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CORRELATION BETWEEN INTERLEUKIN 10 SERUM LEVELS AND SEVERITY OF PERIPHERAL NEUROPATHY IN MULTIBACILLARY LEPROSY PATIENTS

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ABSTRACT

Background: Leprosy is a chronic infectious peripheral neuropathy caused by Mycobacterium leprae. Clinical presentations of leprosy neuropathy are obtained when the nerve damage is more than 30% of peripheral nerve fibers. The anti-inflammatory property of interleukin 10 is supposed to protect tissue from the damage caused by proinflammatory cytokines. Instead, it causes extensive nerve damage due to suppression of the cellular immune system, failure of forming granuloma to limit the growth of Mycobacterium leprae. As a result, it multiplies and spreads. **Purpose:** To analyze the correlation between interleukin levels 10 serum and the severity of peripheral neuropathy. **Methods:** A cross-sectional research on 30 subjects with multibacillary leprosy aged 18-65 at the Neurology Department of Kelet Hospital Jepara from September to October 2021. The questionnaire was used to collect data of the patients. Interleukin level 10 serum evaluation is assessed by examining blood serum. Data analysis used Spearman Correlation Test. The significant result occurs if it is $p<0.05$. **Results:** Patients with multibacillary leprosy are mostly men (73.3%). There is also a strong significant correlation between interleukin 10 levels and the severity of peripheral neuropathy ($p<0.001$) with rho (0.7). **Conclusion:** There is a strong and significant correlation between serum interleukin 10 levels and the severity of peripheral neuropathy in multibacillary leprosy

Keywords: multibacillary leprosy, interleukin 10, peripheral neuropathy

BACKGROUND

Leprosy is a chronic granulomatous infectious disease caused by obligate intracellular Mycobacterium leprae with low virulence and high affinity for Schwann cells. Leprosy is an infectious disease that still gets special attention from World Health Organization (WHO), especially in developing countries. The registered global prevalence of leprosy was 192,713 cases (0.25 / 10,000 population) at the end of 2017, increased to 20.765 compared to 2016. 60% of leprosy patients were multibacillary (MB). The number of visits by MB leprosy patients at RSUD Kelet Jepara is more than PB [1,2,3]

Indonesia has achieved the national level of leprosy elimination (prevalence rate <1/10,000 population) in 2000, according to the global leprosy elimination target mandated by WHA (World Health Assembly) in 1991. The prevalence rate of leprosy in Indonesia has decreased from 5.2 per 10,000 population in 1981 to 0.9 per 10,000 population in 2000. However, from 2001 until now, the epidemiological situation of leprosy in Indonesia is static, with the number of new leprosy patients found in the range of 17,000-20,000 per year, although an increasing trend of leprosy patients with a grade 2 disability is more than 10%. [4,5]

Peripheral neuropathy in leprosy patients involves sensory nerves, motoric nerves, and autonomic nerves. Clinical manifestations are needed when nerve damage is more than 30% of the peripheral nerve fibers. ENMG examination can identify mononeuropathy or polyneuropathy; axonal neuropathy, demyelinating type, or mixed type (axonal-demyelinating), confirming the early diagnosis of neuropathy and detecting the involvement of damaged nerves early. The early diagnosis can minimize the risk of leprosy defections. Leprosy neuropathy depends on the patient's immune response and expresses itself as a focal or multifocal neuropathy with asymmetric involvement. Leprosy neuropathy chronically evolving may develop a repeated period of exacerbations during type 1 or type 2 reactions and lead to neuropathy. The ulnar nerve, sural nerve, and peroneus nerve are the most commonly affected nerves in leprosy. There are various ways to determine the severity of leprosy neuropathy, and in this study, we used a scoring system[6, 7,8,9]

