Journal of Pakistan Association of Dermatologists. 2024;**34(4)**:1002-1008.

Original Article

Correlation between oral infections occurrence with the severity and type of erythema nodusum leprosum in multibacilar leprosy patients in the outpatient clinic of Dr. Soetomo Hospital, Surabaya from 2017-21

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Abstract

Objective The objective of the study is to determine the correlation between of oral infection occurrence and Erythema Nodusum Leprosum (ENL) severity and type.

Methods This retrospective study was carried out using analytical observational research techniques with a retrospective cross-sectional design with samples taken using a consecutive sampling system in multibacillary (MB) leprosy patients with ENL reactions who were also accompanied by oral infections in the Leprosy Division of Dermatovenereology Department, Dr. Soetomo Hospital, Surabaya in 2017-2021, using secondary data in the form of medical record data.

Results The number of ENL patients with oral infections was 93. The number of male patients was greater than female at 61 (65.6%). Most common oral infection was dental caries with 59 (63.4%) patients. The most common type of ENL was chronic ENL with 50 (53.8%) patients. There was a correlation between dental caries occurrence and chronic ENL (p=0.032, r=0.222) and a correlation between oral gingivitis occurrence with mild ENL (p=0.027, r=0.222). There was a significant correlation between ENL of severity type (p=0.019), regardless of oral infection type, with moderate strength (r=0.243).

Conclusion Dental caries is related to ENL type, while gingivitis is related to ENL severity.

Key words
Leprosy; Erythema nodusum leprosum type; Erythema nodusum leprosum severity; Oral infection.

Introduction

Erythema nodosum leprosum (ENL) is a leprosy type 2 reaction and a severe immunological complication of multibacillary (MB) leprosy, especially lepromatous leprosy (LL) and borderline leprosy (BL).[1] Prevalence for leprosy in Indonesia in 2020 was 0.49 cases/10,000 population and the new case discovery rate was 4.12 cases per 100,000 population and around 86% of them were MB-type leprosy.[2] A previous retrospective study at Dr. Soetomo Hospital reported that leprosy cases were still prevalent. In 2010-2013, it was reported that the number of leprosy patients was 594 with 157 new leprosy patients with ENL.[3] The number of new leprosy patients tend to decrease every year.

Manuscript Received on: June 26, 24
Accepted on: August 10, 2024.
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However, the number of patients experiencing ENL continued to increase. ENL could have a negative impact on the patient's quality of life, economic status, and increase mortality rate.[4]

Based on the severity of symptoms, ENL severity could be divided into two: mild and severe reactions based on ENLIST ENL Severity Scale. ENL type could be classified according to the time it occurs: acute, recurrent, or chronic. Acute ENL is defined as a single episode lasting less than 24 weeks; recurrent ENL type is defined as a second or subsequent ENL episode occurring 28 days or more after stopping ENL treatment; and chronic ENL type is defined as ENL that occurs for 24 weeks or more during which a patient requires treatment for ENL either continuously or includes a treatment-free period of 27 days or less. [5]

Risk factors that could play a role in the incidence, severity, and type of ENL include gender, age, leprosy type, bacterial index (BI), morphological index (MI), nutritional status, and co-infections.[6] Co-infections could overstimulate the immune system through many inflammatory markers.[7] One of the co-infections that could occur in leprosy patients is oral coinfection. This is because *M. leprae* is thought to have an affinity for colder areas for its multiplication. Approximately 75% of intraoral involvement is in the hard palate as the average surface temperature is estimated to be approximately 27.4°C. Approximately 67.7% of leprosy patients had periodontal complaints, 54.8% experienced attrition, 54.8% experienced gingivitis, and 74.2% experienced dental caries and pulpitis.[8]

There is still no study or data in Indonesia regarding the correlation between the oral co-infection occurrence and the severity and type of ENL in leprosy patients This retrospective study aimed to determine the correlation between of oral infection occurrence and ENL severity and type in leprosy patients reported in the Leprosy Division of the Dermatovenereology Outpatient Clinic of Dr. Soetomo Hospital, Surabaya from 2017 to 2021.

