

# Risk Factors of Acute and Chronic Erythema Nodosum Leprosum in Dr. Soetomo General Academic Hospital Surabaya

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## ABSTRACT

**Background:** Leprosy is a chronic granulomatous infection and is one of the neglected diseases caused by *Mycobacterium leprae*. ENL is a complex syndrome, that caused inflammation of the skin, nerves, and other organs due to an inflammatory immune response to *Mycobacterium leprae* antigens. Acute ENL was defined as the first episode of ENL with a duration of less than 24 weeks. Chronic ENL was defined as ENL that persisted for more than 24 weeks. These types of ENL can have different risk factors and require different therapeutic interventions. **Purpose:** The onset of ENL is acute, but may progress to a chronic or recurrent phase and require long-term therapy. Early detection of leprosy is very important, because the infection is curable and prompt treatment can reduce nerve damage and associated stigma. Chronic ENL patients require prolonged high doses of corticosteroids to control inflammation in ENL and cause severe complications and side effects associated with morbidity and mortality. **Methods:** This retrospective study was conducted using a non-probability sampling technique consecutively using a case-control formula in leprosy patients with ENL in the Leprosy Division of the Outpatient Dermatology and Venereology Unit RSUD Dr. Soetomo Surabaya for the period 2015 – 2020, using secondary data in the form of medical record data. **Result:** The results of this study obtained leprosy patients with ENL as many as 234 patients, 56 patients with acute ENL and 89 patients with chronic ENL. 45 patients with acute ENL and 45 patients with chronic ENL were obtained from the case-control minimal sample size formula. **Conclusion:** The results of the bivariate analysis test showed that there was a relationship between risk factors for coinfection and steroid therapy with the type of ENL. The presence of coinfection and steroid therapy showed that patients tend to be chronic ENL, conversely, in the absence of coinfection and without steroid therapy, patients tend to be acute ENL. The multivariate logistic regression analysis test showed a significant association between risk factors for ENL onset before MDT and the presence of coinfection with chronic ENL, whereas ENL onset after MDT and absence of coinfection were associated with acute ENL. **Key words:** ENL, Acute ENL, Chronic ENL, Leprosy, Risk factors, Neglected disease.

## INTRODUCTION

Leprosy is a chronic granulomatous infection and is one of the neglected diseases caused by *Mycobacterium leprae*, which infects mucosal tissues and peripheral nerves, causing skin sensation and increased disability during disease progression.<sup>1,2</sup>

ENL is a complex syndrome, that caused inflammation of the skin, nerves, and other organs due to an inflammatory immune response to *Mycobacterium leprae* antigens. Acute ENL was defined as a patient who had a first episode of ENL less than 24 weeks in duration or had a second or subsequent ENL episode, lasting less than 24 weeks and occurring 84 days (i.e., 12 weeks) or more after stopping treatment for ENL. Chronic ENL is defined as ENL occurring for more than 24 weeks in which the patient has required continuous ENL treatment or where the treatment-free period is 27 days or less.<sup>3</sup> These types of ENL can have different risk factors and require different therapeutic interventions.<sup>4</sup> The onset of ENL is acute, but may progress to a chronic or recurrent phase. Early detection of leprosy is very important, because the infection is curable and prompt treatment can reduce nerve damage and associated stigma.<sup>5</sup>

This retrospective study was conducted to determine the incidence of acute ENL and chronic

ENL. Evaluate the general description of acute ENL and chronic ENL according to the basic data to be studied and analyze the risk factors that play a role in acute ENL and chronic ENL. These types of ENL can have different risk factors, so if there are risk factors that play a role in acute and chronic ENL, close monitoring should be carried out, early and adequate management, and better education for patients.

The risk factors to be studied include gender, age, nutritional status based on body mass index (BMI), type of leprosy, bacterial index, morphology index, coinfection, onset of ENL, severity of ENL, duration of Multi Drug Therapy (MDT), and steroid therapy. in patients with acute ENL and chronic ENL within a period of 5 years, namely 2015-2020 in the Leprosy Division of the Outpatient Unit of Dermatology and Venereology in Dr. Soetomo General Academic Hospital Surabaya.

