Levels of E, A, M, G immunoglobulins in children with newly diagnosed tuberculosis at the beginning of antimycobacterial therapy

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Key words: immunoglobulins, children, tuberculosis.

The aim of the work – to investigate IgE, A, M, G levels in children’s blood serum with newly diagnosed tuberculosis at the beginning of antimycobacterial therapy for further development of rationally directed immunocorrective therapy.

Materials and methods. The study of IgE, A, M, G levels in blood serum was performed in 28 children with newly diagnosed tuberculosis aged 1 to 16 years (average age was 9.2 ± 1.1 years old). The levels of IgE, IgA, IgM and IgG in the blood serum were studied using the method of solid phase enzyme-linked immunosorbent assay on the equipment of the Sirio S immuno-enzyme kit with the use of reagent kits “Granum” LLC (Kharkiv, Ukraine). The results of the study were processed by modern methods of analysis on a personal computer using statistical software package Statistica® for Windows 6.0 (StatSoft Inc., AXXR712 D833214FANS).

Results. Children with newly diagnosed tuberculosis at the beginning of the intensive phase of antimycobacterial therapy had a significant increase in IgE and A levels in 2.1 and 1.2 times respectively. With an increase in the prevalence of a specific process and the appearance of destruction, there is a significant increase in the IgG level in 1.2 times. Direct correlations between IgE and IgA, IgA and IgM, IgM and IgG in the disseminated process, and IgA, IgM levels in the local process have been found. A reliable correlation between the decrease in the BCG post-vaccination sign size and the increase in IgE content has been revealed, that may be a prognostic factor in the post-vaccination immunity evaluation. Cellular component of immune system activation is determined in the children, as evidenced by a significant increase in albumins level in 1.5 times against the background of the specific immunological process low activity (α- and α1-globulins levels were within the age norm). There is a significant worsening of dysproteinemia (a decrease in albumin levels by 9 % and an increase in β- and γ-globulins levels in 1.3 times) and specific inflammatory process activity (an increase in α2-globulin level in 1.3 times) with the increase in the specific process prevalence and destruction development. It has been established that the decrease in the albumin level is associated with growth in the IgE, A and G levels; growth in the β-globulin level is associated with growth in the IgA and G levels, and with IgE, M, and G – in γ-globulins. It has been found that IgA, M, and G, and the protein fractions parameters – albumins, β- and γ-globulins are significant and highly informative for the immune changes diagnosis in children with newly diagnosed tuberculosis.

Conclusions. In children with newly diagnosed pulmonary tuberculosis at the beginning of an intensive phase of antimycobacterial therapy with increase in the specific process prevalence and destruction development, significant changes in the levels of immunoglobulins and protein fractions are observed. Data resulting from the study suggest that the humoral component of immune system is also activated on the background of the cellular component of immune system activation with patient’s state aggravation, which is an unfavorable prognosis for patients’ recovery.

Рівні імуноглобулінів Е, А, М, Г у дітей, які хворі на вперше діагностований туберкульоз, на початку антимикобактеріальної терапії

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Туберкульоз у дітей – це хронічний запальний процес, у якому імунологічні механізми посідають одне з провідних місць в патогенезі. Отже, вивчення показників імунного статусу у дітей дає можливість визначити активність захворювання, спрогнозувати його перебіг для ранньої корекції виявлених порушень, визначити ефективність лікування. Одними з імунологічних показників при туберкульозі є імуноглобуліни.

Мета роботи – дослідити рівні IgE, A, M, G у сироватці крові дітей, які хворі на вперше діагностований туберкульоз, на початку антимикобактеріальної терапії для діагностики та врахування хвороби.

Матеріали та методи. Вивчили рівні показників IgE, A, M, G у сироватці крові у 28 дітей, які хворі на вперше діагностований туберкульоз. Патологічні показники IgE, IgA, IgM і IgG у сироватці крові визначали методом твердофазового імуноензимного аналізу на приладі імуноензимний рідер Sirio S із застосуванням наборів реактивів ТОВ НВЛ “Гранум” (м. Харків). Результати дослідження обробляли сучасними методами аналізу з використанням статистичного пакету ліцензійної програми Statistica® для Windows 6.0 (StatSoft Inc., AXXR712 D833214FANS).

