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ALLERGIC REACTIONS TO ANTITUBERCULOSIS DRUGS IN CHILDREN: DIAGNOSTIC POSSIBILITIES

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ABSTRACT. ***Introduction.*** Chemotherapy for tuberculosis in children is often difficult due to poor tolerability. ***The goal of the study*** is to determine the frequency and spectrum of allergic adverse reactions during chemotherapy for tuberculosis in children and to substantiate the method of their laboratory diagnostics. ***Materials and methods.*** We carried out a cohort retrospective study (from 2018 to 2021) which included 146 patients and a prospective study (from 2022 to 2024) of 50 patients. All 196 children (0–14 years) received the intensive phase anti-tuberculosis chemotherapy with a combination of 3–4 drugs. ***Results.*** A retrospective analysis showed that there were no adverse reactions in 56 (38.3%) children, allergic reactions were observed in 32 (21.9%), toxic-allergic reactions in 22 (15.1%), and toxic reactions in 36 (24.7%). In a prospective study in 50 children underwent a basophil activation test using flow cytometry for the drugs they were receiving (196 tests in total). Most basophil activation tests were performed for first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide — 178 (90.8%), for second-line drugs 18 (9.2%). Of the 196 tests, 38 (19.4%) gave a positive result. The test results were compared with the clinical manifestations of adverse reactions in three groups of patients: group I — 18 children with allergic and toxic-allergic reactions to antituberculosis drugs, group II — 14 patients with toxic reactions, group III — 18 children without adverse reactions. In group I the proportion of patients with a positive result of the basophil activation test (for 1 or 2 drugs) was 94.4%, which is higher than in group II — 71.1% and significantly higher than in group III — 16.7% ($P < 0.05$; $\chi^2 = 54.9$). ***Conclusion.*** The importance of the basophil activation test in predicting allergic and toxic-allergic reactions and determining the drug responsible for side effects during combination chemotherapy has been proven.

KEYWORDS: *children, tuberculosis chemotherapy, allergic adverse reactions, basophil activation test*

АЛЛЕРГИЧЕСКИЕ РЕАКЦИИ НА ПРОТИВОТУБЕРКУЛЕЗНЫЕ ПРЕПАРАТЫ У ДЕТЕЙ: ВОЗМОЖНОСТИ ДИАГНОСТИКИ

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РЕЗЮМЕ. ***Введение.*** Химиотерапия туберкулеза у детей часто бывает затруднена из-за явлений плохой переносимости. ***Цель исследования*** — определить частоту и характер аллергических нежелательных побочных реакций при химиотерапии туберкулеза у детей, обосновать метод их лабораторной диагностики. ***Материалы и методы.*** Проведены когортное ретроспективное исследование (с 2018 по 2021 гг.), в которое включены 146 пациентов, и проспективное исследование (с 2022 по 2024 гг.) — 50 пациентов. Все дети (0–14 лет) получали интенсивную фазу противотуберкулезной химиотерапии комбинацией 3–4 противотуберкулезных препаратов. ***Результаты.*** Ретроспективный анализ показал, что нежелательные побочные реакции отсутствовали у 56 (38,3%) детей, аллергические реакции наблюдались у 32 (21,9%), токсико-аллергические у 22 (15,1%), токсические у 36 (24,7%) детей. В проспективном исследовании 50 детям выполнен тест активации базофилов методом проточной цитометрии на те препараты, которые они получали (в целом 196 тестов). Большинство тестов активации базофилов выполнены на препараты первого ряда (изониазид, рифампицин, этамбутол, пиразинамид — 178 (90,8%), на препараты второго ряда — 18 (9,2%)). Из 196 тестов положительный результат дали 38 (19,4%). Результаты тестов сопоставлены с клиническими проявлениями нежелательных побочных реакций в трех группах пациентов: I группа — 18 детей с аллергическими и токсико-аллергическими реакциями на противотуберкулезные препараты, II группа — 14 пациентов с токсическими реакциями, III группа — 18 детей без нежелательных реакций. В I группе доля пациентов с положительным результатом теста активации базофилов (на 1 или 2 препарата) составила 94,4%, что выше, чем во II группе — 71,1% и значительно выше, чем в III группе — 16,7% ($P < 0,05$; $\chi^2 = 54,9$). ***Заключение.*** Доказано значение теста активации базофилов в прогнозировании аллергических и токсико-аллергических реакций и определении препарата — виновника нежелательных побочных реакций при комбинированной химиотерапии.

