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Identification of -2849 IL-10 Gene Promoter Polymorphism in Leprosy Patient

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Abstract

Leprosy is a chronic granulomatous disease. Leprosy is caused by M. leprae. However, not all exposure to M. leprae causes the disease. The condition of the host immune system determines the pathogenesis of leprosy. Interleukin-10 work as a pro- and anti-inflammatory cytokine. Polymorphism in the IL-10 gene promoter affects the amount of IL-10 secretion. The amount of IL-10 secretion determines the body's response to M. leprae. The purpose of this study was to determine the distribution of -2849 IL-10 gene promoter polymorphism in leprosy patient at RSUP dr. Mohammad Hoesin Palembang. This research is an observational descriptive study with cross sectional design. Polymorphism identification was performed using PCR-RFLP. A total of 50 samples were identified. Most of the leprosy patients at RSUP dr. Mohammad Hoesin for the period January – February were < 50 years old (73.47%), male (66%), MB leprosy (92%), and came from Malay-South Sumatra ethnicity (53.06%). The genotype frequency distribution was GG 93.88%, AG 6.12%, and AA 0%. The frequency of allele G was 96.94% and allele A 3.06%. The majority of leprosy patients at RSUP dr. Mohammad Hoesin had wild-type genotypes.

Keyword: leprosy, polymorphism, Interleukin-10

1. Introduction

Leprosy is a chronic granulomatous disease that can cause disability. The etiology of this disease is *Mycobacterium leprae*. Leprosy manifestations can be found in the nerves and skin. Leprosy classified into paucibacillary (PB) and multibacillary (MB) by WHO. The PB type is leprosy with the number of skin lesions less than five while the MB type is leprosy with more than five skin lesions.[1,2,3]

More than 200.000 new cases of leprosy are still found worldwide and one-third suffer from a disability. The spread of leprosy is uneven. As many as 80% of cases were reported from India, Brazil, and Indonesia, while many European countries have reported leprosy free. Indonesia is in the third rank of most cases with 15,910 new cases. The high incidence and the uneven spread of the disease has encouraged the development of epidemiological research on leprosy. Leprosy epidemiology research aims to answer the question of what factors cause the incidence of leprosy has not decreased in several countries. For a while, genetic association and close contact with MB leprosy patients are the strongest risk factors for leprosy (Misch et al., 2010).[1,4,5]

Not all exposure to *M. leprae* causes disease. The difference in the level of the immune response in each individual determines the progression of the disease.[6] The body's first defense against *M. leprae* is the innate immune system. Since *M. leprae* is an obligate intracellular bacillus, the main innate immune cells for destroying bacteria are macrophages. In addition to eradicating bacteria, macrophages will activate the adaptive immune

system. Leprosy will not occur if the innate immune system succeeds in eradicating *M. leprae*.[7,8]

The adaptive immune system determines the type of clinical manifestations of leprosy. The innate immune system will invite T- helper 1 (Th1) and T- helper 2 (Th2). Th1 activates the cellular immune response through the interferon gamma (IFN- ɣ) cytokine and Interleukin-2 (IL-2). The cellular immune response is effective in forming granulomas to prevent the spread of disease. The PB leprosy occurs when the body's dominant immune response is Th1. Meanwhile, Th2 enabled humoral immune responses through the IL-4 and IL-10. The humoral immune response stimulates antibody formation. The MB leprosy occurs when the body's dominant immune response is Th2.[5,7]

Polymorphism is a variation of the DNA sequence that occurs in more than one percent of the population.[9] Wild-type allele in polymorphism encodes the majority of phenotypes in a population, usually called alleles standard. Meanwhile, mutant-type is a polymorphism that is different from standard alleles and is less common.[10,11] Wild-types in one population can be found as mutant types in other populations depending on ethnic heterogeneity.[12] Single nucleotide polymorphism (SNP) is a polymorphism at one specific point of the genome. Changes at one point do not directly cause disease but predispose to susceptibility to a disease. Polymorphisms can occur at the exon, intron, or promoter. The impact of polymorphisms on exons, introns and promoters is different. Polymorphisms in the promoter occur at the transcription stage and affect the amount of gene expression.[13]

