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Original Article

Indoleamine 2, 3-dioxygenase (IDO) levels in leprosy patients with positive serology

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Abstract

Background Seropositive leprosy individuals have a tendency to experience a change into leprosy lepromatous type. Previous studies have demonstrated that the activity of indoleamine 2, 3-dioxygenase (IDO) in patients with lepromatous type leprosy is higher than those with tuberculoid type leprosy. However, no study has been available showing how IDO level can be correlated to seropositive subjects.

Methods Our observational cross-sectional study was conducted in Brebes, Central Java, Indonesia. Leprosy seropositivity was determined by measuring the level of anti-phenolic glycolipid-1 IgM and IDO level using ELISA.

Results Result of The IDO level in seropositive leprosy subjects was higher compared to those who were seronegative ($p = 0.048$).

Conclusion In the early stage of leprosy infection, a high level of IDO level can already be found; therefore, it can affect immune response and ultimately affecting further course of the disease .

Key words
Seropositive leprosy, indoleamine 2, 3-dioxygenase, anti-phenolic glycolipid-1 IgM.

Introduction

Leprosy still remains a major public health problem in Indonesia since the incidence of leprosy is relatively high.[1] It is possibly due to contact with seropositive leprosy patients that have been turning into manifest leprosy.

Measuring the level of anti-phenolic glycolipid-1 immunoglobulin M (PGL-1 IgM) is one of the methods to detect seropositive leprosy subjects.[2,3] The level of such cellular immune response will determine leprosy spectrum. The cellular immunity in leprosy tuberculoid type is still good, on the contrary, there is decreased cellular immunity in leprosy lepromatous type.[4] Individuals with seropositive leprosy contact (IgM anti-PGL-1 level more than 600 unit/ml), have a tendency to experience a change into leprosy lepromatous type.

Previous studies have demonstrated that leprosy patients with lepromatous type have a higher activity of indoleamine 2, 3-dioxygenase (IDO) compared to those with tuberculoid type. The role of IDO levels in leprosy has been studied and an increased number of macrophages/dendritic cells (DC–lineage IDO+ cells were found in lepromatous (LL) compared to tuberculoid (BT) and reversal reaction (RR) patients. LL lesions were characterized by

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massive macrophage infiltration containing a variable number of Virchow cells, full of bacilli accompanied by few lymphocytes, separated from the flat epidermis by a clear zone. BT lesions were characterized by an organized dermal granuloma composed of phagocytic cells with evident epithelioid differentiation surrounded by lymphocytes of giant cells. RR lesions showed activated macrophages with an epithelioid appearance, organized or not as granuloma.[5]

However, no study has been conducted to evaluate how IDO level can be correlated to seropositive leprosy subjects (IgM anti PGL – 1 level more than 600 unit/ml) and have not showed a clinical manifestation on the skin. Our study aimed to identify the difference of IDO level between seropositive and seronegative leprosy subjects.

Methods

Our study was an observational study using a cross-sectional method. In August 2015, the study was conducted in Brebes, Central Java, Indonesia. Ethical clearance was approved by the Ethics Committee of Medical and Public Health Research, Faculty of Public Health, Diponegoro University.

The eligible subjects participated in our study were those who fulfilled the inclusion criteria: individuals who were living together with a leprosy patient, age between 15-55 years, showed no clinical symptom of leprosy, were not taking immunosuppressants during the last three months prior to the study and those who were willing to participate in our study. They also did not suffer from tuberculosis and did not take any anti-tuberculosis medications. The subjects were divided into 2 groups, i.e. those with seropositive leprosy (anti PGL-1 IgM > 600 unit/mL) 6 and those who were seronegative.

