Cytokine profile in children with newly diagnosed tuberculosis

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Nowadays, the most important task of children's phthisiology is to increase the effectiveness of children with tuberculosis treatment, and in the first priority should be given to the first time diagnosed tuberculosis (FTDTB). Examination of the immune system state by cytokine profile in blood serum studying is paid to sufficient attention, as cytokines are the system which regulates the entire complex of organism protective reactions, and immunological dysregulation is the cause of pathological process increasing. There few data of the cytokine profile state studying in children with FTDTB in Ukraine in the available literature and various combinations of cytokines comprehensively with other immunological parameters are studied. According to our studies of the blood serum cytokine profile state in adult patients with tuberculosis, the reliable indices of immune system changes are interleukin (IL)-2, IL-6, IL-4 and IL-10.

The aim of the study is to evaluate the indicators of blood serum cytokine profile (IL-2, IL-6, IL-4) in children with FTDTB.

Materials and methods. The study of the cytokine profile indicators has been performed in 28 children with FTDTB, aged from 1 to 16 years old (an average age was 9.2 ± 1.1 years). The indicators of the cytokine profile were studied by researching the levels of IL-2, IL-6, IL-4, IL-10 in blood serum by ELISA technique on the equipment of Siro S immuno-enzyme reader using “Bender MedSystems GmbH” (Austria) kit (pkg/ml). These indicators were evaluated at the beginning of antimycobacterial therapy intensive phase.

Results. Despite the fact that according to the data from BCG vaccination, 42.8 % of children suffering from FTDTB had full immunity, the changes of cytokine profile indicators at the beginning of the disease were determined in 96.4 % of cases. The peculiarities of cytokine profile changes in sick children were a significant decrease in the content of anti-inflammatory cytokine IL-4, increase in the content of proinflammatory cytokine IL-2 and decrease in the content of IL-6. With a decrease in immunity to tuberculosis infection created by BCG vaccine, a significant increase in IL-2 level in blood serum was determined.

Conclusions. The obtained data indicate that activation of Th1-type cell-mediated immune response (increase in IL-2 content and imbalance of cytokines with the prevalence of its production) is determined in children with FTDTB at the beginning of treatment, and the specific process does not have an active inflammatory reaction which is the cause of its progression (low content of IL-6).

Therefore, in this category of children the factors of tuberculosis favorable course are determined at the beginning of treatment.
Nowadays, the most important task of children's phthisiology is to increase the effectiveness of children with tuberculosis treatment, and in the first priority should be given to the first time diagnosed tuberculosis (FTDTB) [1]. Examination of the immune system state by cytokine profile in blood serum studying is paid to sufficient attention, as cytokines are the system which regulates the entire complex of organism protective reactions, and immunological dysregulation is the cause of pathological process increasing [2,3].

There few data of the cytokine profile state studying in children with FTDTB in Ukraine in the available literature and various combinations of cytokines comprehensively with other immunological parameters are studied [4,5]. According to our studies of the blood serum cytokine profile state in adult patients with tuberculosis, the reliable indices of immune system changes are interleukin (IL) -2, IL-6, IL-4 and IL-10 [6].

The aim of the work

The aim of the work is to study the indicators of blood serum cytokine profile (IL-2, IL-6, IL-4, IL-10) in children with FTDTB by ELISA technique on the equipment of Sirio S immuno-enzyme reader using “Bender MedSystems GmbH” (Austria) kit (pg/ml). These indicators were evaluated at the beginning of antimycobacterial therapy (AMBT) intensive phase. The parents of all sick children signed an informed written consent of the patient to participate in the study.

The results of the study were processed by modern methods of analysis on a personal computer using Statistica® for Windows 6.0 statistical software package (StatSoft Inc., AXXR712 D833214FAN5). The normality of quantitative characteristics distribution was analyzed using the Shapiro-Wilk’s test. The descriptive statistics for quantitative variables distributed under the normal distribution law included the mean (M), the standard deviation (σ). A confidence interval for the average one with a confidence probability of 0.95 was constructed. The reliability of the differences in the comparable values was determined by the Student’s t-test. All tests were double. The difference for p < 0.05 considered statistically significant. Correlation analysis was performed using the Pearson correlation coefficient (r).

