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Interferon-gamma and interleukin-10 profile of children with tuberculosis in North Sumatera, Indonesia

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Abstract. Cellular immunity was mediated the host immune response against Mycobacterium tuberculosis, in which cytokine and T-helper (Th) 1 cells play an important role. Interferon-gamma (IFN-γ) is a leading cytokine involved in the immune response of tuberculosis (TB). The primary function of IFN-γ is to activate macrophages in opposition Mycobacterium tuberculosis. Contrast from IFN-γ, interleukin-10 (IL-10) is considered inhibitory cytokine, important to an adequate balance between inflammatory responses. To analyze cytokine profile, particularly IFN-γ and IL-10 of the children with TB in Indonesia, a cross-sectional study was conducted at two general hospitals and seven primary health care located in Medan and Batubara, North Sumatera, Indonesia. Among 51 children with TB disease and 51 healthy children, found that IFN-γ and IL-10 levels were lower in TB patients compared to healthy children. Statistically significant decreased production of the IFN-γ levels (p=0.042) were found in TB patients 9.41 (1.10-28.06) pg/ml contrast to healthy children 6.30 (1.30-89.76) pg/ml. Homologue finding of the IL-10 levels were also found in TB patients 4.93 (0.22-48.01) pg/ml and 4.93 (0.07-81.60) pg/ml in healthy children, but not statistically significant (p=0.784). High levels of IL-10 were not proven to suppress the levels production of IFN-γ in TB patients.

1. Introduction

Tuberculosis (TB) is a prime cause of illness and death. Over the past decade, the incidence of TB has been increasing worldwide. It is very important to understand the regulation of the human immune response in TB, because of its potential implication to prevent and control TB disease.[1,2]

Cellular immunity was mediated the host immune response against Mycobacterium tuberculosis, in which cytokine and T helper (Th) 1 cells play an important role. Interferon gamma (IFN-γ) is a leading cytokine involved in the protective immune response against mycobacterial infection. IFN-γ primarily produced by CD4 and CD8 T lymphocytes and natural killer (NK) cells.[1]

The primary function of IFN-γ is to activate and enable the macrophages to exert its microbicidal role function. IFN-γ also enhances the antigen presentation through the induction of the expression of molecules from the major histocompatibility complex (MHC) class I and class II which promote the differentiation of CD4 T lymphocytes to the Th 1 subpopulation. IFN-γ also induced the gene transcription in macrophages, including the production of antimicrobial molecule (oxygen free radical and nitric oxide) that represent as the best mechanism to eliminating Mycobacterium tuberculosis.[1,3,4]
IL-10 was described as a cytokine inhibitory factor due to its capability to inhibit the T lymphocyte production of cytokine. IL-10 produced by macrophages and T lymphocytes during Mycobacterium tuberculosis infection. Previous studies showed that IL-10 inhibit the production of pro inflammatory cytokines, including IFN-γ, inhibit the action of antigen presenting cells (APC) and block the activation of T lymphocytes through the inhibition of expression of MHC class II molecules. The increase in IL-10 levels appear to support the survival of mycobacterial in the host.[1,5]

The aim of this study was to analyze cytokine profile, particularly IFN-γ and IL-10 of children diagnosed with TB in two general hospitals and seven primary health care located in Medan and Batubara, North Sumatera, Indonesia. The result can be implemented as a guideline for new treatment to prevent or control TB disease.

2. Methods
In this study, a cross-sectional study was performed to analyze the cytokine profile, particularly IFN-γ and IL-10 of children diagnosed with TB in Medan and Batubara, North Sumatera, Indonesia. The subjects were children diagnosed with TB disease and the control group consisted of healthy children. This study was approved by ethics committee of Medical Faculty, Universitas Sumatera Utara, Indonesia.

From January to November 2016, we recruited samples from two general hospitals and seven primary health care in Medan and Batubara, North Sumatera, Indonesia. Children with 2 months to 14 years old age diagnosed with TB and have approval from the parents or guardian to participate in this study were enrolled within subjects. Subjects withdrawn from the study if immunodeficiency condition were found or the patients suffered for other infection disease.

Subjects consist of 51 children with TB disease. Diagnosis of TB disease based on clinical manifestation, positive result of tuberculin skin test and chest x ray finding in which suggest TB. The control group are 51 healthy children without TB, that proven by negative result of the tuberculin skin test. All the samples will be performed blood test in order to measure the cytokine response. Measurement of cytokine response from the subjects and the control group, in which IFN-γ and IL-10 levels in the supernatant were measured by using human enzyme-linked immunosorbent assay/ELISA kits (Quantikine) according to the manufacture’s instruction.