Five milliliters of venous blood was drawn from each subject. The whole blood was centrifuged to separate the serum, which was then stored at –70°C. Seropositive leprosy was determined by measuring the levels of anti-PGL-1 IgM antibodies using enzyme-linked immunosorbent assay (ELISA) (Polyclonal rabbit anti-human IgM/HRP (Dako ®) and analyzing IDO levels using ELISA commercial kits (Cusabio®, Catalog No: CSB-E09966h). All tests were conducted at the Institute Tropical Disease Laboratory, Airlangga University, Surabaya.

The education level of subjects was categorized into 2 groups, i.e. basic and moderate education. Subjects in basic education group were those who had completed their elementary and junior high school; while moderate education group involved those with senior high school educational background

Results

Table 1 shows that the gender, level of education and age had no effect on the seropositivity (anti-PGL-1 IgM antibodies levels) in leprosy patients; but the levels of IDO were significantly different between seropositive leprosy with seronegative subjects ($p = 0.048$).

In sex variable, there were 20.7% male and 79.3% female with seropositive leprosy and 33.3% male and 66.7% female with seronegative leprosy. There is no significant difference between seropositive leprosy subjects and seronegative leprosy subjects in sex variable ($p = 0.275$).

In level of education variable, seropositive leprosy subjects in primary education is 82.8% and 17.2% is in higher education while in

Table 1 Subject characteristics and indoleamine 2, 3-dioxygenase (IDO) levels.

Variables	*Seropositive leprosy (n=29)*	*Seronegative leprosy (n =30)*	*P*
Sex			
Male (%)	20.7	33.3	0.275[a]
Female (%)	79.3	66.7	
Level of education			
Primary education (%)	82.8	80.0	0.786[a]
Higher education (%)	17.2	20.0	
Age (years), (mean + SD)	33 ± 10	35 ± 11	0.399[b]
IDO (pg/mL), (median + SD)	13.80 ± 9.13	9.10 ± 4.60	0.048[c]

a=chi-square test, b= independent t-test, c=Mann-Whitney test

seronegative leprosy subjects there were 80% in primary education and 20% in higher education (p = 0.786)

The mean age of seropositive leprosy subjects was 33±10 years and the mean age of seronegative leprosy subjects was 35±11 years. (p = 0.399)

The mean IDO level in seropositive leprosy subject was 13.80±9.13 pg/mL while that in seronegative leprosy subject was 9.10±4.60 pg/mL. There was significant difference between seropositive leprosy and seronegative leprosy subjects in terms of IDO level (p=0.048).

Discussion

The first body mechanical defense against *Mycobacterium leprae* is by activating the antigen presenting cells (APCs) of immune system, i.e. the dendritic cells, monocytes and macrophages. IDO is predominantly expressed in APCs. Interferon gamma (IFN-γ) and dependent and/or independent signal pathways can activate and mediate IDO.[7]

Higher level of IDO found in seropositive leprosy subjects of our study supported the results of previous studies which indicate a high IDO protein expression in lepromatous skin lesions and high IDO activity in the sera of lepromatous leprosy patients.[5] People who live together under one and the same roof with leprosy patients with seropositive anti-PGL-I antibody have higher risk for developing leprosy (particularly the lepromatous type) compared to those who have contact with seronegative patients. The anti-PGL-I antibody level in people who live together under one and the same roof with leprosy indicates increased risk of having leprosy in the next 4 years. Another study in Philippines showed an increased risk of developing leprosy to 24-fold is caused by seropositive contacts.[8,9]

In addition due to *M. leprae*, the increased IDO activity in the sera of lepromatous leprosy patients also depends on IFN-γ. There is also a statement that IDO activity was at least partially dependent upon IFN-γ from a study in dengue patients.[10] IDO can be induced in response to various stimuli. The most potent inducer is IFN-γ, although other inflammatory stimuli, including type-I interferons (IFN-α/β) and bacterial lipopolysaccharide (LPS), and some viruses and intracellular pathogens, can induce IDO expression.[15] Support for the "two signal" requirement for IDO-expression has also been obtained in human samples.[14] For example, human monocytes expressed IDO in lepromatous leprosy due to the synergistic actions of IFN-γ and the bacterium (likely through pattern recognition receptor signaling).[5] *M. leprae* and IFN-γ is a cause of an increased of IDO expression in monocytes leprosy patients lepromatous type.[5] Leprosy patients with clinical

manifestation of leprosy or those with seronegative leprosy have a less IFN-γ level than seropositive leprosy.[11]

