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Positive Correlation of Plasma Interleukin-6 Levels with Immunoglobulin M (IgM) Anti Phenolic Glycolipid-1 (PGL-1) Levels in Household Contacts of Multibacillary Leprosy Patients

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ABSTRACT

Background/aim: Leprosy is a chronic infectious disease that can be cured but causes high morbidity because it causes disability. Leprosy is caused by the bacterium Mycobacterium leprae, an obligate intracellular virulence factor in the form of phenolic glycolipid-1 (PGL-1), a capsule component in M. leprae. This study aims for known Increased IL-6 correlation with IgM anti PGL-1 level in household contacts of multibacillary leprosy patient.

Methods: Analytical observational study with a cross-sectional approach. The sample consisted of 42 household contact persons and 22 non-contact samples aged 18-65 years who were selected through consecutive sampling according to the inclusion and exclusion criteria. Samples of 3 milliliters of venous blood were taken, which would then be examined for PGL-1 and IL-6 with the ELISA kit. Data analysis with SPSS version 23 and p-value <0.05 was significant

Results: The average anti-PGL-1 IgM level in the household contact group was 636.76±288.45 u/ml, while in the non-contact group, it was 211.00±237.43 u/ml. The average IL-6 level in the household contact group was 20.28 ± 12.54 pg/ml, while in the non-contact group, it was 8.29 ± 2.88 pg/ml. There was a significant difference in the levels of IL-6 and anti-PGL-1 IgM in the household contact and non-contact groups (p<0.001). This study found a strong positive relationship (r=0.620, p<0.001) between IL-6 levels and anti-PGL-1 IgM levels.

Conclusion: IgM anti-PGL-1 and IL-6 levels in household contacts were higher than in non-contacts, with a significant difference. There is a significant positive relationship between IL-6 and anti-PGL-1 IgM levels.

Keywords: leprosy, contacts, IgM anti-PGL-1, IL-6

INTRODUCTION

Leprosy is a chronic infectious disease that can be cured but causes high morbidity because it causes disability. Leprosy is caused by the bacterium Mycobacterium leprae, an obligate intracellular virulence factor in the form of phenolic glycolipid-1 (PGL-1), a capsule component in M. leprae. These bacteria can cause a broad clinical spectrum, attacking peripheral nerve cells, then attacking the skin, oral mucosa, upper respiratory tract, reticuloendothelial system, eyes, muscles, bones, and testes, except for the central nervous system.[1] The leprosy transmission mechanism occurs through respiratory droplets from the nose and mouth. Transmission occurs after close contact with leprosy patients who have not received therapy because the number of

bacilli is still significant. In contrast, patients who have received therapy are no longer contagious.[2]

Interleukin 6 is an interleukin that acts as a pro-inflammatory cytokine and an anti-inflammatory myokine. In humans, IL-6 is encoded by the IL-6 gene. Muscle cells in the tunica media are abundant in blood vessels and produce IL-6 as a pro-inflammatory cytokine. The role of IL-6 as an anti-inflammatory myokine is mediated through its inhibitory effect on Tumor Necrosis Factor (TNF)-alpha and IL-1, as well as the activation of IL-1 and IL-10.[3]

Interleukin 6 can be used as a potential marker to identify the risk of household contacts becoming clinical leprosy. This risk is higher in low nutritional status (underweight, anemia, and iron deficiency). IL-6 levels can be used to determine the prognosis of M.leprae infection in contact persons and healthy controls in endemic and non-endemic areas.[4,5]

Virulence factors and the host's immune response to M. leprae play an essential role in leprosy. The early phase of disease development is largely determined by the natural immune response, which can determine the outcome of the clinical stage of leprosy. A low natural immune response will cause macrophages to be unable to kill M. leprae bacteria so that M. leprae bacteria will continue to grow in the body and can cause clinical leprosy. M. leprae bacteria have a cell wall component that acts as an antigen, namely phenolic glycolipid 1 (PGL-1), which can trigger an antibody response from the host. Household contacts at home with MB-type leprosy patients have the highest risk of developing subclinical leprosy, which is 5-10 times.[6] Anti-PGL-1 IgM serological examination can indicate the abundance of M. leprae in the contact person's body. Interleukin-6 is one of the first cytokines identified, which has been widely recognized as a biomarker in several mycobacterial diseases, including leprosy.[1] So the researchers wanted to correlate plasma IL-6 levels with anti-PGL-1 IgM levels in household contacts of multibacillary leprosy sufferers at Prof. Dr. IGNG Ngoerah Denpasar Hospital.

