Journal of Pakistan Association of Dermatologists.2023;**33(1)**:215-219.

Original Article

Risk factors of erythema nodosum leprosum in dermatovenereology outpatients

Nur Rakhmat Mulianto, Fatimah Fitriani, Rieska Widyaswari, Sesia Pradestine

Dermatovenereology Departement, Dr. Moewardi General Hospital/ Faculty of Medicine, Sebelas Maret University, Surakarta, Indonesia.

Abstract

Background Erythema Nodosum leprosum (ENL) is a type 2 hypersensitive reaction mostly affecting multibacillary leprosy types. Understanding the risk factors of ENL progression is necessary to prevent complications and further damage.

Methods A case-control descriptive study on leprosy patients visiting the Dermatovenereology outpatient clinic of Dr. Moewardi Hospital, Surakarta, Indonesia from January 2016 to December 2020. The data taken from medical records of patients were sex, age, education, job, type of leprosy based on WHO or Ridley-Jopling, ENL onset, the length of being on multidrug therapy (MDT), and bacterial index. We analyzed the data statistically with the Chi-Square test and Logistic regression analysis, and the significance was determined with P <0.05.

Results We obtained 98 subjects who were dominated by males (69.4%). Leprosy mostly occurred in subjects aged between 26 and 45 years old (41.8%). Most of our subjects were primary school graduates (47%). Farmers predominated our subjects. Bivariate analysis showed no significant relationship between sex as well as age and ENL (p=0.738 and p=0.244, respectively). ENL significantly related to WHO-based leprosy type, LL as well as BL type, onset of ENL, length of MDT consumption, and bacterial index (p=0.000,p=0.000,p=0.013,p=0.009, and p=0.014, respectively).

Conclusion There was a significant correlation between the occurrence of ENL and WHO type of leprosy, Ridley–Jopling type of leprosy, the onset of ENL, duration of MDT, and Bacterial Index. The most significant relationship was between Ridley–Jopling type of leprosy and the occurrence of leprosy.

Key words
Risk factor, erythema nodosum leprosum, multibacillary.

Introduction

Leprosy is a chronic granulomatous disease due to Mycobacterium leprae, which mainly affects the skin and peripheral nerves.[1] World Health Organization (WHO) classifies leprosy into paucibacillary (PB) and multibacillary (MB).[2] Meanwhile Ridley-Jopling categorized leprosy into tuberculoid leprosy (TT), indefinite tuberculoid leprosy (IT), borderline tuberculoid (BT), borderline-borderline (BB), borderline lepromatous (BL), indeterminant leprosy (IL), and polar lepromatous leprosy (LL).[1]

Erythema Nodosum leprosum (ENL) is a type 2 hypersensitive reaction mostly affecting leprosy types BB and LL.[3,4] Its clinical manifestations are painful multiple erythematous nodules, fever, malaise, fatigue, headache, and pain in the muscles, joints, and bone.[5] Erythema nodosum

Address for correspondence
Dr. Fatimah Fitriani
Dermatovenereology Departement,
Dr. Moewardi General Hospital/
Faculty of Medicine, Sebelas Maret University,
Surakarta, Indonesia.
Email: fatimahfitrianidv@gmail.com

leprosum reaction is a complex problem as it requires hospital admission affecting family finance and the patient's quality of life (QOL).[5-7] This reaction can lead to serious complications, such as permanent nerve damage resulting in deformity and disability. Barboza *et al.* study in Mexico (2020) reported that ENL occurred in 80.8% of patients with leprosy.[8] In Ethiopia, Edessa *et al.* 2017 stated that ENL mostly occurred in LL type (50%).[5] A report from Sanglah hospital, Bali by Saraswati *et al.* showed that during the 2016-2018 period patients suffering from ENL were dominated by MB type (65.7%).[7]

Understanding the risk factors of ENL progression is necessary so that we prevent complications and further damage. Therefore we investigated risk factors that may affect on the occurrence of ENL in leprosy patients.

Methods

We conducted a case-control descriptive study on leprosy patients visiting the Dermatovenereology outpatient clinic of Dr. Moewardi Hospital, Surakarta, Indonesia during the period from January 2016-December 2020.

