Risk Factors of Type 1 Leprosy Reaction in Leprosy Patients attending Leprosy Division of Dermatology and Venereology Outpatient Clinic of Dr Soetomo General Hospital in 2017–2019: A Retrospective Study

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Abstract

BACKGROUND: Type 1 leprosy reaction is a delayed hypersensitivity reaction caused by increased response of cellular-mediated immunity to Mycobacterium leprae. Manifestations include skin and nerve lesions, edema, and permanent disabilities. There are several risk factors that should be recognized to prevent disabilities.

AIM: The aim of this study was to analyze the relationship of risk factors to the occurrence of type 1 leprosy reaction in leprosy patients treated at the Outpatient Clinic of Dr. Soetomo General Hospital.

METHODS: This study was an analytical study with retrospective observational study design. Data were secondary from the medical records of leprosy patients at the Outpatient Clinic of Dr. Soetomo General Hospital from January 2017 to December 2019.

RESULTS: Out of 364 patients in the Outpatient Clinic, 190 (52.2%) had leprosy without a reaction and 65 (17.9%) had type 1 reaction. Analysis showed that age, leprosy type, and treatment regimen were significantly associated with the incidence of type 1 reaction (p = 0.023; 0.003 and 0.004, respectively), with the leprosy type as 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.

CONCLUSION: There is a statistically significant correlation between the risk factor and the occurrence of type 1 leprosy reaction in leprosy patient. The risk factor that has significant correlation is age 15–34 years; leprosy types BB, BL, and BT; and the MB MDTL therapeutic regimen. The most significant risk factor for the occurrence of type 1 leprosy reaction from our study is the type of leprosy (BB, BL, and BT).

Introduction

Type 1 leprosy reaction is a delayed hypersensitivity reaction caused by an increase in cellular immunity response to *Mycobacterium leprae* antigen on the skin and nerves of leprosy patients [1].

Clinical manifestations of type 1 reaction are inflammation of the skin and nerves that can cause skin lesions, nerve lesions, edema, and permanent disability [2], [3]. Indonesia ranks 3rd with the highest number of the leprosy patients in the world. In 2017, the Indonesian Ministry of Health reported that the incidence of leprosy in Indonesia is 6.08 new cases per 100,000 population, with East Java as the area with the highest prevalence of leprosy [4]. Leprosy treatment has been developed around the world to eradicate this disease, but along the way there has been some reactions arising from leprosy treatment, one of which is type 1 leprosy reaction. The incidence of type 1 reactions varies in various countries, namely around 19.7–30% [3], [5], [6]. The worst prognosis that arises due to type 1 leprosy reactions is disability, and the estimated number of disabilities due to leprosy reactions is still quite high [2].

Aim

The aim of the study is to analyze the relationship of risk factors to the occurrence of type 1 leprosy reaction in leprosy patients treated at the Outpatient Clinic of Dr. Soetomo General Hospital. Study the use of using private funds.

Materials and Methods

This study was an analytical study, with retrospective observational study design, to analyze the relationship of risk factors to the occurrence of type 1 leprosy reactions in leprosy patients, especially in patients who are treated at the Leprosy Division of Dermatology and Venerology Outpatient Clinic of Dr. Soetomo General Hospital in 2017–2019, using secondary data in the form of medical record.

The inclusions criteria were all of the patients recorded in medical records with a diagnosis of type 1 leprosy reaction in leprosy patient at the Leprosy Division of Dermatology and Venerology Outpatient Clinic of Dr. Soetomo General Hospital from January 2017 to December 2019. Exclusion criteria were incomplete medical records and leprosy patients with type 2 leprosy reaction. Those data were input into a data collection sheet to be analyzed using the Statistical Package for Social Sciences (SPSS) version 17.

Results

The number of cases that met the inclusion criteria showed the incidence of leprosy in Dr. Soetomo General Hospital from January 2017 to December 2019 was 364 cases. (Table 1) showed the demographic distribution in those 364 cases with 52.2% (190 cases) had leprosy without a reaction and 17.9% (65 cases) experienced type 1 reactions.