Methods

This was an analytical observational study with a retrospective cross-sectional design conducted at Dermatovenereology Outpatient Clinic of Dr. Soetomo Hospital, Surabaya. The study population was MB-type leprosy patients with ENL reactions. The study sample was all populations that met the sample inclusion criteria. The inclusion criteria for this study were all patients recorded in the medical record with a diagnosis of MB-type leprosy accompanied by an ENL reaction and oral infection in the Leprosy Division of the Dermatovenereology Outpatient Clinic of Dr. Soetomo Hospital, Surabaya from 2017 to 2021. The exclusion criteria in this study were incomplete medical record data (no diagnosis from a dental and oral physicist) and ENL patients with oral co-infections who had other types of infections. Sampling was conducted using a consecutive sampling system, obtained from secondary data from medical records of patients who were diagnosed with MB-type leprosy and ENL reactions which were also accompanied by oral infections in the Leprosy Division of the Dermatovenereology Outpatient Clinic of Dr. Soetomo Hospital, Surabaya from 2017 to 2021.

Patient data was taken from manual and electronic medical records of patients who were with MB-type leprosy with an ENL reaction. The data and results obtained were then entered into a data collection sheet for analysis. All data was entered into the computer using Microsoft Excel. Distribution and frequency analysis were conducted using SPSS software. Finally, an analysis was conducted regarding the correlation

between oral infection occurrence and ENL type and severity using the Spearman test. P-value <0.05 indicates a significant correlation.

Results

A total of 93 patients were included, which were mostly men with 61 (65.6%) patients. The total number of patients for each year from 2017 to 2021 was 20, 23, 27, 11 and 12, respectively **(Table 1)**. The most common type of ENL was chronic ENL with 50 patients (53.8%) **(Table 2)**. In terms of ENL severity, most patients had mild ENL severity with 47 (50.5%) patients. However, this result was similar with severe ENL with 46 (49.5%) patients **(Table 3)**. Regarding the type of oral infection, most patients experienced dental caries with 59 (63.4%) patients **(Table 4)**. Analysis of the correlation between oral infection occurrence and ENL type showed that only dental caries was related to ENL type (p=0.032) with moderate strength (r=0.222), whereas dental caries occurrence was related to chronic ENL type **(Table 5)**. Regarding the correlation between oral infection occurrence and ENL severity, overall oral infections were associated with ENL severity (P <0.05) with a moderate correlation (r=0.288). If we look at each type of infection, only gingivitis occurrence was related to ENL severity (p=0.027). Gingivitis occurrence was found mostly in mild ENL with moderate correlation strength (r=0.222) **(Table 6)**. Analysis between ENL severity and type showed that patients with mild ENL were most often found to have acute ENL with 23 patients (62.2%), while most severe ENL patients were found to have chronic ENL type with 31 patients (62%). There was a significant correlation between ENL of severity type (p=0.019), regardless of oral infection type, with moderate strength (r=0.243) **(Table 7)**.

Discussion

In this study, there was a significant correlation between dental caries and ENL type (P-value 0.032 and r=0.222). Dental caries is most common disease in oral cavity. Many bacteria multiply in the oral cavity, but there are only a few bacteria that cause caries. Bacteria are the main pathogens and could cause progressive damage to the tissue under the teeth. These bacteria include *Streptococcus mutans* and

Table 1 Gender distribution.

		Year					*Total*
		2017	*2018*	*2019*	*2020*	*2021*	
Gender	Men	15 (75.0%)	16 (69.6%)	16 (59.3%)	7 (63.6%)	7 (58.3%)	61 (65.6%)
	Women	5 (25.0%)	7 (30.4%)	11 (40.7%)	4 (36.4%)	5 (41.7%)	32 (34.4%)
Total		20 (100%)	23 (100%)	27 (100%)	11 (100%)	12 (100%)	93 (100%)

Tabel 2 ENL type distribution.

		Year					*Total*
		2017	*2018*	*2019*	*2020*	*2021*	
ENL type	Acute	5 (25.0%)	10 (43.5%)	13 (48.1%)	6 (54.5%)	3 (25.0%)	37 (39.8%)
	Recurrent	4 (20.0%)	0 (0.0%)	2 (7.4%)	0 (0.0%)	0 (0.0%)	6 (6.5%)
	Chronic	11 (55.0%)	13 (56.5%)	12 (44.4%)	5 (45.5%)	9 (75.0%)	50 (53.8%)
Total		20 (100%)	23 (100%)	27 (100%)	11 (100%)	12 (100%)	93 (100%)

Table 3 ENL severity distribution.

