Low plasma level of insulin-like growth factor – I (IGF-I) is a risk factor for multibacillary type of leprosy

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ABSTRACT

Introduction: Leprosy is one of infectious diseases with complex issues. The previous study showed poverty, malnutrition, lack of proper food and nutrient intake, as well as low income. Recently, many studies reported insulin-like growth factor-I (IGF-I) as an excellent nutrient marker.

Objective: This study aims to prove that low plasma level of insulin-like growth factor-I is a risk factor for the multibacillary type of leprosy.

Material and methods: This case-control study design involved 38 patients with leprosy subjects as cases and 38 control subjects. The sample collection is done by consecutive sampling and has fulfilled the inclusion and exclusion criteria, which matched by age and gender in Dermatovenereology Polyclinic of Sanglah Hospital. The collected data was analyzed using SPSS version 23.0 with Pearson Chi-square test to obtain the odds ratio.

Results: This study showed that IGF-I plasma levels in the case group were significantly lower than the control group (p<0,05) with Odds ratio for IGF-I plasma 34,61 (95% CI= 7,17-167,01, p<0,001)

Conclusion: Low plasma level of insulin-like growth factor-I is a risk factor for the multibacillary type of leprosy.

Keywords: multibacillary leprosy, insulin-like growth factor, IGF-I.
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INTRODUCTION

Leprosy is a chronic infectious disease caused by Mycobacterium leprae. The bacteria can attack the skin and peripheral nerves where clinically numb skin lesions can be found accompanied by peripheral nerve thickening.[1] The incidence of leprosy around the world in 2015 was 213,899 cases, around 81% of the three main endemic countries such as India, Brazil, and Indonesia. Indonesia is the highest contributor (14,213 cases or 83.4%) for multibacillary (MB) type of new leprosy cases in Southeast Asia.[2] The prevalence of leprosy in Bali based on data from the Bali Provincial Health Office accounted for 0.21 per 10,000 population with new cases 89 people in 2014. The total number of leprosy patients in Dermatology and Venereology outpatient clinic of Sanglah General Hospital from January 2015 to January 2016 were 44 cases.[3,4]

Mycobacterium leprae is obligate intracellular with virulence factors in the form of phenolic glycolipid-1 (PGL-1) in Mycobacterium leprae capsule components.[5] In addition to bacterial factors, leprosy is strongly influenced by host factors, such as immunity status and genetic variation. The host's natural immune system such as epithelial integrity, immunoglobulin A (IgA), natural killer cells (NK cells), cytotoxic T lymphocytes, and macrophages become the first barrier to fight the infection. The cellular immunity system determines the leprosy spectrum, low host cellular immunity system lead to polar lepromatous, otherwise high cellular immunity lead to tuberculoid leprosy spectrum.[6]

The neuroendocrine system plays a role in helping the immune response effective against pathogens and controls the intensity of the immune response to prevent extensive tissue damage. In nerve damage caused by immunological reaction marked with the release of proinflammatory cytokines such as TNF, IL-12, IL-15, IL-16, IL-18, and IL-1β by macrophages. The cytokines are also induced by the 19-kDa protein, which binds to TLR1/2 and causes Schwann cells apoptosis. Nerve damage that occurs due to the edema and influx of inflammatory cells in nerve cells resulting in compression and ischemia.[7,8]

Insulin-like growth factor-1 (IGF-I) is a component of the neuroendocrine system in

the form of a hormone with anti-apoptotic and proliferative abilities, which has an important role in tissue homeostasis.[9] IGF-I is known to play a role in the process of proliferation, chemotaxis and T cell maturation.[10] Innate immunity such as macrophages and neutrophils is also affected by IGF-I through the pathway of phosphatidylinositol-3 kinase and can delay the apoptotic process in these cells.[11,12] This study aimed to prove that low plasma IGF-I levels were a risk factor for the occurrence of multibacillary leprosy.

