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ЦИТОКИНЫ ПРИ РАЗЛИЧНЫХ ФОРМАХ ЛЕГОЧНОГО ТУБЕРКУЛЕЗА

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РЕЗЮМЕ: Цитокины Т-клеток эффекторов существенны в защите хозяина против *Mycobacterium tuberculosis*, однако механизмы их действия остаются неясными. Противоречивые результаты демонстрируются уже многие годы, возможно, вследствие того, что не учитываются различные формы туберкулеза (ТБ), уровни витамина Д больных и методы оценки продукции цитокинов. Целью работы было исследование спонтанной и стимулированной туберкулином (PPD) продукции 9 цитокинов мононуклеарами периферической крови у больных с инфильтративным туберкулезом (ИТ), фиброзно-кавернозным туберкулезом (ФКТ) и у здоровых доноров. Пробы были получены в апреле-июне в Санкт-Петербурге (59° северной широты). Уровень 25(OH)D был низким даже у здоровых взрослых доноров — 19,3±1,4 нг/мл; однако у всех больных он был существенно ниже. Индуцированная продукция IFN-γ, IL-2, IL-17 и IL-8 мононуклеарными клетками периферической крови была значительно повышена у больных обеих групп по сравнению с контролем, но уровни спонтанной продукции TNF-α, IL-1β и IL-6 были ниже у больных ТБ, чем у здоровых доноров. Мы нашли значительные различия между двумя группами больных ТБ в уровнях стимулированной продукции IFN-γ и IL-6 и спонтанной продукции TNF-α. Более тяжелое и продолжительное течение ТБ и более глубокий дефицит витамина Д у больных ФКТ, чем у ИТ, сопровождались более высокими уровнями IFN-γ, TNF-α, IL-17 и IL-8, и их избыточное и отрицательное действие не блокировал ИЛ-10, продукция которого не возрастала.

КЛЮЧЕВЫЕ СЛОВА: цитокины; инфильтративный туберкулез; фиброзно-кавернозный туберкулез; витамин Д.

CYTOKINES IN DIFFERENT FORMS OF PULMONARY TUBERCULOSIS

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ABSTRACT: The acquired T cell responses are critical for the host defense against Mycobacterium tuberculosis, yet their mechanisms of action remain unclear. Conflicting results have been demonstrated over the years, possibly due to the disregarded vitamin D levels, different forms of tuberculosis (TB), and methods used. The objective of the study was to investigate the production of 9 cytokines by the peripheral blood mononuclear cells, both PPD-stimulated and spontaneous, in patients with infiltrative (IT), fibrous cavernous tuberculosis (FCT), and in healthy donors. Blood samples were obtained in April-June in the Saint Petersburg region (59° north latitude). The level of 25 (OH) D was very

low even in healthy adult donors — 19.3±1.4 ng/ml; however in all patients it was yet significantly lower. The induced production of IFN-γ, IL-2, IL-17, and IL-8 by the peripheral blood mononuclear cells was significantly increased in the patients of both tuberculosis groups, but the levels of TNF-α, IL-1β and IL-6 production, not stimulated by PPD, were lower in the tuberculosis patients than in healthy donors. We found a significant difference between the two groups of TB patients in the levels of the induced production of IFN-γ and IL-6, and the spontaneous production of TNF-α. The more severe course of TB and the lower vitamin D level in the FCT patients than in the IT patients was accompanied by higher levels of IFN-γ, TNF-α, IL-17, and IL-8 whose detrimental action was not restrained by IL-10 that failed to respond by the increase of its production.

KEYWORDS: cytokines; infiltrative tuberculosis; fibrous cavernous tuberculosis; vitamin D.

INTRODUCTION

Tuberculosis (TB), a global public health menace, is in 90–95 % of cases clinically asymptotic [23]. The disease course is determined by the balance between the *Mycobacterium tuberculosis* (Mtb) and the host innate and adaptive immunity mechanisms.

The innate immune cells primarily infected by Mtb are the alveolar macrophages. In the macrophage phagosome Mtb find favorable niche for surviving and replication [20]. Human alveolar macrophages activate signaling pathways to combat bacterial replication and attract other immune cells into the site of infection. In the progress of cellular immunity against Mtb, macrophages also function as antigen presenting cells.

Th1, Th2, Th17, and regulatory T cells are involved in the response to Mtb, but the Th1 and their cytokines are recognized as the main cell subset associated with macrophage microbicidal mechanisms [8].

