# The Risk Factor Analysis of Erythema Nodosum Leprosum in a Tertiary Hospital in Surabaya, Indonesia

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A three-year retrospective study of multibacillary leprosy patients suffering from erythema nodosum leprosum (ENL) in a tertiary hospital in Surabaya city, East Java, Indonesia, with a minimum of 2 to 5 years follow up period, was conducted to analyse the risk factors associated with ENL. Multivariate analyses result showed leprosy type lepromatous leprosy (odds ratio [OR]=78.664; 95% confidence interval [CI] = 13.635-453.827; p<0.0001) and borderline lepromatous leprosy (OR= 24.756; 95% CI= 5.052-121.320; p<0.0001), as well as coinfection (OR = 42.963; 95% CI = 3.778-488.585; p=0.002) are significant risk factors of ENL. While gender, age, bacterial index (BI), morphological index (MI), nutritional status were not significantly associated with ENL. The ENL patients were predominantly male, 20-40 years old, suffered from lepromatous leprosy (LL) type leprosy, with BI 3+ and positive MI, and have normal weight. Finding risk factors that may be associated with ENL will help increase physician's alertness to provide better health care. A comprehensive examination and early recognition of possible risk factors will enhance health care quality in monitoring, educating, as well as providing prompt and appropriate treatment in order to help reduce ENL morbidity.

**Keywords** : Erythema Nodosum Leprosum, ENL, Risk Factor, Leprosy

## Introduction

The biggest problem in leprosy is the development of acute and subacute complications called reactions. Type 2 leprosy reaction or ENL is a serious, debilitating, systemic disorder due to an inflammatory immune response to *M. leprae* antigen, occurring predominantly in the lepromatous end of the spectrum, namely borderline lepromatous leprosy (BL) and lepromatous leprosy (LL). It is scharacterised by the development of multiple erythematous nodules all over the body and accompanying systemic symptoms of fever, joint pain and neuropathy (Kar & Chauhan 2017). In some patients, ENL episodes occur multiple times or over a long period of time, fulfilling its chronic and recurrent nature; hence it can have a negative impact on the patient's quality of life, economic status and is associated with increased hospital admission and mortality (Chandler et al 2015, Pocaterra et al

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2006, Walker et al 2014, Yap et al 2016). Special attention must be given to ENL patients to be treated promptly and appropriately. Finding the risk factors of developing ENL at diagnosis will help increase alertness for leprosy patients to be strictly supervised and educated about the complication of ENL regarding its course, sign, symptoms, and treatment to enhance patient's compliance both during and after their treatment with MDT, as well as during the treatment course of the reaction.

Research data on risk factors for ENL are still sparse, a study in Nepal showed a reduced risk of ENL in patients older than 40 years old, and a large study in India showed male predominance over females (Arora et al 2008, Manandhar et al 1999). A high BI value increased the risk of developing ENL; on the other hand, ENL is more frequently found in a patient with MI less than 5% related to a higher number of dead bacilli (Balagon et al 2010, Kumar et al 2004, Manandhar et al 1999, Pocaterra et al 2006). In addition, many research identified LL leprosy type as the major risk factor of ENL (Manandhar et al 1999, Neves et al 2019, Pocaterra et al 2006, Thomas et al 2017). Other possible risk factors include intercurrent infection and research by Motta et al supported this finding, especially regarding chronic oral infection (Kar & Chauhan 2017, Motta et al 2012). While a Brazilian study found that leprosy reactions were less common in underweight individuals (Montenegro et al 2012), adequate nutrition can help reduce the risk of leprosy or increase the immune system against other infections could increase the risk of developing ENL (Diffey et al 2000, Wagenaar et al 2015). This study was conducted in Leprosy Division, Dermatology and Venereology Outpatient Department Dr Soetomo General Academic Hospital, Surabaya, East Java, Indonesia from January 2015 to December 2017

with a follow-up period of 2-5 years, to determine the risk factors associated with ENL.