		Year					*Total*
		2017	*2018*	*2019*	*2020*	*2021*	
ENL severity	Mild	9 (45.0%)	8 (34.8%)	21 (77.8%)	5 (45.5%)	4 (33.3%)	47 (50.5%)
	Severe	11 (55.0%)	15 (65.2%)	6 (22.2%)	6 (54.5%)	8 (66.7%)	46 (49.5%)
Total		20 (100%)	23 (100%)	27 (100%)	11 (100%)	12 (100%)	93 (100%)

Table 4 Frequency of oral types of infections.

		Year					*Total*
		2017	*2018*	*2019*	*2020*	*2021*	
Oral infection	Periodontitis	1 (5.0%)	9 (39.1%)	5 (18.5%)	0 (0.0%)	2 (16.7%)	17 (18.3%)
	Dental caries	18 (90.0%)	12 (52.2%)	16 (59.3%)	7 (63.6%)	6 (50.0%)	59 (63.4%)
	Radix gangrene	1 (5.0%)	2 (8.7%)	2 (7.4%)	0 (0.0%)	1 (8.3%)	6 (6.5%)
	Gingivitis	0 (0.0%)	0 (0.0%)	4 (14.8%)	4 (36.4%)	3 (25.0%)	11 (11.8%)
Total		20 (100%)	23 (100%)	27 (100%)	11 (100%)	12 (100%)	93 (100%)

Table 5 Correlation between oral infection occurrence and ENL type.

	ENL type			*Total*	*P value*
	Acute	*Recurrent*	*Chronic*		
Non-periodontitis	33 (89.2%)	6 (100%)	37 (74.0%)	76 (81.7%)	0.059
Periodontitis	4 (10.8%)	0 (0.0%)	13 (26.0%)	17 (18.3%)	
Non-dental caries	10 (27.0%)	0 (0.0%)	24 (48.0%)	34 (36.6%)	0.032*
Dental caries	27 (73.0%)	6 (100%)	26 (52.0%)	59 (63.4%)	r=0.222
Non-radix gangrene	36 (97.3%)	6 (100%)	45 (90.0%)	87 (93.5%)	0.161
Radix gangrene	1 (2.7%)	0 (0.0%)	5 (10.0%)	6 (6.5%)	
Non-gingivitis	32 (86.5%)	6 (100%)	44 (88.0%)	82 (88.2%)	0.883
Gingivitis	5 (13.5%)	0 (0.0%)	6 (12.0%)	11 (11.8%)	

*= significant.

Lactobacilli. Caries could occur at all ages.[12] TNF-α could be detected in the saliva and gingival fluid of individuals with dental infections. Other studies also showed that IL-6 and TNF-α were identified in leprosy patients with dental infections, and similar study also showed that in ENL patients with periodontal disease showed significant IFN-γ and IL-1β. Development and further planning of molecular and chemical biomarkers that have predictive and prognostic value could help early detection/identification of patients with an increased risk of dental infection in leprosy patients.[13]

Overall oral infections were associated with ENL severity (P <0.05) with a moderate correlation (r=0.288). Furthermore, there was a significant correlation between gingivitis occurrence and ENL severity, where gingivitis was found more common in mild severity (p-value 0.027 and r=0.222). Gingivitis is a type of inflammatory disease that is limited to the gingiva without further damage to the tissue supporting the teeth. Gingivitis is the most common dental disease after dental caries. Factors that could cause gingivitis might be due to the buildup of plaque on the surface and include bacterial, fungal, viral infections, genetic lesions, and several mucocutaneous disorders that manifest as gingival inflammation.[14] The results of this study could be due to the possibility that a person with ENL, whether they have dental symptoms or not, will delay dental control or examination. This results in delayed treatment. The incidence of mild and severe ENL were similar in this study. ENL patients with oral infections might not think it is a serious problem because there are no significant symptoms. Many people still consider treatment for oral infections only when there are complaints of toothache. The difference in results with previous studies, which reported moderate cases as the most cases, could be caused by the use of different criteria. There is a possibility that what is referred to as moderate in this study could actually be categorized as mild if using the assessment criteria in this study. Patients who are known to have an oral infection must have regular check-ups and also be reminded to have them checked or treated. Patients are also always given information and

Table 6 Correlation between oral infection occurrence and ENL severity.

