



Overview of Leprosy Reactions at Universitas Sumatera Utara Medical Faculty Hospitals between 2017 and 2021

Ramona Dumasari Lubis*^{ORCID}, Ariyati Yosi^{ORCID}

Department of Dermatology and Venereology, Faculty of Medicine Universitas Sumatera Utara/Adam Malik General Academic Hospital, Medan, Indonesia

Abstract

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***Correspondence:** Ramona Dumasari Lubis, Head of Department of Dermatology and Venereology, Chief of Leprosy Division, Faculty of Medicine Universitas Sumatera Utara. E-mail: ramonadlubis02@gmail.com
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BACKGROUND: Leprosy, or Morbus Hansen, is a chronic granulomatous disease caused by *Mycobacterium leprae* that involves the skin and peripheral nerves, with or without motor disorders. Leprosy reactions are immune-mediated acute or subacute inflammatory episodes that interfere with chronic disease and are classified into three types: type 1 (RR), type 2 (ENL), and the Lucio phenomenon.

AIM: The purpose of the study is to describe the epidemiology of leprosy reactions at Universitas Sumatera Utara (USU) teaching hospitals and provide a description of factors associated with the reactions that might provide valuable information for future studies.

METHODS: This is a cross-sectional analytic study with total sampling on medical records of patients in the Dermatology and Venereology Polyclinic at H. Adam Malik Hospital Medan and USU Education Hospital in 2017–2021.

RESULTS: The incidence of leprosy reactions at the USU Medical Faculty Education Hospital in 2017–2021 was 41 cases. The majority of reaction types were type 2 reactions (68.3%). Risk factors for type 1 reactions were a history of reactions, being elderly, multiple lesions or nerve involvement, and co-infections, whereas the risk factors for type 2 reactions were LL, younger age, bacterial index >4+, stress, and co-infections. The highest age group proportion was 18–59 years (95.1%) and was more common in men (70.7%), which mostly appeared before treatment (39.1%). The incidence of leprosy reactions was 26 new cases per 100 patients.

CONCLUSION: The highest proportion of leprosy reactions was type 2, within the adult age group (18–59 years), males, and before treatment.

Introduction

Leprosy, also known as Morbus Hansen or leprosy, is a chronic granulomatous disease caused by *Mycobacterium leprae*, which usually affects the skin and peripheral nerves with symptoms of loss of sensation in the skin with or without skin lesions and may be accompanied by motor disturbances [1]. Gerhard Armauer Hansen first identified the *M. leprae* bacilli in 1873 [2]. *M. leprae* is an acid-fast bacterium (AFB) that lives and proliferates at a temperature of 27–30°C. The incubation period is long and varies from *M. leprae* between a few weeks to 20 years, with an average duration of 5–7 years [1], [2], [3]. Transmission usually occurs through prolonged and close contact with someone with untreated leprosy through coughs, sneezes, or droplets containing bacteria, especially in individuals with certain susceptibilities. Leprosy is an example of a neglected tropical disease, and currently, the methods of prevention of disease transmission are still being evaluated through either chemoprophylaxis or vaccines [4].

Leprosy is an endemic disease in tropical countries, especially developing countries. A total of

202,185 new cases were reported from 144 countries in 2019, with a prevalence rate of 22.4/1,000,000 population, which accounted for more than 10,000 new cases of leprosy patients in 2019 [5]. Several risk factors for leprosy infection are close contact or living in the same house with leprosy patients, age 5–15 years and over 30 years, genetic predisposition, living in endemic areas, poor environmental sanitation, and lack of access to health services [1]. Clinical manifestations of leprosy depend more on the host's cellular immune response to bacteria. The clinical symptoms of leprosy are mainly related to skin lesions and involvement of the peripheral nervous system. The World Health Organization (WHO) classifies leprosy into 2 types, namely paucibacillary (PB) and multibacillary (MB) leprosy, that would affect the duration of treatment for leprosy with PB for 6 months and MB for 12 months [4], [5], [6].