Interleukin-10 is a cytokine that is activated by immune cells, particularly monocytes, macrophages, and T cells.[14] Interleukin-10 is encoded by chromosome 1 locus 1q32.[15] This cytokine has dominant roles as anti-inflammatory cytokine depending on the time IL-10 is produced by inflammatory mediators, location of infection, and stimulus.[5,15] As an anti-inflammatory cytokine, IL-10 plays a role in suppressing macrophage function, decreasing Th1 proliferation, and inhibiting immune mediators. The aim is to protect monocytes and macrophages from complement lysis due to an excess immune response.[16]

The IL-10 gene promoter is responsible for regulating the amount of IL-10 secretion. The location of the IL-10 gene promoter is located at many points starting from proximal to distal to the 1q32 locus. Each point synthesizes a different amount of IL-10.[17] To determine the link between genetics and leprosy, the haplotype IL-10 gene promoter study was extended to the distal and proximal 1q32 locus.[18] The points that are thought to influence the secretion of IL-10 are -3575 T>A, -2849 G>A, -2763, C>A, -1082 G>A, -819 C>T and -592 C>A.[19]

Research in Brazil found the IL-10 gene promoter polymorphism with a haplotype at the point of -3575A/-2849G/-2763C increased resistance while IL10-3575T / -2849A / -2763C showed susceptibility to leprosy.[15] Research in India shows the haplotype IL-10 -3575T/-2849G/-2763C/-1082A/-819C/-592C increases the susceptibility and severity of leprosy.[20]

Genotype -2849 consists of the A and G alleles. The GG genotype is a wild-type in Brazil and Europe.[15,18] The GG genotype is a common genotype of point -2849 in India.[20] While -2849G acts as a protective factor in Brazil, -2849G acts as a predisposing factor for leprosy in India. [15,20]

Epidemiological studies of the -2849 IL-10 gene promoter polymorphism are needed to explain the reason of higher incidence of leprosy in one population compared to other population. Identification of the -2849 IL-10 gene promoter polymorphism also plays a role in the initiation of more advanced research in the form of haplotype that possibly could explain the further effect of IL-10 gene promoter polymorphism not only with leprosy susceptibility, but also with degree of severity and secretion of IL-10. So far, there are no data on allele and genotype distribution of -2849 IL-

10 gene promoter polymorphism in Indonesia. The only IL-10 gene promoter polymorphisms that already identified in South Sumatra are the -1082 and -819 IL-10 gene promoter polymorphism.[3,21] In its application, the identification of genetic factor could useful for education of contact persons and can be used as a method for screening for leprosy. Thus, the study of polymorphism in point -2849 IL-10 gene promoter needs to be done.

2. Method

This research is a cross-sectional observational descriptive study. This study only observes and describes the results from observations of the IL-10 gene promoter polymorphism. A total 50 leprosy patients from dr. Mohammad Hoesin Palembang were obtained from the previous study.[3] Nested PCR-RFLP were used to identify polymorphisms. This study was approved by the Ethics Committee of Medical Faculty of Sriwijaya University Affiliated with Dr. Mohammad Hoesin Hospital. Informed consent was obtained from each participant.

The Nested PCR method was carried out twice at primary and secondary reaction. The mixture for primary PCR reaction was ddH 2 O 10 µl, go taq green 10 µl, F primer 0.5 µl, R primer 0.5 µl and DNA sample 4 µl. Meanwhile, the mixture for the secondary PCR reaction was ddH 2 O 16.5 µl, go taq green 15 µl, F primer 0.75 µl, primary R 0.75 µl and amplicon 4. 5 µl. The PCR stage was carried out 35 cycles with initial denaturation, denaturation, annealing, extension, and additional extension stages.