Th2 cells, Th3 cells, monocytes, dendritic cells, eosinophils, mast cells, and keratinocytes produce Interleukin-10. IL-10 acts on active macrophages to terminate the response toward the microbe and return the system to a resting state. Interleukin 10 is a cytokine with anti-inflammatory properties that plays an important role in limiting the host immune response to pathogens, preventing host tissue damage while maintaining normal tissue homeostasis. Multibacillary leprosy, which has a higher level of interleukin 10 than paucibacillary leprosy and interleukin 10 is a dominant cytokine found in MB. The anti-inflammatory properties of interleukin 10, which are supposed to protect tissues from damage caused by proinflammatory cytokines, evidently cause widespread nerve damage due to suppression of the cellular immune system, failure to form granulomas, and failure to limit the growth of Mycobacterium leprae. As a result, the bacterias multiply and spread. [10,11, 12]

The research on cytokine levels and neurological examination in leprosy is often done separately. Hence, the authors are interested in seeing the correlation between interleukin level 10 serum and the severity of peripheral neuritis in multibacillary leprosy.

METHODS

The research used the method of an observational study with non-invasive neuropathy measurement and venous blood sampling to examine interleukin level 10. This study is a cross-sectional study with purposive sampling as the method of study. The subjects of this study were multibacillary leprosy patients in the outpatient installation of RSUD Kelet Jepara who met the inclusion and exclusion criteria. Inclusion criteria were patients with a diagnosis of multibacillary leprosy under treatment, aged 18-65, agreed to participate in the study and signed the informed consent of the study. Meanwhile, the exclusion criteria were that the patient had diabetes mellitus, nerve injury, or other severe infection and was not experiencing a leprosy reaction, either type I or type II. Diagnosis of the severity of peripheral neuropathy is by examining the sensory and motor ulnar nerves, peroneus nerves, and sural nerves, then scoring: axonal lesions score 2, mixed lesions 1, demyelinating lesions 0.5. Mild neuropathy score 0.5-5.2, moderate score 5.3-10.4, severe score more than 10.4.

This research had been approved by the Ethics Commission of dr. Kariadi Hospital Semarang with the serial number 358/EC/KEPK/FK-UNDIP/IX/2021 dated 15 September 2021. Patients were selected based on inclusion and exclusion criteria, then given informed consent. The research started by having anamnesis and a physical examination of the patients. Then they had to fill out a questionnaire and did the electromyography examination and take a blood sample for serum IL 10 examination.

The data collected from the patients was checked thoroughly, followed by cleaning, coding, editing, tabulating, and restoring it into the computer using the IBM SPSS Statistics for Windows version 26 programs. Data analysis included descriptive statistics and hypothesis testing.

Data analysis is divided into two stages: descriptive statistics and analytical statistics. Descriptive statistics is to determine the basic characteristics of the research object. Nominal scale variables are described by frequency distribution (n) and percentage (%), and numerical variables are described by mean and median. The results are presented in the form of tables and graphics.

Bivariate analysis is used to determine the correlation between interleukin 10 serum levels and the severity of peripheral neuropathy using the bivariate test with the Spearman correlation test, with a 95% confidence level. It is considered significant when p is <0.05.

RESULTS

Characteristics of Research Subjects

Table 1. IL 10 serum of research subjects

No. Subject	IL 10 serum level
1.	17.67
2.	422.02
3.	44.29
4.	37.19
5.	51.27
6.	47.46
7.	50.25
8.	44.61
9.	62.59
10.	84.27
11.	53.86
12.	56.23
13.	49.83
14.	49.42
15.	31.97

16.	60.44	24.	763.59
17.	57.73	25.	45.71
18.	39.36	26.	596.06
19.	49.37	27.	132.30
20.	57.47	28.	380.12
21.	62.03	29.	731.64
22.	168.06	30.	43.13
23.	50.63		

Tabel 2. Characteristics of research subjects

Variable	F	%	Mean ± SD	Median (Min-Max)
Gender				
Male	22	73,3		
Female	8	26,7		
Age			42,13± 14,69	42 (20-64)
Education				
No School	1	3,3		
Elementary School	13	43,3		
Junior High School	6	20,0		
Senior High School	10	33,3		
Onset				
< 6 months	1	3.3		
6 months – 1 year	8	26,7		
> 1 year	21	70,0		
MDT Administration Time				
< 6 months	5	16,7		
> 6 months	25	83,3		
IL 10			144,7±209,7	52,6 (17,7-763,6)
Severity Level				
Peripheral Neuropathy				
Mild	7	23,3		
Moderate	14	46,7		
Severe	9	30,0		