Leprosy reactions are episodes of acute or subacute immune-mediated inflammation that interrupt a relatively unproblematic course of chronic disease that affects the skin, nerves, mucous membranes, and/or other organs in the body. Reactions can occur in all types of leprosy, except the indeterminate type. Unless treatment is carried out promptly and adequately,

leprosy reactions can cause deformities and disabilities. For patients, the appearance of a reaction not only indicates worsening of the disease but also raises doubts about the cure of the disease. Repeated bouts of reactions also affect drug adherence [7].

There are three types of leprosy reactions that are known and classified into type 1 leprosy reaction (T1R), type 2 leprosy reaction (erythema nodosum leprosum = ENL = T2R), and Lucio phenomenon. T1R is a delayed type of hypersensitivity reaction associated with a shift in the patient's position in the leprosy spectrum. Type 2 reaction is an immune complex syndrome found in LL and rarely in borderline lepromatous (BL) leprosy. Occasionally, both T1R and type 2 (T2R) reactions are observed on the BL spectrum; very rarely, both may occur simultaneously in the same person. Lucio's phenomenon is a type of reaction observed in the untreated form of LL with diffuse non-nodular infiltrates, which is found mainly in Mexico and is also known as Lucio's leprosy. This was associated with arteriolar necrosis, in which the endothelium was massively invaded by *M. leprae* [6].

According to a retrospective study in 2015–2017 at Dr. Soetomo Hospital in Surabaya, 385 new leprosy patients were recorded, with 86.2% were MB leprosy and 28.8% of the MB patients had type 2 or ENL leprosy reactions [8]. According to research at Haji Adam Malik General Hospital Medan in 2015–2018, out of 79 leprosy patients who had been treated, 48.1% had leprosy reactions. The percentage of patients with type 2 leprosy reactions who had received the treatment was 41.8% [9].

Based on the previous explanation, the researcher was interested in looking for leprosy reactions and their relation to the type, age, sex, and onset of the appearance of leprosy reactions in Faculty of Medicine at Universitas Sumatera Utara (USU) teaching hospitals between 2017 and 2021.

Methods

Statistical methods

This is an observational study with a cross-sectional approach that was conducted at Haji Adam Malik Medan (HAM) General Hospital and Universitas Sumatera Utara (USU) Hospital. These hospitals were chosen because they are the teaching hospitals for the Faculty of Medicine at USU. The research was conducted from the time the research proposal was prepared until the preparation of the research report in November 2022. The data collection was carried out in April 2022. The population of this study was all the data gathered from the medical records of leprosy patients

who were treated in the Dermatology and Venereology Polyclinic at the Faculty of Medicine at USU Teaching Hospitals between 2017 and 2021. In this study, the sample was part of the population in the form of medical record data taken by means of total sampling that had met the inclusion and exclusion criteria. The researcher determined several variables to be studied, such as age, gender, type of leprosy reaction, and onset of the leprosy reaction. The inclusion criteria for this study were patients with a diagnosis of leprosy reactions, and the exclusion criteria were incomplete medical record data (age and sex were not known). Data collection was carried out retrospectively using secondary data from medical records at Haji Adam Malik (HAM) General Hospital and USU Hospital in 2017–2021. Data processing was carried out using manual and computerized methods. Univariate data was used to obtain an overview of each variable and the frequency distribution of the various variables studied. A diagram of the research stages can be seen in Figure 1.

