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Inflammatory Cytokines Response among Positive Tuberculin Skin Test Children with Household Contacts Tuberculosis in an Endemic TB Setting

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Abstract

Cell-mediated immunity, which involves interactions between T cells, macrophages, Interferon-gamma (IFN-γ) and Interleukin-17 (IL-17) are essential to the host against *Mycobacterium tuberculosis* (Mtb) infection. Understanding the correlation between cytokine response and tuberculin skin test (TST) in latent tuberculosis (TB) infection children with household contact exposure may provide insights into immune mechanisms and diagnosis tuberculosis. This study was conducted at Dr.Soetomo Hospital, Indonesia. Children diagnosed with history of closed contact TB were performed TST. Serum levels of IFN-γ, IL-10, and IL-17 were measured using enzyme-linked immunosorbent assay (ELISA). Data were analyzed using Mann-Whitney U test, with statistical significance set at $p < 0.05$. Tuberculin skin test was positive in 20 (66.67%) children. Mean level serum of IFN-γ, IL-17, and IL10were38.04 pg/mL, 4.96 pg/mL and 6.86 pg/mL.There were significant elevated of IFN-γ and IL-10 in children with positive TST group.Children with TB infection have a complex immunological response, as evidenced by their positive TST and elevated IFN-γ and IL-10 levels. Cytokine profiling could be helpful in differentiating between latent or early exposure and active disease in pediatric populations.

Keywords: Immunology, Immune System, Infection Disease, Tuberculosis, Mantoux

Introduction

Tuberculosis (TB) remains a substantial global health issue caused by the bacillus Mycobacterium tuberculosis (Mtb)(1,2). Recently, the World Health Organization (WHO) declared that tuberculosis (TB) has become the foremost cause of mortality from a single infectious agent, succeeding a three-year period during which it was surpassed by coronavirus disease (COVID-19). Worldwide, over 10.8 million individuals contracted tuberculosis. There are approximately 1.3 million cases among children and young adolescents (aged 0-14 years), accounting for 12% of the total estimated cases (3).

Upon exposure and infection with Mtb, the organism can form an asymptomatic, latent infection in the lung or may advance to active tuberculosis (4). Household contacts are at a heightened risk of contracting TB infection from index patients. Infants and children are more predisposed to severe manifestations of tuberculosis due to an underdeveloped immune response (5-7).Cellular immunity facilitated the host immune response against MTB, with cytokines and Th1 playing a crucial role. Interferon gamma (IFN-γ) and Interleukin-17(IL-17) are pro-inflammatory cytokines implicated in the protective immune response to Mycobacterium tuberculosis (MTB) infection. Interleukin-10 is an anti-inflammatory cytokine involved in preventing infections within the host organism (8,9).

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To develop effective methods and risk mitigation in regions with a high risk of tuberculosis transmission, it is essential to delineate the immunopathogenic mechanisms. The objective of this study is to investigate the inflammatory reactions in children who have household contact.

Materials and Methods

The current study employed a cross-sectional design and involved children ages 1 month to 18 years who had close contact with an index case of tuberculosis. All children had examination and diagnosis by pediatric respirologist consultants from the pediatric department of Dr.Soetomo Academic General Hospital in Surabaya, Indonesia. All children had a medical interview, physical examination, and diagnostic assessments, including chest X-ray, tuberculin skin test (TST) and microbiology confirmation.

The TST or Mantoux test was conducted with 2 tuberculin units (TU) of the purified protein derivative (PPD) RT23. The pediatrician assessed the transversal diameter of skin induration after 48 to 72 hours. A result was deemed affirmative when the induration size was ≥10mm. A positive TST test indicated latent Mtb infection, while a negative TST result signified the absence of Mtb infection.

Prior to sample collection, informed consent was obtained from the parents of each participant. Peripheral blood sampleswere obtained from the children and collected in a vacutainer tube. Serum levels of IFN-γ, IL-17, and IL-10 were quantified using human enzyme-linked immunosorbent assay (ELISA) kits in accordance with the manufacturer's instructions. Interferon gamma and IL-10 were measured using the Elabscience® High Sensitivity Human ELISA kit, while IL-17 was assessed with the Quantikine® High Sensitivity Human ELISA. The protocol for this study received approval from the Research and Ethical Committee of Dr.Seotomo Academic General Hospital, Indonesia.For demographic analysis, the Fisher's exact test was completed. For age, weight, height, were performed by Mann-Whitney U test. Statistical analysis was performed by SPSS software, version 26.0 (IBM Corp, New York, NY, USA).

