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TUBERCULOSIS INFECTION IN CHILDREN WITH NEGATIVE REACTIONS TO THE DIASKINTEST

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Variants of the course of tuberculosis infection in 54 children from two to 14 years old, negatively reacting to a sample with an allergen tuberculosis recombinant (Diaskintest) were analyzed. There were 3 groups: 1st – 27 children infected with *Mycobacterium tuberculosis* (MBT), 50.0% of cases; 2nd – 16 children with newly diagnosed residual post-tuberculosis changes (OPTI), 29.6% of cases; 3rd group – 11 patients with active tuberculosis, 20.4% of cases. **Methods of examination:** intradermal Mantoux test with 2TE and Diaskintest, according to the testimony of a number of patients *in vitro* tests: QuantiFERON test (QFT), – SPOT test.TV, multispiral computed tomography, bacteriological, molecular genetic methods of investigation on MBT. The method of mass tuberculin diagnostics revealed 70.4 ± 8.8% of children of the 1st group, 93.8 ± 4.7% of the 2nd group and 54.6 ± 15.0% of children of the 3rd group. The duration of infection with MBT in children was different and was less than 1 year in children of the 1st and 2nd groups – 51.9 ± 9.6% and 43.8 ± 12.4% of cases, respectively, which was significantly more frequent than in patients of the 3rd group (18.2 ± 11.6% of cases). Tuberculosis disease occurred in the form of complicated forms of the primary period-in 45.5 ± 15.0 % of cases, uncomplicated forms – in 27.3 ± 3.4% of cases, generalized lesions – in 27.3 ± 13.4% of cases. Diagnosis of a specific lesion occurred equally in the manifest phases of inflammation: infiltration, infiltration and decay (45.5 ± 15.0% of cases), and in the phase of ongoing reverse development (incomplete calcination – in 45.5 ± 15.0% of cases), one child had a combination of infiltration and calcination phases (9.1 ± 8.7% of cases). Residual posttuberculosis changes in children of group 2 were more often formed in the form of calcifications in the organs of the thoracic cavity – in 87.5% of cases, in 12.5 ± 8.3% of patients OPTI was formed by the formation of seals. **Conclusion:** in children with negative reactions to the Diaskintest requires individual comprehensive diagnosis of tuberculosis infection.

Keywords: children; tuberculosis; Diaskintest; allergen tuberculosis recombinant; Mantoux test with 2TE; tuberculin.

ТУБЕРКУЛЕЗНАЯ ИНФЕКЦИЯ У ДЕТЕЙ С ОТРИЦАТЕЛЬНЫМИ РЕАКЦИЯМИ НА ПРОБУ ДИАСКИНТЕСТ

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Проанализированы варианты течения туберкулезной инфекции у 54 детей 2–14 лет, отрицательно реагирующих на пробу с аллергеном туберкулезным рекомбинантным (Диаскинтест). Выделены три группы: группа 1 — 27 детей, инфицированных микобактериями туберкулеза (50,0 % наблюдений); группа 2 — 16 детей с впервые выявленными остаточными посттуберкулезными изменениями — 29,6 % наблюдений; группа 3 — 11 пациентов с активным туберкулезом — 20,4 % наблюдений. **Методы обследования:** внутрикожные пробы Манту с 2ТЕ и Диаскинтест, по показаниям у ряда пациентов тесты *in vitro*: QuntiFeron test (QFT), тест T-SPOT.TB, мультиспиральная компьютерная томография, бактериологические, молекулярно-генетические исследования на выявление микобактерий туберкулеза. Методом массовой туберкулинодиагностики было обнаружено 70,4 ± 8,8 % детей группы 1, 93,8 ± 4,7 % группы 2 и 54,6 ± 15,0 % группы 3. Длительность инфицирования микобактериями туберкулеза у детей была различной и составляла менее года в группах 1 и 2 — 51,9 ± 9,6 % и 43,8 ± 12,4 % случаев соответственно, что достоверно чаще, чем у пациентов группы 3 (18,2 ± 11,6 % случаев). Заболевание туберкулезом протекало в виде осложненных форм первичного периода в 45,5 ± 15,0 % случаев, в виде неосложненных форм — в 27,3 ± 3,4 % случаев, в виде генерализованных поражений — в 27,3 ± 13,4 % случаев. Диагностика специфического поражения происходила в равной мере как в манифестные фазы воспаления: инфильтрации, инфильтрации и распада (45,5 ± 15,0 % случаев), так и в фазы

