

Correlation between serum interleukin-6 levels and the severity of Enlist ENL Severity Scale (EESS) in Erythema Nodosum Leprosum (ENL) patients



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Received: 2023-09-27
Accepted: 2023-12-08
Published: 2024-01-03

ABSTRACT

Introduction: Leprosy is a chronic infection caused by *Mycobacterium leprae* (*M. Leprae*) which no biological examination can yet be appointed as an early marker. This research is aimed to analyze the correlation between serum IL-6 levels and the severity of the ENLIST ENL Severity Scale (EESS) in ENL.

Methods: A cross-sectional study was conducted on all leprosy patients with ENL who sought treatment at the Dermatology and Venereology Polyclinic, North Sumatra University Hospital, dr. Pirngadi General Hospital, and H. Adam Malik General Hospital Medan. ENL patients who were uncooperative, with infectious, autoimmune, malignant diseases, or who were pregnant or breastfeeding were excluded. Data processing was carried out with the help of statistical software with a significance value <0.05 .

Results: A total of 40 ENL patients were studied. The mean age of the patients was 33.10 ± 12.23 years, male (70%), high school (75%), and not working (95%). The degree of severity based on mild EESS was more dominant than severe, namely 57.5% vs 42.5%, respectively. The median IL6 level was 64.65 ± 34.06 in ENL patients and was higher in severe compared with mild EESS, namely 105.18 ± 24.14 versus 50.08 ± 16.84 , respectively ($p=0.103$, $p=0.167$, respectively). There was a very strong and significant positive correlation between serum IL6 levels and EESS ($r: 0.813$ and $p<0.05$).

Conclusion: There was a correlation between serum IL6 levels and EESS. Further study is needed in measuring serum IL6 levels to detect early severity of ENL.

Keywords: Erythema Nodosum Leprosum, leprosy reaction, IL6, ENLIST ENL Severity Scale.

Cite This Article: Nahrisyah., Lubis, R.D., Siregar, R. 2024. Correlation between serum interleukin-6 levels and the severity of Enlist ENL Severity Scale (EESS) in Erythema Nodosum Leprosum (ENL) patients. *Bali Medical Journal* 13(1): 373-376. DOI: 10.15562/bmj.v13i1.5001

INTRODUCTION

Leprosy is a chronic infection caused by *Mycobacterium leprae* (*M. Leprae*) which usually attacks the skin and peripheral nerves with accompanying symptoms of loss of sensation and motor disorders. It is an acid-fast bacilli (AFB) that lives and proliferates at temperatures of 27–30 °C. The incubation period of *M. leprae* varies between several weeks to 20 years with an average duration of 5–7 years.¹⁻⁴

Based on a data from the World Health Organization (WHO), 202,256 new cases were reported in 118 countries (26.0/1,000,000 population) in 2019, including India, Brazil and Indonesia which accounted for 79% of all new cases and the total number of cases that have been reported. India had 65,147 cases, Brazil had 17,979 cases, and Indonesia which was in third place had 11,173 cases.³

In Indonesia, the number of new cases of leprosy in the past ten years has relatively decreased. The leprosy prevalence rate in Indonesia is 0.49 cases/10,000 population and new cases are 4.12 cases/100,000 population in 2020. It was reported that in 2020 there were 11,173 new cases of leprosy, 85% of which were of the multi bacillary (MB) type. One of the indicators used to show success in detecting new cases of leprosy early is the level 2 disability rate. The level 2 disability rate in 2020 is 2.32/1,000,000 population, this figure tends to decrease every year. This illustrates that case discovery is getting earlier and delays in case handling can be prevented.⁴

Study at the Haji Adam Malik Medan General Hospital in 2015–2018, recorded 79 cases of leprosy patients who had received treatment, with a percentage of 48.1% of the total number of cases

being patients with leprosy reactions. The percentage of patients with type 2 leprosy reactions who had received treatment during that time was 41.8%. Based on other study regarding a retrospective study of leprosy patients in 2015–2017 at Dr. Soetomo Surabaya, 385 new leprosy patients were recorded, 86.2% were MB leprosum patients and 28.8% of the percentage of new MB type patients had type 2 leprosy reactions or erythema nodosum leprosum (ENL).^{3,4}