Results

A total of 30 participants had a mean age of 11.7 ± 0.50 years, with 17 (54.8%) were female children. The mean body weight was 36.8 ± 16.6 kg and the mean height was 140 ± 22.60 cm. Fifty percent of children were diagnosed with tuberculosis, comprising both pulmonary tuberculosis (PTB) and extrapulmonary tuberculosis (EPTB). The tuberculin skin test yielded positive results in 20 children, representing 66.67% of the cohort. The characteristic of subject described in (Table 1).

To investigate variations in cytokine responses among children with household contact, we assessed cytokine levels in plasma (Table 2). This study indicates that the mean serum level of IFN-γ is 38.04

Table 1: Demographic characteristics of subjects

	Tuberculin test (N=30)		p
	Positive (n=20)	Negative (n=10)	
Age(Years)	12.4 (±0.95)	10.30 (±1.39)	0.000*
Sex (%) Boy Girl	 9 (30%) 11 (36.7%)	 4 (13,3%) 6 (20%)	0.794
Weight(kg)	35.30(±2.98)	39.80 (±7.06)	0.000*
Height(cm)	142.55(±4.73)	136.20(±8.18)	0.000*
Nutritional status Normal nutrition Malnutrition	 13 (43.3%) 7 (23.3%)	 10 (33.4%) NA	0.033*
Scar BCG	17 (56.7%)	10 (33.4%)	0.197

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Table 2: Cytokine inflammatory level plasma in children with household contact TB						
Inflammatory cytokine	Mean (pg/mL)	SD	Minimum	Maximum	95% Confidence Interval	
					Lower bound	Upper bound
IFN-γ	38.04	62.71	0.44	222.31	14.62	61.46
IL-17	4.96	9.42	0.18	51.63	1.45	8.48
IL-10	6.86	10.17	0.95	51.63	3.05	10.65

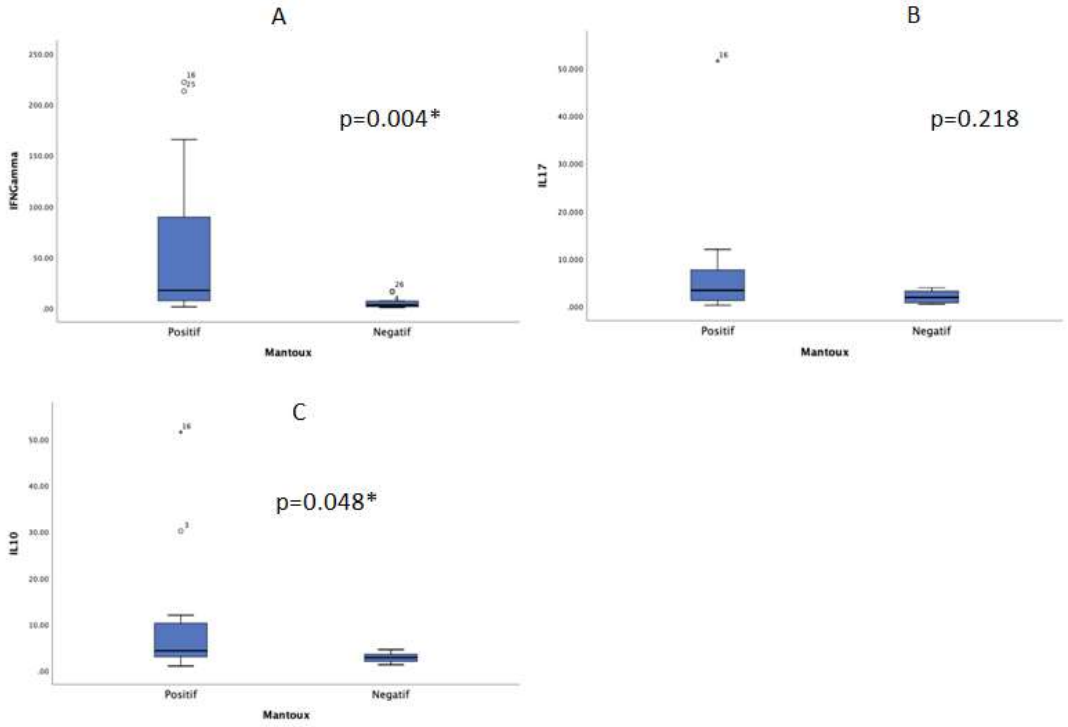

Fig. 1: (A) Inflammatory response of IFN-γ in children with positive TST; (B) Inflammatory response of IL-17 in children with positive TST; (C) Inflammatory response of IL-10 in children with positive TST

pg/mL, surpassing the mean levels of IL-17 and IL-10. The peak concentration of IFN-γ was 222.31 pg/mL.