продолжающегося обратного развития (неполной кальцинации — в 45,5 ± 15,0 % случаев), у одного ребенка было выявлено сочетание фаз инфильтрации и кальцинации (9,1 ± 8,7 % случаев). Остаточные посттуберкулезные изменения у детей группы 2 чаще были представлены обызвествлениями в органах грудной полости — 87,5 % случаев, у 12,5 ± 8,3 % пациентов остаточные посттуберкулезные изменения были в виде уплотнений. **Заключение.** При отрицательных реакциях на Диаскинтест у детей необходима индивидуальная комплексная диагностика туберкулезной инфекции.

Ключевые слова: дети; туберкулез; Диаскинтест; аллерген туберкулезный рекомбинантный; проба Манту с 2ТЕ; туберкулин.

Currently, tuberculosis infection in children is detected and diagnosed using the Mantoux test with 2TE and a test with recombinant tuberculosis allergen (Diaskintest) [1, 2, 6, 9]. A tuberculin test is highly sensitive to tuberculosis antigens, which allows us to evaluate the duration of post-vaccination immunity and determine the time of tuberculosis infection [5, 7]. However, due to insufficient specificity, it does not always reliably confirm tuberculosis infection [4, 8, 12]. Diaskintest reveals actively metabolizing Mycobacterium tuberculosis in the body [1, 3, 10]. According to the invention patent, there is 100% specificity of Diaskintest and the sensitivity is not <80%[1]. The authors noted that the sensitivity of Diaskintest is different and depends on the bacterial load on the body, as well as the activity and the immune state of the body [3, 4, 6]. The highest sensitivity of this test was observed in children and adolescents with tuberculosis reaching 71.6–96.9%. After the intensive phase of treatment, it decreases to 83.8%; after the end of the treatment course, it decreases to 78.3% [3, 5, 6, 8, 10]. A negative reaction of Diaskintest can occur in children in the early stages of tuberculosis infection or active tuberculosis, with the small local forms of tuberculosis, as well as in patients with severe immunosuppressive conditions due to either severe tuberculosis or a combination of immunodeficiency diseases [4, 7, 8]. According to several researchers, in children infected with Mycobacterium tuberculosis without signs of the disease, the sensitivity of Diaskintest varied from 22.7% to 91.7%, depending on whether the contact with a patient with bacterial excretion was established and depending on the duration of the tuberculosis infection [3, 5, 8, 10, 11]. According to several authors, the number of positive reactions ranged from 22.7% to 45.9% in the early period of primary tuberculosis infection; for the children infected in previous years, the number ranged from 53.7% to 91.3%; after conducting courses of preventive therapy, the number of positive reactions decreased from 40.0% to 0% of patients [3, 5, 8, 10, 11]. When diagnosing spontaneously formed residual post-tuberculous changes, negative results on Diaskintest were observed in 0–54.5% of patients [3, 5, 11].

Given the likelihood that children with negative reactions to Diaskintest may develop a tuberculosis infection, we performed a relevant analysis to evaluate the features of its course in these patients.

Thus, this study aims to analyze the course of tuberculosis infection in children with negative reactions to Diaskintest to improve the diagnosis and the prevention of the disease.