The widely reported incidence of ENL has become a concern for researchers to discuss ENL further. Disability in leprosy sufferers is caused by damage to the peripheral nerves and the leprosy reaction is one of the triggers for nerve damage. A leprosy reaction is an immunological process that occurs either before, during or after treatment. The leprosy reaction is an acute inflammatory process that

manifests in the skin and nerve tissue, which can cause disability. There are two types of leprosy reactions, namely type 1 (Reversal Reaction/RR) and type 2/ENL.^{1,4}

There is a scoring system to assess the severity of ENL. ENLIST ENL Severity Scale (EESS) proposed by Walker et al., in 2016, which was then modified by them into a 10-point severity scale in 2017. With an EESS score if ≤ 8 it is said to be mild and if the score is > 8 it is said to be severe.⁵

Vilani et al., explained that IL-6 will increase in severe ENL.⁶ In this study, the correlation between severity level of EESS and IL-6 levels will be investigated. Until now there is still no biological examination that can be an early marker. It is hoped that a study on IL-6 in ENL patients can detect ENL earlier so that treatment can be carried out more quickly before the situation gets worse and causes complications, especially disability in ENL patients.^{5,7,8}

METHODS

Patients and study design

This was a cross sectional study with consecutive sampling methods involving 40 patients at Universitas Sumatera Utara General Hospital from October 2020 to November 2023. The inclusions criteria were leprosy patients with ENL, aged ≥ 18 years old, and signed informed consent. The exclusions criteria were uncooperative ENL patient; had co-infection with pulmonary tuberculosis, COVID-19 and other inflammation due to infections, viruses, bacteria and fungi; had autoimmune diseases such as rheumatoid arthritis; had malignancy; and pregnant or breastfeeding. This study was approved by the Research Ethics Commission of the Faculty of Medicine Universitas Sumatera Utara and Universitas Sumatera Utara General Hospital with a number 204/UNS.5.4.1.1.2/KPM/2023.

Study procedure

This study was conducted at the Dermatology and Venereology Outpatient Department, North Sumatra University General Hospital, dr. Pirngadi General Hospital and the Haji Adam Malik Medan General Hospital. Blood samples for evaluation of IL-6 levels were carried out at the Integrated Laboratory, Faculty of

Medicine, University of North Sumatra, Medan. History taking and physical examination was done. Diagnosis of ENL was established through history taking and dermatological examination. ENLIST ENL severity scale was assessed by physical examination.

Statistical analysis

The correlation of serum IL-6 levels with the severity of ENL was analyzed using the Spearman test. The correlation coefficient obtained will be used to measure the strength of the correlation between the two variables. The $p < 0.05$ was considered statistically significant.

RESULTS

The characteristics of ENL were presented in **Table 1**. The largest age range for ENL patients were 18–25 (35%). It was found more frequently in men, namely 28 patients (70%), compared to 12 women patients (30%). The highest education level was high school (SMA), namely 30 patients (75%), followed by elementary school (SD), 6 patients (15%), and junior high school (SMP), amounting to 4 patients (10%). Jobless was frequently

found in ENL patients, namely 38 patients (95%) compared to working, namely 2 patients (5%). Mild degree of severity in ENL patients was more dominant, namely 23 patients (57.5%), compared to a severe degree of severity, namely 17 patients (42.5%) based on EESS. The average of IL-6 levels in ENL was 64.65 pg/mL (range 25.89 to 169 pg/mL) (**Table 2**).