Taken from Table 1, it is concluded that in this study the most patients with multibacillary leprosy are male (73.3%) with an average age of 42, with the youngest patient being 20 years old and the oldest being 64 years old, having elementary school diploma, (43.3%), having a disease onset more than 1 year with a duration of MDT > 6 months (83.3%) and are in moderate severity. The average level of Interleukin 10 in this study is 144,7 with the lowest being 17.7 and the highest being 763.6.

Correlation between Serum Interleukin 10 and the Severity of Peripheral Neuropathy

Table 3. Correlation of Serum Interleukin 10 with Severity of Peripheral Neuropathy

Variable	Rho	P	Meaning
The severity of peripheral neuropathy	0,700	0,001	Significant

From table 2, the correlation between serum interleukin 10 and the severity of peripheral neuropathy analyzed by using Spearman's analysis shows significant results where $p < 0.05$ ($p = 0.001$), with a strong strength of $rho > 0.6$ ($rho = 0.7$). The hypothesis that there is a correlation between Serum Interleukin 10 and the severity of peripheral neuropathy is acceptable.

DISCUSSION

In this study, it is shown that there are more males than females with multibacillary leprosy with a ratio of 2.75:1. Previous research conducted by Siskawati et al, 2017 shown there were more males than females with a ratio of 3.75:1. Haroun et al 2019 stated that men have a higher risk of developing leprosy because women may be more worried about their health and are diagnosed earlier with various

levels of risk factors exposure to leprosy in men and women. [13,14,15]

Joshi 2010 stated that the greater number of men than women in India who have multibacillary leprosy may be due to their greater mobility and increasing contact risk. In contrast to the opinion of Haroeun et al, according to Joshi, men in India are also more willing to check their health at health facilities and seek treatment compared to women.[16]

Education is often associated with a person's socioeconomic status. Low education is considered a measurement of poverty. Leprosy is generally seen as a disease of poverty. Leprosy is endemic in the poorest countries in the world, and within these countries, leprosy can be found in the poorest areas or urban slum areas. Although a causal relationship between poverty and leprosy is difficult to prove, socioeconomic determinants have been studied and are believed to have a major influence on the continuation of the transmission of this disease. (Screwer, 2016)[3]

Data from the Ministry of Health of the Republic of Indonesia in 2018 stated that social-economic factors play a significant role in the case of leprosy, where leprosy decreases rapidly due to an increase in socioeconomic status. Leprosy is known to occur at all ages ranging from infants to the elderly (3 weeks to more than 70 years of age). However, the majority are at young and productive ages. Following this study, the average age was 42 years old. Research conducted by Sutedja revealed that people with an average age of 38, the youngest being 16 years old, and the oldest being 72 years old are most likely to get this disease.[17]

Leprosy can occur at any age but is more commonly seen in the group of age between 20 and 30. In endemic areas, infection generally occurs during childhood. In low-endemic areas, the infection may occur in adults or older. The increase in the proportion of leprosy cases in the population has epidemiological significance indicating the presence of active transmission of the disease in the community. When disease transmission decreases, it will be seen more often in the older age group. [16]

We determined the onset of the disease by asking when the patient first felt symptoms and signs in the form of spots or complaints of numbness or other complaints related to multibacillary leprosy until the patient received treatment based on the history (questionnaire). In this study, the onset was more than a year which indicated that the patient was late in getting a diagnosis of multibacillary leprosy. In a study conducted by Tarique, 2018, of 25 BL/LL patients, the onset of patients was between 0.8-1.9 years. It is difficult to establish definite boundaries of disease onset. Kumar, 2016, states that based on *the Eighth Report of the WHO Expert Committee on Leprosy*, leprosy is suspected in patients with symptoms or signs of pale or reddish patches on the skin, decreased sensation or loss of skin sensation, thick or tingling sensation in the feet or hands, nerve pain, swelling or nodules on the face or ear lobes, a burning or sharp feeling in the hands and feet. These symptoms are not specific so that at the beginning of the course of leprosy it is often not diagnosed and people with leprosy are also late for treatment.[18]