METHOD

This is an analytic observational study with a cross-sectional design conducted at the Dermatology and Venereology Polyclinic, Prof. Dr. IGNG Ngoerah Hospital at Denpasar. Inclusion criteria: (1) All individuals who live in the same house (household contact) and have a history of contact for at least 6 months with type MB leprosy patients who, during the study period, visited the Dermatology and Venereology Polyclinic at Prof. Dr. IGNG Ngoerah Denpasar. (2) Indonesian citizens, (3) Aged 18-65 years, (4) Good general condition, (5) approval signed in informed consent. Exclusion criteria: (1)Subjects who are pregnant/breastfeeding, (2) the subject is a smoker, (3) the subject shows clinical symptoms of leprosy from anamnesis and physical examination, (4) the subject is suffering from a tuberculosis infection, (5) There is a history of chronic/autoimmune diseases such as coronary heart disease, rheumatoid arthritis, chronic kidney failure, chronic liver disease, systemic lupus erythematosus, diabetes mellitus, malignancy, vitiligo, psoriasis, atopic dermatitis, chronic diarrhea, bronchial asthma, (6) The subject is currently receiving systemic corticosteroid / hormonal contraceptive/diuretics in the past 4 weeks, (7) Genetic family history of leprosy.

This research has obtained a research ethics permit at Udayana University with the number LB.02.01/XIV2.2.2/30827. Samples were recruited by consecutive sampling. Data collection process and performed anamnesis, physical examination, and samples of 3 milliliters of venous blood were taken, which would then be examined for PGL-1 and IL-6 with the ELISA kit. The collected data will be examined, processed, and analyzed using statistical tests with the Statistical Package for Social Sciences (SPSS) 24.0 program.

RESULT

This study involved 42 subjects, household contacts, and 22 non-household contacts who met the inclusion and exclusion criteria. The results of the characteristics of the subjects are in Table 1.

Table 1 Characteristics of Data

Characteristics	Contact State N (%), mean ± SB	
	contact person (N= 42)	Not a contact person (N= 22)
Age (years)	31.60 ± 12.62	35.68 ± 10.86
Gender		
Man	18 (42.85)	9 (40.90)
Woman	24 (57,15)	13 (59,10)
Nutritional status based on body mass index (kg/m2)		
Mean ± SB	21.81 ± 1.05	21.85 ± 0.94
Profession		
Private sector employee	28 (66,67)	9 (40.90)
Does not work	5 (11.90)	8 (36,36)
Self-employed	6 (14,28)	2 (9,10)
Trader	1 (2,38)	1 (4.54)
Student	1 (2,38)	0 (0)
Seamstress	0 (0)	1 (4.54)
Retired	1 (2,38)	0 (0)
Midwife	0 (0)	1 (4.54)
Length of contact with MB-type leprosy patients mean ± SD	4.33±6.06	-
< 1 year	3 (7,14)	-
1-5 years	32 (76,19)	
> 5 years	7 (16,67)	
Anti-PGL-1 IgM levels (u/ml)		
Mean ± SD	636.76 ± 288.45	211.00 ± 237.43
IL-6 levels (pg/ml)		
Mean ± SD	20.28 ± 12.54	8.29 ± 2.88

SD: standard deviation

Correlation analysis with the Spearman Rho test between IL-6 levels and IgM anti-PGL-1 because the data is not normally distributed can be seen in Table 2. Based on the test results, it was found that there was a strong positive relationship with the value of the correlation coefficient (r), which was 0.620, and a p value <0.001 between IL-6 levels and anti-PGL-1 IgM levels. This indicates that the higher the IL-6 level, the higher the anti-PGL-1 IgM level. Plasma Interleukin 6 Levels Proven to Have a Strong Positive Correlation and As a Risk Factor for Increased Levels of Immunoglobulin M (IgM) Anti Phenolic Glycolipid-1 (PGL-1) in Household Contacts at Home with Multibacillary Leprosy Patients

Table 2 Correlation test of IL-6 levels with anti-PGL-1 IgM levels

Variable	IL-6 levels	
Anti-PGL-1 IgM levels	Correlation (r)	0.620
	p-value	<0.001*
	Amount (n)	64