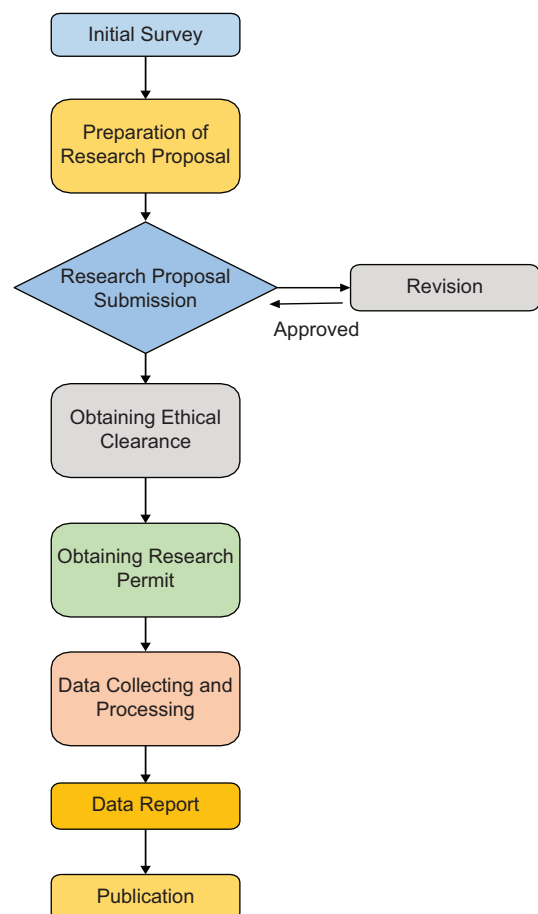


Figure 1: Research procedures

Ethics

The research was conducted after obtaining approval from the Research Ethics Committee at Universitas Sumatera Utara (No. 530/KEPK/USU/2022).

Results

Incidence of leprosy reactions at Faculty of Medicine USU Teaching Hospitals between 2017 and 2021

In this study, we reported 41 new cases of leprosy reaction who had been treated at the Faculty of Medicine at USU Teaching Hospitals from 2017 to 2021. The distribution of patients with leprosy reactions each year was 12 patients (0.53%) in 2017, 14 patients (0.28%) in 2018, 6 patients (0.13%) in 2019, 3 patients (0.12%) in 2020, and 6 patients (0.28%) in 2021. The incidence of leprosy reactions was 26 new cases per 100 patients at the Faculty of Medicine at USU Teaching Hospitals. The table for the incidence of leprosy reactions can be seen in Table 1.

Table 1: Incidence of leprosy reactions at the USU medical faculty teaching hospital in 2017–2021

Year	Total of new patients with leprosy reactions	Total of dermatology and venereology patients	Incidence of leprosy reaction patients each year (%)
2017	12	2228	0.53
2018	14	4986	0.28
2019	6	4565	0.13
2020	3	2424	0.12
2021	6	2069	0.28
Total	41	16272	0.25

Proportion of leprosy reaction types in faculty of medicine USU teaching hospitals in 2017–2021

Based on the type of leprosy reaction, the proportion of leprosy patients who had a type 1 reaction was 13 patients (31.7%), a type 2 reaction was 28 patients (68.3%), and there was no patient with Lucio's phenomenon. The majority of the types of reactions in this study were type 2 reaction, which can be seen in Table 2.

Table 2: Proportion of leprosy reactions type at faculty of medicine USU teaching hospitals between 2017 and 2021

Reaction Type	Frequency (n)	Proportion (%)
Type 1 Leprosy Reaction	13	31.7
Type 2 Leprosy Reaction	28	68.3
The Lucio Phenomenon	0	0
Total	41	100

Proportion of leprosy reactions according to age in the teaching hospital of the USU faculty of medicine between 2017 and 2021

The proportion of patients with leprosy reactions according to age was 2 patients (4.9%) in the <18 years age group, and within the 18–59 years age group, it was 39 patients (95.1%). There was no patient with leprosy reactions in the age group of >59 years old. The majority of the subjects in this study were in the 18–59-year age group. This can be seen in Table 3.

Table 3: Proportion of leprosy reactions based on age in the USU medical faculty teaching hospital 2017–2021

Age	Frequency (n)	Proportion (%)
Children (<18 years)	2	4.9
Adult (18–59 years)	39	95.1
Elderly (>59 years)	0	0
Total	41	100

Proportion of leprosy reactions according to sex in faculty of medicine USU teaching hospitals 2017–2021

The majority of the subjects in this study were male (n = 29; 70.7%). The proportion of women was 12 patients (29.3%), which can be seen in Table 4.

Table 4: Proportion of leprosy reactions according to sex in faculty of medicine USU teaching hospitals between 2017 and 2021

Gender	Frequency (n)	Proportion (%)
Male	29	70.7
Female	12	29.3
Total	41	100

Proportion of leprosy reactions according to reaction time in faculty of medicine USU teaching hospitals between 2017 and 2021

The majority of the proportion of the time the leprosy reaction appeared in this study was in the pre-treatment group of 16 patients (39.1%), followed by during treatment group of 14 patients (34.1%), and 11 patients (26.8%) in the end-of-treatment group. This can be seen in Table 5 below.