The T-cell cytokines have been demonstrated to regulate the vitamin D metabolism [10]. Conversely vitamin D acting as modulator of the immune system inhibits T cell cytokines such as IL2 and IL17 [4, 13].

Recent investigations attracted worldwide attention to vitamin D which besides its classical effect, is involved in pathogenesis of chronic diseases including tuberculosis and autoimmune diseases. Vitamin D insufficiency is widely spread and is associated with increased tuberculosis risk in different populations [18, 19]. We found significant deficiency of vitamin D in our TB patients [3].

Conversion of 25-hydroxyvitamin D to active 1,25-dihydroxyvitamin D in the immune cells is essential for their antibacterial activity [12]. The most important effect of the localized activation of vitamin D in response to Mtb is the induction of cathelicidin (LL-37), a potent antimicrobial peptide necessary for the bacterial killing in a variety of cell types [15]. Cathelicidin can fulfill antimicrobial, antifungal and antiviral properties through different ways [2]; it plays a particular part in defense against intracellular Mtb inducing autophagy in monocytes/macrophages [22].

Interferon-γ (IFN-γ), the main cytokine of the Th1 profile, induces autophagy, phagosomal maturation, the production of antimicrobial peptides such as cathelicidin, and antimicrobial activity against *Mycobacterium tuberculosis* in human macrophages via a vitamin D–dependent pathway [11]. TNF-α acts synergistically with IFN-γ to stimulate the production of NO by macrophages and influences the expression of chemokines [8]. The involvement of IL-17 and IL-23 as well as IL-10 in mediating the immunopathology of TB has also been demonstrated [5].

Acquired T cell responses are critical for host defense against microbial pathogens, yet their mechanisms of action remain unclear. Conflicting results have been demonstrated over the years, possibly due to disregarded vitamin D level, different forms of TB, and methods used.

Objectives: to study the production of 9 cytokines by peripheral blood mononuclear cells (PBMC), both PPD-stimulated and spontaneous, in patients with two form of TB and healthy donors.

Distinction was made in our investigations between TB patients with short-time and long-time duration of disease.

MATERIAL AND METHODS

A total of 41 participants were enrolled in the study with informed consent: 10 patients with infiltrative tuberculosis (IT), 10 patients with fibrous cavernous tuberculosis (FCT), and 21 healthy donors. Blood samples obtained in April-June from the in-patients of the Saint Petersburg Research Institute of Phthisiopulmonology (SPbRIP) and those of TB sanatorium near Saint Petersburg (59° north latitude). The institutional review board of the SPbRIP approved all studies involving humans. All processing of information obtained from the participants has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

The mean age of patients was 35.4 years (range 17–65), 73 % were males. The mean age of healthy donors was 31.5 years (range 17–56), 44 % were males. The chest X-ray findings, direct smear microscopy, mycobacterial culture results, and clinical data were abstracted from the medical records. TB manifests in many forms. In our study two groups of TB patients had different clinical and X-ray characteristics, but all TB patients were in active phase of the disease.

The IT is the most common type of the secondary TB. In our investigation the IT patients (mean age 22.9 years, range 17–33) had 1–3 segments of the lung affected (81.4 %), and more benign course of disease compared to FCT group. 38 % of IT patients excreted Mtb. Physical signs of TB were absent in 49.1 % of patients.

The FCT patients had progressive disease lasting from 4 to 19 years, with average 11.2 years of duration. The multiple in-

volvement of lung segments and signs of lung destruction were observed in all of them. Mtb excretion was found in 91 %. 89 % had some manifestations of TB on physical examination. All FCT patients had multi-drug Mtb resistance and some degree of respiratory insufficiency. The mean age of FCT patients group was 47.9 (range 29–65). Overwhelming majority of population in Russia is BCG-vaccinated, which was the case for all donors involved.

The cytokine production by PBMCs was measured using the whole-blood ELISA (Vector Best Baltica, Russia). We determined cytokine concentrations in the supernatants of PPD-stimulated PBMCs (induced) and in the unstimulated (spontaneous) duplicates from patients and healthy donors. The sensitivity and range of the cytokine detection was different for various cytokines as reported by the manufacturer, namely, IFN-γ, IL-18: sensitivity 2pg/mL, range 0–1000pg/mL; IL-2, IL-10: 1pg/mL, 0–500 pg/mL; IL-1β, IL-6 0.5pg/mL, 0–300pg/mL; IL-8: 2pg/mL, 0–250pg/mL; TNF-α: 1pg/mL, 0–250.