***Significant if p<0.05; correlation analysis with Spearman rho test**

In this study, ROC curve analysis was performed to determine the cut-off point of IL-6 levels by grouping based on IgM anti-PGL-1 levels using the cut-off point of 605 u/ml. The results of the ROC curve analysis showed a sensitivity of 95.2% and a specificity of 81.8% with a cut-off value of 8.75 pg/ml (Figure 1 and Table 3). Furthermore, based on these values, a risk model was developed for anti-PGL-1 IgM levels. In this study, anti-PGL-1 IgM levels > 605 u/ml were categorized as high anti-PGL-1 IgM levels in household contacts of multibacillary leprosy.

Table 3 Sensitivity, specificity, and cut-off points of serum IL-6

Variable	AUC	Sensitivity	specificity		*cut-off* point	CI 95%	p.s
IL-6 levels	91.8%	95.2%	81.8%		8.75	0.842 - 0.993	<0.001

The results of the risk analysis found a significant relationship between the IL-6 category and the IgM anti-PGL-1 category in household contacts of multibacillary leprosy patients ($p<0.05$) (Table 4). Based on the risk analysis using the 2x2 table, it was found that IL-6 increased the risk 5.6 times for increased anti-PGL-1 IgM levels (PR: 5.6 95% CI: 1.82 – 17.19, p= 0.002).

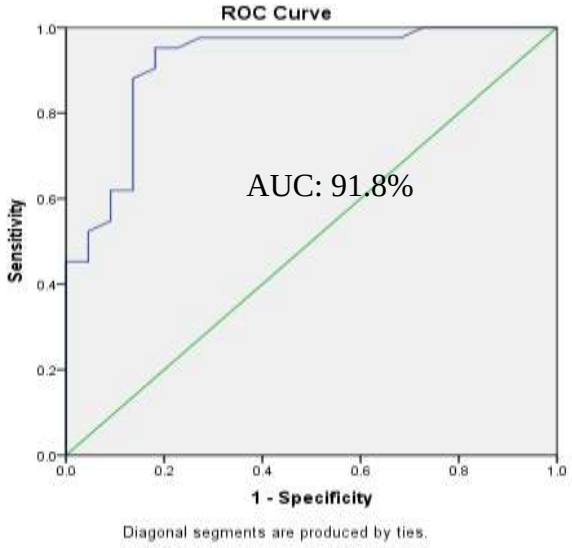

Figure 1 ROC curve for IL-6 levels based on the IgM anti-PGL-1 category

Table 4 Risk analysis of increased IL-6 to increased anti-PGL-1 IgM levels

	IgM anti-PGL-1		homework	CI 95%	p-value
	Tall >605u/ml.	Low ≤605 u/ml.			
High IL-6 (>8.75 pg/ml)	32 (76.19%)	8 (36.36%)	5,60	1.82 – 17.19	0.002*
low IL-6 (≤8.75 pg/ml)	10 (23.81%)	14 (63.64%)			
*Significant if the value of p<0.05; cross tabulation analysis with Chi-Square test					

DISCUSSION

The results of this study showed that the average age of household contact subjects was 31.60 ± 12.62 years and the average age of non-household contact subjects was 35.68 ± 10.86 years, meaning that the subjects in this study were not different. Most household contacts in Indonesia have been examined in several areas, namely in Bali, East Java, and Central Java; it was found that the average age range of household contacts of leprosy sufferers is 30-40 years old.[6–12] This study is not much different from a study conducted by Oktaria et al. (2022), where household contacts of leprosy patients have an average age of 37.3 years. In endemic controls, the most age is 39.6 years.[5] The results also showed no significant relationship between age in the study subjects, which compared leprosy patients, household contacts, and endemic leprosy with increased IL-6 levels. Meanwhile, in research conducted by Moet et al. (2006) of 21,870 household contacts, the most were aged 20-29 years, namely 6,940 (17.2%), and the second most were aged 30-39 years, namely 6,452 (15.18%).[13] The age of 30-40 years is still productive, and this age range can be at risk of developing subclinical leprosy due to the long incubation period of M. Leprae and the immune system, which is still high.[14,15]

