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The Influence of IL-4, IL-18, IFN-Γ AND TNF-A Properties in Blood Plasma in HIV-Infected Children

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Abstract: Despite advancements in treatment and care, HIV infection continues to pose significant challenges, especially in pediatric populations. Children living with HIV often experience immune dysregulation and heightened inflammatory responses, leading to increased susceptibility to opportunistic infections and disease progression. Cytokines are critical signaling molecules that orchestrate the immune response and influence the pathogenesis of HIV infection (Tudela et al., 2014).

The epidemiological situation of tuberculosis in different regions of the world is constantly changing as a result of the complex relationship between population movements, the number and distribution of tuberculosis patients , the socio-economic and cultural level of the population, the availability of medical care, and the prevalence of HIV infection.

Keywords: HIV, children, CD4 cells, interleukins.

Among the various cytokines involved in HIV pathogenesis, interleukin-4 (IL-4), interleukin-18 (IL-18), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) play crucial roles in shaping the immune milieu. IL-4 is involved in promoting Th2 responses and antibody production, while IL-18 is a proinflammatory cytokine that modulates innate and adaptive immunity. IFN-γ is a key cytokine in promoting antiviral mechanisms, whereas TNF-α plays a central role in the inflammatory cascade and immune activation (Tudela et al., 2014).

Understanding the dynamics of these cytokines in HIV-positive children can provide valuable insights into the underlying immunopathogenic mechanisms and help guide personalized treatment approaches. Ultimately, elucidating the features of IL-4, IL-18, IFN-γ, and TNF-α in blood plasma may contribute to improved clinical management and outcomes for pediatric patients living with HIV (da Cunha et al., 2015).

In this study, we sought to investigate the levels of IL-4, IL-18, IFN-γ, and TNF-α in the blood plasma of HIV-positive children and evaluate their relationship with disease progression and immune status. By examining the cytokine profiles in these pediatric patients, we aim to delineate the immune signatures associated with HIV infection and identify potential biomarkers for disease progression and therapeutic intervention.

Aim of the study

The aim of the study was to study the characteristics of cytokines IL-4, IL-18, IFN-γ and TNF-α in the blood plasma of HIV-positive and HIV-negative children.

Materials and methods.

Study population. A total of 77 participants, including 69 HIV-infected individuals and 8 HIV-negative controls, were randomly selected for this study. Blood sampling and research were carried out at the Republican AIDS Center of Uzbekistan and the Institute of Immunology and Genomics of the Academy of Sciences of Uzbekistan, Tashkent. Blood samples were collected at one point during antiretroviral therapy.

1. HIV positive patients. HIV-infected individuals (n=69) were aged 9–19 (m=16.33) years and their blood samples were collected during ART. The number of male and female participants was 42 and 27, respectively.

2. Participants for control. Children in the control group (n=8) were HIV-seronegative and aged from 8 to 14 years (m=12.0). Among them are 5 boys and 3 women.

Inclusion and exclusion criteria. Individuals younger than 19 years of age who initiated ART were eligible to participate. Individuals with active opportunistic infections, inflammatory conditions, and diarrhea were excluded. Control subjects were apparently healthy HIV-seronegative individuals younger than 19 years of age and eligible for the study.

Study design. The study design was a cross-sectional study in which blood samples were collected from study subjects during ART.

Sample collection. From all study participants, 5 milliliters of fasting blood was collected by veinpuncture. Blood samples were appropriately aliquoted into serum separation tubes (SST) to obtain pure serum for cytokine determination (IL-4, IL-18, TNF-α, and INF-γ). Sera were separated and stored at $\leq -20°C$ until analysis.

Cytokine measurement. Cytokines IL-4, IL-18, TNF-α and INF-γ were determined using an ELISA kit (Vector Best, Russian Federation). The quantitative sandwich enzyme-linked immunosorbent assay method was used.

Statistical analysis. Results were presented as mean ± standard deviation. Differences between the results of the control group and HIV-positive subjects receiving ART were analyzed using Student's t-test. The statistical package MS Excel version 2010 was used to analyze the data. Significant levels were considered at $P < 0.05$.

Results

Average value of IL-4 in the blood of participants in the main and control groups was 1.68 pg/ml and 1.16 pg/ml, respectively. There was no statistically significant difference between the IL-4 values in the groups (p=0.1425). The average concentration of IL-18 in the groups of participants with HIV and without HIV was 301.20 pg/ml and 165.25 pg/ml, respectively. The level of IL-18 in the blood plasma of patients with HIV was significantly higher than that of participants with negative HIV status (p=0.0002). In the blood serum of participants in the main and control groups, the average IFN-gamma content was 54.72 pg/ml and 12.07 pg/ml, respectively. It was found that the concentration of IFN-gamma in the main group was statistically significantly higher than in the control group (p=0.00001). The results of this study showed that the concentration of TNF-alpha in the blood plasma of patients in the main group (M=19.45 pg/ml) was significantly higher than that in the group of HIV-negative participants (M=9.99 pg/ml) (p=0.00001).

Discussion

Investigations have shown (Tudela et al., 2014) (Osuji et al., 2018) that pro-inflammatory cytokines are released in significant quantities at various stages of HIV infection, but as the viral load decreases, the number of CD4+ T helper cells in the blood increases, which leads to increase the release of pro-inflammatory cytokines. The results of our study were similar to the results of recent studies (Tudela et al., 2014) (Osuji et al., 2018). Thus, in our study, the content of the pro-inflammatory cytokine TNF-alpha in the HIV-positive group was significantly higher

than in the HIV-negative group (p = 0.00001). Also, the concentration of the pro-inflammatory cytokine IL-18 was significantly higher in the main group than in the control group (p=0.0002). However, these results contrast with a study by Fantauzzi, Floridia (Fantauzzi et al., 2015) and Musve, Oktedalen (Amoani, Sakyi, Barnie, et al., 2021), who found relatively low levels of TNF-α among HIV+ patients.

According to a study (JR & NG, 2016), ART significantly reduces the incidence and severity of opportunistic diseases. It gives the body the opportunity to restore its immune function. During antiretroviral therapy, there is a decrease in plasma IFN-γ levels, which helps suppress inflammation and activate the immune system. This decrease in the level of the above-mentioned cytokine may be due to the restoration of the immune system after suppression of the virus. On the contrary, according to the results of our study, the concentration of IFN-gamma, a regulator of the humoral immune response, in the group of patients with HIV infection was statistically significantly higher than in the control group (p = 0.00001).

Conclusion

Concentration of IFN-gamma, a regulator of the humoral immune response, in the group of patients with HIV infection was statistically significantly higher than in the control group (p=0.00001). On the contrary, the concentration of another regulator of the humoral immune response, IL-4, differs slightly in the main and control groups (p = 0.1425). The content of the pro-inflammatory cytokine TNF-alpha in the HIV-positive group was significantly higher than in the HIV-negative group (p = 0.00001). Also, the concentration of the pro-inflammatory cytokine IL-18 was significantly higher in the main group than in the control group (p=0.0002).

The dynamics of rise and fall of cytokine levels during ART makes cytokines a good prognostic tool for monitoring their effectiveness. Although cytokine profiles during antiretroviral therapy among people living with HIV (PLHIV) have been documented, no clearly defined pattern of effects of antiretroviral therapy on cytokine profiles has been identified. While some studies report a pro-inflammatory effect of antiretroviral therapy, others illustrate the opposite.

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