The point -2849 was cut using the Alwl enzyme and visualized at 2.5% agarose. The A allele was visible at 193 bp while the G allele was visible at 153 bp and 40 bp.

The data, in the form of frequency distribution, is processed using the SPSS program.

3. Result

A total of 50 samples were identified. From the 50 samples, 66% were male and only 34% were female. The majority of patients with MB leprosy were 92% and come from the South Sumatra Malay ethnicity (53.06%).

From the 50 samples, 46 samples (93.88%) were identified as having the GG genotype at point -2849. It was found that 6.12% of the samples were AG genotype while the AA genotype was not found at all. The A and G alleles were found to be 3.06% and 96.94%, respectively.

Table 1. Distribution of Basic Characteristic

Variable	Category	n	%
Age	<50 years	36	73.47
	≥ 50 years	13	26.53
Gender	Male	32	65.30
	Women	17	34.70
Classification	PB	4	8.16
	MB	45	91.84
Ethnic group	Malay-Batak	1	2.04
	Bugis-Malay	7	14.29
	Malay-Javanese	14	28.57
	Malay-South Sumatra	26	53.06
	Non-Malay Chinese	1	2.04

Table 2. Distribution of Genotype

Genotype	Distribution	
	n	%
AA	0	0
AG	4	6.12
GG	46	93.88
Total	50	100

Table 3. Distribution of Allele

Alleles	Distribution	
	n	%
A	5	3.06
G	95	96.94
Total	100	100

4. Discussion

Age is one of the risk factors for leprosy. Most of the leprosy patients in this study were in the group of less than 50 years. Epidemiological studies of leprosy in Flores, Indonesia, show that the highest incidence of leprosy is in the 15-19 age group.[22] Studies in Nepal, Philippines, and Brazil also show a peak incidence at age 15.[23] However, another study in Vietnam suggested that even though the highest incidence of leprosy was in the adolescent group, elderly patients had a higher risk of leprosy complications.[24] The elderly age group has a higher risk of leprosy complications because they already have comorbid diseases and a decreased immune system.[25] Overall, all over the world, there was a peak bimodal incidence of leprosy in adolescents and the elderly.[4]

Globally, only about 35-37% of female leprosy patients are detected. In Ethiopia, only 35.5% of female leprosy patients are detected.[26] A study in Pakistan found only 0.5% of female leprosy patients. Studies in Sudan and Bangladesh also consistently report lower cases of leprosy in women than men.[27]

The proportions of MB leprosy in India, Brazil, and Indonesia are 48%, 66%, and 83% respectively.[28] Data from other epidemiological studies show Brazil has a prevalence rate of 1.54 cases per 10,000 population with 33,955 new cases in 2011. As many as 61% of these new cases were identified as MB leprosy.[7] Epidemiological studies in hyperendemic areas of leprosy have linked high rates of MB leprosy with male sex, low levels of education, and high rates of disabilities due to leprosy.[29]

Epidemiological studies of leprosy have concluded that the incidence of leprosy is related to several factors, including gender, race, ethnicity, and housing conditions.[30] Individuals who live in places with high levels of poverty have a five times higher risk of leprosy. Low income and poor living environment increase the risk of leprosy twofold.[31] A positive correlation was found between the leprosy reagent and the non-white population in Brazil.[30] Asians and Pacific Islanders are associated with a higher probability of MB leprosy.[32] This information supports the hypothesis of the associative nature of disease with social conditions. Leprosy does not only originate from the disease process, but also social factors that directly affect health.