In the contracting group, there were 18 (42.85%) male subjects and 24 (57.15%) female subjects, and in the non-household contact group, there were 9 (40.90%) male subjects and 13 (59.10%) female subjects. The results of this study show that the distribution of subjects is the same and that the most common household contacts are women. Most household contacts in Indonesia are women because they are often at home and are tasked with caring for sick family members, while men, because of

work demands, are more likely to be outside the house and live far from home.[16] The most extensive distribution of women in household contact leprosy is by research conducted by Oktaria et al. (2022), namely 42 female subjects (62.6%), and there was no significant difference in the distribution of male and female gender in terms of increased IL-6 in household contact leprosy.[5] This is also to the research of Moet et al. (2006), namely that there were 11,433 female subjects (52.3%), and the results showed no significant effect between the distribution of men and women in household contact leprosy with the result p=0.071.[13] The results of PGL-1 levels were also not found to be related to gender and age.[11,17–20].

The average body mass index of household contact subjects was 21.81 ± 1.05 kg/m2, and the average body mass index of non-household contact subjects was 21.85 ± 0.94 kg/m2. These results indicate that the BMI data distribution is dama, meaning that all research subjects have good nutrition. These results are the same as a study conducted by Oktaria et al. (2022) which obtained all leprosy subjects, household contacts, and endemic leprosy at normal nutritional status.[5] In statistical tests, it was found that the risk of leprosy increasing increased IL-6 levels in malnutrition by 2.6 times compared with normal or overweight/obese (OR, 2.599 [95% CI, 0.991–6.820; P <0.05], the results of a comparison of household contacts found that there was a risk of an increase in IL6 in severe malnutrition by 2.1 times compared to normal or overweight/obese OR 2,176 [IK95%, 1,010–4,692; P < 0.05]. Besides being able to increase levels of nutritional IL-6Poor household contact was also significantly associated with the risk of anemia, which was 10.7 times compared to endemic leprosy (OR 10,771 [95% CI, 4,926–23,552; P <0.001]) and the risk of decreased serum iron levels was 17 times compared to endemic leprosy (OR, 17.274 [95% CI, 7.295–40.904; P < 0.001]). PGL-1 levels were also found to be higher in household contact subjects who had a 7 times increase in malnutrition compared to normal or overweight/obese (OR 7.083 [95% CI, 2.930–17.126; P < .001].[21]

The relationship between increased IL-6 levels and nutritional status is associated with markers of vascular endothelial dysfunction and the effects of unsaturated fatty acids.[22] Many experimental and observational studies in humans have found an inverse relationship between the consumption of dietary fatty acids and the marker of systemic inflammation, IL-6.[22,23] The poor nutritional status will change the inflammatory status in blood circulation, increasing IL-6 levels by 20-60%.[24]

In the results of the work, it was found that most of them were private employees, which meant that there was no significant difference between the subjects in this study. Occupation is closely related to the patient's nutritional and economic status. Studies found that income below the minimum wage standard affects the spread of leprosy to a greater extent, namely 2.3-5.7 times (Bareto et al., 2011). On research Schuring et al. (2006), it was found that PGL-1 levels increased in household contact subjects who had low economic status with poor nutrition with a risk of 4.27 times (95% CI, 0.68-7.87, P<0.001).[25] In Oktaria et al.'s (2018) research on dietary diversity and poverty on risk factors for leprosy in Indonesia, it was found that unstable income is at risk with (OR 5.67; 95% CI 2.54-12.64; p = 0.000), anemia (OR, 4.01; 95% CI, 2.10-7.64; p = 0.000), food availability (OR, 1.13; 95% CI, 1.06-1.21; p = 0.000, iron deficiency (OR, 1.06; 95% CI, 0.10–11.37; p = 0.963).[5]

The duration of household contact was close to MB-type leprosy patients with an average of 4.71 ± 6.28, and the most contacts were for 1-5 years, as many as 32 people (76.19%). Moet's study found that the risk of developing subcutaneous leprosy would be 3.3 times higher than clinical leprosy with an increasing range of 1.7-5.9 fold (p=0.003) in subjects with contact exposure for 1-5 years.[13] Oktaria's study found no

increase in IL-6 levels in household contacts with exposure for less than 5 years and endemic leprosy.[5] In a systematic study by Penna et al. (2016), it was found that PGL-1 levels increased in household contacts after four years of exposure to leprosy by 50.34% in Venezuela, 10.51% in Brazil, and 6.54% in Zaire, whereas in Uberlandia contact during 5 years obtained an increase of 12.31%.[26]