Table 1: Distribution of type 1 leprosy reactions in patients attended Dr. Soetomo General Hospital from January 2017 to December 2019

Patients category	Year			Total (%)
	2017 (%)	2018 (%)	2019 (%)	
Leprosy division	135 (37.1)	125 (34.3)	104 (28.6)	364 (100)
Leprosy without a reaction	70 (19.2)	70 (19.2)	50 (13.7)	190 (52.2)
Leprosy with type 1 reaction	26 (7.14)	18 (4.9)	21 (5.8)	65 (17.9)

On the other hand, (Table 2) showed the age distribution in leprosy patients with type 1 reaction in Dr. Soetomo General Hospital from January 2017 to December 2019. The results showed that the age range 35–55 years had the highest prevalence with 56.9% (37 patients).

Table 2: Age distribution in type 1 leprosy reaction patients in Dr. Soetomo General Hospital from January 2017 to December 2019

Age (year)	Year			Total (%)
	2017 (%)	2018 (%)	2019 (%)	
<15	0 (0)	1 (1.5)	0 (0)	1 (1.5)
15–34	8 (12.3)	4 (6.2)	7 (10.8)	19 (29.2)
35–55	15 (23.1)	10 (15.4)	12 (18.5)	37 (56.9)
>55	3 (4.6)	3 (4.6)	2 (3.1)	8 (12.3)
Total	26 (40.0)	18 (27.7)	21 (32.3)	65 (100)

Moreover, (Table 3) showed the gender distribution in leprosy patients with type 1 reaction in Dr. Soetomo General Hospital from January 2017 to December 2019. The results showed that male patients had the highest prevalence with 75.4% (49 patients).

Table 3: Gender distribution in type 1 leprosy reaction patients in Dr. Soetomo General Hospital from January 2017 to December 2019

Gender	Year			Total (%)
	2017 (%)	2018 (%)	2019 (%)	
Male	21 (32.2)	12 (18.5)	16 (24.6)	49 (75.4)
Female	5 (7.7)	6 (9.2)	5 (7.7)	16 (24.6)
Total	26 (40.0)	18 (27.7)	21 (32.3)	65 (100)

Furthermore, (Table 4) showed the nutritional status in leprosy patients with type 1 reaction in Dr. Soetomo General Hospital from January 2017 to December 2019. The results showed that patients with good nutritional status had the highest prevalence with 98.5% (64 patients).

Table 4: Nutritional status distribution in type 1 leprosy reaction patients in Dr. Soetomo General Hospital from January 2017 to December 2019

Nutritional status	Year			Total (%)
	2017 (%)	2018 (%)	2019 (%)	
Under	1 (1.5)	0 (0)	0 (0)	1 (1.5)
Normal	25 (38.5)	18 (27.7)	21 (32.3)	64 (98.5)
Over	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	26 (40.0)	18 (27.7)	21 (32.3)	65 (100)

Table 5 showed the bacterial index status in leprosy patients with type 1 reaction in Dr. Soetomo General Hospital from January 2017 to December 2019. The results showed that patients with negative bacterial index had the highest prevalence with 72.3% (47 patients).

Table 5: Bacterial index distribution in type 1 leprosy reaction patients in Dr. Soetomo General Hospital from January 2017 to December 2019

Bacterial index	Year			Total (%)
	2017 (%)	2018 (%)	2019 (%)	
Negative	19 (29.2)	12 (18.5)	16 (24.6)	47 (72.3)
1+	3 (4.6)	1 (1.5)	4 (6.2)	8 (12.3)
2+	4 (6.2)	4 (6.2)	1 (1.5)	9 (13.8)
3+	0 (0)	1 (1.5)	0 (0)	1 (1.5)
4+	0 (0)	0 (0)	0 (0)	0 (0)
>4+	0 (0)	0 (0)	0 (0)	0 (0)
Total	26 (40.0)	18 (27.7)	21 (32.3)	65 (100)

Table 6 showed the types of leprosy in leprosy patients with type 1 reaction in Dr. Soetomo General Hospital from January 2017 to December 2019. The results showed that the type of leprosy BB had highest prevalence with 61.6% (40 patients).