MATERIALS AND RESEARCH METHODS

We analyzed 54 case histories of children ranging in age from 2 to 14 years in 2014–2017. We performed comprehensive physiological examinations, using modern methods, and diagnosed tuberculosis infection with negative reactions to Diaskintest. When collecting epidemic anamnesis data, we evaluated the dynamics of the Mantoux with 2TE and also considered the criteria indicating the need for a child's admission to a tuberculosis dispensary for the diagnosis of tuberculosis infection [10]. Children with long-term monotonous sensitivity to tuberculin were not included in the sample to exclude a possible long-term post-vaccination allergy. X-ray examination included multispiral computed tomography of the chest organs; bronchoscopy was performed if it was medically required. For a number of patients (seven children), immunodiagnosis of tuberculosis infection (the Mantoux test with 2TE and Diaskintest) was supplemented by in vitro tests, such as QuantiFeron test (QFT) and T-SPOT.TB test. These tests were prescribed for children with negative results in the Mantoux test with 2TE, in order to clarify the activity of tuberculosis infection in the body with newly detected calcifications, foci of compaction in the organs of the chest cavity, or with severe tuberculosis. All of the patients underwent laboratory tests; their bacteriological and molecular genetic materials were studied for the presence of mycobacterium tuberculosis. According

[1] Patent for invention no. 2277540, valid from July 29, 2003; patent for invention.

to the results of a comprehensive diagnosis, three observation groups were identified:

- Group 1 included 27 children infected with mycobacterium tuberculosis without tuberculosis (50.0% of all patients).
- Group 2 included 16 children with diagnosed residual post-tuberculous changes (29.6% of all patients).
- Group 3 included 11 children with active forms of tuberculosis (20.4% of all patients).

Thus, the largest proportion of the patients included children infected with Mycobacterium tuberculosis without signs of transferred or active tuberculosis. The ratio of boys and girls was approximately equal (51.9% and 48.1%, respectively), and the distribution in the groups was equal.

The data were statistically processed using Microsoft Excel 2007. To determine the significance of differences between the compared average values, we used Student's *t*-test. The differences were considered to be statistically significant at $p < 0.05$.

RESEARCH RESULTS

The majority of patients from all of the observation groups were vaccinated against tuberculosis, including 96.3% of children from group 1, all of the patients from group 2, and 81.8% of children from group 3. Tuberculosis infection in all of the patients was most often diagnosed using mass tuberculin testing. In children from group 1, tuberculosis infection was diagnosed in 70.4 ± 8.8% of patients; in children from group 2, it was diagnosed in 93.8 ± 4.7% of patients (Table 1). For children with active tuberculosis (group 3), this method was rarely used, i. e., in 54.6 ± 15.0% of patients, which was due to the large proportion of children identified by complaints, amounting to 27.3 ± 13.4% ($p < 0.05$). The epidemic method in group 1 was used in 25.9% of patients, which is more often than in groups 2 and 3 (6.3% and 18.2% of patients, respectively). One group 1 patient was identified from an outpatient risk group.

Group 2 included 18.8 ± 9.7% of children from tuberculosis foci; group 3 included 36.4 ± 14.2% of children, which is more than during the initial examination, since some patients (12.5 ± 8.3% and 18.2 ± 11.6% in groups 1 and 2, respectively) were established as the source of the disease when collecting their anamnesis data in a hospital. Bacillary contacts with drug-resistant tuberculosis were more likely to occur in children with active tuberculosis (27.3 ± 13.4% of patients), in contrast to children infected with Mycobacterium tuberculosis ($p < 0.05$), and less often in children with residual post-tuberculous changes (6.3 ± 6.1% of patients), confirming the role of the bacterial load on the child's body in the development of tuberculosis disease.

The dynamics of the Mantoux with 2TE in most patients revealed infection with Mycobacterium tuberculosis, provided that the influence of nonspecific factors on this test was eliminated. (Table 2). The classic conversion, reflecting that tuberculin samples became positive, was more often observed

Table 1 / Таблица 1

Methods of detection of tuberculosis infection in examined children
Методы выявления туберкулезной инфекции у обследованных детей

Detection methods / Методы выявления	Group 1, $n = 27$ / Группа 1, $n = 27$	Group 2, $n = 16$ / Группа 2, $n = 16$	Group 3, $n = 11$ / Группа 3, $n = 11$
Tuberculin diagnosis / Массовая туберкулинодиагностика	70.4 ± 8.8 $p_{1-2} < 0.05$	93.8 ± 4.7 $p_{1-2} < 0.05$ $p_{2-3} < 0.05$	54.6 ± 15.0 $p_{2-3} < 0.05$
Epidemic methods / Эпидемический метод	25.9 ± 8.4	6.3 ± 6.0	18.2 ± 11.6
Identifying at-risk outpatient clinics / Выявление из групп риска поликлиники	3.7 ± 3.6	0	0
Identification of complaints / Выявление по обращению с жалобами	0	0	27.3 ± 13.4

Note. $p < 0.05$ – significance of differences in methods of detection of tuberculosis infection in patients with negative results of the Diaskintest. *Примечание.* $p < 0,05$ — достоверность различий методов выявления туберкулезной инфекции у пациентов с отрицательными результатами Диаскинтеста.