## Material and Methods

This study is an analytical cohort retrospective study. The data were obtained from medical records with the inclusion criteria consisting of all-new untreated MB leprosy patients who came to Leprosy Division, Dermatology and Venerology Outpatient Department Dr Soetomo General Academic Hospital from January 2015 to December 2017 with a follow-up period of 2 to 5 years. Exclusion criteria included MB leprosy patients who were referred only for laboratory examination, patients who transferred to other health care centres, and patients with type 1 reactions. The analytical data include age, gender, leprosy type, bacteriological index, morphological index, coinfection, and nutritional status based on body mass index (BMI). The diagnosis was made according to the Indian Association of Leprologists (IAL) based on clinical and bacteriological assessment (IAL 1982). Bacterial index was calculated as defined by Ridley (Ridley 1964) and the morphological index was calculated as the percentage of solid stained bacilli (Browne 1966). The BMI value was calculated using the formula: BMI = Weight (kg) / Height (m)$^2$, while for patients younger than 20 years old, BMI for age percentile graphs available at http://www.cdc.gov/growth-charts were used. Ethical clearance was obtained from the Ethical Committee of Dr. Soetomo General Hospital Surabaya in July 2020.

## Results

Among 385 patients who came to Leprosy Division in 2015-2017, 262 patients were excluded due to paucibacillary (PB) classification (47), transfer to another centre (88), undergoing laboratory examination only and ulcer therapy (18), MB patient with type 1 leprosy reaction (61), and previously treated multibacillary (MB)

**Table 1 : Univariate Analysis**

| Variabel | ENL | | $X^2$ | P |
|---|---|---|---|---|
| | Yes | No | | |
| **Gender** | | | 0.041 | 0.839 |
| Male | 42/63 (66.7%) | 42/60 (70.0%) | | |
| Female | 21/63 (33.3%) | 18/60 (30.0%) | | |
| **Age** | | | 0.915 | 0.339 |
| <40 | 39/63 (61.9%) | 43/60 (71.7%) | | |
| ≥40 | 24/63 (38.1%) | 17/60 (28.3%) | | |
| **Leprosy type** | | | 53.349 | 0.000 |
| BB | 3/63 (4.8%) | 39/60 (65.0%) | | |
| BL | 29/63 (46.0%) | 16/60 (26.7%) | | |
| LL | 31/63 (49.2%) | 5/60 (8.3%) | | |
| **BI** | | | 19.365 | 0.000 |
| (<3+) | 30/63 (47.6%) | 52/60 (86.7%) | | |
| (≥3+) | 33/63 (52.4%) | 8/60 (13.3%) | | |
| **MI** | | | 29.687 | 0.000 |
| Positive | 55/63 (87.3%) | 23/60 (38.3%) | | |
| Negative | 8/63 (12.7%) | 37/60 (61.7%) | | |
| **Coinfection** | | | 22.984 | 0.000 |
| Yes | 24/63 (38.1%) | 1/60 (1.7%) | | |
| No | 39/63 (61.9%) | 59/60 (98.3%) | | |
| **Nutritional status** | | | 2.772 | 0.250 |
| Underweight | 9/60 (15.0%) | 4/60 (6.7%) | | |
| Normal | 44/60 (73.3%) | 51/60 (85.0%) | | |
| Overweight | 7/60 (11.7%) | 5/60 (8.3%) | | |

patient (48). A total of 123 previously untreated MB patients were analysed, including 63 patients who developed ENL and 60 patients who did not develop ENL as control. All the 123 patients received 12 months WHO/MDT multi-bacillary (MB) treatment and were examined for risk factor characteristics; however, the nutritional status of 3 MB patients who developed ENL was not known. Tables 1 and 2 show that patients with ENL were predominantly younger than 40 years old, male, suffered from LL type leprosy, had BI ≥ 3, positive MI, and normal nutritional status, and more than one third had coinfection.

Patients with BL and LL leprosy type had a significantly higher prevalence of ENL than patients with borderline leprosy (BB) type (p < 0.0001). Patients with coinfection had a significantly higher prevalence of ENL than those without coinfection (p = 0.002). The prevalence of ENL was not significantly different between males