Table 5: Proportion of leprosy reactions based on onset of the appearance of leprosy reactions in faculty of medicine USU between 2017 and 2021

Onset	Frequency (n)	Proportion (%)
Before treatment	16	39.1
During treatment	14	34.1
After treatment	11	26.8
Total	41	100

Discussion

Based on Fransisca *et al.*, out of the 385 leprosy patients, there were 61 MB patients with type 1 leprosy reactions and 63 patients with type 2 reactions [8]. According to the data obtained from the Dermatology and Venereology Outpatient Clinics in 13 Education Hospitals in Indonesia, Jakarta was the city with the highest number of leprosy cases, with a total of 396 patients (16.1%), while the lowest cases of leprosy were found in Semarang, with 54 cases (2.2%). The result of a study conducted at the Division of Leprosy, Dermatology, and Venereology Outpatient Clinic in Hospital Dr. Soetomo from 2018 to 2020 showed that 86.2% of leprosy cases were MB leprosy, followed by

PB type, with the most common type of leprosy reaction being erythema nodosum leprosum (ENL=20.3%), followed by a reverse reaction (RR) with 13.3% [9].

A previous study in 2022 stated that the most common type of leprosy reaction found in Dermatology and Venereology Polyclinics in 13 Teaching Hospitals in Indonesia in 2018–2020 was ENL (20.3%), followed by RR (13.3%), and Lucio's phenomenon (0.7%) [9]. Leprosy reactions are immunological phenomena that can occur before, during, or after the full course of MDT treatment. Some of the risk factors that influence the occurrence of leprosy reactions in type 1 (RR) are borderline types of leprosy (especially BL and BB); reactions that can occur before, during, or after treatment; older age; multiple lesions and nerve involvement; the presence of coinfections such as hepatitis B or C; and puerperium [7]. Risk factors that influence type 2 leprosy reactions are LL leprosy with skin infiltration, reactions that occur during the 1st year of MDT administration, younger age, bacterial index above 4+, and physical and mental stress [7]. One of the most important problems during the clinical course of leprosy is the appearance of episodes of acute inflammation, which are defined as leprosy reactions [1]. Leprosy reactions are one of the main contributors to irreversible and severe nerve damage, which can lead to impaired nerve function, deformity, and disability and should be treated adequately [7].

Leprosy reactions can be classified into 3 types: type 1 reaction, or reverse reaction (RR), type 2 reaction, or Erythema Nodosum Leprosum (ENL), and Lucio's phenomenon [1]. Reverse reactions can occur in up to 30% of leprosy patients; most episodes of reaction occur in the borderline form, especially borderline-lepromatous (BL) and borderline-borderline (BB). Erythema Nodosum Leprosum (ENL) is an aggressive vasculitis with immune complex deposition that affects multiple organs, causing symptoms elsewhere. A high bacillary index and diffuse skin infiltration are important risk factors, and 65% of cases have more than one episode of ENL [1].

The distribution of leprosy according to age is generally based on the prevalence, and only a few of the cases are based on the incidence of leprosy reactions. This is because it is difficult to know the onset of the disease. Therefore, it is easier to associate the onset with the age when the disease is found. In previous studies, it was stated that leprosy is most commonly found in young and productive individuals, and leprosy reactions generally occur in individuals <40 years old, which is one of the risk factors for leprosy reactions [10], [11]. Some studies found that there was an increased risk in close contacts of the leprosy patients who had a genetic predisposition, namely in children, parents, and siblings who are related by blood and live together with the patients, who were said to have an increased incidence rate, especially at a younger age [12]. Due to the increasing prevalence

of leprosy and leprosy reactions, especially ENL in the younger populations, special attention must be given to this disease as it would reduce the patients' productive ability in the work environment as well as their quality of life due to social stigma [13].

This study found that the prevalence of leprosy was higher in men. This is in line with the research conducted by Prakoeswa *et al.* in 13 teaching hospitals in Indonesia from January 2018 to December 2022. It was found that out of 1643 leprosy patients, 66.8% of the subjects were male [9]. Research by Gunawan *et al.* in West Java from January 2015 to December 2019 also reported that out of 53 patients with leprosy reactions, 36 patients (68%) were male [14]. Leprosy reactions are more common in males than females, with a ratio of 2:1. This may be caused by several factors, such as differences in the behavior and lifestyle of men and women, in which men tend to be more active, therefore they are more susceptible to infection. In addition, men also pay less attention to their health [9], [14].