## METHODS

This retrospective study was to analysis of the risk factors for acute and chronic erythema nodosum leprosum in new leprosy patients at the Leprosy Division of the Outpatient Dermatology and Venereology Dr. Soetomo General Academic Hospital Surabaya during the period of January 2015 to December 2020 has been carried out by evaluating the medical records of leprosy patients and from

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Electronic Medical Record (EMR) data. This study has received ethical approval from the Hospital Ethics Committee RSUD Dr. Soetomo Surabaya (0932/LOE/301.4.2/VI/2022). Sampling in this retrospective study was carried out using a consecutive non-probability sampling technique using the case-control formula. Random probability sampling technique was also used to obtain a total of 45 patients with acute ENL and 45 patients with chronic ENL from the formula for the minimum sample size of cases and controls.

This study analyzed the relationship of risk factors in acute and chronic ENL patients, such as gender, age, nutritional status based on body mass index (BMI), type of leprosy, bacterial index, morphological index, coinfection, onset of ENL, severity of ENL, duration of MDT, and steroid therapy. The relationship was investigated by Pearson's chi-square bivariate analysis and Wald's backward stepwise multivariate logistic regression analysis, with p value < 0.05 indicating a significant relationship between the analyzed factors and the related ENL type.

## RESULT

New leprosy patients with erythema nodosum leprosum (ENL) who came to the Leprosy Division of the Outpatient Dermatology and Venereology Unit, RSUD Dr. Soetomo for the 2015-2020 period totaled 234 patients. Based on the criteria for acceptance and rejection of the sample, the number of leprosy patients with acute ENL were 56 patients (24%), and leprosy patients with chronic ENL were 89 patients (38%). In accordance with the case-control formula for the minimum sample size, the number of samples of acute ENL patients was 45 patients and samples of chronic ENL patients were 45 patients. The number of sample rejections was 89 patients, including 5 pediatric patients with ENL, 3 patients with incomplete data, 81 patients who only had 1 polyclinic control and did not continue therapy (loss of follow-up) in the Leprosy Division Outpatient Dermatology and Venereology Dr. Soetomo General Academic Hospital Surabaya.

Gender distribution in acute and chronic ENL patients, mostly male, 28 patients (62.2%) for acute ENL and 35 patients (77.8%) for chronic ENL. The number of male patients in chronic ENL patients was more than male patients with acute ENL. Age of patients with acute and chronic ENL was more at the age of < 40 years. The number of patients aged < 40 years was more in chronic ENL as many as 29 patients (64.40%) compared to acute ENL. The highest BMI in acute and chronic ENL patients was in the normal category, with the same number of patients, namely 36 patients (80%). The most common type of leprosy in acute ENL patients was LL type with 25 patients (55.6%), while in chronic ENL patients it was BL type with the same number of 25 patients (55.6%). The highest number of bacterial indices in acute ENL patients was > 3, as many as 15 patients (46.9%). In patients with chronic ENL also found the same number of > 3 in 17 patients (37.8%). The highest morphological index was 0 in 27 patients (60%) in acute ENL and 21 in chronic ENL (46.7%). Most ENL onset was after MDT or RFT treatment in 21 patients (46.7%) acute ENL and 18 (40%). In acute ENL, the number of patients with or without coinfection was almost equal, namely 23 patients (51.1%) with coinfection and 22 patients (48.9%) without coinfection. In chronic ENL, it was found that almost all patients were co-infected with 43 patients (95.6%). The most severe degrees of acute ENL patients were moderate degrees, which were 27 patients (60%), similarly to chronic ENL, the highest number was moderate, namely 32 patients (71.1%). Patients with mild degrees of chronic ENL were not found. The highest duration of MDT when patients experienced ENL for the first time was during RFT or before MDT, 23 (51.1%) in acute ENL, and 33 (73.3%). The highest cumulative amount of steroid therapy within the first 8 weeks in acute and chronic ENL patients was <1,995 mg, 35 patients (77.8%) in acute ENL and 37 patients (82.2%) in chronic ENL.