Statistical analysis was carried out using the Statistical Package for Social Sciences software. The Mann-Whitney test was used. Statistical significance was set at $p<0.05$.

RESULTS

The peripheral blood characteristics of the two TB groups studied were different. Both groups displayed monocytosis, thrombocytosis, and increased erythrocyte sedimentation rate (ESR), but changes in the FCT group were much more significant. Monocytosis was present in 76.5 % of FCT patients, thrombocytosis — in 85.7 %, increased ESR — in 82.4 %.

CYTOKINE PRODUCTION BY PBMC

IT patients (Fig.1) The production of **IFN-γ** by the cultured PBMC stimulated by PPD was significantly greater than in healthy donors; the mean was 125pg/mL, versus 47.7pg/mL; according to Mann-Whitney U test U=35, p=0.013 (Fig.1A). There was no difference between IT patients and healthy donors in the spontaneous production of IFN-γ (Fig.1B).

The stimulated production of **TNF-α** in the IT patients did not differ from that of healthy donors, whereas the production of TNF-α by the non-stimulated PBMC was lower in IT (the mean was 0.6pg/mL) than in healthy individuals (the mean was 11.2pg/mL), U=19, p=0.0003 (Fig.1B).

The stimulated production of **IL-2** was found significantly increased in IT patients, (mean 37.8pg/mL), compared to healthy donors (4.8pg/mL), U=21, p=0.0014 (Fig.1A).

The induced production of **IL-17** was much higher in IT patients (14.9pg/mL) than in controls (2.7pg/mL), U=10, p=0.00004 (Fig.1A).

The stimulated production of **IL-8** was significantly enhanced in IT patients (the mean was 72000pg/mL) compared to healthy donors (19300pg/mL), U=31, p=0.002 (Fig.1A). The spontaneous production of **IL-1β** was significantly lower in IT patients (0.55pg/mL), than in controls (5.86pg/mL), U=34, p=0.004 (Fig.1). In addition, the spontaneous production of IL-6 was lower in IT patients (3.7pg/mL) than in the healthy individuals (80.2pg/mL), U=32, p=0.004 (Fig.1B).

FCT patients (Fig.2) The mean **IFN-γ** level in stimulated cultures was significantly higher compared to both healthy donors (the mean was 2212pg/mL vs 48pg/mL, U=16, p=0.0003) (Fig.2A) and to patients with IT (125 pg/mL, U=20, p=0.045) (Fig3A). Half of the FCT patients had many-fold increased level compared to any other patient studied.

The concentration of the **TNF-α** stimulated by PPD in FCT patients was significantly increased compared to healthy donors (1359pg/mL vs. 371pg/mL, U=35, p=0.018) (Fig.2A) and was insignificantly higher than in the IT patients. The spontaneous production of **TNF-α** was significantly lower in FCT than in controls (4.4 vs 11.2, U=54, p=0.045) (Fig.2B).

The induced production of **IL-2, IL-17,** and **IL-8** (pg/mL) was also increased in FCT, and more significantly than in IT: **IL-2** (107 vs. 4.8, U=10, p=0.0001); **IL-17** (35.5 vs. 2.7, U=14 p=0.0001); **IL-8** (102500 vs. 19300, U=14, p=0.0002) (Fig. 2A).

The spontaneous production of **IL-2**, **IL-1β** and **IL-6** (pg/mL) was decreased in FCT patients compared to healthy donors (Fig. 2B); **IL-2** (0.0 vs 2.2, U=50, p=0.007), **IL-1β** (0.7 vs 5.7, U=41, p=0.012), **IL-6** (16.6 vs 80.2, U=35, p=0.0052)

No difference was revealed between patients of both groups and healthy donors regarding the levels of IL-10 and IL-18, both in stimulated and not stimulated cultures. We saw no difference also in the spontaneous production of IFN-γ, and IL-8 in the FCT patients against that of controls (not shown).