MATERIAL AND METHODS

This study used a match-paired case-control study with leprosy as a dependent variable and plasma IGF-I levels as independent variables (risk factors). The study was conducted at the Dermatology and Venereology Outpatient Clinic of Sanglah General Hospital Denpasar from May 2018 to July 2018 by consecutive sampling. The inclusion criteria for the case were all MB leprosy patients, Indonesian citizenship, aged 18 to 70 years, generally good condition, and willing to take part in research and signed informed consent. Inclusion criteria for control were healthy populations who did not suffer from leprosy who lived in the same area with leprosy and paired for ages (with a range of 5 years) and gender, good general condition and willing to included in the study and signed informed consent. MB leprosy patients who have completed MDT treatment or release from treatment (RFT), experience leprosy reactions in both type 1 and type two leprosy reactions, relapse, pregnancy, smokers, suffer from pituitary gland disorders, liver disease, burns or post-treatment surgery and diabetes mellitus, receiving non-steroidal anti-inflammatory treatment, corticosteroid drugs, and contraceptive drugs in the last month were excluded from this study. MB type of leprosy patients was based on the WHO criteria. The chemiluminescent immunometric assay measured plasma IGF-I levels through venous blood collection. Collected data analyzed descriptively and analytically using SPSS. Research ethical clearance from the Research Ethics Commission of Udayana University/ Sanglah General Hospital with number 370/ UN14.2/KEP/2018 was given before the study was conducted.

RESULTS

Total of 76 study subjects with 38 leprosy cases and 38 leprosies included in this study. The general characteristics of the study subjects presented in Table 1.

In the case group, the minimum value of plasma IGF-I levels was 128.75 ng/mL, and the maximum value was 196.82 ng/mL. The minimum value of plasma IGF-I levels in the control group was 151.97 ng / mL, and the maximum value was 229.24 ng / mL. Based on the results of the analysis using the Mann Whitney test found significant mean differences between cases and controls in plasma IGF-I levels (p<0.001) (Table 2). Chi-square test performed to evaluate low plasma IGF-I levels as a risk factor for multibacillary type leprosy. Based on the test, low plasma IGF-1 increase the occurrence of multibacillary leprosy 34,61 times (OR=34.61, 95% CI= 7.17-167.01, p<0.001) compared to normal plasma IGF-1 level (Table 3).

Table 3 shows that low plasma insulin-like growth factor I (IGF-I) levels are a risk factor for multibacillary type leprosy of 34.61 times (OR = 34.61, 95% CI = 7.17-167.01, p<0.001) compared to normal plasma IGF-I levels.

Table 1   General characteristics of the subjects

Variable	Group		p-value
	Case n=38 (%)	Control n=38 (%)	
Age			
16-25	9 (23.68)	9 (23.68)	
26-35	10 (26.32)	10 (26.32)	
36-45	8 (21.05)	8 (21.05)	
46-55	4 (10.53)	4 (10.53)	
55-65	6 (15.79)	6 (15.79)	
>66	1 (2.63)	1 (2.63)	
Median [IQR]	35.50 [23.50]	34.50 [25.00]	0.988
Gender			
Male	22 (57.89)	22 (57.89)	
Female	16 (42.11)	16 (42.11)	
Food intake			
Low	3 (7.89)	0 (0)	
Moderate	26 (68.42)	23 (60.53)	
High	9 (23.68)	15 (39.47)	
Body mass index (kg/m²)			
Underweight	3 (7.89)	0 (0)	
Normal	29 (76.32)	25 (65.79)	
Overweight	6 (15.79)	13 (34.21)	
Median [IQR]	21.89 [3,18]	23.73 [3.88]	0.011
Income			
< minimum salary	31 (81.58)	12 (31.58)	
>= minimum salary	7 (18.42)	26 (68.42)	
IGF-I (ng/mL)			
Median [IQR]	146.82 [19.03]	194.35 [13.06]	<0.001

*normality test with a significant result or normally distributed if p>0,05

Table 2 IGF-1   comparison between case and control group

Variable	Group		p-value
	Case	Control	
IGF-1 level mean±SD	150.42 ±15.07	192.13 ± 16.33	<0.001*