In this study, the duration of MDT administration in MD consisting of Dapsone, Rifampicin, and Clovazimin is more than six months and under twelve months. The MDT treatment regimen in Indonesia follows WHO's recommendation for MB. The MB treatment is by giving dose based on age group on the table below. Since One blister is for 28 days, as a result, 12 blisters are needed to be taken for the duration of 12-18 months. [19]

Meta-analysis Study based on 5 studies comparing MDT with ROM (Rifampicin, Ofloxacin, and Minocycline) does not show statistically significant differences between them after 6 months of treatment and at the end of the period of the study (Lazo-Porras, 2020). Dapsone, like all active sulfonamide and sulfone drugs, inhibits dihydrofolic acid synthesis by blocking the enzyme dihydropteroate synthetase. This drug is a weak bactericide for M. leprae. Rifampicin inhibits deoxyribonucleic acid-binding (DNA-dependent) ribonucleic acid (RNA) synthesis, by blocking RNA polymerase. A single dose of 1,500 mg in humans can reduce the number of bacilli to a level so low that they are undetectable. Clofazimine has a mildly immunosuppressive effect that can assist in the management of reactions to erythema nodosum leprosum (Saunderson, 2010). [20.21]

IL 10 level in a study conducted by Sutedja at Hasan Hospital in Bandung, which examined 38 patients with multi-bacillary leprosy, the lowest IL-10 level was 6.7 pg/ml on one patient and the highest level of 60.1 pg/ml was on another patient, with an average of 22.50. His study is much lower than this

study, which has the lowest IL 10 value of 17.7 and the highest 763.6 with an average of 144.7.10. Another study conducted by Kodrati, 2021, comparing serum IL 10 levels of leprosy and non-leprosy patients, the results obtained IL 10 in the group of patients with leprosy, the average was 13.24 with the lowest score of 5.59 and the highest of 19.41, while the non-leprosy group had an average IL level of 10 40.15 with the lowest score 29.41 and the highest 44.71. [22]

Interleukin 10 (IL-10) can inactivate macrophages, inhibit IL-12 and IFN-ϒ production. In addition, IL-10 directly inhibits the function of CD4+ T cells and antigen-presenting cells (APC) in cells infected with M. leprae. In lepromatous leprosy, TH2 Treg lymphocytes participate in the anti-inflammatory response and produce large amounts of IL 10, which inhibits macrophages activation and facilitates the survival of M. leprae. Administration of MDT can result in suppression of the bacterial index as well as a reduction in the stimulation of specific immune responses, resulting in a decrease in the production of cytokines (including IL-10) among leprosy patients. This theory is supported by evidence showing that patients with a higher bacterial index exhibit higher levels of IL-10.[10,22]

The results of the research conducted by Sutedja on 43 subjects showed that age and duration of MDT administration did not correlate with IL-10, while IB had a positive correlation with IL-10. The correlation coefficient between IB and IL-10 is 0.504 with p-value = 0.001 (significant). Age and IL-10 have a value of r = 0.048 with a p-value of 0.758 (not significant). The administration of MDT and IL-10 had an r-value of 0.136 and a p-value of 0.383 (not significant). The bacterial index has a positive correlation with IL-10, which means that if the IB value is high, the same high goes to IL-10 as well. [10]

Lesions in Lepromatous leprosy expresses Th 2 cell cytokines (IL-4, IL-5, IL-6, IL-9, and IL-10), which play a role in antibody production, inhibition of macrophage function (formation of macrophage granulomas), and suppression of SIS, thereby allowing intracellular bacteria to multiply. IL-10 is immunosuppressive against M. leprae (Darmaputra, 2018). 71 LL lesions show strong IL-10 expression but weak IL-12 and IFN- expression, so that IL-10 plays a role in the induction and/or maintenance of energy in lepromatous leprosy patients.[23]