A higher IDO level in seropositive group found in our study supports the results of some previous studies, which showed that IDO induction after bacterial infection could be beneficial to the host. Amino acid tryptophan will break into stable metabolite called kynurenine when the IDO level increases.[12] Moreover, tryptophan depletion and starvation will occur since bacteria need tryptophan.[13,14] The growth of bacteria is dependent on the greater amount of tryptophan rather than T cells.[13]

IDO could be considered to be a double-edged sword in the immune response against pathogens. Immune cells, including antigen-presenting cells like DCs, are able to express IDO in response to various stimuli.[10]

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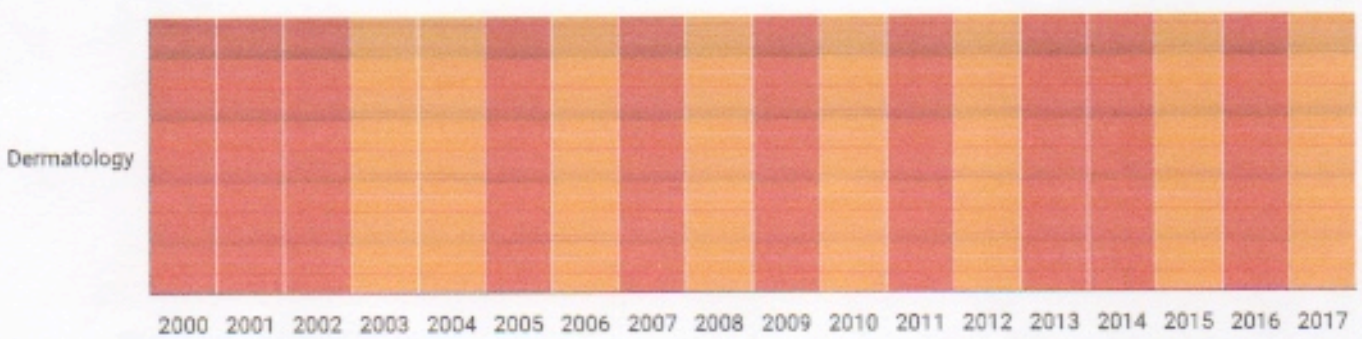

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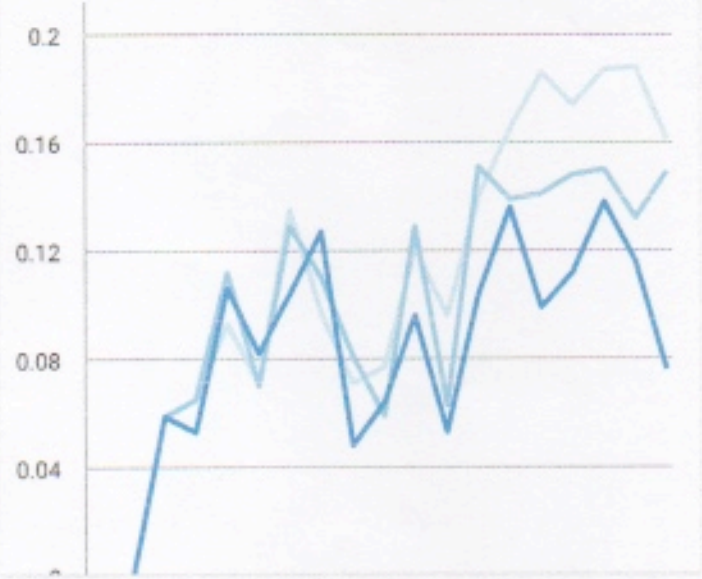