Результати. У дітях, які хворі на вперше діагностований туберкульоз, на початку інтенсивної фази антимикобактеріальної терапії визначається вірогідне зростання рівнів IgE та A у 2,1 та 1,2 рази, відповідно. При нарощуванні погорішнього специфічного процесу та появи деструкції спостерігається вірогідне зростання рівні IgG у 1,2 рази. При поширеному
Уровні імуноглобулінів Е, А, М, G у дітей, больних впершеdiagnozированным
туберкулезом, в начале антимикобактериальной терапії

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Туберкулез у дітей – це хронічний вісцеральний процес, в якому імунологічні механізми займають одну з ведучих позицій у патогенезі. На це впливає можливість імунологічних реакцій в організмі, які можуть бути прогнозоюми для ефективності проводимого лікування. Одними із імунологічних показників при туберкулезі вже давно слідкували за імуноглобулінами.

Цель работы – исследовать уровни IgЕ, А, М, G в сыворотке крови детей, больных впервыеdiagnozированным туберкулезом, в начале антимикобактериальной терапии для дальнейшей разработки рационально направленной иммунокорректирующей терапии.

Материалы и методы. Изучение уровней показателей IgЕ, А, М, G в сыворотке крови проведено у 28 детей, больных впервыеdiagnozированным туберкулезом, в возрасте от 1 до 16 лет (средний возраст 9,2 ± 1,1 года). Уровни показателей IgЕ, IgА, IgМ и IgG в сыворотке крови изучали методом твердофазного иммуноферментного анализа на приборе иммуноферментный расход Siro S с применением наборов реактивов ООО НПЛ «Гранум» (г. Харьков, Украина). Результаты исследования обработаны современными методами анализа с использованием статистического пакета лицензионной программы Statistical® для Windows 6.0 (StatSoft Inc., № AXXR712 D833214FANS).

Результаты. У детей, больных впервыеdiagnozированным туберкулезом, в начале интенсивной фазы антимикобактериальной терапии определяется достоверное повышение уровня IgЕ и А в 2,1 и 1,2 раза соответственно. При нарастании распространенности специфического процесса и появлении деструкции наблюдается достоверный рост уровня IgG в 1,2 раза. При распространенном процессе установлены прямые корреляционные связи уровней IgЕ и IgА, IgА и IgМ и IgG, IgМ и IgG, а при ограниченном – между IgЕ и IgМ. Установлена достоверная корреляционная связь между уменьшением размера послеvakцинального знака БЦЖ и нарастанием содержания IgЕ, что может быть прогностическим фактором в оценке патогенетического иммунитета. У детей определяется активация клеточного звена иммунной системы, о чем свидетельствовало достоверное повышение в 1,5 раза уровня альбуминов на фоне низкой активности специфического воспалительного процесса (уровни альбуминов находились в пределах возрастной нормы). При этом при нарастании распространенности специфического процесса и появлении деструкции наблюдается достоверное нарастание диспротеинемии (снижение уровня альбумина на 9 % и ростом уровней β- и γ-глобулинов в 1,3 раза) и активности воспалительного специфического процесса (повышение уровня альбуминов в 1,3 раза) Установлено, что снижение уровня альбумина связано с повышением уровней IgЕ, А и G, рост уровня β-глобулинов связан с ростом уровней IgА и G, а γ-глобулинов – IgЕ, М и G. Установлено, что диагностически значимыми и высокоинформативными для диагностики изменений иммунитета являются IgА, М и G, а среди показателей белковых фракций – альбумины, β- и γ-глобулины.