Mann Whitney test. *Significant if p<0.05

Table 3   Plasma IGF-1 as a risk factor of multibacillary leprosy

Variable	Group		OR	95% CI	p-value
	Case	Control			
Plasma IGF-1 level Low	25	2	34.61	7.17-167.01	<0.001
Normal	13	36			

OR= odds ratio, CI= confidence interval

DISCUSSION

IGF-I has a regulatory role in the inflammatory response of the immune system to infection.[13,14] Silva et al. conducted a study to measure IGF-I on leprosy infection and found that IGF-I expression levels in dermal lesions of leprosy patients correlated with the severity of infection.[9] Research conducted by Rodrigues et al. found that plasma IGF-I levels were lower in patients with the lepromatous spectrum compared with tuberculoid.[15] However, other studies resulted LL type leprosy group has higher IGF-I secretions and expressions than BT type leprosy group.[9]

In this study, the median age in the case group was 35.50. This study also showed that multibacillary type leprosy was found in the 26-35 year age group (26.32%). The research conducted by Ardeshna in Mumbai, India found the highest incidence of leprosy in the age group between 15-30 years with a median age of 34.3 years.[16] This finding indicates that in endemic areas, the transmission process occurs from childhood and along with long leprosy incubation period, and new symptoms occur in adulthood. Multibacillary type leprosy was found in men as with 22 cases (57.89%) compared to women 16 cases (42.11%). Nobre reported more research in Brazil with male subjects (54.8%) compared to female subjects (45.2%) supporting this study results.[17] This condition might due to the existence of the local community culture where women must get permission and approval from the husband or family to do the examination, besides that men are more afraid to lose economic status and social status, therefore seek the medical advice more often. Body mass index is the most commonly used indicator for nutrition. The median value of body mass index in the case group was 21.89 kg/m². In the control group, the median value of body mass index 23.73 kg/m². Another study conducted by Diffey reported that BMI of people with leprosy with disabilities was lower than the BMI of people affected by leprosy without disability.[18]

In this study, the mean value of plasma IGF-I levels in the case group was significantly lower compared to the control group, 146.82 vs. 194.36 (p<0.001). The results of this study showed plasma IGF-1 levels in the case group were lower than in the control group. This result is also supported by a study conducted by Rodrigues which stated that plasma IGF-I levels were lower in multibacillary type leprosy patients compared to those with paucibacillary type leprosy.[15]

Analysis of plasma IGF-I levels with the Pearson Chi-Square test and an Odds Ratio of 34.61 with a 95% confidence interval (7.17-167.01) were obtained. This result shows that low plasma IGF-I levels are a risk factor for multibacillary type leprosy. Individuals with low plasma IGF-I levels are at risk of multibacillary type leprosy 34.61 times higher compared to individuals with normal IGF-I levels. This result substantiates evidence regarding the role of IGF-I in the pathogenesis of leprosy. IGF-I has an endocrine role that is important in mediating growth hormone activity and increasing anabolic processes. Growth hormone, IL-1β, and TNF-α influence the secretion of IGF-I. Lack of food intakes such as hunger and malnutrition lead to metabolic disorders, including decreased IGF-I levels that disrupt muscle mass formation, lipolysis, and fat oxidation disorders accompanied by central body fat accumulation. IGF-I regulation by nutrients and hormones is related to inflammation and cytokines simultaneously regulate anabolic processes and growth.[9,15,19,20] Perez and Borghem reported that IGF-I, as part of the neuroendocrine system, which, together with the immune system, plays a large role in the process of immunity homeostasis against the stress and infection.[21,22] IGF-I expression levels in dermal lesions of leprosy patients correlated with the severity of the infection.[9] Other studies found that IGF-I levels are lower in BL/LL patients who have not received MDT therapy compared to BT patients and healthy controls. In the BL and LL group, approximately 75-83.3% had serum IGF-I levels below normal.[15] Further research to evaluate the correlation of IGF-1 with the occurrence of multibacillary leprosy with a larger sample and a cohort model is needed to know the risk factor value.

CONCLUSION

Low plasma IGF-I levels are a risk factor for multibacillary type leprosy.

CONFLICT OF INTEREST

None declared.

FUNDING

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