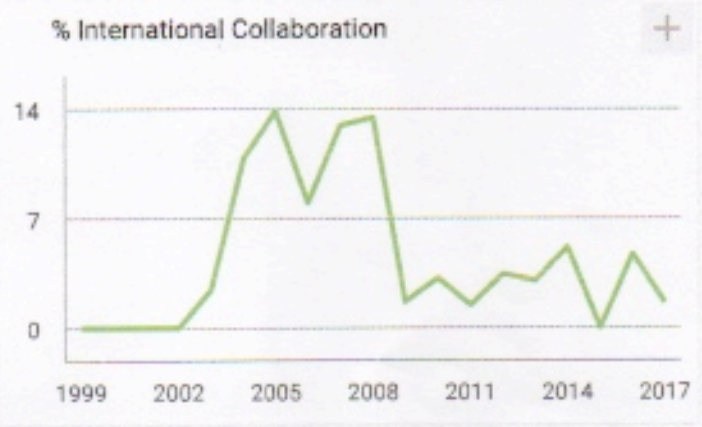

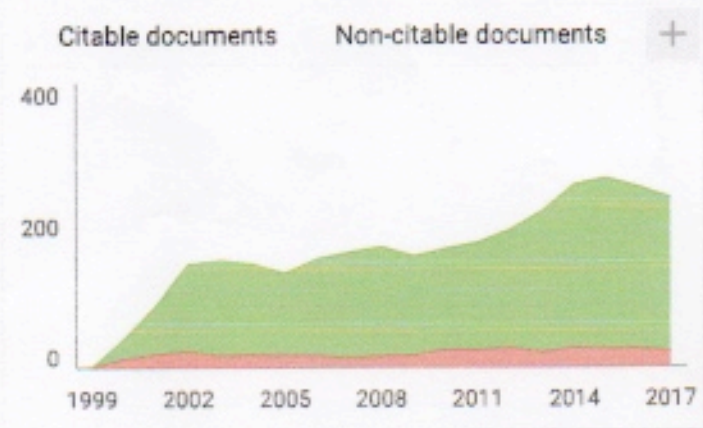

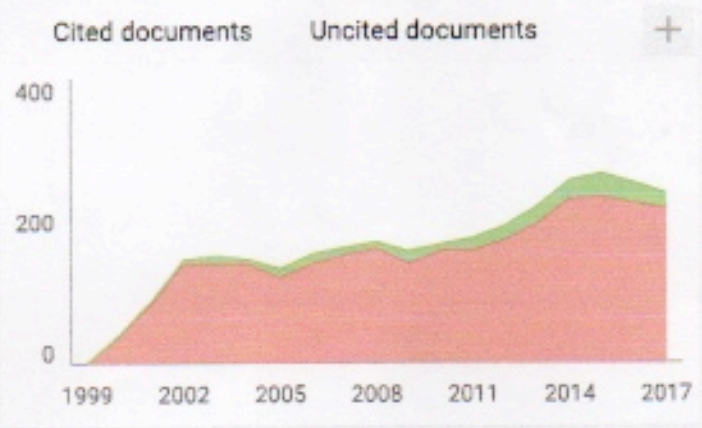

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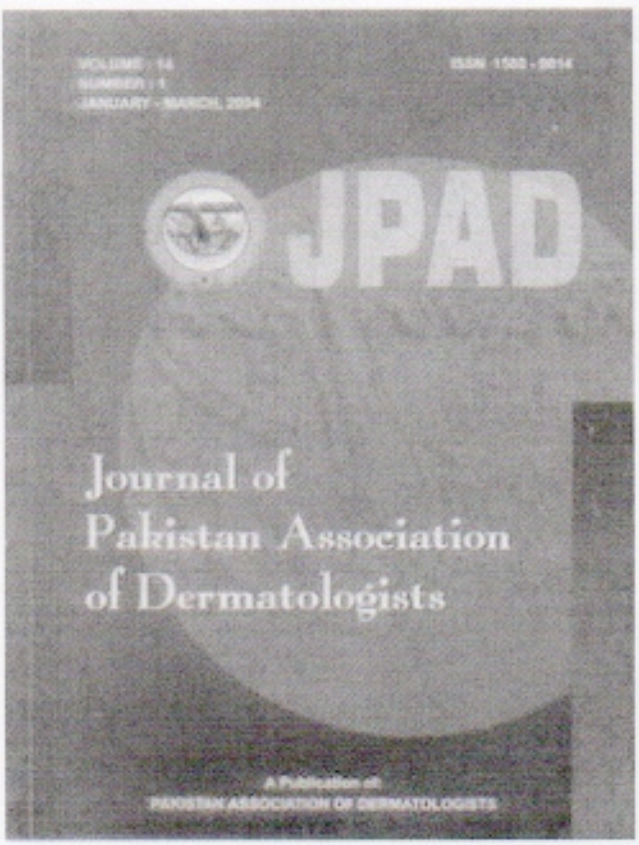

Indoleamine 2, 3-dioxygenase (IDO) levels in leprosy patients with positive serology

by Ago Harlim

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Original Article

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Abstract

Background Seropositive leprosy individuals have a tendency to experience a change into leprosy lepromatous type. Previous studies have demonstrated that the activity of indoleamine 2, 3-dioxygenase (IDO) in patients with lepromatous type leprosy is higher than those with tuberculoid type leprosy. However, no study has been available showing how IDO level can be correlated to seropositive subjects.

Methods Our observational cross-sectional study was conducted in Brebes, Central Java, Indonesia. Leprosy seropositivity was determined by measuring the level of anti-phenolic glycolipid-1 IgM and IDO level using ELISA.

Results Result of The IDO level in seropositive leprosy subjects was higher compared to those who were seronegative ($p = 0.048$).

Conclusion In the early stage of leprosy infection, a high level of IDO level can already be found; therefore, it can affect immune response and ultimately affecting further course of the disease .

Key words
Seropositive leprosy, indoleamine 2, 3-dioxygenase, anti-phenolic glycolipid-1 IgM.

Introduction

Leprosy still remains a major public health problem in Indonesia since the incidence of leprosy is relatively high.[1] It is possibly due to contact with seropositive leprosy patients that have been turning into manifest leprosy.