The majority of genotypes in the study were the same as the genotypes that were mostly found in India, Brazil and China. The wild-type genotype of the interleukin-10 gene promoter at point -2849 in India, Brazil, and China is GG. However, although the genotypes of the IL-10 gene promoter at point -2849 in India, China, and Brazil are the same, the effect on leprosy susceptibility is different. The GG genotype at -2849 gene promoter IL-10 point in India and China increased susceptibility to leprosy while GG genotype studies in Brazil increased resistance to leprosy.[15,20,33]

Riyazi et al (2005) found a correlation between the amount of IL-10 secretion and the genotype of the IL-10 gene promoter at -2849. In two independent studies, De Jong et al (2002) and Lard et al (2003) found that the GG genotype produced greater amounts of IL-10 than the AA genotype. Based on this research, wild-type genotype could increase the risk of susceptibility and severity of leprosy. This is because the increase in IL-10 will suppress Th1 so that the body responds to *M. leprae* using the humoral immune system. The humoral immune system is not effective in treating leprosy. So that patients will be more susceptible to leprosy and if affected by leprosy, the type of leprosy manifestation that arises is MB leprosy.[34,35,36]

Interleukin-10 is produced at chromosome 1 locus 1q31-1q32. The length of the IL-10 coding gene is 4.7 kb. The promoter region is a DNA sequence that indicates the start of gene transcription by RNA polymerase. The promoter region consists of the nuclear region, the proximal region, and the distal region. The point -2849 gene promoter is one of points that located in the distal region of this gene promoter. Changes in the promoter region affect the amount of IL-10 secretion.[37]

Changes at one point did not significantly change the outcome of IL-10 secretion. To determine the impact of polymorphisms, further research on the IL-10 gene promoter haplotype is needed.[18] Research on the haplotype of IL-10 gene promoter polymorphism has been conducted in Brazil, India and China.

In Brazil, haplotype IL10 -3575A/-2849G / -2763C increases resistance to leprosy while IL10-3575T/-2849A/-2763C shows susceptibility to leprosy.[15] In India, haplotype IL10-3575T/-2849G/-2763C/-1082A/-819C/-592C acts as a protective halotype for leprosy while -3575T/-2849G/-2763C/-1082A/-819T/-592A acts as a disease-prone haplotype leprosy.[20] In China, haplotype -3575A/-2849G/-2763A/-1082G/-819C/-592C is associated with leprosy susceptibility.[33] From those researches, it can be seen that point -2849 has the same genotype G but when it is combined into a haplotype the effect will change.

The IL-10 cytokine has a dual effect on immunoregulation: anti-inflammatory and pro-inflammatory. In the acute stage of inflammation, IL-10 will help NK cells act as pro-inflammatory cytokines. In the chronic stage, IL-10 acts as an anti-inflammatory cytokine by suppressing Th1 action.[14]

Changes in the amount of IL-10 secretion have been investigated at points A1082G, C819T and C592A. Polymorphisms at those points increase the amount of IL-10 secretion. Increasing IL-10 will decrease Th1 function so that the susceptibility to leprosy increases.[15,18]

Not only SNPs, haplotype variations affect IL-10 secretion. A study reported that the IL-10-1082G/ -819C / -892C / -592C haplotype showed relatively low IL-10 secretion, whereas the 1082A / -819C / -592C haplotype showed relatively high IL-10 secretion.[38]

Another study showed the haplotype IL-10 promoter -3575T / -2849G / -2763C was shown to be associated with IL-10 hypersecretion while the haplotype -3575A / -2849G / -2763A was associated with lower IL-10 secretion. The points -3575, -2849, and -2763 are located distal to the gene promoter. Distal SNPs have a greater effect on IL-10 secretion than proximal SNPs.[39]

From previous studies, it can be concluded that SNP studies on the IL-10 gene promoter and haplotype can be associated with IL-10 secretion and susceptibility to leprosy. Before the relationship is explored, it is necessary to identify the points that are suspected of being influential. Polymorphisms at the IL-10 gene promoter point -2849 in leprosy patients in South Sumatra have been identified. Many patients have wild-type alleles. The next study was to examine adjacent points and then examine the haplotype pattern in leprosy patients.

5. Conclusion

Leprosy patient dr. Mohammad Hoesin has the majority of the wild-type genotype.

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