The data taken from medical records of patients were sex, age, education, job, type of leprosy based on WHO or Ridley-Jopling, ENL onset, the length of being on multidrug therapy (MDT), and bacterial index. We excluded patients whose medical records are incomplete. We analyzed the data statistically with the Chi-Square test and Logistic regression analysis, and the significance was determined with $P < 0.05$.

Results

During the study period, we obtained 98 subjects meeting our inclusion criteria who were dominated by males (69.4%). Leprosy mostly occurred in subjects aged between 26 and 45 years old (41.8%). Most of our subjects were primary school graduates (47%). Farmers predominated our subjects **(Table 1)**.

Bivariate analysis showed no significant relationship between sex as well as age and ENL (p=0.738 and p=0.244, respectively). However ENL significantly related to WHO-based leprosy type, LL as well as BL type, onset of ENL, length of MDT consumption, and bacterial index (p=0.000, p=0.000, p=0.013, p=0.009, and p=0.014, respectively) **(Table 2)**.

Multivariate analysis revealed that leprosy type BL and LL were most significant factor for the occurrence of ENL (p=0.000; OR=0.481; 95% CI=0.192–1.205). Type of leprosy, the onset of ENL, the duration of MDT consumption, and bacterial index were not determinant factors for ENL reaction. However, there is 2 probability of 71.20% of experiencing leprosy reaction if a patient has those four risk factors **(Table 2)**.

Table 1 The demographic characteristics of the study subjects.

Characteristics	*Number (n = 98)*	*Percentage (%)*
Sex		
Male	68	69.4%
Female	30	30.6%
Age		
6-11 years old	2	2.1%
12-25 years old	20	20.4%
26-45 years old	41	41.8%
46-65 years old	29	29.6%
>65 years old	6	6.1%
Education		
Primary	46	47%
Junior High School	41	41.8%
Senior High School	11	11.2%
Occupation		
Student	9	9.2%
Entrepreneur	10	10.2%
Farmer	42	42.8%
Labor	17	17.5%
Housewife	8	8.1%
Employee	12	12.2%

Table 2 Bivariate and Multivariate analysis of risk factors related to ENL

Variable	*Reaction*		*p-value*	*OR*	*CI 95%*
	ENL (+) n=49(%)	*ENL (-) n=49 (%)*			
Sex					
Male	36 (73.4)	32 (65.3)	0.738		
Female	13 (26.6)	17 (34.7)			
Age at diagnosis					
≥ 35 year old	46 (93.9)	42 (85.7)	0.244		
< 35 year old	3 (6.1)	7 (14.3)			
Type of Leprosy WHO					
PB	0 (0)	16 (32.6)	0.000*	0.000	0.000
BB	49 (100)	33 (67.3)			
Ridley – Jopling					
BL	14 (28.5)	28 (57.2)	0.000*	0.481	0.192-1.205
LL	35 (71.5)	21 (42.8			
Onset of ENL					
On therapy	29 (59.2)	0	0.013*	0.000	0.000
Post therapy	20 (40.8)	0			
The Duration of MDT					
> 12 months	15 (30.6)	37 (75.5)	0.009*	0.020	0.004-0.110
≤ 12 months	34 (69.4)	12 (24.5)			
Bacterial Index					
≥ +4	45 (91.8)	17 (34.7)	0.014*	0.347	0.198-0.609
< +4	4 (8.2)	32 (65.3)			
Constant			0.997	6.465	
Nagelkerke R Square			0.712		
P < 0.05 = significant					

Discussion

Leprosy is a chronic infectious disease caused by M. leprae which initially affects peripheral nerves then skin, mucosa, upper airway, reticuloendothelial system, eyes, muscles, and bones. During the course of the disease, leprosy can develop into a reaction in the form of acute episodes occurring prior to, during, or post MDT therapy. Leprosy reaction can be differentiated into two, they are reversal reactions and type 2 leprosy reactions, known as ENL.[7]