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Short description of IDO and its effect on leprosy

massive macrophage infiltration containing a variable number of Virchow cells, full of bacilli accompanied by few lymphocytes, separated from the flat epidermis by a clear zone. BT lesions were characterized by an organized dermal granuloma composed of phagocytic cells with evident epithelioid differentiation surrounded by lymphocytes of giant cells. RR lesions showed activated macrophages with an epithelioid appearance, organized or not as granuloma.[5]

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Methods

Our study was an observational study using a cross-sectional method. In August 2015, the study was conducted in Brebes, Central Java, Indonesia. Ethical clearance was approved by the Ethics Committee of Medical and Public Health Research, Faculty of Public Health, Diponegoro University.

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The education level of subjects was categorized into 2 groups, i.e. basic and moderate education. Subjects in basic education group were those who had completed their elementary and junior high school; while moderate education group involved those with senior high school educational background.

Results

Table 1 shows that the gender, level of education and age had no effect on the seropositivity (anti-PGL-1 IgM antibodies levels) in leprosy patients; but the levels of IDO were significantly different between seropositive leprosy with seronegative subjects ($p = 0.048$).

In sex variable, there were 20.7% male and 79.3% female with seropositive leprosy and 33.3% male and 66.7% female with seronegative leprosy. There is no significant difference between seropositive leprosy subjects and seronegative leprosy subjects in sex variable ($p = 0.275$).