	ENL severity		*Total*	*P value*
	Mild	*Severe*		
Non-periodontitis	42 (89.4%)	34 (73.9%)	76 (81.7%)	0.055
Periodontitis	5 (10.6%)	12 (26.1%)	17 (18.3%)	
Non-dental caries	18 (38.3%)	16 (34.8%)	34 (36.6%)	0.728
Dental caries	29 (61.7%)	30 (65.2%)	59 (63.4%)	
Non-radix gangrene	43 (91.5%)	44 (95.7%)	87 (93.5%)	0.419
Radix gangrene	4 (8.5%)	2 (4.3%)	6 (6.5%)	
Non-gingivitis	38 (80.9%)	44 (95.7%)	82 (88.2%)	0.027*
Gingivitis	9 (19.1%)	2 (4.3%)	11 (11.8%)	r=0.222

*= significant.

Table 7 Correlation between ENL severity and type.

		ENL type			*Total*	*Nilai p*
		Acute	*Recurrent*	*Chronic*		
ENL severity	Mild	23 (62.2%)	5 (83.3%)	19 (38.0%)	47 (50.5%)	0.019*
	Severe	14 (37.8%)	1 (16.7%)	31 (62.0%)	46 (49.5%)	r=0.243
Total		37 (100.0%)	6 (100.0%)	50 (100.0%)	93 (100.0%)	

*= significant.

education about dental and oral hygiene, hence oral infections do not get worse and minimize the occurrence of repeated ENL reactions and ENL occurrence does not last longer.

The results of this study showed that the most patients had recurrent ENL (83.3%), followed by the acute ENL type and the chronic ENL type. In patients with severe ENL, most of them had chronic ENL type (62%), followed by the acute and recurrent ENL. In addition, there was a significant correlation (p=0.019 and r=0.234) between ENL severity and type in all oral infection patients, without differentiating between each type of oral infection. A cohort study by Pocaterra *et al.* in Hyderabad, India, for 11 years reported that in acute ENL patients, the majority had moderate ENL with 27 patients (60%). Chronic ENL patients in their study also mostly had moderate ENL with 32 patients (71.1%).[15] Study by Indrawati *et al.* reported that in chronic ENL patients, most patients had moderate ENL with 32 patients (71.1%) and 13 patients had severe ENL (28.9%). However, they reported no correlation between ENL severity with acute and chronic ENL patients (p=0.130).[10] MDT could kill intracellular mycobacteria, which break down and release antigens. This antigen could form immune complexes that cause ENL. Recurrent ENL is more commonly found in mild degrees than severe degrees. This could be because the patient has finished undergoing treatment, but within a period of ≥28 days a recurrence occurs. In patients who have completed reaction treatment, clinical symptoms also decrease. This was also reported by Motta *et al.* regarding the improvement in inflammatory markers IL-1, TNF-α, IL-6, IFN-γ and IL-10 after treatment. A small percentage of patients do not receive treatment for their oral infections, so the inflammatory process still remains, so this could become a serious ENL reaction and prolong the reaction.[16]

There were several limitations in this study. Not all ENL patients with oral infections went to the dentist. Patients with oral infections could occur before leprosy reaction occurred or even before leprosy was diagnosed. Patients might not continue treatment or changed the location of treatment, hence ENL and oral infection occurrences could not be evaluated. Several patients also had other infections or other comorbid factors, so they were not included in the inclusion criteria.

Conclusion

Dental caries is related to ENL type, while gingivitis is related to ENL severity. There is also correlation between ENL severity and type. Further study comparing leprosy patients with and without ENL accompanied by oral infections needs to be carried out to assess differences in ENL severity and type after dental and oral treatment. Further studies on leprosy patients with ENL needs to be carried out on other types of infections.

Ethical Approval: This study was approved by the Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya. (1365/LOE/301.4.2/VII/2023).

Declaration of patient consent The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship None.

Conflict of interest Authors declared no conflict of interest.

Author's contribution

DNK: Substantial contribution to study design, acquisition of data, manuscript writing, has given final approval of the version to be published.

MYL: Substantial contribution to analysis and interpretation of data, critical review, has given final approval of the version to be published.

CRSP, DY, MDA: Substantial contribution to analysis and interpretation of data, critical review, has given final approval of the version to be published.