Erythema Nodosum Leprosum can affect both sexes though the prevalence is higher in males than females. In this study, ENL was also dominated by males (73.4%). Males have a higher risk of ENL because of their job and physical activities. Leprosy can attack people of all ages, mainly those of productive age. The incidence of leprosy increases along with age and reaches its peak at the age between 20 and 30 years old.[1] Pocatera's study reported the mean age of ENL subjects was 34.7 years old.[9] In our study, ENL was mostly found in patients aged 26-45 years old. Leprosy is caused by M. leprae. The multiplication of M. leprae is slow and the mean incubation period is 5 years. The symptoms may appear in a year, but it may also occur after 20 years, thus the onset is commonly present in adults.[10] This is also related to high mobility and activity as well as external exposure in these groups of people.[9,11]

Type 2 leprosy reaction or ENL is common in MB leprosy and complication of BL and LL types which can be acute or chronic. Its occurrence is associated with the immunological response of the sufferer to infection and high exposure to M. leprae organism.[1,12] in this study, ENL reaction occurred in MB leprosy (100%) with the percentage of 71.5% LL type and

28.5% BL type. ENL reaction occurring in BL and LL types results from an increase in neutrophil apoptosis, in which these neutrophils release TNF-α and IL-8 through the stimulation of lipopolysaccharides (LPS) by M. leprae. Neutrophil as an effector cell actively produces proinflammatory cytokine and it is not only a chemoattractant cell in ENL reaction.[13]

Bacterial index (BI) is one of the risk factors for ENL.[14] High BI can increase the probability of ENL reaction, particularly in LL leprosy type with BI of ≥ 4.

This study supports the previous study by Manandar and Pocaterra which reported that BI ≥4 was a risk factor for ENL.[15,16] We found a significant relation between BI ≥4 and the occurrence of ENL. A high BI level is responded to by the body through the immune system mechanism which eliminates the remained bacterial product excessively. This bacterial product is deemed as M. leprae antigen in the tissue resulting in the elevation of T helper/ T suppressor ratio specifically Th2 which then induces plasma cell formation and immunoglobulin production.[17]

The reaction of ENL can present before, during, and after completing the therapy. In this study, ENL reaction occurred mostly during MDT treatment which is 59.2%. This finding is in line with previous studies by Pocaterra in India and Listyowati in Indonesia which stated that ENL is more commonly found in the third month of MDT therapy than in pre - MDT therapy.[16,18] During treatment, MDT eliminates M. leprae intracellularly, so that the bacteria breakdowns and release antigens. Those antigens proliferate so rapidly that induce incredible reactions in the body in order to eliminate the remained bacterial product of M. leprae.

Multidrug therapy can cure leprosy within months, but this therapy may result in a leprosy reaction. This study revealed that ENL reaction was more common in patients taking MDR for less than a year than those consuming MDT for more than 2 years. This finding is similar to that of the Pocaterra study in India which reported that ENL occurred in patients receiving MDT MB for ≤12 months.[16]

Our statistical analysis obtained a significant relationship between the duration of MDT therapy and ENL occurrence. Since ENL can also appear after completing MDT, thus monitoring leprosy patients is crucial in order to recognize any reaction which may occur, though these patients release from treatment.

This study was limited by several circumstances, such a as lack of complete medical records. This study relied on as it is a retrospective study. It is also a single-center study so it can not represent the general population. The study period is too short for investigating leprosy with ENL reaction.

Conclusion

In conclusion, there was a significant correlation between the occurrence of ENL and risk factors, such as WHO type of leprosy, Ridley–Jopling type of leprosy, the onset of ENL, duration of MDT, and Bacterial Index. The most significant relationship was between Ridley – Jopling type of leprosy and the occurrence of leprosy.

References

1. Salgado, Claudio Guedes., Brito, Arival Cardoso de., Salgado, Ubirajara Imbiriba., Spencer JS. Leprosy. In: Kang, Sewon., Masayuki, Amagai., Bruckner AL, editor. Fitzpatrick's Dermatology in General Medicine. 9 ed. New York: Mc Graw Hill; 2019. hal. 2926–58.
2. Poobalan A. Guidelines for the diagnosis, treatment and prevention of leprosy

[Internet]. New Delhi; 2018. Tersedia pada: http://apps.who.int/iris.