Выводы. У детей, больных впервыеdiagnozированным туберкулезом легких, в начале интенсивной фазы антимикобактериальной терапии при нарастании распространенности специфического процесса и появлении деструкции наблюдаются достоверные изменения уровней иммуноглобулинов и белковых фракций. Полученные данные свидетельствуют: на фоне активации клеточного звена иммунной системы с утяжелением состояния происходит активация гуморального звена, что является неблагоприятным прогностическим фактором в оценке поствакцинального иммунитета. У детей определяется активация клеточного звена иммунной системы, о чем свидетельствовало достоверное повышение в 1,5 раза уровня альбуминов на фоне низкой активности специфического воспалительного процесса (уровни альбуминов находились в пределах возрастной нормы). При этом при нарастании распространенности специфического процесса и появлении деструкции наблюдается достоверное нарастание диспротеинемии (снижение уровня альбумина на 9 % и ростом уровней β- и γ-глобулинов в 1,3 раза) и активности воспалительного специфического процесса (повышение уровня альбуминов в 1,3 раза) Установлено, что снижение уровня альбумина связано с повышением уровней IgЕ, А и G, рост уровня β-глобулинов связан с ростом уровней IgА и G, а γ-глобулинов – IgЕ, М и G. Установлено, что диагностически значимыми и высокоинформативными для диагностики изменений иммунитета являются IgА, М и G, а среди показателей белковых фракций – альбумины, β- и γ-глобулины.
are excreted in a human body: serum and secretory. Serum IgA provides local immunity, and secretory participates in providing protection of mucous membranes (respiratory, urogenital tract and digestive tract) from microorganisms, including mycobacterium tuberculosis (MBT). The decrease in IgA level indicates a lack of humoral local immunity, and in the absence of appropriate treatment it leads to the immune system depletion, which causes infectious process inhibition, etc. Increase in IgA level is observed in infectious diseases, both in acute and chronic exacerbation processes [4]. Under the influence of IgM the compliment system is activated in response to an acute infectious process, providing primary immunity. Serum IgG provides long-term humoral immunity to infectious agents. In chronic infectious and autoimmune diseases an increase in the serum IgG level is detected and its deficiency contributes to the weakening of a body resistance to infectious diseases.

### Purpose

To investigate IgE, A, M, G levels in children’s blood serum with newly diagnosed tuberculosis at the beginning of anti-mycobacterial therapy for further development of rationally directed immunocorrective therapy.

### Materials and methods

The study of IgE, A, M, G levels in blood serum was performed in 28 children with NDTB aged 1 to 16 years (average age was 9.2 ± 1.1 years old) who were on inpatient treatment in a children’s unit of the clinical base of Phtisio-logy and Pulmonology Department of Zaporizhzhia State Medical University at Communal Institution “Zaporizhzhia Regional Antituberculous Clinical Dispensary” and constituted the main group. There were 16 (57.1 %) girls and 12 (42.9 %) boys. The comparison group included 30 healthy children aged 1 to 16 (average age was 8.9 ± 1.0 years old). The comparison group were comparable to age and gender.

The levels of IgE, IgA, IgM and IgG in the blood serum were studied using the method of solid phase enzyme-linked immunosorbent assay on the equipment of the Sirio S immuno-enzyme reader with the use of reagent kits “Granum” LLC (Kharkiv, Ukraine). Units of measurement: IgE (MU/ml), IgA, M, G (g/l). The analysis of blood serum protein fractions parameters was carried out using rheum sampling electrophoresis method with distribution on acetate-cellulose film on the fraction. The levels of albumins and globulins (α1, α2, β, γ) (%) were determined [5].

All indicators were evaluated at the beginning of the intensive phase (IF) of antitymocobacterial therapy (AMBT). Parents of all sick children signed a patient’s written informed consent to participate in the study.

The diagnostic significance of indicators assessment was carried out using the diagnostic utility coefficient (DUC) calculation according to A. M. Zemskova formula [6]:

\[ DUC = \frac{(d_2^2 + d_2^2)(\bar{M}_1 - \bar{M}_2)}{\bar{m}_1^2 - \bar{m}_2^2} \]

where \( d_2 \) is the mean average deviation of a healthy person’s parameters; \( d_2 \) is the mean square deviation of children with NDTB parameters; \( \bar{M}_1 \) and \( \bar{M}_2 \) are the average means, respectively. The coefficient which had a value of 1, was considered highly informative, in the range from 1.1 to 10 was medium-informative, exceeding 10 was low informative.

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

### Results and discussion

On hospital admission 5 (17.8 %) children with NDTB were diagnosed with extrapulmonary forms of tuberculosis, 3 (10.7 %) of them had tuberculosis of the intracranial lymph glands and 2 (7.1 %) had specific pleurisy. 23 patients (82.2 %) were diagnosed with pulmonary forms: 5 (17.8 %)

### Table 1. Blood serum levels of total IgE, A, M, G among children with NDTB at the beginning of anti-mycobacterial therapy (AMBT) (M ± m)

| Groups          | Number of persons | IgE (MU/ml) | IgA (g/l) | IgM (g/l) | IgG (g/l) |
|-----------------|-------------------|-------------|-----------|-----------|-----------|
| Comparison group| 30                | 55.8 ± 4.8  | 1.24 ± 0.1| 1.23 ± 0.1| 8.21 ± 0.64|
| Basic group     | 28                | 121.9 ± 30.9| 1.19 ± 0.1| 1.14 ± 0.03| 8.74 ± 0.3 |

*: the difference in the content of Ig certain type in comparison with the healthy children indicator \( (P < 0.05) \).

