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Features of pro- and anti-inflammatory cytokines in the blood of HIV-positive children

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ABSTRACT

This article describes the results of the study and the characteristics of the cytokines IL-4, IL-18, IFN-γ and TNF-α in the blood plasma of HIV-positive and HIV-negative children. The study design was a cross-sectional study in which blood samples were collected from study subjects during ART. Cytokines IL-4, IL-18, TNF-α and INF-γ were determined using an ELISA kit (Vector Best, Russian Federation). The results showed 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). 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). 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.

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Oiv-musbat bolalar qonida yallig‘lanish va yallig‘lanishga qarshi sitokinlarning xususiyatlari

Kalit so‘zlar:
interleykinlar,
OIV,
CD4 hujayralari.

ANNOTATSIYA

Ushbu maqolada tadqiqot natijalari va OIV-musbat va OIV-manfiy bolalarning qon plazmasidagi IL-4, IL-18, IFN-gamma va TNF-alfa sitokinlarining xususiyatlari tasvirlangan. Tadqiqot dizayni kesma tadqiqot bo‘lib, unda qon namunalari ART paytida o‘rganilayotgan subyektlardan olindi.

Особенности про- и противовоспалительных цитокинов в крови у ВИЧ-позитивных детей

Ключевые слова:
интерлейкины,
ВИЧ,
CD4 клетки.

АННОТАЦИЯ

В данной статье описаны результаты исследования и особенности цитокинов IL-4, IL-18, IFN-γ и TNF-α в плазме крови у ВИЧ-положительных и ВИЧ-негативных детей. Дизайн исследования представлял собой перекрестное исследование, в ходе которого у субъектов исследования вовремя АРТ собирались образцы крови. Цитокины IL-4, IL-18, TNF-α и INF-γ определяли с помощью набора ИФА («Вектор Бест», Российская Федерация). Результаты показали концентрация ИФН-гамма – ррегулятора гуморального иммунного ответа в группе больных с ВИЧ-инфекцией статистически значимо выше, чем в контрольной группе (p=0.00001). Напротив, концентрация другого регулятора гуморального иммунного ответа – ИЛ-4 в основной и контрольной группах различается незначительно (p=0.1425). Содержание провоспалительного цитокина ФНО-альфа в ВИЧ-положительной группе оказалось значительно выше, чем в ВИЧ-отрицательной группе (p=0.00001). Также, концентрация провоспалительного цитокина ИЛ-18 оказалась в основной группе значительно выше, чем в контрольной (p=0.0002). Хотя профили цитокинов во время антиретровирусной терапии среди людей, живущих с ВИЧ (ЛЖВ), документированы, четко определенной закономерности влияния антиретровирусной терапии на профили цитокинов выявлено не было.

INTRODUCTION

Cytokines are a broad group of soluble proteins and peptides that contribute significantly to the immune response to intracellular and extracellular pathogens. They are mainly classified into anti-inflammatory cytokines and pro-inflammatory cytokines (Tudela et al., 2014), and a physiological balance between these two groups is required for homeostasis. Cytokines produced by CD4+ T cells play an important role in the fight against intracellular infections such as HIV.

One of the known factors required to direct CD4+ T helper 1 cells to an appropriate immune response are cytokines produced by cells of the innate immune system (Tudela et al., 2014). Antigen-presenting cells such as dendritic cells release interleukin 12, which induces naïve T cells into CD4+ T helper 1 (TH1) cells. In fact, TH1 cells produce interleukin 2 and interferon-gamma, which are pro-inflammatory cytokines responsible for the intracellular clearance of pathogens.

Prescribing antiretroviral therapy for the treatment of HIV infection has become a very effective tool for controlling HIV infection among patients. According to da Cunha and Maselli (da Cunha et al., 2015), currently highly active antiretroviral therapy (HAART) is the most effective and safe option for combating HIV-1 infection. It improves immune system recovery while reducing the risk of mortality. It is important to note that although ART aims to reduce viral load, the impact on the cytokine profile must be taken into account in drug production, as dysregulated cytokine profile is a hallmark of marked progression to more severe disease (AIDS).

PURPOSE OF THE STUDY

The purpose of the research 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.

A. 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.

B. 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 venipuncture. 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 ≤ −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

The 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

Studies 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

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). 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). The concentration of the pro-inflammatory cytokine IL-18 was significantly Also 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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