Analysis of the results of the bivariate test, several risk factors were found that were associated with ENL patients, which were coinfection,

**Table 1: Bivariate analysis tests of risk factors according to types of ENL.**

Risk Factors	Types of ENL		P Value
	Acute ENL (%)	Chronic ENL (%)	
<b>Coinfection</b>			
Yes	23 (51.1)	43 (95.6)	0.001*
No	22 (48.9)	2 (4.4)	
<b>Steroid therapy</b>			
No steroid therapy	8 (17.8)	1 (2.2)	0.004*
<1.995 mg	35 (77.8)	37 (82.2)	
>1.995 mg	2 (4.4)	7 (15.6)	
<b>MDT duration</b>			
RFT/Before MDT	23 (51.1)	33 (73.3)	0.031*
< 6 months	16 (35.6)	9 (20%)	
6 – 12 months	6 (13.3)	3 (6.7)	
<b>Gender</b>			
Male	28 (62.2)	35 (77.8)	0.200
Female	17 (37.8)	10 (22.2)	
<b>Age</b>			
<40 tahun	23 (51.1)	29 (64.4)	0.107
>40 tahun	22 (48.9)	16 (35.6)	
<b>BMI</b>			
Underweight	1 (2.2)	4 (8.9)	0.134
Normal	36 (80)	36 (80)	
Overweight	3 (6.7)	4 (8.9)	
Obese	5 (11.1)	1 (2.2)	
<b>Leprosy Type</b>			
BB	1 (2.2)	0 (0)	0.305
BL	19 (42.2)	25 (55.6)	
LL	25 (55.6)	20 (44.4)	
<b>Bacterial Index</b>			
0	14 (31.1)	13 (28.9)	0.618
1	5 (11.1)	3 (6.7)	
2	11 (24.4)	12 (26.7)	
>3	15 (46.9)	17 (37.8)	
<b>Morphological Index</b>			
0	27 (60)	21 (46.7)	0.179
<5%	14 (31.1)	17 (37.8)	
>5%	4 (8.9)	7 (15.6)	
<b>Onset ENL</b>			
Before MDT	4 (8.9)	15 (33.3)	0.130
During MDT	20 (44.4)	12 (26.7)	
After MDT/RFT	21 (46.7)	18 (40)	
<b>Severity Scale</b>			
Mild	7 (15.6)	0 (0)	0.130
Moderate	27 (60)	32 (71.1)	
Severe	11 (24.2)	13 (28.9)	

\*significant if P value < 0.05

**Table 2: Multivariate analysis tests of risk factors according to types of ENL.**

Risk Factors	B	Nilai p	OR	95% CI
ENL onset (before MDT)	2.137	0.016	8.474	1.498 – 47.932
Coinfection	3.390	0.001	29.655	5.040 – 174.496

\*significant if P value < 0.05

duration of MDT and steroid therapy.

There is a significant relationship between the risk factors for coinfection and the incidence of ENL, where if there is coinfection, the patient tends to become chronic ENL and vice versa if there is no coinfection, the patient tends to become acute ENL. A significant relationship was also found in the duration of MDT when patients first experienced ENL, that patients who had RFT and before MDT tended to become chronic ENL, and patients with MDT duration of

6-12 months tended to have acute ENL. A significant relationship was also seen between steroid therapy and the incidence of ENL, in which patients with steroid therapy with a cumulative dose of <1,995 mg in 8 weeks, the patient tends to become chronic ENL and vice versa if the patient is not treated with steroids, the patient tends to become acute ENL. Significant results ( $p$  value = 0.001) were shown in the association between coinfection risk factors and the incidence of ENL, also in the relationship between MDT duration and the type of ENL ( $p$  value = 0.031), and in the relationship between steroid therapy and the incidence of ENL ( $p$  value = 0.004).