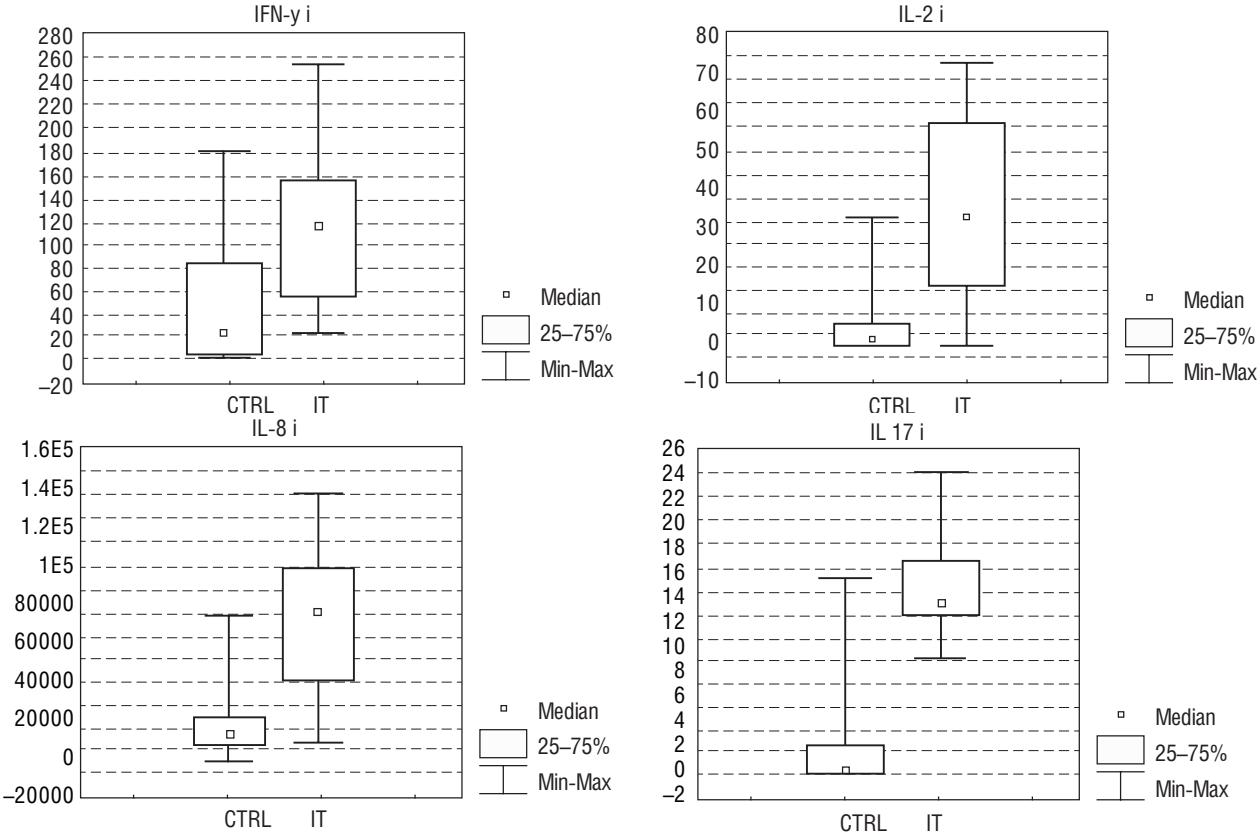
Two studied groups of patients differed in the production of cytokines. Significantly higher stimulated level of IFN-γ occurred in FCT patients (Mann-Whitney U Test: U=20.5, p=0.045). The same was registered for stimulated IL-6 level (U=21.5, p=0.031) (Fig.3A). The spontaneous production of TNF-α was lower in IT than in FCT (U=22.5, p=0.038).

DISCUSSION

In our investigation the production of **IFN-*γ*** stimulated by PPD was enhanced in patients of both groups compared to healthy donors, but highest level was in FCT patients. Half of our patients had a many-fold increased level compared even to other patients in this group. We saw no association of this high level with clinical data. The essential role for IFN-*γ* in the resistance to Mtb has been confirmed by many researchers [8]. IFN-*γ,* the main cytokine of the Th1 subset, enhances the macrophage defense mechanisms via a vitamin D-dependent pathway, but also is known for enhancement of autoimmunity [10, 11].

In the current study we found increased stimulated level of **TNF-α** in FCT but not in IT patients. This observation can be important since TNF-α is known to be critical in the control of Mtb infection [8]. The induced production of one more Th1 cell cytokine, namely **IL-2**, was significantly increased in our TB patients, while spontaneous production did not change.