Table 6: Types of leprosy distribution in type 1 leprosy reaction patients in Dr. Soetomo General Hospital from January 2017 to December 2019

Type of leprosy	Year			Total (%)
	2017 (%)	2018 (%)	2019 (%)	
TT (Tuberculoid leprosy)	0 (0)	0 (0)	0 (0)	0 (0)
BT (Borderline tuberculoid)	0 (0)	0 (0)	0 (0)	0 (0)
BB (Borderline lepromatous)	12 (18.5)	13 (20.0)	15 (23.1)	40 (61.6)
BL (Lepromatous leprosy)	12 (18.5)	4 (6.2)	4 (6.2)	20 (20.8)
LL (Lepromatous leprosy)	2 (3.1)	1 (1.5)	2 (3.1)	5 (7.7)
Neural	0 (0)	0 (0)	0 (0)	0 (0)
Total	26 (40.0)	18 (27.7)	21 (32.3)	65 (100)

Table 7 showed therapeutic regimens in leprosy patients with type 1 reaction in Dr. Soetomo General

Hospital from January 2017 to December 2019. The results showed that MB was the therapeutic regimen with the highest prevalence at 100% (65 patients).

Table 7: Therapeutic regimens distribution in type 1 leprosy reaction patients in Dr. Soetomo General Hospital from January 2017 to December 2019

Therapeutic regimen	Year			Total (%)
	2017 (%)	2018 (%)	2019 (%)	
PB	0 (0)	0 (0)	0 (0)	0 (0)
MB	26 (40.0)	18 (27.7)	21 (32.3)	65 (100)
Total	26 (40.0)	18 (27.7)	21 (32.3)	65 (100)

Then from these variables, data were analyzed by bivariate and multivariate analysis. Table 8 showed the results of the bivariate analysis. The results of data analysis showed that age, type of leprosy and treatment regimen were significantly associated with the incidence of type 1 reactions (p = 0.023; 0.003 and 0.004, respectively), with leprosy type as the most dominant risk factor. Gender, nutritional status and bacterial index were not significantly associated with the incidence of type 1 reactions in leprosy patients.

Table 8: Bivariate analysis results for type 1 leprosy reaction patients in Dr. Soetomo General Hospital from January 2017 to December 2019

Bivariate analysis				
Variable	Type 1 reaction (%)		χ^2	p
	Yes	No		
Age (year)			5.140	0.023
<15	1/65 (1.5)	11/190 (5.8)		
15–34	19/65 (29.2)	86/190 (45.3)		
35–55	37/65 (56.9)	69/190 (36.3)		
>55	8/65 (12.3)	24/190 (12.6)		
Gender			0.564	0.453
Male	49/65 (75.4)	134/65 (70.5)		
Female	16/65 (24.6)	56/65 (29.5)		
Nutritional status			0.052	0.819
Under	1/65 (1.5)	7/190 (3.7)		
Normal	64/65 (98.5)	183/190 (96.3)		
Over	0/65 (0)	0/190 (0)		
Bacterial index			1.421	0.233
Negative	47/65 (72.3)	122/190 (64.2)		
Positive	18/65 (26.7)	68/190 (35.8)		
Types of leprosy			9.082	0.003
TT	0/65 (0)	8/190 (4.2)		
BT	0/65 (0)	12/190 (6.3)		
BB	40/65 (61.6)	95/190 (50.0)		
BL	20/65 (20.8)	33/190 (17.4)		
LL	5/65 (7.7)	37/190 (19.5)		
Neural	0/65 (0)	3/190 (1.6)		
Therapeutic regimen			8.237	0.004
PB	0/65 (0)	22/190 (11.5)		
MB	65/65 (100)	168/190 (88.5)		

Bivariate analysis was followed by multivariate analysis. The analysis began with a multivariate selection of candidate variables from the results of the previous bivariate analysis. Variable candidates pass the selection if the p < 0.25. Table 9 showed the results of the initial multivariate analysis.