BU: Substantial contribution of concept, study design, critical review, has given final approval of the version to be published.

References

1. Bhat RM, Vaidya TP. What is New in the Pathogenesis and Management of Erythema Nodosum Leprosum. Vol. 11, Indian Dermatology Online Journal. Wolters Kluwer Medknow Publications; 2020. p. 482–92.
2. Kementerian kesehatan nasional. Pedoman nasional pelayanan kedokteran tata laksana kusta. Jakarta; 2020.
3. Pratamasari MA, Listiawan MY. Studi Retrospektif: Reaksi Kusta Tipe 1 (Retrospective Study: Type 1 Leprosy Reaction). *J Unair*. 2015;137–43.
4. Walker SL, Balagon M, Darlong J, Doni SN, Hagge DA, Halwai V, *et al*. ENLIST 1: An International Multi-centre Cross-sectional Study of the Clinical Features of Erythema Nodosum Leprosum. *PLoS Negl Trop Dis*. 2015;**9(9)**:e0004065.
5. Walker SL, Sales AM, Butlin CR, Shah M, Maghanoy A, Lambert SM, *et al*. A leprosy clinical severity scale for erythema nodosum leprosum: An international, multicentre validation study of the enlist ENL Severity Scale. *PLoS Negl Trop Dis*. 2017;**11(7)**: e0005716.
6. Wankhade VH, Debnath P, Singh RP, Sawatkar G, Bhat DM. A retrospective study of the severe and uncommon variants of erythema nodosum leprosum at a tertiary health center in central India. *Int J Mycobacteriol*. 2019;**8(1)**:29–34.
7. Motta ACF, Pereira KJ, Tarquínio DC, Vieira MB, Miyake K, Foss NT. Leprosy reactions: Coinfections as a possible risk factor. *Clinics*. 2012;**67(10)**:1145–8.
8. Bommanavar S, Hosmani J, Khan S, Bhandi S, Patil S, Alamir AWH, Sarode S, Awan KH. Current updates on dental perspectives of leprosy-Revisited. *Dis Mon*. 2020;**66(7)**:100918.
9. Fransisca C, Zulkarnain I, Ervianti E, Sari M, Denisa Alinda M, Haryo Kusumaputra B, *et al*. A Retrospective Study: Epidemiology, Onset, and Duration of Erythema Nodosum Leprosum in Surabaya, Indonesia. 2020.
10. Indrawati D, Astari L, Hidayati AN, Sawitri, Damayanti, Utomo B, *et al*. Risk Factors of Acute and Chronic Erythema Nodosum Leprosum in Dr. Soetomo General Academic Hospital Surabaya. *Pharmacog J*. 2022;**14(6)**:766–70.
11. Motta ACF, Simão JCL, Furini RB, Ferreira MAN, Palma PVB, Komesu MC, *et al*. Oral coinfection can stress peripheral lymphocyte to inflammatory activity in leprosy. *Rev Soc Bras Med Trop*. 2013;**46(1)**:73–8.
12. Gao L, Xu T, Huang G, Jiang S, Gu Y, Chen F. Oral microbiomes: more and more importance in oral cavity and whole body. *Protein Cell*. 2018;**9(5)**:488-500.

13. Cortela DC, de Souza Junior AL, Virmond MC, Ignotti E. Inflammatory Mediators of Leprosy Reactional Episodes and Dental Infections: A Systematic Review. *Mediators Inflamm*. 2015;**2015**:548540.
14. Ashraf F. Fouad, Asma A. Khan. Etiology and Pathogenesis of Pulpitis and Apical Periodontitis. Essential Endodontology: Prevention and Treatment of Apical Periodontitis. 2019;**3**:59–90.
15. Pocaterra L, Jain S, Reddy R, Muzaffarullah S, Torres O, Suneetha S, *et al*. Clinical course of erythema nodosum leprosum: an 11-year cohort study in Hyderabad, India. *Am J Trop Med Hyg*. 2006;**74(5)**:868-79.
16. Motta AC, Furini RB, Simão JC, Ferreira MA, Komesu MC, Foss NT. The recurrence of leprosy reactional episodes could be associated with oral chronic infections and expression of serum IL-1, TNF-alpha, IL-6, IFN-gamma and IL-10. *Braz Dent J*. 2010;**21(2)**:158-64.