*Fransisca et al*

**Table 2 : Multivariate Analysis**

| Variable | Estimation | p | OR | CI |
|----------|-----------|-----|-----|-----|
| **Leprosy type** | | | | |
| BB | | | | |
| BL | 3.209 | 0.000 | 24.756 | 5.052-121.320 |
| LL | 4.365 | 0.000 | 78.664 | 13.635-453.827 |
| **BI** | | | | |
| (<3+) | | | | |
| (≥3+) | 0.145 | 0.820 | 1,157 | 0.331-4.035 |
| **MI** | | | | |
| Positive | 0.463 | 0,498 | 1,588 | 0.416-6.063 |
| Negative | | | | |
| **Coinfection** | | | | |
| Yes | 3.760 | 0.002 | 42.963 | 3.778-488.585 |
| No | | | | |
| **Nutritional status** | | | | |
| Underweight | 0.718 | 0.489 | 2.051 | 0.268-15.664 |
| Normal | | | | |
| Overweight | 0.855 | 0.363 | 2.351 | 0.373-14.833 |

and females; age ≥ 40 and < 40 years old; BI < 3 and ≥ 3; MI positive and negative; and patients who were underweight, normal, or overweight nutritional status. Although univariate analysis showed that patients with BI ≥ 3 had a significantly higher prevalence of ENL than those with BI < 3 and MI positive than those with MI negative however in multivariate analysis, the results were not significant, the difference in the analysis results could be due to indirect influence of other risk factors that influence ENL significantly, in this case, leprosy type or coinfection.

## Discussion

In this study, patients suffering from LL type leprosy (CI: 13.635-453.827; OR: 78.664) and BL (CI: 5.052-121.320; OR: 24.756) had a significantly higher prevalence of ENL than BB type (p <0.0001). This finding is in accordance with many other studies which stated that ENL is more common in LL type. The ENL ratio in LL type was found to be about 5 times higher than that of BL type and other types of MB leprosy (Kumar et al 2004, Neves et al 2019, Penna et al 2008, Pocaterra et al 2006, Thomas et al 2017). This could be explained by the total number of precipitation antibodies and mycobacterial antigens higher in LL than other MB types resulting in antibody-antigen interactions, which will produce immune complexes that underlie ENL pathogenesis (ILEP 2002, Kementerian Kesehatan RI Direktorat Jenderal Pengendalian Penyakit dan Penyehatan Lingkungan 2012, Kar & Chauhan 2017). Correct diagnosis of MB leprosy types (LL, BL, BB) with the help of clinical,

bacteriological, immunological, or histopatho-logical examination is important since LL type followed by BL type have a significantly higher risk of developing ENL compared to BB type; therefore patients with BL and LL type leprosy should be educated about the risk of ENL and be strictly supervised.

Beside leprosy type, coinfection significantly increase the risk of ENL (OR = 42.963; 95% CI = 3.778-488.585; p=0.002). More than one-third of ENL patients had coinfection (24/63, 38.1%), and the most common infection was oral infection (17/24: 70.8%), including periodontitis, caries, and pulp gangrene; while other infections found include pharyngitis, hepatitis, tuberculosis, trichomoniasis, bacterial conjunctivitis, otitis, and cellulitis. One known risk factor for ENL is intercurrent infections such as streptococcal, viral, intestinal parasites, filariasis, and malaria (Kar & Chauhan 2017). Motta et al (2010, 2011, 2012) have shown association between oral infections and lepra reactons. The study by Motta et al showed that coinfection was significantly associated with ENL (p<0.0001), and chronic oral infection was the most prevalent (40/88, 45.5%) (Motta et al 2012). Coinfection can over-stimulate the immune system through the release of many inflammatory markers, including cytokines, acute phase proteins, as well as chemokines and maintain a proinflammatory state (Motta et al 2010, 2011). A study by Listiawan showed that the innate immune system also played a role in ENL, hence the coexistence of leprosy with other infections associated with increased expression of inflammatory markers could aggravate leprosy and consequently inducing, stimulating or sus-taining inflammatory reactions that can be associated with leprosy reactions (Kar & Chauhan 2017, Listiawan 2019, Motta et al 2012). Thus, it is necessary to evaluate both local and systemic coinfection in leprosy patients and treat it immediately.

Age is not a risk factor for ENL (Balagon et al 2010, Kumar et al 2004, Pocaterra et al 2006, Saunderson et al 2000, Scollard et al 2015). However, a study in Nepal showed a reduced risk of ENL in patients > 40 years old, and a study in India showed a reduced risk of chronic ENL in patients aged > 35 years (Manandhar et al 1999, Pocaterra et al 2006). In this study, most ENL patients are younger than 40 years old, productive age with higher workload and the inability to work optimally could be related to ENL risk factors, namely physical or mental stress; alternatively, people in their productive age are more active in seeking treatment.