Table 9: Initial multivariate analysis results for type 1 leprosy reaction patients in Dr. Soetomo General Hospital from January 2017 to December 2019

Variable	p-value	OR (95% CI)
Type of leprosy	0.016	0.273 (0.095–0.786)
Therapeutic regimen	0.998	0.000 (0.000)
Bacterial index	0.309	0.707 (0.362–1.380)
Age	0.513	1.234 (0.658–2.313)

Based on the initial multivariate analysis results, variables of therapeutic regimen, bacterial index, and age had a significance value> 0.05, so these variables had to be excluded and reanalyzed. Table 10 showed the final multivariate analysis results.

Table 10: Final multivariate analysis results for type 1 leprosy reaction patients in Dr. Soetomo General Hospital from January 2017 to December 2019

Variable	B-value	p-value	OR (95% CI)
Type of leprosy	−1.400	0.005	0.247 (0.094–0.065)
Constant	2.262	0.000	

Based on the results of the final multivariate analysis, it showed that the variable, type of leprosy, has a significance value <0.05 (0.005), so it can be concluded that the non-borderline type of leprosy provides a protective effect against the incidence of skin reactions higher than the borderline type of leprosy. The protective effect can be measured using the probability formula:

$$y_{borderline} = B_{constant} + B_{leprosy\ type}$$

$$y_{borderline} = 2.62 + (−1.4) = 1.22$$

while

$$y_{non-borderline} = B_{constant} + B_{leprosy\ type} \quad (2)$$
$$y_{non-borderline} = 2.62 + (−1.4)(2) = −0.18$$

thus,

$$P_{borderline} = \frac{1}{1+e^{-y}} = \frac{1}{1+2.72^{-1.22}} = \frac{1}{1.3} = 76.92\%$$

$$P_{non-borderline} = \frac{1}{1+e^{-y}} = \frac{1}{1+2.72^{-(-0.18)}} = \frac{1}{2.2} = 45.45\%$$

It was found that the borderline leprosy type raises the risk of incidence of type 1 leprosy to 76.92% and the non-borderline type of leprosy raises the risk of incidence of type 1 leprosy to 45.45%.

Discussion

Study conducted by Ranque _et al_. in 2007 supported these results, they found that 56.5% of patients aged more than 15 years experienced type 1 reactions with a significant analysis result (univariate p < 0.001; multivariate p = 0.001). They concluded that age is an independent risk factor for incidence of type 1 reactions with patients over 20 years of age are more likely to experience type 1 leprosy reactions. It can be said that age is an important risk factor in determining the incidence and severity of type 1 reaction [7].

There are two main reasons why type 1 leprosy reactions are more common at an older age. Type 1 leprosy reaction is mainly caused by high Th1 level. In children, the main immune response for reaction is Th2, while in older age group is Th1. This first reason may

explain the lower frequency of type 1 leprosy reactions in children than in the older age group. The second reason is the high number of memory T cells in adulthood. This in turn causes a secondary antigen cross reaction from Mycobacterium infection other than *M. leprae*; for example Mycobacterium tuberculosis. The cross-reaction of the antigen triggered by Mycobacterium other than *M. leprae* can also cause type 1 reactions [7]. Increased cellular immune response that occurs in adulthood, namely by the entry of CD4 + T cells and the production of IL-1, TNF-α, IL-2, and IFN- in lesions, and an increased Th1 response pattern known as the "*inflam-aging*," effectively causes an increase in the incidence of type I leprosy reactions [8].