A — the induced production of cytokines



B — the spontaneous production of cytokines

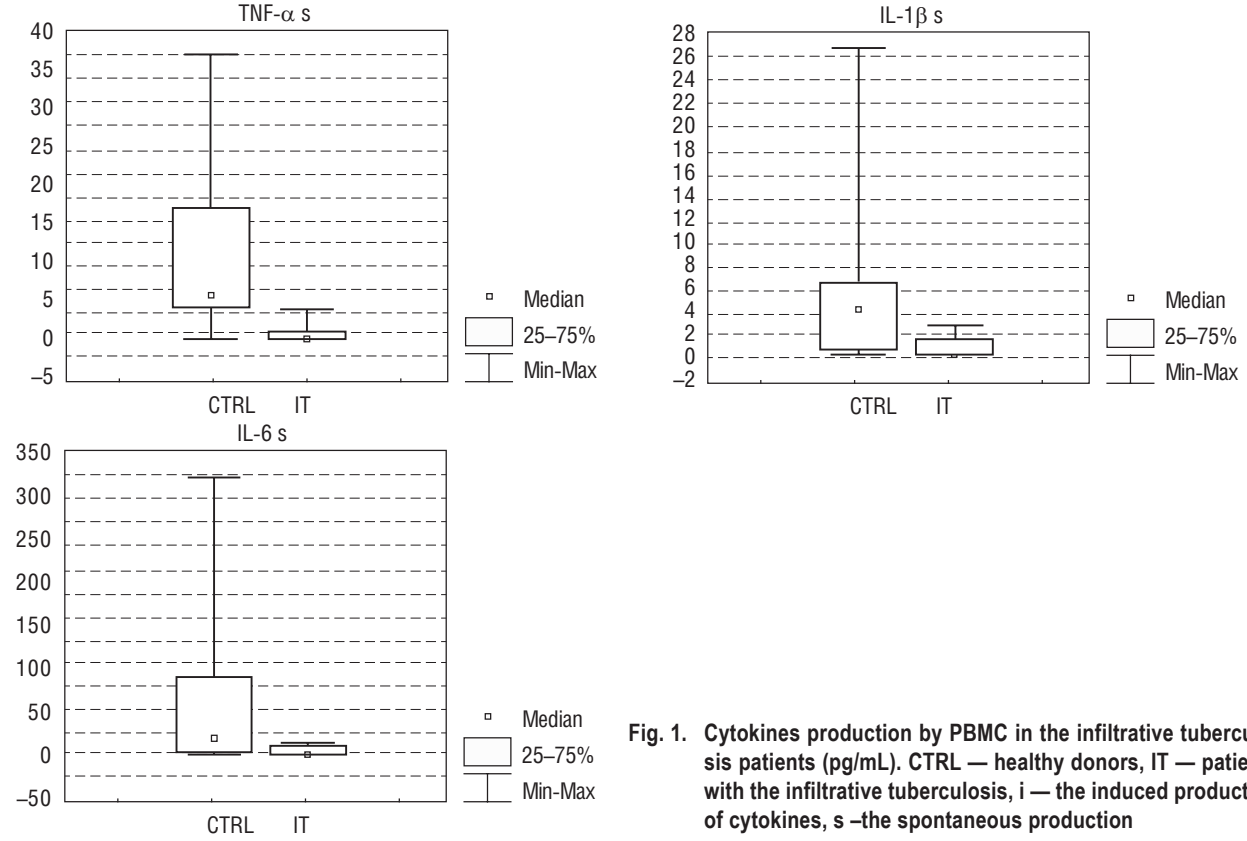


Fig. 1. Cytokines production by PBMC in the infiltrative tuberculosis patients (pg/mL). CTRL — healthy donors, IT — patients with the infiltrative tuberculosis, i — the induced production of cytokines, s –the spontaneous production