In level of education variable, seropositive leprosy subjects in primary education is 82.8% and 17.2% is in higher education while in

Table 1 Subject characteristics and indoleamine 2, 3-dioxygenase (IDO) levels.

Variables	*Seropositive leprosy (n=29)*	*Seronegative leprosy (n=30)*	*P*
Sex			
Male (%)	20.7	33.3	0.275[a]
Female (%)	79.3	66.7	
Level of education			
Primary education (%)	82.8	80.0	0.786[a]
Higher education (%)	17.2	20.0	
Age (years), (mean ± SD)	33 ± 10	35 ± 11	0.399[b]
IDO (pg/mL), (median ± SD)	13.80 ± 9.13	9.10 ± 4.60	0.048[c]

a=chi-square test, b= independent t-test, c=Mann-Whitney test

seronegative leprosy subjects there were 80% in primary education and 20% in higher education ($p = 0.786$)

The mean age of seropositive leprosy subjects was 33±10 years and the mean age of seronegative leprosy subjects was 35±11 years ($p = 0.399$)

The mean IDO level in seropositive leprosy subject was 13.80±9.13 pg/mL while that in seronegative leprosy subject was 9.10±4.60 pg/mL. There was significant difference between seropositive leprosy and seronegative leprosy subjects in terms of IDO level (p=0.048).

Discussion

The first body mechanical defense against *Mycobacterium leprae* is by activating the antigen presenting cells (APCs) of immune system, i.e. the dendritic cells, monocytes and macrophages. IDO is predominantly expressed in APCs. Interferon gamma (IFN-γ) and dependent and/or independent signal pathways can activate and mediate IDO.[7]

Higher level of IDO found in seropositive leprosy subjects of our study supported the results of previous studies which indicate a high IDO protein expression in lepromatous skin lesions and high IDO activity in the sera of lepromatous leprosy patients.[5] People who live together under one and the same roof with leprosy patients with seropositive anti-PGL-I antibody have higher risk for developing leprosy (particularly the lepromatous type) compared to those who have contact with seronegative patients. The anti-PGL-I antibody level in people who live together under one and the same roof with leprosy indicates increased risk of having leprosy in the next 4 years. Another study in Philippines showed an increased risk of developing leprosy to 24-fold is caused by seropositive contacts.[8,9]

In addition due to *M. leprae*, the increased IDO activity in the sera of lepromatous leprosy patients also depends on IFN-γ. There is also a statement that IDO activity was at least partially dependent upon IFN-γ from a study in dengue patients.[10] IDO can be induced in response to various stimuli. The most potent inducer is IFN-γ, although other inflammatory stimuli, including type-I interferons (IFN-α/β) and bacterial lipopolysaccharide (LPS), and some viruses and intracellular pathogens, can induce IDO expression.[15] Support for the "two signal" requirement for IDO-expression has also been obtained in human samples.[14] For example, human monocytes expressed IDO in lepromatous leprosy due to the synergistic actions of IFN-γ and the bacterium (likely through pattern recognition receptor signaling).[5] *M. leprae* and IFN-γ is a cause of an increased of IDO expression in monocytes leprosy patients lepromatous type.[5] Leprosy patients with clinical

manifestation of leprosy or those with seronegative leprosy have a less IFN-γ level than seropositive leprosy.[11]

A higher IDO level in seropositive group found in our study supports the results of some previous studies, which showed that IDO induction after bacterial infection could be beneficial to the host. Amino acid tryptophan will break into stable metabolite called kynurenine when the IDO level increases.[12] Moreover, tryptophan depletion and starvation will occur since bacteria need tryptophan.[13,14] The growth of bacteria is dependent on the greater amount of tryptophan rather than T cells.[13]

IDO could be considered to be a double-edged sword in the immune response against pathogens. Immune cells, including antigen-presenting cells like DCs, are able to express IDO in response to various stimuli.[10]

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