КЛЮЧЕВЫЕ СЛОВА: *дети, химиотерапия туберкулеза, аллергические нежелательные побочные реакции, тест активации базофилов*

INTRODUCTION

Monitoring of tuberculosis epidemic situation in the Russian Federation has shown that after a decrease in incidence in children 0-14 years of age in 2013–2020, the indicator stagnates at 6.7 per 100,000 in the following years [1], which requires increased attention to all aspects of pediatric tuberculosis, including its treatment [2].Undesirable adverse reactions (UARs) resulting from the use of antituberculosis drugs (ATDs) in children can significantly complicate the course of tuberculosis chemotherapy and reduce its effectiveness [3, 4]. UARs for antituberculosis drugs in children, as well as adults, are divided into toxic, allergic, and toxic-allergic ones according to mechanisms of origin [5, 6].

Toxic UARs are organ-specific and depend on the dose, structure and metabolism which is specific for each TB drug. For example, isoniazid, cycloserine, prothionamide have toxic effects on the nervous system; aminoglycosides are ototoxic and nephrotoxic, many ATDs have hepatotoxic effects, etc.

Allergic UARs are hypersensitivity reactions. They can occur with any TB drug, regardless of the dose. From a practical point of view, it is difficult to identify the drug that caused an allergic reaction in combination chemotherapy, and it is often necessary to cancel all drugs.

Toxic-allergic adverse reactions occur when an allergic state develops, which is accompanied by a vascular reaction, enzymatic and biochemical shifts that aggravate the toxic effect of drugs on organs and tissues.

According to literature data, allergic adverse reactions during TB treatment in children account for 20–30% [7], while toxic and toxic-allergic reactions predominate. However, some studies emphasize the high frequency of adverse reactions of allergic genesis (50.5%) is a peculiarity of childhood [8]. Allergic reactions are often manifested by isolated eosinophilia, as well as skin reactions in the form of rashes and itching, are often systemic, and may be accompanied by organ damage, fever [9]. Therefore, they are often treated as toxic-allergic and toxic, thus, it is not possible to identify the allergic factor in the development of UARs using routine methods.

The main method of drug allergy detection is pharmacological anamnesis, but it is usually difficult to apply it in newly diagnosed tuberculosis patients. Taking into account multicomponent chemotherapy regimens for tuberculosis, it can be quite difficult to identify the drug responsible for drug allergy [10]. The methods of recording allergic reactions to ATDs are underdeveloped and there are few studies based on the general principles of drug allergy diagnosis [11]. *In vivo* tests — patch-test [12], provocation test [13] — can cause aggravation of allergic reactions up to life-threatening conditions, which is why their use is limited. The advantages of *in vitro* tests over *in vivo* diagnostic tests are their safety, as well as the possibility to test several drugs simultaneously [14]. Allergic reactions to ATDs have been determined by lymphocyte blast-transformation reaction (LTR), initially by staining smears with azur-2-eosin [15, 16], and in later studies the proliferative activity of lymphocytes was determined by the incorporation of H3-thymidine into cell DNA [17, 18]. The method did not find further application in phthisiatric practice. One publication mentions the use of leukocyte agglomeration reaction to detect allergy to rifampicin and kanamycin [19]. In order to diagnose drug allergy to some antibacterial drugs, the determination of allergen-specific IgE antibodies to the corresponding allergens is used. However, kits for the determination of specific IgE are only available for a limited number of drugs, including amoxicillin, ampicillin, cefaclor, and penicillin [20]. In addition, only IgE-mediated allergy is detected using allergen-specific IgE antibodies, whereas it can be caused by different mechanisms (IgE-mediated and non-IgE-mediated) [21].

The basophil activation test (BAT) is a promising and sought-after method of allergy diagnosis, which makes it possible to detect a reaction to any drug. The great advantage, especially in comparison with diagnostic tests of allergen-specific IgE determination, is that BAT evaluates both IgE-dependent and IgE-independent mechanisms of allergy [22–25]. The basophil activation test is based on the contact of allergen with various receptors on the basophil membrane (including the IgE-FcεRI complex) with activation of a range of enzymatic reactions [26]. Activation of basophils leads not only to the release of soluble mediators, but also to the expression of activation markers — CD63

and CD203c — on the membrane, which are taken into account using flow cytofluorimetry [27, 28]. When diagnosing drug allergy to some antibiotics in patients, the sensitivity varies from 33 to 67%, and the specificity of this method varies from 79 to 100%, which indicates that it is promising, according to a number of authors [14, 29, 30].

AIM

To determine the frequency and nature of allergic UARs during chemotherapy of tuberculosis in children, to substantiate the method of their laboratory diagnostics.

MATERIALS AND METHODS

The study is cohort, retrospective and prospective. It covered the period from 2018 to 2024. The study was carried out on the basis of the tuberculosis department of the St. Petersburg State Budgetary Institution "Children's Infectious Diseases Hospital No. 3" (DIB NO. 3). Overall, 196 children with active forms of respiratory tuberculosis were included.