Sex also influences the distribution of the Ridley-Jopling classification, as found in a retrospective study by Liu *et al.* in Sichuan, China, between 2000 and 2015. The study found that the ratio of males to females in each of the Ridley-Jopling LL, BL, BT, TT, BB, and LL groups was 2.5, 2.5, 2.5, 2.9, 1.6, and 2.0. A lower BB ratio indicates that women have a higher risk of developing BB-type leprosy [15]. The proportion of leprosy reactions found in this study was different from the results obtained by Putri *et al.* in Indonesia and India. Putri *et al.* found that out of 66 samples, 42 had leprosy reactions during the MDT treatment period, followed by 17 patients before MDT treatment and 7 patients after completion of MDT treatment. In this study, there was only 1 sample in Indonesia who had experienced a leprosy reaction 10 years after completing the MDT treatment, and only 1 sample in India who experienced a leprosy reaction 14 years after completing the MDT treatment [16].

According to Mastrengelo *et al.*, the occurrence of a leprosy reaction before treatment is based on an immunological reaction; therefore, the reactions can occur before the treatment is started, during the treatment, or even after the treatment is completed. Type 1 and type 2 reactions can be initiated by mycobacterial antigens. In leprosy patients who have not received treatment, there is an increased count of *M. leprae* due to persistent bacterial multiplication. The multiplication of these bacteria causes a high bacterial load, especially in MB-type leprosy patients. High levels of antigenic bacterial load in MB patients trigger an increase in antibody production. As a result, a large number of antigen-antibody complexes are formed, which trigger a reaction [17]. Leprosy reactions can occur before treatment, during treatment, or after completion, but most commonly occur during the 2nd year of MDT treatment. This happens because, at the time of treatment, a lot of dead *M. leprae* trigger antigen

reactions with antibodies and form immune complexes. The immune complexes that are formed then enter the blood circulation, where it will settle in various organs of the body and cause reaction symptoms [11].

In our study, we found that the most common leprosy reactions occurred before therapy, as most of our patients had a higher bacterial load, which might also contribute to the higher prevalence of ENL reactions [11]. The incidence of newly reported cases of leprosy reactions in this study was declining, which might have contributed to the active surveillance and leprosy awareness programs as well as early detection and treatment using corticosteroids, according to the WHO. However, within 2019–2020, the decrease in reported incidence might have contributed to the COVID-19 outbreak that hindered the caregivers' program and patients' ability to seek treatment.

Another concern for the leprosy reaction is the long-term use of corticosteroids and their known side effects. At present, there is no certain consensus for the dose and duration of corticosteroid treatment for ENL or other medications for leprosy reactions. This should be alarming for the health organizations that are responsible for the regulations.

Conclusion

Faculty of Medicine USU Teaching Hospitals (Haji Adam Malik General Hospital and Universitas Sumatera Utara Hospital) are the two biggest teaching hospitals in North Sumatra and were the referral centers to provide secondary and tertiary care for dermatology and venereology diseases. In this study, the incidence of leprosy reactions observed between 2017 and 2021 was 26 cases per 100 patients. The majority of leprosy reactions were type 2 leprosy reactions, followed by type 1 reactions, and there was no subject with Lucio's phenomenon. The proportion of leprosy reactions in this study was more commonly found in the adult age group (18–59 years). The proportion of leprosy reactions was found more frequently in males than in females. The proportion of leprosy reactions based on the onset of the appearance of leprosy reactions was most commonly found in the pre-treatment group.

We suggest that the Faculty of Medicine at USU Teaching Hospitals would improve the data of their medical records for future studies; therefore, they can be beneficial in describing the actual state of the population. Information related to leprosy reactions is important in preventing defects because it is considered necessary to provide education to leprosy patients in order to recognize the early signs and symptoms of leprosy reactions.

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Author Contribution

The authors contribute to the concepts or ideas, design, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, and manuscript review before submission.

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