Results and discussion

At the time of the survey, the positive reactions to Mantoux test with 2 tuberculin units (TU) and to the tubercular recombinant allergen test (TRA) in all children of the main group were determined. Therefore, tuberculin sensitivity was assessed as an infectious allergy. The TRA test response was negative in all children of comparison group.

In the main observed group antituberculosis vaccinisation BCG was performed on 23 children (82.1 %), and 5 children (17.9 %) were not vaccinated. Among the children vaccinated with BCG vaccine, one child (3.6 %) did not have a postvaccinal mark indicating the absence of postvaccinal immunity. Immunity reduction to tuberculosis infection created by BCG was assessed based on weak intensity of local reaction (LL) to tuberculin when vaccinating, the size of the postvaccinal mark was up
to 5 mm. Such a response to the BCG vaccination was in 10 children with FTDTB (35.7 %), and 12 children (42.8 %) had a complete postvaccinal response.

Thus, taking into account the BCG vaccination data, only 42.8 % of children suffering from FTDTB had full immunity to tuberculosis infection, 35.7 % were weak and 21.5 % had a lack of it at the time of suffering from tuberculosis.

At the beginning of AMBT intensive phase the indicators of cytokine in blood serum were within the normal range only in one child (3.6 %), while the rest of the children with FTDTB had reliable changes of IL-6, IL-4 and IL-2 indices (Table 1).

According to the obtained data in children suffering from FTDTB against a background of a significant decrease in the content of anti-inflammatory cytokine IL-4 by 3 times (0.56 ± 0.04 against 1.72 ± 0.05) pkg/ml and normal content of IL-10, a significant increase in the content of proinflammatory cytokine IL-2 by 6.3 times (2.73 ± 1.1 against 0.43 ± 0.09) pkg/ml was determined, indicating the Th1-type of immune cell-mediated response activation. A significant reduction in the content of IL-6 in 2.4 times (0.64 ± 0.3 against 1.59 ± 0.04) pkg/ml demonstrated that specific process had no active inflammatory reaction in children with FTDTB, that was the cause of its progression.

The balanced state of pro- and anti-inflammatory cytokines ratio gave in indication of IL-2/IL-10 index calculation not significantly, which was in children with FTDTB, compared with healthy persons, but 7 times higher (2.57 ± 1.2 against 0.14 ± 0.03) indicated the imbalance of cytokines with prevalence of pro-inflammatory cytokine production – IL-2, which confirmed the activation of the Th1-type cell-mediated response.

At the same time, a reliable correlation between the IL-2 blood serum level increase and the local reaction to BCG vaccination intensity (r = 0.402; p < 0.05) in the children of the main group has been found. With other indicators of the cytokine profile any reliable correlations with the local reactions to BCG vaccination intensity has not been found.

Conclusions

1. Despite the fact that according to the data on BCG vaccination 42.8 % of children suffering from FTDTB had full immunity the changes of cytokine profile indicators were determined in 96.4 % of cases at the beginning of disease.

2. The peculiarities of cytokine profile changes in sick children are a significant decrease in the content of anti-inflammatory cytokine IL-4, increase in the content of proinflammatory cytokine IL-2 and decrease in the content of IL-6.

3. A decrease in immunity to tuberculosis infection created by BCG vaccine, a significant increase in the level of IL-2 in blood serum is determined.

4. The obtained data indicate that activation of Th1-type immune cell-mediated response (increase in the content of IL-2 and imbalance of cytokines with the prevalence of its production) is determined in the children with FTDTB at the beginning of treatment, and specific process does not have an active inflammatory reaction which is the cause of its progression (low content of IL-6). Therefore, in this category of children the factors of tuberculosis favorable course are determined at the beginning of treatment.

Prospects for further researches. Study further the immune system state in children with FTDTB in the process of AMBT in order to develop a pathogenetic correction of re-

Table 1. Content of cytokines in blood serum in children with FTDTB at the beginning of the intensive phase of AMBT (M ± m)

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of sick patients</th>
<th>Levels of cytokines in the blood serum, pkg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IL-6</td>
</tr>
<tr>
<td>Comparison Group</td>
<td>30</td>
<td>1.59±0.04</td>
</tr>
<tr>
<td>Main Group</td>
<td>28</td>
<td>0.64±0.3*</td>
</tr>
</tbody>
</table>

*: the difference in the content of one cytokine compared with the indicator of healthy children group (p < 0.05).

References


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