The results of the multivariate analysis test showed a significant relationship between risk factors for the onset of ENL before MDT and the incidence of chronic ENL (OR = 8,474, 95% CI = 1,498-47,932,  $p$  value = 0.016), and there was also a significant relationship between the risk factors for coinfection and the incidence of Chronic ENL (OR = 29.655, 95% CI = 5.040-174.496,  $p$ -value = 0.001). In contrast, acute ENL was associated with risk factors for ENL onset after MDT and without coinfection.

## DISCUSSION

Gender of ENL patients in Leprosy Division of Dermatology and Venereology unit, RSUD Dr. Soetomo Surabaya is dominated by male patients. In acute ENL, 28 male patients (62.2%), and chronic ENL found 35 male patients (77.8%). There was no significant relationship between gender and the incidence of acute and chronic ENL. The high number of patients aged < 40 years in chronic ENL is in accordance with the results of research by Pocaterra *et al* and Kumar *et al*,<sup>4,6</sup> in which ENL is caused by factors of economic productive age and a higher workload can trigger conditions of stress or physical or mental fatigue. This can have serious health and economic consequences for patients and their families.<sup>4,6</sup>

Montenegro *et al.*,<sup>7</sup> showed a controversy with the finding of a less frequent occurrence of reactions in the underweight group ( $p=0.091$ ) with the assumption that underweight patients may not have an adequate immune response to trigger reactions.<sup>7</sup> This is related to the majority of acute and chronic ENL patients in this study who had normal BMI categories, so that patients had an adequate immune response to trigger ENL reactions. The type of leprosy was found the most with BL and LL types in acute and chronic ENL patients. High BL and LL leprosy types can be risk factors for ENL because high concentrations of mycobacterial antigens in tissues can lead to high production of IgM and IgG antibodies.<sup>1,6</sup>

Bacterial index (IB) in patients with ENL in the Leprosy Division of Dermatology and Venereology unit, RSUD Dr. Soetomo Surabaya has the highest number 0 and > 3. acute and chronic ENL patients with IB 0, most of the patients who had Release from Treatment (RFT). These results can be seen that the number is almost the same as patients with IB > 3, most of whom are in the stage before or currently on MDT treatment. High antigen load will interact with antibodies to produce immune complexes that can trigger ENL so that high IB can increase the risk of ENL. Most of the morphological indices (IM) of acute and chronic ENL patients was IM 0. Several studies stated that ENL was more often found in patients with low MI, which was <5%, this was related to the number of germs that died so that the number of antigens increased and triggered an immune reaction.<sup>8</sup>

The onset of ENL in acute and chronic ENL patients obtained the highest number of patients with onset after MDT or RFT. Results of the bivariate analysis test, it was found that there was no relationship between the onset of ENL and the incidence of acute and chronic ENL ( $p = 0.093$ ). The multivariate logistic regression test showed that there was a relationship between the onset of ENL before MDT treatment and the incidence of chronic ENL ( $p = 0.016$ , OR = 8.474, 95% CI =

1.498-47.932), on the other hand, the onset of ENL after MDT then the patient tended to have acute ENL. The results of bivariate and multivariate analysis showed different results. This is because the risk factor for ENL onset before MDT treatment in multivariate logistic regression analysis is a dependent risk factor that can cause chronic ENL incidence by being influenced by the presence of other risk factors, namely the presence of co-infection that can appear even before the patient is diagnosed with ENL. The onset of ENL after MDT is more likely in patients with acute ENL, according to most studies due to increased bacterial fragmentation due to MDT treatment which can increase the formation of antigen-antibody complexes to trigger the ENL reaction.