As depicted in Figure 1, there were elevated production of IFN-γin children with positive TST children compared with negative TST children (54.37 pg/mL vs 5.37 pg/mL, p = 0.004). Significant elevated of IL-10 were highlighted in children with positive TST compare with children with negative TST (8.87 pg/mL vs 2.81 pg/mL, p = 0.048). from this study showed elevated IL17 in children with positive TST but no significantly statistic (6.47 pg/mL vs 1.95 pg/mL, p = 0.218).

Discussion

Host systemic and pulmonary immunity is crucial in tuberculosis pathogenesis by regulating the clearance, survival, and replication of Mtb (10).Following that, numerous pathways of signaling get active, leading to the release of cytokines and chemokines (11,12).The cytokine response in tuberculosis differs from that in other respiratory infections. In

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tuberculosis infection, the response is typically extended and inclined towards Th1-type responses, characterized by increased levels of IFN-γ (13). This study demonstrated higher levels of the pro-inflammatory cytokines IFN-γ and IL-17 in children with a positive TST. Comparable to earlier studies, CD4+ T-cell production of IFN-γ and TNF-α was observed in children and adults with confirmed TB. Another study demonstrated that IFN-γ levels are significantly elevated in children with active tuberculosis and those in close contact with TB patients (14).Conversely, another study shown that the production of IFN-γ and IL-17 was markedly reduced in children with tuberculosis compared to their healthy counterparts (15-16). Protective immunity to Mtb relies on Th1, Th17, and Treg cells, which mediate both antibacterial and pro-inflammatory host defensive mechanisms (17).

This study highlights an increase in IL-17 levels in children with a positive TST, while the results are not statistically significant. Another study demonstrated significantly higher levels of IL17A in children with confirmed or unconfirmed tuberculosis (18). This aligns with recent data indicating increased IL-17A production in people with active tuberculosis (19). Inflammatory cytokines such as IFN-γ, TNF-α, IL-2, and IL-17A can effectively differentiate proven in children within a highly endemic area (18). Th1 and Th17 cells are the primary effector CD4+ T cells in tuberculosis infection. Key Th1-inducing cytokines are IFN-γ and IL-12, succeeded by IL-2, TNF-α, and IL-27. Interleukin-12 reduces the bacterial load of tuberculosis by sustaining IFN-γ production, which restricts prolonged bacterial proliferation, with their levels regulated by IL-10 (20-26).

This study revealed a considerable elevation of the anti-inflammatory cytokine IL-10 in children with a positive TST. Consistent with prior research, the inflammatory mediator IL-10 is positively correlated with the tuberculin test in children with tuberculosis. Regulatory T cells and circulating levels of IL-10 have been proposed to be elevated in children with extrapulmonary tuberculosis both during the illness and thereafter (21).In contrast to another study, the balanced ratio of pro- and anti-inflammatory cytokines indicated no higher levels of IL-10 in children newly diagnosed with tuberculosis (27). Interleukin-10 is an immunomodulatory cytokine that suppresses cell differentiation. Elevated levels of TB have been correlated with disease progression and unfavorable outcomes (28-30).

The limitation of this study is based on a cross-sectional analysis andsmall sample size. It may lack sufficient ability to discern differences between the groups, hence constraining the generalizability of our findings. Future cohort studies with substantial sample sizes would enable the detailed monitoring of changes in cytokine inflammatory plasma levels from a state of health to infection and subsequently to disease onset.

Conclusion

In conclusion, cytokine inflammatory responses, particularly IFN-γ and IL-10, are significantly enhanced in children with a positive tuberculin test as a protective mechanism against Mtb infection. Serum-derived immune markers may indicate the biological processes linked to the host response to Mtb and could aid in diagnosing TB in children.

Ethic approval

This study was approved as ethically appropriate by the Research and Ethical Committee of Dr.Seotomo Academic General Hospital, Indonesia (No. 0785/KEPK/IX/2023).

Conflicts of interest

The authors declare they had no conflict of interest.

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