Inclusion criteria were: presence of active respiratory tuberculosis; full intensive phase (IP) of chemotherapy (CT) in the pediatric tuberculosis department; absence of parasitic invasions. Exclusion criteria: inactive tuberculosis or latent tuberculosis infection; leaving the hospital before the end of IP chemotherapy; parasitic invasions detected before or during treatment. The age of children varied from 0 to 14 years inclusive. Girls constituted 106 (54.1%), boys — 90 (45.9%). Children of early age (from 0 to 3 years) accounted for 31 (15.8%), from 3 to 7 years — 84 (42.8%), from 8 to 14 years — 81 (41.4%).

The research was conducted in two stages. The first stage (retrospective) included the analysis of archived case histories of 146 children for 2018–2021 in order to determine the number of all ARDs when taking ATD. The frequency and spectrum of reactions caused by allergic and toxic-allergic mechanisms were defined. The second stage (prospective) involved the observation of children (50 patients) during the course of the study, recording UARs and performing the basophil activation test.

Patients were examined according to the Clinical Recommendations that were relevant for the period of the study [31]. Examination was conducted before the administration of chemotherapy (CT) for tuberculosis and in the course of dynamic follow-up. It included: anamnesis collection (epidemiological, social, allergological, pharmacological ones); physical examination methods, standard clinical and biochemical blood and urine tests, chest computed tomography, immunodiagnostics using Mantoux test with 2 units and test with recombinant tuberculosis allergen (RTA, Diaskin-test). Bacteriological studies aimed at detection of Mycobacterium tuberculosis (MBT) included sputum smear microscopy (or bronchoscopy), molecular genetic methods of pathogen detection, culture on dense and liquid growth-supporting microenvironment. Fibrobronchoscopy and test for interferon-gamma induction by MBT antigens (TB-Feron test) were performed when indicated. Triple stool tests for helminth eggs and parasites were performed. All children underwent electrocardiography (ECG) and pulmonary function tests. In the course of chemical treatment, a clinical blood test, urine analysis, extended blood biochemical analysis with determination of alanine and asparagine transaminases (ALT and AST), bilirubin, uric acid and other indices of liver and kidney function were performed once a month (more often if indicated) to monitor possible UARs to the drugs.

The basophil activation test via flow cytometry was used as a special method for diagnosing sensitization to drugs. BAT with drugs was performed within 2 hours from the moment of blood collection in vacutainers with lithium heparin. Allergenicity kit (Beckman-Coulter) was used to perform the test by flow cytometry. According to the instructions for the test system, the basophil population was detected in a multicolor protocol with multistage gating using monoclonal antibodies to CD3, CD294, CD203c. Cell activation was assessed in vitro based on the increase in CD203c expression after drug stimulation. The technique of basophil activation test (BAT) was as follows [32]. Since tested TB drugs were in tablet form (except amikacin), a contact aqueous solution based on the drug and distilled water was used. Supernatant from the prepared drugs was used at a dilution of 1:25 in relation to the

patient's blood sample. Presence/absence of sensitization to drugs in BAT was determined on the basis of basophil activation index with a threshold value of 1.1. The basophil activation index is the ratio of the number of activated basophils in the sample with allergen to the number of these cells in the sample with buffer solution.

All 50 children included in the prospective study got through BAT for those drugs, which they received according to the regimen of ChT, in order to diagnose sensitization of the organism to antituberculosis drugs. The study was performed 2 weeks after the therapy had started. 46 out of 50 children were tested for sensitization to 4 drugs and 4 children – to 3 drugs. The follow-up period lasted for 2 months. ChT prescription, monitoring and evaluation of possible adverse reactions were performed according to the Federal Clinical Guidelines "Tuberculosis in Children" (2018, 2020, 2022).

Statistical processing. The database was composed in Excel 2010 program (Microsoft Office). Differences between relative values were determined using the Pearson χ^2 criterion in STATISTICA 6.1. The generally accepted confidence level of 95% ($p < 0.05$) was considered. The odds ratios (ORs) for the development of UARs and their 95% confidence interval (95% CI) were determined.

The study was approved by the local ethical committee of the St. Petersburg State Pediatric Medical University, conclusion No. 06/04 dated 02.12.2021.