The average anti-PGL-1 IgM level in the household contact group was 636.76 ± 288.45 u/ml, while in the non-household contact group, it was 211.00 ± 237.43 u/ml. This shows that the average level of the household contact group has exceeded the anti-PGL-1 antibody titer in seropositive leprosy patients ranging from 605 u/mL (cut point for the East Java population) and the cut point in Bali is 613 u/ml.[9] The median anti-PGL-1 IgM level was significantly higher in the household contact group (533 u/ml) than in the non-household contact group (152 u/ml) with a $p<0.05$.

The average IL-6 level in the household contact group was 20.28 ± 12.54 pg/ml compared to the non-household contact group, which was 8.29 ± 2.88 pg/ml. The median IL-6 level in the household contact group was also higher at 14.76 pg/ml compared to the median IL-6 level in the non-household contact group with a value of 7.31 pg/ml with a $p<0.001$. These results show that IL-6 levels were found to be higher than what had been done by Oktaria 2022, with marks in leprosy patients with a median of 9.2 (IQR: 4.5-119.9), household contacts with a median of 5.6 (IQR 3 .4-10.3) and leprosy endemic with a median of 5.6 (IQR 3.8-8.0) pg/ml.

The results showed a strong positive relationship between IL-6 levels and anti-PGL-1 IgM, with a correlation coefficient (r) of 0.620 and a $p<0.001$ value. IL-6 levels increased the risk 5.6 times of increasing anti-PGL-1 IgM levels (PR: 5.6 95% CI: 1.82 – 17.19, p= 0.002). This indicates that the higher the IL-6 level, the higher the anti-PGL-1 IgM level, with a 5.6-fold risk. Research conducted by Sharma et al., 2018 stated that in multibacillary type leprosy (BL/LL), IL-6/100 pg/mL could significantly increase PGL-1 with an average of 338.71 ± 23.1 u/ml. Compared to TT/BT paucibasiler-type patients with a mean of 39.93 ± 6.47 u/ml and healthy controls 38.43 ± 1.07 u/ml. Research conducted by Siswati found that positive expression of IL-6 was found in neutrophils, lymphocytes, epithelioid histiocytes, Langhans cells, and plasma cells in the form of granulomas or scattered in the dermis. Initial IL-6 expression value ≥ 40.21% increases the risk of early leprosy reactions up to 22.2 times.[27]

The correlation between IL-6 and IgM PGL-1 is related to acute M.leprae infection, which actively increases these two mediators. In leprosy infection, inflammatory cells will be active and induce an acute inflammatory response by activating the predominant phenotype of the immune response, namely T-helper 1, which in macrophages will increase the expression of MHC class I and II and increase the antigen transporter process, whereas at IgM antibody levels towards PGL-1 antigen in the blood circulation increases due to the early detection of leprosy bacilli which is related to the bacterial index and clinical symptoms in leprosy patients.[4,5,14]

Interleukin-6 present on the cell surface and intracellular compartments and induces intracellular signaling cascades that lead to the production of inflammatory cytokines that trigger an increase in PGL-1 in response to antibodies from the host M. leprae bacteria.[28,29]. Household contacts of MB patients are the people most at risk of contracting seropositive cases in leprosy endemic areas, around 7-36% of the total population[16].

High levels of IL-6 as a pro-inflammatory cytokine play a role in inhibiting macrophage granuloma formation, antibody production, and suppression of the cellular immune system, pathogen-associated molecular patterns (PAMPs) specific microbes in leprosy.[30] Interleukin-6 increases the risk of leprosy reactions by

disrupting the balance between T reg cells and Th17 cells. Increased IL-6 appears to facilitate the recruitment of inflammatory cells and the formation of immune complexes, indirectly contributing to the pathomechanism of the leprosy reaction. [15] So that increased levels of IL-6 can be used as a potential marker for developing leprosy among individuals who have close contact with index cases or live in leprosy-endemic areas.[5]

CONCLUSION

IgM anti-PGL-1 and IL-6 levels in household contacts were higher than in non-contacts, with a significant difference. There is a significant positive relationship between IL-6 and anti-PGL-1 IgM levels.

Declaration by Authors

Ethical Approval: Approved

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