A large hospital-based study in India showed significant male predominance over women (Arora et al 2008). The same finding was shown in a previous study in RSDS Surabaya (74.1% vs 25.1%) and in a tertiary hospital in North India (85% vs 15%) (Listiyawati et al 2015, Thomas et al 2017). However, a retrospective study in India and in Thailand showed a higher risk in women (Kumar et al 2004, Suchonwanit et al 2015). Several other studies showed that gender is not a risk factor for ENL (Balagon et al 2010, Pocaterra et al 2006, Saunderson et al 2000, Sharma et al 2000). It is not yet known why certain sexes are more predominant in ENL; a possible explanation is that men are more active in seeking treatment (Arora et al 2008). In addition, the high workload and responsibility of a man as the backbone of the family and the inability to work effectively could be related to the risk factor stress, while female predominance may be due to hormonal factors. Erythema nodosum leprosum is mainly asso-ciated with Th2 immune response, and stress associated with increased cortisol levels could activate Th2 (Rook & Baker 1999). The same is found in pregnancy, with a shift in the immune

response from Th1 to Th2 (Khanna 2017). Thus stress and hormonal factors could both be related to ENL.

In this study, most of the ENL patients had BI = 3 at diagnosis (31/63, 49.2%), while only 2 patients had BI = 4 (3.2%), and none of the patients had BI > 4; hence BI of 3 was used as benchmark value, which also showed that the diagnosis of LL type leprosy was enforced based on clinical findings, not merely bacteriological examination (Porichha & Natrajan 2017). In addition, the finding of very few BI ≥ 4 in this study might also affect the insignificant finding of BI as ENL risk factor. Previous studies have shown that BI ≥ 3 is a risk factor for ENL, but it did not describe the total number of patients with BI ≥ 4 (Kumar et al 2004). Most of the ENL risk factor studies on BI used the benchmark value ≥ 4, and it is a significant risk factor for ENL (Balagon et al 2010, Manandhar et al 1999, Pocaterra et al 2006). A high BI is generally found in LL and BL types, and it shows the density of acid-fast bacilli, which include live and dead bacteria, hence the antigen load, and based on the pathogenesis of ENL, a high antigen load will interact with antibodies to produce immune complexes, therefore, a high BI could increase the risk of ENL.

Histologically, ENL generally does not appear until the bacilli become granular hence the biological activity of *M. leprae* live bacilli assessed by MI is not a significant factor (Kar & Chauhan 2017, Manandhar et al 1999). ENL is mainly found in patients whose MI has become negative because, in general, the bacteria in ENL are dead, and in addition, administering MDT to patients with high MI might require close monitoring because treatment can increase the number of dead antigens.

Malnutrition, especially micronutrient deficiency, results in Th2 mediated immune response, while supplementation with micronutrients reverses it to a Th1 response with enhanced innate immunity (Khanna 2017). Protein-energy malnutrition, as well as inadequate intake of vitamins and minerals, are associated with decreased cellular immunity associated with increased risk of leprosy, other infections, and worsening of leprosy (Farhadi & Ovchinnikov 2018, Khanna 2017, Wagenaar et al 2015). Research on nutritional risk factors for ENL is still very sparse, with one study showing a controversial finding that reaction is less frequently found in the undernourished group (p = 0.0906) with the assumption that malnourished patients do not have an adequate immune response to trigger a reaction(Montenegro et al 2012). Although nutritional status was not a risk factor for ENL in this study, it should be semphasised that adequate nutrition can help reduce the risk and worsening of leprosy and other infections that can trigger ENL.

This study has limitations because it uses retrospective data that is available and presented as it is in medical records; therefore, some deficiencies in information regarding BI, MI, leprosy type, coinfection, and nutritional status (including 3 unknown nutritional statuses of MB leprosy patients with ENL) are inevitable.

## Conclusion

The analytical result of ENL risk factors in this study showed that BL and LL types with coinfection significantly increase the risk of ENL, while gender, age, BI, MI, and nutritional status were not found to increase the risk of developing ENL.

Completing medical records thoroughly and comprehensive examination including history taking, physical examination, and laboratory examination are critical to obtaining integrated information on ENL risk factors, especially regarding the correct diagnosis of leprosy type and evaluation of intercurrent infections. Patients

should be educated about the presence of intercurrent infections that could trigger or aggravate the reaction and advised to get treated immediately; in addition, this report also highlighted the importance of strict monitoring in patients with risk factors in order to reduce the morbidity associated with leprosy reaction and increase the patient's quality of life.

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