The characteristics of IL-6 levels based on EESS are presented in **Table 3**. It was reported that IL-6 levels were higher in severity compared to mild EESS, namely 105.18 ± 24.14 pg/mL compared to 50.08 ± 16.84 pg/mL. The distribution of data was considered normal based on the Shapiro Wilk test for mild and severe EESS ($p = 0.167$ and $p = 0.103$). A significant correlation was found between IL-6 levels and the severity of EESS ($p < 0.05$) in **Table 4**. The correlation strength value (r) produced between IL-6 levels and the severity of EESS was 0.813, indicating a very strong positive correlation between IL-6 levels and the severity of EESS. A positive correlation shows that the higher the IL-6 levels, the more severe the severity of EESS in ENL patients.

The relationship between serum IL-6 levels and the severity of ENL based on

Table 1. Characteristic of ENL patients

Variable	n	%
Age (Years)		
18–25	14	35
26–35	11	27.5
36–45	8	20
46–55	6	15
66–75	1	2.5
Gender		
Male	28	70
Female	12	30
Education		
Elementary school	6	15
Junior high school	4	10
High school	30	75
Employment		
Work	2	5
Jobless	38	95
EESS		
Mild	23	57.5
Severe	17	42.5

Table 2. Characteristic of ENL patients based on IL-6 levels

Variable	Median	Minimum	Maximum
IL-6 (pg/mL)	64.65	25.89	169

EESS could also be seen using a scatter plot. The dots on the graph will represent each study subject, with x and y coordinates representing serum IL-6 levels and ENL severity based on EESS. By looking at the pattern of dots, it can be concluded that the correlation between these two variables is very strong (as in Figure 1).

DISCUSSION

Walker et al., found something in line with this study, that the age range for ENL was 12–73 years. The majority of ENL were male, with a ratio between males and females of 2.8:1.⁹ A study carried by Melo et al., also reported that the prevalence of ENL was at ages 18–30 years (23.1%) and 31–49 years (42.3%). The cause may lie in its social and economic impact, as ENL strikes individuals at an age when they are at the peak of their working capacity. The prevalence of ENL was higher in men, namely 17 people (65.4%) and 9 women (34.6%). The prevalence of ENL was higher in men because they were more likely to be infected with multibacillary leprosy and seek medical help when it is already severe so it is diagnosed at a late stage of the disease. As many as 13 patients (50%) reported not having completed elementary school, five (19.2%) had completed high school, three (11.5%) had not completed high school, three (11.5%) were illiterate, and two (7%) had studied until the end of elementary school. So, it could be concluded that patients with ENL generally have a low level of education.¹⁰

Until this study was carried out, there was still no study discussing the relationship between ENL and patient's work. Factors that cause many ENL patients to experience difficulty in maintaining employment involve aspects of health and stigma. Erythema nodosum leprosum (ENL) causes nerve damage to the extremities, such as the hands and feet, resulting in physical limitations that affect the ability to carry out certain jobs that require motor skills. The social stigma against leprosy in society can exacerbate this condition, with discrimination and rejection in the work environment. In addition, a lack of understanding about leprosy can create uncertainty and fear that prevents leprosy patients, especially ENL patients, from entering the work

Table 3. Characteristic of IL-6 levels based on EESS and normality test

IL-6 (pg/mL)	EESS	
	Mild	Severe
Mean	50.08	105.18
Standard deviation	16.84	24.14
Minimum	25.89	56.21
Maximum	94.90	169
p*	0.167	0.103