A — the induced production of cytokines

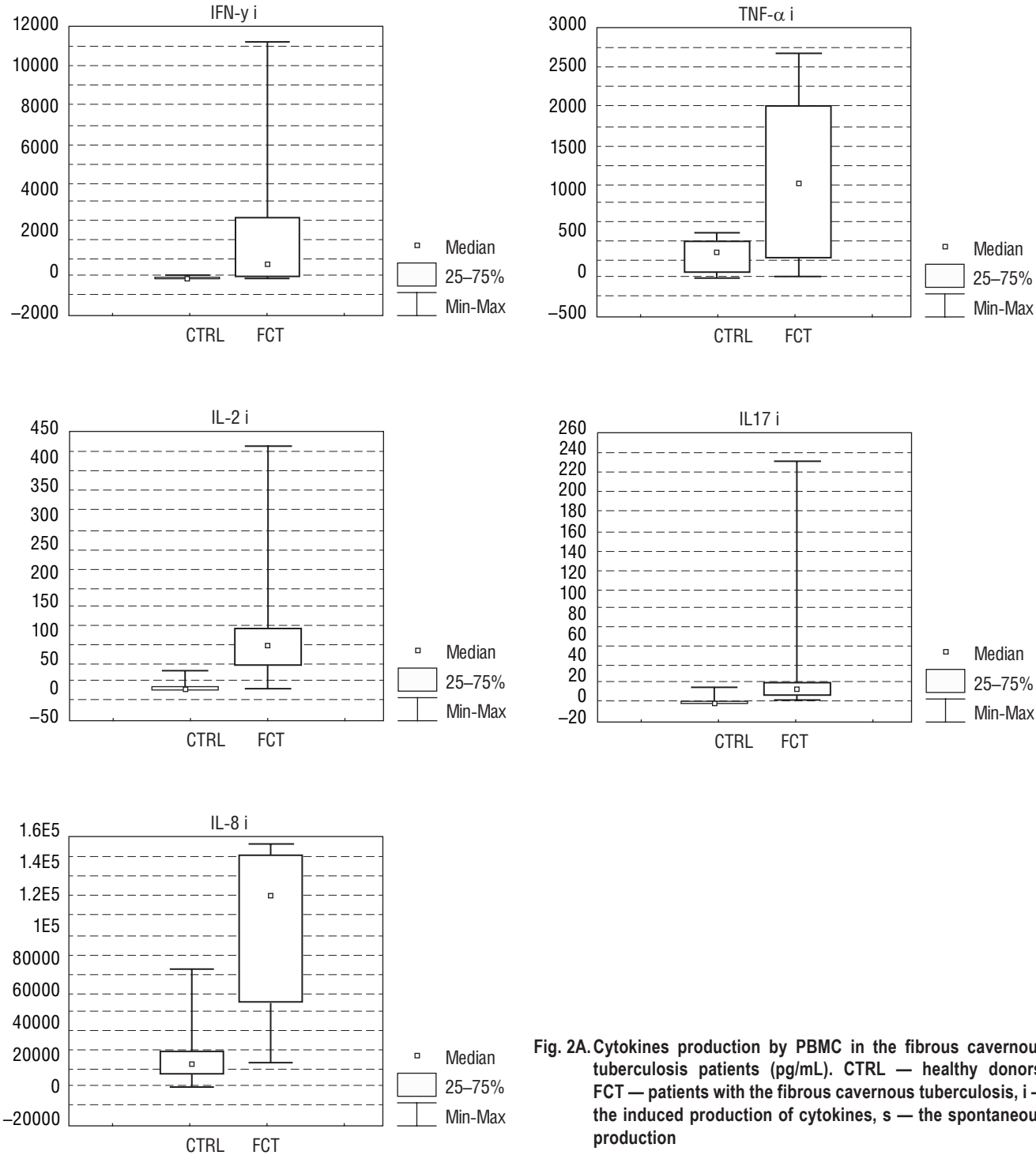


Fig. 2A. Cytokines production by PBMC in the fibrous cavernous tuberculosis patients (pg/mL). CTRL — healthy donors, FCT — patients with the fibrous cavernous tuberculosis, i — the induced production of cytokines, s — the spontaneous production

In our study induced production of **IL-17** was greatly increased in patients of both TB groups, but especially in FCT. Th17 cells are known to be crucial for control of Mtb [7, 21]. The major cytokine of Th17 cell, IL-17, has the dual capacity, both defensive and pathogenic [17, 6]. It plays important part in pathogenesis of the autoimmune inflammation [21]. Earlier we have shown the autoantibodies presence to many antigens in both groups of patients [1]. It is possible that in our study IL-17 was responsible for the autoimmune components revealed in TB.