The highest prevalence for gender was in males with 75.4% (49 patients), the study bivariate showed there's no significant correlation (p: 0,453). Study conducted by Scollard *et al*. in 2015 supported these results. They found that sex has no significant relationship with the incidence of leprosy either without reaction or with a type 1 reaction [6]. Based on research conducted by Aisyah and Agusni in 2018 and Antunes *et al*., there was a predominance of leprosy in male patients. The reasons why there's a predominance of male leprosy patients might be related to stress. Stress is associated with immune responses and nonspecific responses to lymphocyte proliferation, the emergence of T cells, specific antigens, activation of macrophages, changes in the balance of Th1 and Th2, and the release of cytokines such as IL-6s [6], [9]. All of those reasons could then trigger type 1 leprosy reaction [10].

The highest prevalence for nutritional status is normal with 98.5% (64 patients); the study bivariate showed there's no significant correlation (p: 0.819). These results were contradictory with study conducted by Rao and John in 2012. They found that there's a significant difference between the number of under-nutrition patients (body mass index< 18.5) in leprosy patients compared to non-leprosy patients (p = 0.0001) [11]. This discrepancy is influenced by lack of research related to data collection on nutritional status in the outpatient installation of Dr. Soetomo Surabaya. Data related to nutritional status come from measurements of patient's height and weight; however, there are incomplete data on body weight and height in medical records. The reason why nutritional value could be a risk factor for type 1 leprosy reaction is that lack of nutrients can lead to damage of body's defenses and results in immune suppression. Several micronutrients are important in maintaining the body's defenses and immune function such as immune response and antibody production [12].

The highest prevalence for bacterial index is negative with 72.3% (47 patients); the study bivariate showed that there's no significant correlation (p = 0.233). These results were contradictory with study conducted by others [7], [13], [14], [15], [16], [17].

Most of the studies found that patients with positive bacterial index have a higher chance of developing type 1 leprosy reaction than patients with negative bacterial index [7], [13], [14], [15], [16], [17]. This discrepancy could be because the low number of data. For example, Antunes in 2013 used 440 cases with 211 cases of type 1 leprosy reaction, while Hungria in 2016 used 753 cases with 418 cases of type 1 leprosy reaction. The highest prevalence for type of leprosy was for BB with 61.6% (40 patients); the study bivariate showed there's a significant correlation (p = 0. 003). Study conducted by Antunes *et al*. in 2013 supported these results; they found that 68.5% of the samples who experienced reactions had borderline type of leprosy. Research by Hungria *et al*. in 2016 also found similar results; they found that 98.5% of the sample had borderline type of leprosy. Leprosy types BT, BB, and BL were the types of leprosy that experienced the most type 1 reactions [14], [15]. The tendency of borderline type leprosy patients to experience type 1 reactions may occur because the borderline type has very unstable immunity, so that when the level of bacteria increases, it will stimulate the phenomenon of cell-mediated hypersensitivity [18].

The highest prevalence for therapeutic regimen is MB with 100% (65 patients); the study bivariate showed that there's a significant correlation (p = 0.004). Study conducted by Hungria *et al*. in 2016 supported these results; they found that MB patients had a higher tendency to develop leprosy reactions. Several other studies have also shown that leprosy reactions mainly occur in patients receiving MB therapy [15], [19]. Type 1 leprosy reaction is related to the success of therapy in the MB therapeutic regimen, because the antigen from bacterial degradation will stimulate the body to produce antibodies and generate cell-mediated immune (CMI) response [20], [21]. The CMI that appears will cause an inflammatory reaction to the skin and nerves, which eventually arises as a type 1 leprosy reaction [20].

Conclusion

There is a statistically significant correlation between the risk factor and the occurrence of type 1 leprosy reaction in leprosy patient who are treated at the Leprosy Division of Dermatology and Venerology Outpatient Clinic of Dr. Soetomo General Hospital. The risk factor that has significant correlation is age 15–34 years; leprosy types BB, BL, and BT; and the MB MDTL therapeutic regimen. The most significant risk factor for the occurrence of type 1 leprosy reaction from our study is the type of leprosy (BB, BL, and BT).

Acknowledgment

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