*Shaphiro Wilk

Table 4. Correlation between IL-6 levels and EESS in ENL

IL-6	EESS	
	p*	r
IL-6	0.000	0.813

*Spearman's rho

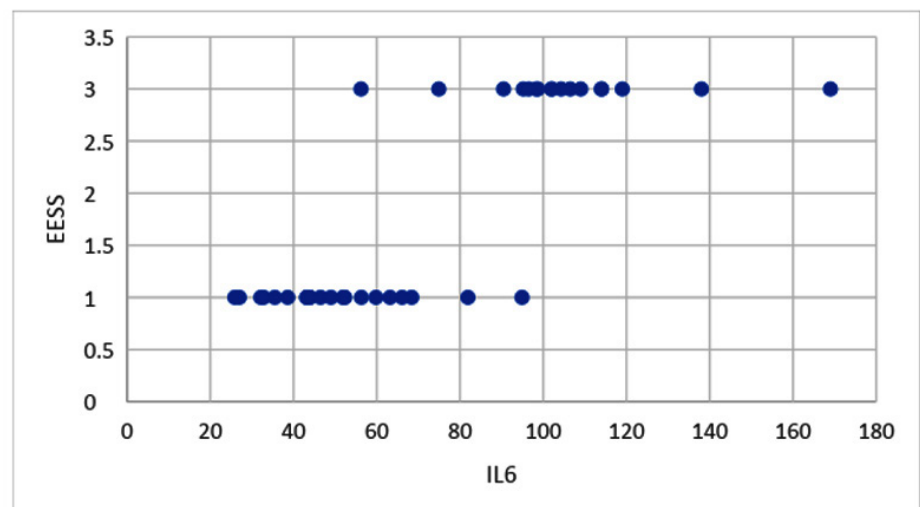


Figure 1. Scatter plot graph

environment. Overcoming this challenge requires a comprehensive approach through community education efforts about leprosy, social support and policies that support leprosy patients in the workplace.^{2,11,12}

Study conducted by Walker et al., found that the mild EESS score was obtained by 65 patients and for the moderate-severe category by 145 patients. The ENLIST ENL Severity Scale aims to increase understanding of the causal mechanisms of ENL, provide more information to support decision making in the management of individuals with ENL, and increase the availability of effective therapy.¹³

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that promotes neutrophil maturation and activation

and stimulates antibody production. Neutrophilic infiltration was involved in the early phase of the ENL reaction and decreased progressively over 9 days, representing the transition from the acute phase to the regressive phase of the reaction. Furthermore, because IL-6 is synthesized in response to infection or tissue damage and stimulates the production of acute phase proteins in hepatocytes, it is possible that the decrease in serum IL-6 levels observed in patients who have received treatment is related to the regression of the inflammatory process.⁶

Serum IL-6 receptors increase significantly at the onset of ENL and decrease after therapy.¹⁴⁻¹⁶ Interleukin-6 is a pro-inflammatory cytokine that

stimulates the activation of lymphocytes to form immune complexes that activate complement C3. This triggers a response from neutrophils and TNF- α and provides a signal to macrophages due to stimulation from *M. Leprae*. Interleukin-6 works early in the occurrence of ENL and this is a consideration for becoming a biomarker.¹⁶

Stefani et al., evaluating serum IL-6 levels in ENL showed conflicting results, with some studies reporting increased levels, similar to our findings. While Iyer et al., reported no association between IL-6 and ENL. Sales et al., revealed an association of single nucleotide polymorphisms in the IL-6 gene with ENL, with increased serum IL-6 levels, consistent with our findings. To further support this hypothesis, we observed an association between IL-6 and the severity of ENL reactions, with higher serum IL-6 levels in patients with severe ENL than in patients with mild reactions.^{6,17-19}

Vilani et al. explained that IL-6 levels will increase in severe ENL.⁶ This was in line with this study which found that there is a very strong and significant positive correlation between IL-6 levels and EESS values. Apart from that, until this study was carried out, there were still few journals discussing the relationship between IL-6 levels and EESS.

CONCLUSION

A correlation between serum IL6 levels and EESS was observed in this study. Further study is needed in measuring serum IL6 levels to detect early severity of ENL.

ACKNOWLEDGEMENTS

We want to express gratitude to the Head Department of Dermatology and Venereology of Faculty of Medicine Universitas Sumatera Utara and Universitas Sumatera Utara Hospital.

CONFLICT OF INTEREST

None to declare

ETHICS CONSIDERATION

This study was approved by the Research Ethics Commission of the Faculty of Medicine Universitas Sumatera Utara and Universitas Sumatera Utara General Hospital with a number 204/UNS.5.4.1.1.2/KPM/2023.

FUNDING

No specific funding was received for this study.

AUTHORS' CONTRIBUTION

All members have contributed equally to the writing of this manuscript.

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