Most of the patients with chronic ENL had co-infection of 43 patients (95.6%). In acute ENL the number of patients with and without coinfection showed almost the same number, 23 patients with coinfection (51.1%) and 22 patients without coinfection (48.9%). From the bivariate test analysis, it was found that there was a significant relationship between coinfection risk factors and the incidence of ENL ( $p = 0.001$ ), and the results of the multivariate logistic regression analysis also showed a relationship between coinfection and the incidence of chronic ENL ( $p = 0.001$ ). The presence of risk factors for co-infection in ENL patients tends to become chronic ENL, and conversely, in the absence of coinfection, patients tend to become acute ENL. The most common type of coinfection experienced by ENL patients was oral infection, chronic periodontitis. Coinfection itself can also be experienced by patients even before the patient is diagnosed with ENL so that it can aggravate the patient's condition before treatment. This is related to the risk factors for ENL onset before MDT treatment, so this coinfection has a significant effect on the relationship between ENL onset before MDT and chronic ENL patients. Coinfection can overstimulate the immune system through the release of various inflammatory markers. Most likely, these inflammatory products can spread to the peripheral circulation, so that it will worsen the course of leprosy and can stimulate or maintain an inflammatory reaction during the disease process.<sup>9</sup>

The severity of ENL in acute and chronic ENL patients mostly at moderate ENL degrees. Patients with acute and chronic ENL with moderate severity are common after MDT or RFT treatment. The highest degree of severity in acute ENL patients was found during MDT treatment, and in chronic ENL patients it was found after MDT or RFT treatment. MDT therapy can kill intracellular mycobacteria, which break down and release antigens. These antigens can form immune complexes that cause ENL.<sup>4</sup> Patients with acute and chronic ENL in the Leprosy Division, the incidence of ENL was first experienced by patients more common during RFT or before MDT. The results of the Spearman's correlation test showed a significant relationship between the duration of MDT and the incidence of acute and chronic ENL ( $p = 0.031$ ). In patients treated with MDT, patients tend to have acute ENL, and in patients who have had RFT and before receiving MDT, patients tend to have chronic ENL. Coinfection can affect the occurrence of ENL reactions, according to Machado *et al*,<sup>10</sup> coinfections in leprosy can modify host immunity either by increasing inflammation and tissue damage that causes reactions and neuritis, or suppressing defense mechanisms resulting in higher bacterial burden or relapse.<sup>10</sup>

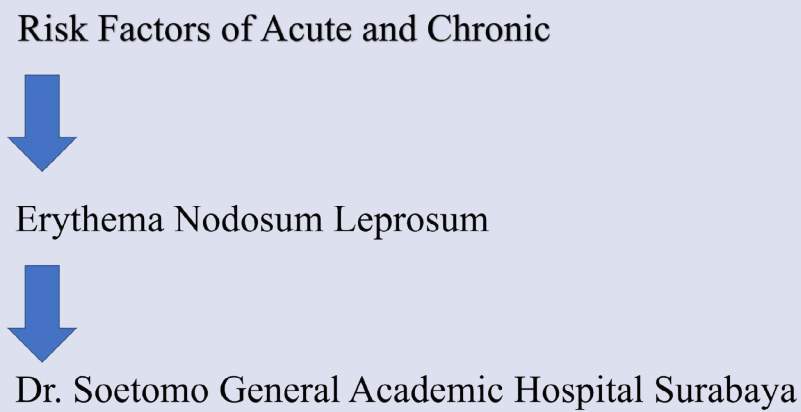
Patients with acute and chronic ENL mostly received steroid therapy, with the cumulative dose in 8 weeks was < 1,995 mg. The results of the Spearman's correlation test analysis showed a significant relationship between risk factors for steroid therapy and the incidence of ENL ( $p = 0.004$ ). ENL patients with the cumulative amount of steroid therapy <1,995 mg in 8 weeks, the patient tends to become chronic ENL, on the other hand patients without steroid therapy, the patient tends to become acute ENL. From the results of the study, it can be seen that the incidence of ENL can still be controlled in acute and chronic ENL

patients, and most chronic ENL patients must receive steroid therapy. In addition to steroid therapy, ENL patients are treated with anti-inflammatory or painkillers, which are generally classified as mild ENL, this shows that ENL reactions are easier to control in acute ENL.

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## GRAPHICAL ABSTRACT



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