B — the spontaneous production of cytokines

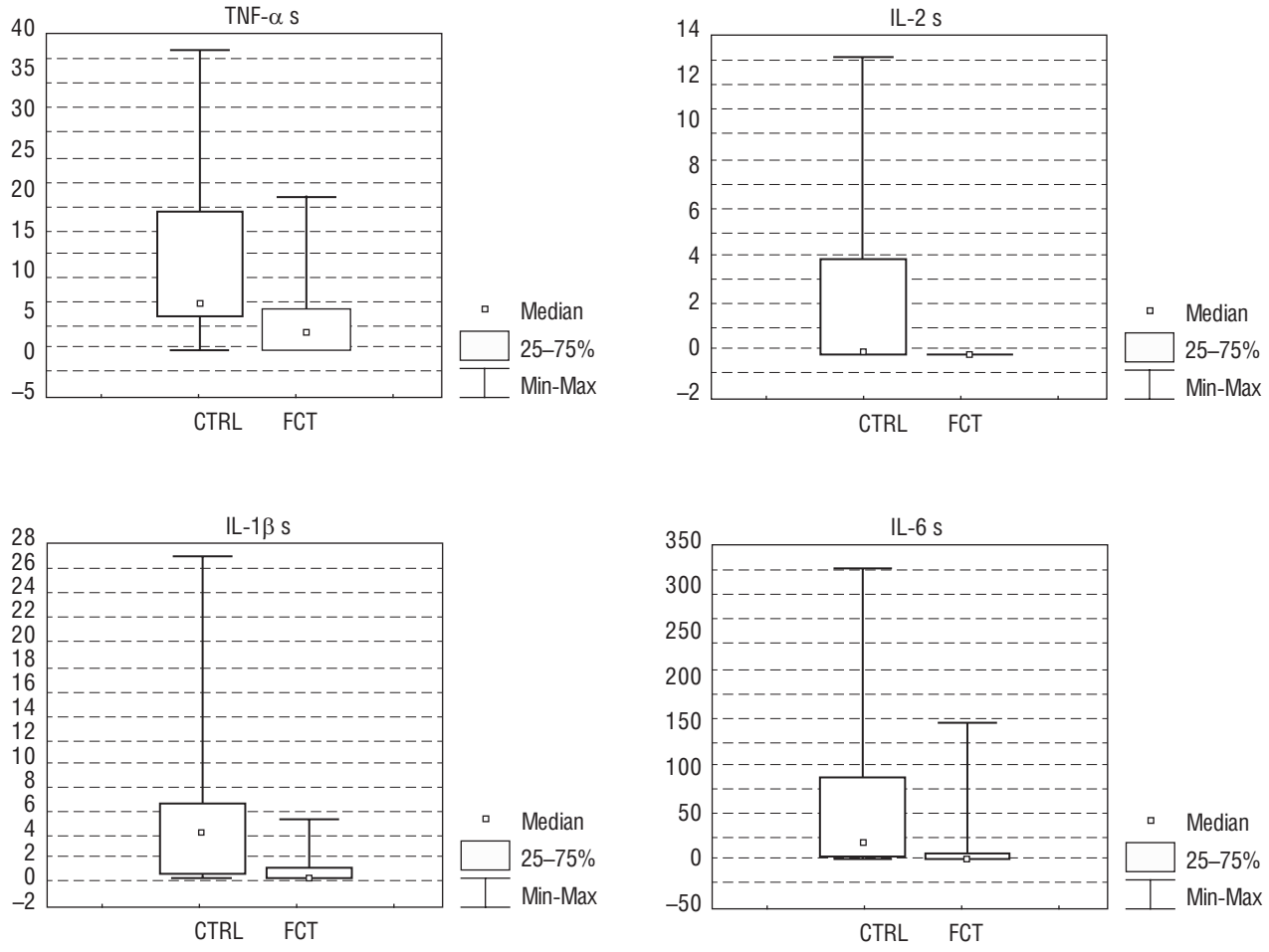


Fig. 2B. Cytokines production by PBMC in the fibrous cavernous tuberculosis patients (pg/mL). CTRL — healthy donors, FCT — patients with the fibrous cavernous tuberculosis, i — the induced production of cytokines, s — the spontaneous production

The excessive activity of TNF-α and IFN-γ can be harmful to the host. In the early stage of TB the IL-17 production facilitates the granuloma formation and control of bacterial growth. During the chronic phase of TB, balance between Th1 and Th17 responses is vital because an excessive IL-17 production may cause extensive neutrophil accumulation and tissue damage [21]. We found greatly increased production of those cytokines in the long course of disease, fibrous cavernous tuberculosis.