Data analysis were performed using Statistical Package for Social Sciences (SPSS) software version 22. When the variance was not equal, non-parametric Mann Whitney test was used to analyze IFN-γ and IL-10 levels of TB patients and the healthy control. Statistically significant result will be considered whereas p<0.05.

3. Results
During the study period, 51 children diagnosed with TB were recruited for the subjects and 51 healthy children were recruited for the control group. The characteristics of samples are shown in Table 1. Most of TB patients were female (72.5%) with age younger than 5 years old or older than 10 years old age (54.9%). Malnutrition condition were found more common in children diagnosed with TB (64.7%)

| Table 1. Characteristics of samples. |
|-------------------------------------|
| Characteristics | TB Patients n (%) | Healthy Control n (%) |
|-----------------|--------------------|------------------------|
| Gender          |                    |                        |
| Male            | 14 (27.5)          | 27 (52.9)              |
| Female          | 37 (72.5)          | 24 (47.1)              |
| Age             |                    |                        |
IFN-γ levels of TB patients were 9.41 (1.10-28.06) pg/ml, in which lower compared to healthy control. The difference of IFN-γ levels between TB patients and the healthy children was found statistically significant with p=0.042* (Table 2).

Table 2. IFN-γ levels of TB patients and healthy control.

|                              | Median (min-max) | p    |
|------------------------------|------------------|------|
| IFN-γ levels of TB patients  | 9.41 (1.10-28.06)| 0.042|
| IFN-γ levels of healthy control | 6.30 (1.30-89.76) |      |

Table 3 showed that IL-10 levels were lower in TB patients compared to healthy control 4.93 (0.22-48.01), but the difference was not statistically significant (p=0.784).

Table 3. IL-10 levels of TB patients and healthy control.

|                 | Median (min-max) | p    |
|-----------------|------------------|------|
| IL-10 levels of TB patients | 4.93 (0.22-48.01) | 0.784|
| IL-10 levels of healthy control | 4.93 (0.07-81.60) |      |

4. Discussion

TB is one of the major causes of serious public health obstacle in the developing country.[6] Indonesia ranked on the fifth position for the country with highest TB incidence (410,000 - 520,000 cases). The other top four ranked countries with highest TB burden are India (2,230,000 cases), China (0.9 – 1.1 million cases), Nigeria (340,000 – 880,000 cases) and Pakistan (370,000 – 650,000 cases).[7]

In order to prevent and to control TB disease, an improved understanding of the human response in TB is one of the vital aspects to understand.[8] Cytokines play an important role in modulation of the immune response.[9] IFN-γ secreted from activated T cells and NK cells have the power to activate macrophages that enhance mycobacterial eradication by permitting phagosomal maturation and production of the antimicrobial.[8] Macrophage activation is a major mechanism by which Mycobacterium tuberculosis was eradicated during the immune response.[10]

This study was analyzed association between IFN-γ levels and IL-10 levels, because decreased of IFN-γ levels might be correlate with higher IL-10 levels of TB patients. In this study, we did not found correlation between IFN-γ levels and IL-10 levels. This was similar to previous study by Yu CC et al in Taiwan that showed IFN-γ levels were not affected by IL-10 levels.[10] Th1 cells responding to antigen and antigen presenting cells (APC) cause inhibition of IFN-γ by IL-10, but Th2 cytokine synthesis was not significant affect.

In this study, we found statistically significant difference between IFN-γ levels of TB patients contrast to the healthy control (p=0.042*). IFN-γ levels of TB patients were lower 9.41 (1.10-28.06) pg/ml compared to the healthy control, 6.30 (1.30-89.76) pg/ml. Low levels of IFN-γ of TB patients will cause decreased of activation of macrophages, leading to occurred of TB disease.

Our data demonstrated IL-10 levels of TB patients were lower 4.93 (0.22-48.01) pg/ml than healthy control 4.93 (0.07-81.60) pg/ml, but the difference were not statistically significant (p=0.784). Other researchers in Brazil [1] and Croatia [9] reported different findings. They found IL-10 levels...
were higher in TB patients. Beamer et al [11] also found higher IL-10 levels in mice. Our founding suggested that might be other cytokine role that influences IFN-γ levels others than IL.

5. Conclusion
High levels of IL-10 were not proven to suppress the levels production of IFN-γ of the TB patients. Further studies needed to prove other specific cytokine that inhibits production of IFN-γ are needed, in order to prevent and control TB disease in children.

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