We used a scoring system to determine the severity of leprosy neuropathy from result of electromyography. Axon loss: Amplitude of compound muscle action potential (CMAP) correlates with the number of motor nerve axons, and similarly, the amplitude of the sensory nerve action potential (SNAP) reflects the number of sensory nerve axons. Lesions causing axon loss generally result in reduced CMAP and SNAP amplitudes. Secondary axonal loss often occurs in severe or chronic demyelinating lesions. Demyelination: Loss of myelin is associated with slowing of conduction velocity (slower than 75% of the lower limit of normal), marked prolongation of distal (longer than 130% of the upper limit of normal), or both. Amplitude changes can also occur with demyelination due to secondary axonal loss. Reduced motor amplitude may also occur in demyelination if there is conduction block. In conduction block, the amplitude will be low when the nerve is stimulated proximal to the site of demyelination, but will be normal when stimulated below the block. The severity of leprosy neuropathy in this study was mainly moderate. Peripheral neuropathy in leprosy involves sensory nerves, motor nerves, and autonomic nerves. Clinical manifestations are received when nerve damage is more than 30% of the peripheral nerve fibers (Nascimento, 2013).[6,24]

The mechanism of nerve damage in multibacillary leprosy, namely Th2, produces cytokines IL-4, IL-10, IL-5, and IL-13. IL-5 activates eosinophils, IL-4 and IL-10 activate macrophages, IL-4 activates B cells to produce IgG and IgE, while IL-4, IL-10, and IL-13 activate mast cells. The first signal in the absence of the second signal will induce T cell energy. The incomplete activation of APC will cause a response towards Th 2. In lepromatous leprosy, Th 2 will be higher than Th 1. Phagocytic macrophages produce partial bacterial lysis. Ingested bacterial phospholipids enter the cytoplasmic vacuole, producing leprosy cells (Virchow cells). During the initial phase, no immune stimulation plays a role. It is suspected that mitochondrial dysfunction of “Mitsuda negative” macrophages leads to excessive free radical production and depression of lysosomal phospholipase. In the advanced phase of lepromatous leprosy, other macrophages can phagocytize Virchow cells, thereby providing neoantigen information expressed on MHC

class II, stimulating new APCs, secreting IL-4, and stimulating humoral immunity. [25]

According to Srinivasan, the affected peripheral nerves will experience several levels of damage, such as: [26]

Stage of involvement

At this stage, the nerves become thicker than normal and there is a possibility accompanied by tenderness and spontaneous pain in the peripheral nerves, but not accompanied by impaired nerve function such as anesthesia or muscle weakness yet.

Stages of damage

At this level, the nerves have been damaged and the function of the nerves is disrupted. The diagnosis of stage of damage is made when the nerve has been in incomplete or complete paralysis for more than 6-9 months. The treatment at this level can avoid the permanent damage of nerve.

Stage of destruction

At this stage, the nerves have been completely damaged. The diagnosis of stage of destruction can be made if there is a complete nerve damage or paralysis for more than one year. At this stage, nerve function cannot be repaired even by treatment.

The limitations of this study are that this is a cross-sectional observational study, the researchers did not record the drugs taken by the patients other than MDT, the researchers only used anamnesis (questionnaires) in determining the onset of the disease, thus it depends on the patient's memory.

CONCLUSION

Peripheral neuropathy in leprosy patients involves sensory nerves, motoric nerves, and autonomic nerves. Clinical manifestations are needed when nerve damage is more than 30% of the peripheral nerve fibers. EMG needs to predict early leprosy neuropathy to prevent severity. Interleukin 10 is a dominant cytokine found in MB. In our study, correlation between serum interleukin 10 and the severity of peripheral neuropathy analysis shows significant results with a strong strength. In conclusion, random controlled trials are needed to provide reliable evidence for leprosy neuropathy treatment in leprosy patients and for relevant impact on activity limitations and psychological well-being.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

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