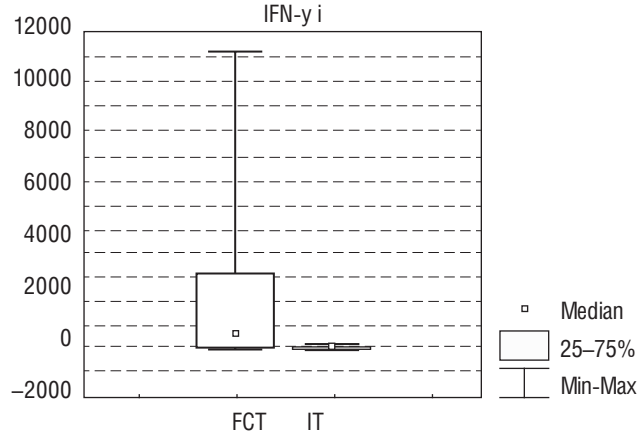
Our results showed a marked increase in the stimulated production of IL-8 by patients of both TB groups, maybe partially due to the capacity of TNF-α to up-regulate the IL-8 secretion [9]. IL-8 has a central role in the neutrophil chemo-taxis to areas of TB granulomata formation however extensive accumulation of neutrophils in TB lesions is associated with a high pathogen load [16].

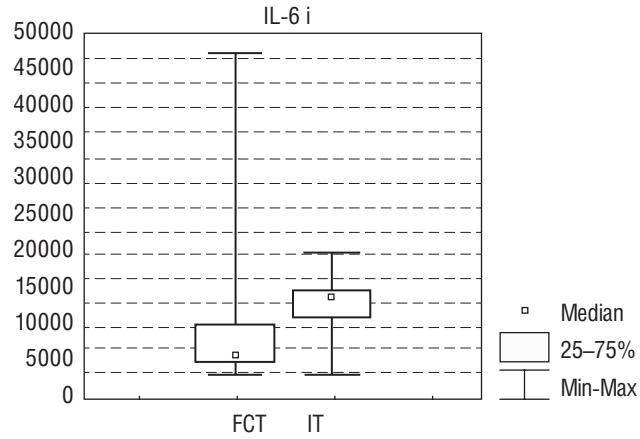
We found a significant difference between the two groups of TB patients in the levels of induced production of IFN-γ and IL-6, and spontaneous production of TNF-α. Spontaneous production of TNF-α, IL-2, IL-1β, and IL-6 was significantly lower in the patients of both groups compared to controls. Low and even undetectable levels of IL-2 in TB were reported also by others [14]. The cause of that is not clear. One possible explanation is that the blood samples were taken from the TB patients after beginning of the treatment, and the serum cytokine levels decrease during the anti-TB therapy. Another explanation is that in TB most active cells are recruited into granulomata, so those staying in blood may have relatively low spontaneous cytokine-producing activities, although stimulation reveals their potential; similar consideration coined in [14].

CONCLUSION

TB in We registered significant changes in cytokines production in pulmonary TB as well as some difference between the studied forms of TB. The more severe course of the FCT patients than in IT patients was accompanied by the higher levels

B — the spontaneous production





A — the induced production

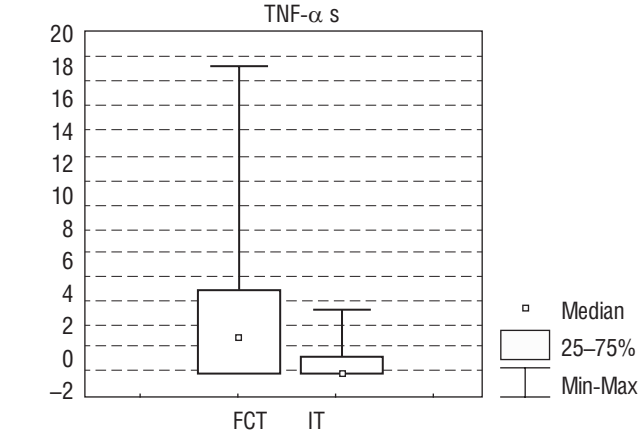


Fig. 3. Comparison of the cytokines production by PBMC in the fibrous cavernous and infiltrative tuberculosis patients. FCT — patients with the fibrous cavernous tuberculosis, IT — patients with the infiltrative tuberculosis, i — the induced production of cytokines, s –the spontaneous production

of IFN-γ, TNF-α, IL-17, and IL-8 whose detrimental action was not restrained by IL-10 that failed to respond by increase of its production.

There was a difference between the two groups of TB patients in the levels of induced production of IFN-γ and IL-6, and spontaneous production of TNF-α.

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The authors declare that they have no conflict of interests.

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