### Table 2. IgE, A, M, G blood serum levels in children with NDTB depending on tuberculosis prevalence (M ± m)

| Prevalence of tuberculosis | Ig blood serum levels | IgE (MU/ml) | IgA (g/l) | IgM (g/l) | IgG (g/l) |
|---------------------------|-----------------------|-------------|-----------|-----------|-----------|
| Local (n = 13)            | 105.5 ± 25.3          | 1.52 ± 0.1  | 1.18 ± 0.05| 7.77 ± 0.2 |
| Disseminated (n = 15)     | 134.5 ± 53.2          | 1.64 ± 0.1  | 1.10 ± 0.04| 9.59 ± 0.4 |

*: the difference in the content of Ig certain type in the processes \( (P < 0.05) \).

### Table 3. Concentration of blood serum protein fractions in children with NDTB at the beginning of anti-mycobacterial therapy (AMBT) (M ± m)

| Indicator, % | Comparison group (n = 30) | Main group (n = 28) |
|--------------|---------------------------|---------------------|
| Albumins     | 40.93 ± 0.7               | 61.91 ± 1.7*        |
| α1-globulins | 3.68 ± 0.2                | 3.79 ± 0.3          |
| α2-globulins | 8.05 ± 0.1                | 8.43 ± 1.3          |
| β-globulins  | 7.36 ± 0.2                | 11.43 ± 0.7*        |
| γ-globulins  | 11.42 ± 0.7               | 15.64 ± 1.0*        |

*: the indicator difference in comparison with the group indicators healthy children \( (P < 0.05) \).

### Table 4. Blood serum concentration of protein fractions in children with NDTB depending on tuberculosis prevalence of (M ± m)

| Indicators, % | Comparison group (n = 13) | Main group (n = 15) |
|---------------|---------------------------|---------------------|
| Albumins      | 66.7 ± 1.4                | 57.8 ± 2.4*         |
| α1-globulins  | 3.2 ± 0.3                 | 4.3 ± 0.4*          |
| α2-globulins  | 6.8 ± 0.5                 | 9.8 ± 2.4           |
| β-globulins   | 9.7 ± 0.6                 | 12.9 ± 1.2*         |
| γ-globulins   | 13.5 ± 1.3                | 17.5 ± 1.2*         |

*: the difference between the groups \( (P < 0.05) \).
had pleurisy, 5 (17.8 %) had primary tuberculosis complex, 11 (39.5 %) had infiltrative form and 2 (7.1 %) – disseminated. Bacterial secretion and destructive process in the lungs were registered in 7 children (25 %). Local forms of tuberculosis without a destructive process in the lungs were diagnosed in children with an average age of 5.4 ± 1.5, and disseminated tuberculosis including a destructive process presence were diagnosed among two older children with an average age of 12.5 ± 1.1.

During blood serum IgE, A, M, G total levels investigation in children with NDTB at the beginning of the IF AMBT (Table 1), reliable changes have been found only in the IgE and A. Thus, the level of IgE was within normal range in 13 patients (46.5 %), and it was elevated in 15 (53.5 %). The average IgE level exceeded the age norm by 2.1 times (P < 0.05). IgA levels were high only in 2 (7.1 %) and the level of all the other 26 children (92.9 %) indicators were within the normal range. The mean IgA level exceeded the age-matched norm in 1.2 times (P < 0.05). IgM levels in all 100 % cases were within the age range. IgG level was decreased in 1 patient (7.1 %), and the average level of its content did not exceed the norm. Furthermore the direct correlation of IgE and IgA levels (r = 0.309; P < 0.05), IgA and IgM (r = 0.341; P < 0.05) have been found.

When analyzing the changed levels of Ig depending on tuberculosis prevalence, (Table 2), the following features have been established. At normal average values the level of IgG content reliably depended on tuberculosis severity, namely its prevalence and destructive process presence. Thus, its level growth in 1.2 times, respectively. With an increase in the specific process prevalence and destruction appearance there was a direct correlation between the decrease in the sign size and the IgG level increase (r = 0.670; P < 0.05) has been established. Direct correlation in levels of IgA and G, and γ-globulins IgE, M and G. The level of albumin was diagnosed in 14 children (50 %).