Table 2 / Таблица 2

The dynamics of the Mantoux test with 2TE in examined children
Динамика пробы Манту с 2ТЕ у обследованных детей

The dynamics of the Mantoux test with 2TE / Динамика пробы Манту с 2ТЕ	Group 1, *n* = 27 / Группа 1, *n* = 27	Group 2, *n* = 16 / Группа 2, *n* = 16	Group 3, *n* = 11 / Группа 3, *n* = 11
The superelevation after the extinction of post-vaccination immunity / Вираж после угасания поствакцинального иммунитета	22.2 ± 8.0	12.5 ± 8.3	9.1 ± 8.7
The superelevation in children not vaccinated with BCG vaccine / Вираж у детей, непривитых вакциной БЦЖ	3.7 ± 3.6	0	9.1 ± 8.7
Increase by 6 mm or more / Нарастание на 6 мм и более	18.5 ± 7.5	31.3 ± 11.6	9.1 ± 8.7
Gradual increase of 7–11 mm / Постепенное нарастание на 7–11 мм	7.4 ± 5.0	0 $p_{2-3} < 0.05$	27.3 ± 13.4 $p_{2-3} < 0.05$
Rise up to 12 mm and more (not less than 4 mm) / Нарастание до 12 мм и более (не менее чем на 4 мм)	25.9 ± 8.4 $p_{1-3} < 0.05$	31.3 ± 11.6 $p_{2-3} < 0.05$	0 $p_{1-3} < 0.05$ $p_{2-3} < 0.05$
Rise to hyperergic reaction / Нарастание до гиперергической реакции	18.5 ± 7.5	25.0 ± 10.8	9.1 ± 8.7
Negative sensitivity / Отрицательная чувствительность	3.7 ± 3.6	0 $p_{2-3} < 0.05$	27.3 ± 13.4 $p_{2-3} < 0.05$
Lack of dynamics due to the early age of the child / Отсутствие динамики вследствие раннего возраста ребенка	0	0	9.1 ± 8.7

Note. $p < 0.05$ – significance of differences in criteria for MBT infection in children with negative results of the Diaskintest, MBT – *Mycobacterium tuberculosis*. *Примечание.* $p < 0{,}05$ — достоверность различий критериев инфицирования МБТ у детей с отрицательными результатами Диаскинтеста. МБТ — микобактерии туберкулеза.

in patients from group 1, i. e., in 22.2 ± 8.0% of patients, than in patients with residual post-tuberculous changes and active tuberculosis, which was observed in 12.5 ± 8.3% and 9.1 ± 8.7% of patients, respectively. The increase of the Mantoux induration in dynamics up to 12 mm (but not <4 mm) was observed in 25.9 ± 8.4% of children from group 1 and in 31.3 ± 11.6% of children from group 2; however, it was not observed in group 3 patients ($p < 0.05$). Hyperergic reaction to tuberculin was registered more often in group 2 children, i. e., in 25.0 ± 10.8% of patients; in group 1, it was registered less often, i. e., in 18.5 ± 7.5% of patients; in group 3, it was registered in 9.1% of patients.

Three children (27.3 ± 13.4%) from group 3 (tuberculosis patients) were negatively sensitive to tuberculin. In these cases, the etiology of the disease was confirmed by the results of other immunological QFT and T-SPOT.TB tests, as well as by the specific test therapy results. Among group 1 patients, one child from the tuberculosis site was negatively sensitive to tuberculin; the infection was confirmed by a positive QFT test result.

