.b. T1R: Type 1 Reaction; T2R: Type 2 Reaction

Figure 2. Distribution of leprosy reaction recurrence episodes and types of leprosy.



n.b. T1R: Type 1 Reaction; T2R: Type 2 Reaction

Figure 3. Distribution of types of leprosy reaction and disability.

DISCUSSION

Leprosy reaction episodes (REs) are a formidable challenge because these reactions are most likely the major cause of permanent nerve impairment that leads to paralysis, disability, and deformity.[14,16–19] T1R are more prone to deformities and are responsible for the stigma attached to leprosy.[18,20] Even with adequate treatment, 40% of T1R may cause a permanent disability.[19] Meanwhile, T2R may develop other systemic complications.[16,18,20] Thus, it is very crucial to identify leprosy reactions as early as possible, irrespective of the type, to minimize complications.[18,20]

There has been an increased incidence of leprosy reactions during the last three years (2020 to 2022) in this study. The incidence of leprosy reactions between 2019 and 2020 was significantly diminished due to the endemic of COVID-19 in Indonesia, which discourages leprosy patients from going to the hospital. The global occurrence of leprosy reaction remains unknown.[15] Our study's subjects who underwent REs were all categorized as MB type. The prevalence of the MB type appears to be dominant in the post-elimination era.[21,22] The stronger virulence of *M. leprae* in endemic areas might be the reason for the dominance of MB type.[23] MB type had a higher tendency to develop reactions. This correlates with another study.[24] The reason behind this phenomenon was that the MB type was associated with a high bacillary load that made this group more prone to reaction episodes.[24] Surveillance and early detection of leprosy reactions are needed when handling the MB type.[11]

Leprosy reactions are classified as type 1 and type 2 reactions. These episodes could occur before, during, and after MDT, or even seven years after treatment completion. REs in this study mostly happen during the MDT treatment. This result was in line with another study.[16] MDT consists of dapsone, rifampicin, and clofazimine. Dapsone has a bacteriostatic effect that promotes moderate bacillary destruction and decreases inflammatory reactions. On the other hand, rifampicin works as a bactericidal drug to promote massive bacillary destruction and release many antigenic fractions that cause an acute inflammatory reaction in chronic leprosy disease.[16] Leprosy reactions were also observed at the initial diagnostic visit before the MDT started, so it is evident that leprosy reactions are not necessarily the result of treatment.[14] This finding correlates with another study.[14] Early detection combined with proper treatment of leprosy reaction could be an effective strategy to hinder disability in leprosy patients.[10] Prompt treatment is essential to prevent irreversible neurological deficits, with recovery rates of 60%-70% in those identified and treated within six months from the onset.[13] Type 2 reaction (ENL) dominated this study. This finding was in line with the previous study.[16] It can be explained by the fact that this study was conducted at a referral center that treats patients with more severe complications. ENL is related to the MB type due to its high load of the bacterial index.[16,25] ENL reactions tend to have prolonged or recurrent reaction episodes over several years.[15,16,18] ENL involves a type 2 immune-mediated reaction specified by a peripheral inflammatory reaction.[16] The immune system's responses are provoked by high loads of fragmented bacilli in skin tissue.[15,25]

Managing chronic erythema nodosum leprosy remains a problem of leprosy in Indonesia.[3] The steroid is the prime proven treatment for acute neuritis in leprosy. Prolonged use of potent immunosuppressants can bring another problem, a steroid-induced side effect that could increase mortality and morbidity.[15] In this study, 3 out of 55 subjects with reactions had the complication of prolonged steroid use, with clinical manifestations such as moon face and Cushing syndrome. All of them had recurrence episodes of the ENL reaction. This study found that, 31 (56.4%) out of 55 subjects had recurrence episodes of leprosy reaction. Most of them had 2-4 incidences of recurrence episodes. ENL was the most dominant type that underwent multiple reaction episodes and mostly happened after MDT treatment. This finding correlates with previous studies stating that ENL often recurs more than four times.[15,16,25] ENL occurs dominantly during MDT treatment but could also occur years after release from treatment.[15,16] Therefore, it is important for healthcare staff and patients to be aware of the development of late episodes of ENL, do standardized follow-up management, and understand the varied

clinical manifestations of leprosy reaction.[15] Possible trigger factors in ENL are hormonal changes, including pregnancy, lactation, menopause, and puberty. Other things are infection, vaccination, and psychological stress.[15,25] A chronic or recurrent ENL must increase the awareness of the healthcare professional that it could be a warning of drug-resistant strains of *Mycobacterium leprae*.[25]

As a clinician who manages leprosy, we need to have good judgment about which patients may be considered to have a higher risk of developing leprosy reaction episodes in the future. It has an important implication in reducing the morbidity of the reaction.[16] This study indicates that having co-infections and comorbidities in leprosy patients will lead to a higher risk of developing leprosy reactions. The most common sources of infection in this study were upper respiratory infections and dental infections, followed by gastrointestinal infections. Leprosy reactions may be triggered by different co-infections and antigens of *Mycobacterium leprae*.[24] The presence of a co-infection will modulate inflammatory reactions by increasing inflammatory markers. Some of these inflammatory markers would spill over to the peripheral circulation, thus exacerbating the insidious and chronic evolution of the leprosy reaction.[16] Treatment of this co-infection might improve the outcome of leprosy patients and prevent recurrences of reactional episodes.[16] Leprosy still had many unresolved problems behind its elimination status. A crucial problem was an increasing trend in the number of leprosy reactions. The MB group and type two dominated most leprosy reactions. Leprosy reactions mostly occur in the young adult population. The high recurrence rate of reactional episodes found in this study was followed by a high incidence of co-infection and co-morbidity cases. Leprosy cases in a young population with a higher risk of developing reaction episodes need collaboration in the management to prevent deformity in youth.

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