So far as the γ-globulin fraction contains immunoglobulins IgG, IgA, IgM, IgE, the analysis of protein fraction indicators (Table 3) has been performed. It has been established that children with VDTB at the beginning of IF AMBT had an increase in the albumin level in 1.5 times in comparison with healthy children (P < 0.05). Furthermore, a high level of albumin was diagnosed in 26 children (92.8 %) of the main group. In contrast, an increase in the proteins globulin fraction levels was determined by increasing the β- and γ-globulins levels in 1.5 and 1.3 times (P < 0.05) respectively, which was recorded in 19 patients (67.8 %). The levels of α1- and α2-globulins were within the age norm, indicating specific inflammatory process low activity in children at the beginning of treatment. The level of α2-globulin has been determined in 14 children (50 %).

Analysis of protein fractions altered levels depending on the prevalence of tuberculosis (Table 4) has showed the following results. Children with a common specific process had an increase in dysproteinemia, which was manifested by a decrease in albumin levels by 9 % (P < 0.05) and an increase in the levels of β- and γ-globulins in 1.3 times (P < 0.05). In this context, an increase in the inflammatory specific process activity was determined, indicating an increase in the level of α2-globulin in 1.3 times (P < 0.05).

DUC was also calculated for all protein fractions parameters. It has been established that DUC for albumin indicators, β- and γ-globulin values were up to 1.0 (0.16, 0.13 and 0.37 respectively), indicating their high informativeness for diagnosis. The informativeness of the α1- and α2-globulin indices was average, since their DUC were 1.11 and 4.49 respectively.

The investigation of correlation between levels of Ig content and protein fractions parameters (Table 5) made it possible to establish that children with NDTB at the beginning of IF AMBT had a decrease in albumin levels which was associated with an increase in IgE, A, and G levels. The growth in β-globulin levels was associated with an increase in levels of IgA and G, and γ-globulins IgE, M and G.

**Table 5. Correlation between Ig content levels and protein fractions parameters among children with NDTB**

| Indicators of protein fractions | Ig indicators | IgE | IgA | IgM | IgG |
|--------------------------------|--------------|-----|-----|-----|-----|
|                                |              | r   | p   | r   | p   |
|                                |              | r   | p   | r   | p   | r   | p   |
| Albumens                       |              | -0.386 | <0.05 | -0.486 | <0.01 | -0.355 | >0.05 | -0.619 | <0.001 |
| α1-globulins                   |              | 0.08 | >0.05 | 0.336 | >0.05 | -0.167 | >0.05 | 0.318 | >0.05 |
| β1-globulins                   |              | -0.107 | >0.05 | 0.246 | >0.05 | 0.08 | >0.05 | 0.088 | >0.05 |
| γ-globulins                    |              | 0.200 | >0.05 | 0.524 | <0.01 | 0.284 | >0.05 | 0.481 | <0.01 |
| IgE                            |              | 0.384 | <0.05 | 0.233 | >0.05 | 0.399 | <0.05 | 0.383 | <0.05 |

**Conclusions**

1. Children with NDTB, at the beginning of the IF AMBT had a significant increase in IgE and A levels in 2.1 and 1.2 times, respectively. With an increase in the specific process prevalence and destruction appearance there was a significant increase in the IgG level in 1.2 times. Direct correlation of IgE and IgA, IgA and IgM, IgM and IgG in the disseminated process, and IgA, IgM levels in the local process has been established.

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2. A reliable correlation between the decrease in the BCG post-vaccination sign size and the increase in IgE content has been found which can be a prognostic factor in the evaluation of post-vaccination immunity.

3. The activation of immune system cellular component is determined among the children as evidenced by a significant increase in albumins level in 1.5 times against the background of specific inflammatory process low activity (levels of α1- and α2-globulins were within the age range).

There is a significant increase in dysproteinemia (a decrease in albumin levels by 9 % and an increase in β- and γ-globulins levels in 1.3 times) and specific inflammatory process activity (an increase in α1-globulin levels in 1.3 times) with the increase in the specific process prevalence and destruction appearance.

4. It has been established that the decrease in the albumin level is associated with the growth in IgE, A and G levels; the growth in β-globulin levels is associated with the growth in IgA and G levels, and with IgE, M and G – in γ-globulins.

5. It has been found that IgA, M and G and the protein fractions parameters – albumins, β- and γ-globulins are significant and highly informative for the immune changes diagnosis among children with NDTB.

Prospects for further researches. The revealed changes are the basis for the development of rationally directed immunocorrective therapy among children with NDTB, and it will contribute to improvement of treatment effectiveness.

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