The duration of tuberculosis infection in children in the observation groups was different (Table 3). Tuberculosis infection lasted <1 year in children from groups 1 and 2, in 51.9 ± 9.6% and 43.8 ± 12.4% of patients, respectively. These indicators are significantly higher than in group 3 (18.2 ± 11.6% of patients). In a significant part of patients with tuberculosis (45.5 ± 15.0%), it was not possible to determine the time of tuberculosis infection due to the negative and dubious sensitivity to the Mantoux with 2TE (27.3 ± 13.4% of patients) and the lack of complete dynamic data on sensitivity to tuberculin (18.2 ± 11.6% of patients).

In 87.5% of children from group 2, residual post-tuberculous changes were represented by calcifications in the organs of the chest cavity with the prevalence of single calcifications in the lung tissue (Ghon foci) in 56.3 ± 8.3% of patients; in 12.5 ± 8.3% of patients, residual post-tuberculous changes were due to carnifications (Table 4).

Patients from group 3 were registered with both widespread and generalized lesions, as well as limited forms of tuberculosis. Tuberculosis of the intrathoracic lymph nodes, complicated by single foci of screening into the lung tissue, was diagnosed the most frequently, in 45.5 ± 15.0% of patients; uncomplicated limited forms of primary tuberculosis were found in 27.3 ± 13.4% of patients; generalized tuberculosis was registered in 27.3 ± 13.4% of patients (Table 5).

Table 3 / Таблица 3

The dynamics of the Mantoux test with 2TE in examined children
Динамика пробы Манту с 2TE у обследованных детей

The duration of MBT infection in the examined children / Длительность инфицирования МБТ обследованных детей	Group 1, $n = 27$ / Группа 1, $n = 27$	Group 2, $n = 16$ / Группа 2, $n = 16$	Group 3, $n = 11$ / Группа 3, $n = 11$
Less than 1 year / Менее 1 года	51.9 ± 9.6 $p_{1-3} < 0.05$	43.8 ± 12.4	18.2 ± 11.6 $p_{1-3} < 0.05$
More than 1 year / Более 1 года	48.1 ± 9.6	56.3 ± 12.4	36.3 ± 14.5
Definition not possible / Определение невозможно	0 $p_{1-3} < 0.05$	0 $p_{2-3} < 0.05$	45.5 ± 15.0 $p_{1-3} < 0.05$ $p_{2-3} < 0.05$

Note. $p < 0.05$ – significance of differences in the timing of MBT infection in children with negative results of the Diaskintest. MBT – *Mycobacterium tuberculosis*. *Примечание.* $p < 0{,}05$ — достоверность различий сроков инфицирования МБТ у детей с отрицательными результатами Диаскинтеста. МБТ — микобактерии туберкулеза.

Table 4 / Таблица 4

Structure of residual post-tuberculosis changes in children
Структура остаточных посттуберкулезных изменений у обследованных детей

Residual post-tuberculosis changes / Остаточные посттуберкулезные изменения	Group 2, $n = 16$ / Группа 2, $n = 16$
Calcification in the thoracic cavity, including:/ Обызвествления в органах грудной полости, в том числе:	87.5 ± 8.3
• isolated calcification in the lung tissue / единичные кальцинаты в легочной ткани	56.3 ± 12.5
• multiple calcifications in the lungs / множественные кальцинаты в легких	18.8 ± 9.8
• calcinates in the lung tissue and in the intra-thoracic lymph nodes / кальцинаты в легочной ткани и во внутригрудных лимфатических узлах	6.3 ± 6.1
• calcification in hilar lymph nodes and isolated pockets of drop-outs in the lung tissue / кальцинаты во внутригрудных лимфатических узлах и единичные очаги отсева в легочной ткани	6.3 ± 6.1
• seals in the organs of the thoracic cavity, including: / уплотнения в органах грудной полости, в том числе:	12.5 ± 8.3
– compacted intragastric lymph node / уплотненный внутригрудной лимфатический узел	6.3 ± 6.1
– a single compacted lesion in the pulmonary tissue / единичный уплотненный очаг в легочной ткани	6.3 ± 6.1

Table 5 / Таблица 5

Structure of active forms of tuberculosis in children
Структура активных форм туберкулеза у обследованных детей