3. Balagon, Marivic., Saunderson, Paul R., Gelber RH. Does clofazimine prevent Erythema Nodosum Leprosum (ENL) in leprosy? A retrospective study, comparing the experience of multibacillary patients receiving either 12 or 24 months WHO-MDT. *Lepr Rev1*. 2011;**82(1)**:213–21.
4. Polycarpou, Anastasia., Walker, Stephen L., Lockwood DNJ. A Systematic Review of immunological Studies of erythema Nodosum Leprosum. *Front Immunol*. 2017;**8(233)**:1–41.
5. Negera, Edessa., Walker, Stephen L., Doni, Shimelis N., Tsegaye, Degafe., Lambert, Saba M., Idriss, Munir H., Tsegay, Yohanis., Dockrell, Hazel M., Aseffa, Abraham., Lockwood DN. Clinico-pathological features of erythema nodosum leprosum: A case-control study at ALERT hospital, Ethiopia. *Plos Negl Trop D*. 2017;**11(10)**:1–13.
6. Sales, Anna Maria., Illarramendi, Ximena., Walker, Stephen L., Lockwood, Diana., Sarno, Euzenir Nunes., Nery J. The impact of Erythema Nodosum Leprosum on health related quality of life in Rio de Janeiro. *Lepr Rev*. 2017;**88(1)**:499–509.
7. Saraswati, Putu Ayu., Rusyati, Luh Made Mas., Karmila ID. Karakteristik Penderita Kusta Multi Basiller (MB) dengan Reaksi Erythema Nodosum Leprosum (ENL) di Poliklinik Kulit dan Kelamin RSUP Sanglah selama Tahun 2016-2018. *Intisari Sains Medis*. 2019;**10(3)**:655–8.
8. Barboza A, Garza J, Lozano J, Pineda R, Gomez L, Zuniga I, *et al*. Leprosy Reactions in Northeast Mexico: Epidemiology and Risk Factors for Chronic Erythema Nodosum Leprosum. *J Eur Acad Dermatol*. 2020;**34(5)**:1–8.
9. Pocaterra, Leonor., Jain, Suman., Reddy, Rajgopal., Muzaffarullah, Syed., Torres, Obdulita., Suneetha, Sujai., Lockwood DNJ. Clinical Course of Erythema Nodosum Leprosum: An 11 Year Cohort Study in Hyderabad, India. *Am J Trop Med Hyg*. 4066;**74(5)**:868–79.
10. Aisyah I AI. Penelitian retrospektif: gambaran pasien baru kusta. *Period Dermatol Venereol*. 2018;**30(1)**:40–8.
11. Quyum, Farhana., Hasan, Mashfiqul., Hury, Wahida Khan Chowd., Wahab MA. Leprosy Reactions: Frequency and Risk Factors. *Clin Dermatol Ther*. 2016;**3(1)**:1–3.
12. Suchonwanit, Poonkiat., Triamchaisri, Siripich., Wittayakornrerk, Sanchawan., Rattanakaemakorn P. Leprosy Reaction in Thai Population: A 20-Year Retrospective Study. *Dermatol Res Pr*. 2015;**2(1)**:1–5.
13. Scollard DM, Martelli CM, Stefani MA, Maroja MF, Villahermosa L, Pardillo F TK. Risk Factors for Leprosy Reactions in Three Endemic Countries. *Am J Trop Med*. 2015;**92(1)**:108–14.
14. Walker SL, Lockwood DN. Leprosy type 1 (reversal) reactions and their management. *Lepr Rev*. 2008;**79(4)**:372–86. Tersedia pada: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19274984
15. Manandhar R, LeMaster JW, Roche PW. Risk factors for erythema nodosum leprosum. *Int J Lepr Other Mycobact Dis*. 1999;**67(3)**:270–8.
16. Voorend, Carlijn G N., Post EB. A Systematic Review on the Epidemiological Data of Erythema Nodosum Leprosum, a Type 2 Leprosy Reaction. *PLoS Negl Trop Dis*. 2013;**7(10)**:2440–8.
17. Balagon, M. V. F., Cellona, R. V., Gelber, R. H., Abalos RM. Reactions Following Completion of 1 and 2 Year Multidrug Therapy (MDT). *Am J Trop Med*. 2010;**83(3)**:637–44.
18. Mohanty KK, Joshi B, Katoch K SU. Leprosy Reactions: Humoral and Cellular Immune Responses to M. leprae, 65kDa, 28kDa, and 18 kDa Antigens. *Int J Lepr*. 2004;**72(2)**:149–58.