Structure of clinical forms of active tuberculosis / Структура клинических форм активного туберкулеза	Group 3, $n = 11$ / Группа 3, $n = 11$
Non-complicated forms of intrathoracic TB, including: / Неосложненные формы внутригрудного туберкулеза, в том числе:	27.3 ± 13.4
• tuberculosis of the intrathoracic lymph nodes (small form) / туберкулез внутригрудных лимфатических узлов (малая форма)	18.2 ± 11.6
• primary tuberculosis complex (limited) / первичный туберкулезный комплекс (ограниченный)	9.1 ± 8.7
• tuberculosis of intracranial lymph nodes with foci of pulmonary tissue / туберкулез внутригрудных лимфатических узлов с очагами отсева в легочную ткань	45.5 ± 15.0
• generalized tuberculosis / генерализованный туберкулез	27.3 ± 13.4

Mycobacterium tuberculosis were detected through polymerase chain reaction in the cerebrospinal fluid and urine of one young child (9.1 ± 8.7% of patients) with generalized tuberculosis.

Specific lesions were detected equally in the overt inflammatory phases, including infiltration, infiltration, and decay (45.5 ± 15.0% of patients), and in the continuing reverse development phases, i. e., during incomplete calcination (45.5 ± 15.0% of patients); one child was registered with a combination of infiltration and calcination phases (9.1 ± 8.7% of patients). All of the children with combined HIV infection (three patients) were diagnosed with tuberculosis in the infiltration phase (27.3 ± 13.4% of patients).

DISCUSSION

Negative results of Diaskintest were more often observed in children infected with Mycobacterium tuberculosis (50.0% of patients), less often in patients with residual post-tuberculous changes (29.6% of patients), and patients with active tuberculosis (20.4% of patients). The leading method for detecting tuberculosis infection in children with negative Diaskintest results was mass tuberculin diagnostics, which allowed detecting 70.4 ± 8.8% of children infected with mycobacterium tuberculosis and 93.8 ± 4.7% of children with residual post-tuberculous changes. Patients with active tuberculosis were detected using this method less frequently, i. e., in 54.6 ± 15.0% of patients, which is due to a large proportion of patients with the disease identified in cases of complaints (27.3 ± 13.4% of patients). In patients with negative Diaskintest results, tuberculosis was both locally limited (27.3 ± 13.4% of patients) and complicated with intrathoracic forms (45.5 ± 15.0% of patients) and with generalized lesions (27.3 ± 13.4% of patients).

Different variants of the tuberculosis infection course in children with negative Diaskintest results can be explained in some cases by a relatively high level of immunity while in others by the low immune status of patients due to a combination of tuberculosis with HIV infection or severe tuberculosis.

FINDINGS

1. Among the children examined with tuberculosis infection and negative reactions to Diaskintest, most of the children were infected with Mycobacterium tuberculosis (50.0% of patients); the others were registered with residual post-tuberculous changes (29.6% of patients) and active forms of tuberculosis (20.4% of patients).

2. The leading method for identifying patients with negative Diaskintest results is mass tuberculin diagnosis, owing to which tuberculosis in children infected with Mycobacterium tuberculosis is diagnosed in 70.4 ± 8.8% of patients; in children with residual post-tuberculous changes, it is diagnosed in 93.8 ± 4.7% of patients; in children with active tuberculosis, it is diagnosed in 54.6 ± 15.0% of patients.

3. In case of complaints, negative Diaskintest results indicated active tuberculosis in 27.3 ± 13.4% of patients, which was due to either low sensitivity to tuberculin or lack of data on the dynamics of the Mantoux with 2TE.

4. In 45.5 ± 15.0% of patients, complications of tuberculosis in children with negative Diaskintest results were registered in the primary period; uncomplicated forms were registered in 27.3 ± 13.4% of patients; generalized lesions were registered in 27.3 ± 13.4% of patients.

5. In case of negative reactions to Diaskintest in children, epidemic anamnesis data, dynamics of the Mantoux test with 2TE, results of immunological in vitro tests, results of dynamic X-ray examinations, and results of bacteriological and molecular genetic methods for diagnosis of Mycobacterium tuberculosis should be considered when performing an individual comprehensive diagnosis of tuberculosis infection.

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