RESULTS

The retrospective study revealed that 146 children who received inpatient TB treatment in 2018–2022 had the following clinical forms of the disease: intrathoracic lymph node tuberculosis (ITNT) – 103 (70.5%), primary tuberculosis complex (PTC) – 35 (24.0%), infiltrative TB- 5 (3.4%), focal TB – 2 (1.3%), disseminated TB – 1 (0.7%). Only 2 children had their own bacterial excretion (MBT sensitivity to ATDs was preserved), so chemotherapy regimens (ChTR) were prescribed on the basis of information about the MBTs of an adult patient with whom the child was in contact. Standard I/III chemotherapy regimens consisting of four main ATDs (isoniazid, rifampicin, ethambutol, pyrazinamide) were given to 124 children (84.9%). If multidrug-resistant (MDR) MBT was found, children were treated with IV ChTR (22 (15.1%) children in total). A combination of 4–5 ATDs was administered as part of IV ChTR (22 children), taking into account the source MBT resistogram. 56 (38.3%) out of 146 examined children had no adverse effects during therapy, while the remaining 90 children had adverse effects, the spectrum of which is shown in Figure 1.

Thus, three types of adverse reactions to TB drugs could be distinguished.

Allergic reactions were observed in 32 (21.9%) children. Isolated eosinophilia prevailed – 26 (81.2%). It constituted 7–10% of cells in the leukocytic formula (up to 500 cells in μl of blood) – in 15 people, 10–19% (500–1500 cells in μl) – in 8 people, 20% and more (more than 1500 cells in μl) – in 3 people. In addition to isolated eosinophilia, it was combined with other manifestations of allergy (skin rashes, bronchospasm, rhinitis, conjunctivitis) in 4 (12.5%) children. Cutaneous allergic reactions (urticaria, pruritus) without eosinophilia occurred in 6.3% (2 people).

Toxic-allergic reactions occurred in 22 (15.1%) patients. Allergic symptoms in the form of eosinophilia were combined with dysfunction of various organs. Increased serum levels of liver enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST)) were additionally observed among 13 (59.1%) children. 4 (18.3%) patients had elevation of uric acid. Increased levels of enzymes combined with hyperuricemia was observed in 5 (22.7%) patients. Elevation of liver enzymes up to 1.5 norms was observed in

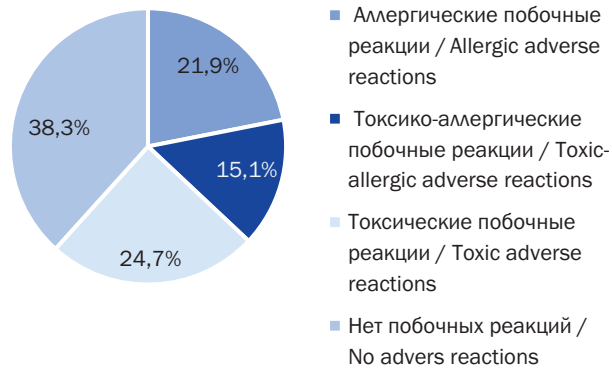

Fig. 1. Structure of adverse reactions during tuberculosis chemotherapy in 146 children

Рис. 1. Структура нежелательных побочных реакций при химиотерапии туберкулеза у 146 детей

6 (27.2%), from 1.5 to 3 norms — in 4 (13.6%), over 3 norms — in 3 (9%) children. In addition to these laboratory shifts, some of these children had clinical symptoms in the form of skin manifestations (urticaria, dermatitis, itching) — 4 children (18.2%), joint pain — 1 (4.5%), dyspeptic phenomena (vomiting, nausea, abdominal pain) — 5 (22.7%), central nervous system manifestations — 4 (18.2%) (sleep disturbance — 1, photophobia — 1, hyperexcitability — 1, auditory hallucinations — 1).

Toxic reactions without allergy manifestations were registered in 36 children (24.7%). Elevation of liver enzymes was the main manifestation of toxic UARs, it was found in all children of this group 36 (100%). Liver hyperfermentemia was combined with hyperuricemia in blood biochemical analysis in 17 (47.2%) cases, dyspeptic phenomena — in 10 (27.7%) children, neurotoxic reactions — in 4 (11.1%) patients, one case each — nest alopecia, color perception disorders, nosebleeds.

All UARs were reversible on the background of symptomatic treatment, however, temporary withdrawal or replacement of drugs was required in allergic UARs in 8 (25.0%) cases, in toxic-allergic reactions — in 10 (45.5%) cases ($P < 0.05$).

Thus, the retrospective analysis allowed us to conclude that the allergic mechanism is significant in the development of adverse reactions during chemotherapy of tuberculosis in children, since purely toxic UARs without allergic manifestations were less frequent (24.7%) than reactions with clinical and laboratory signs of increased sensitization to the drugs, which were observed in 37% of children. Among them, allergic reactions were registered in 21.9% of children and toxic-allergic reactions in 15.1%. Development of laboratory tests allowing to determine the level of sensitization of a child's organism to TB drugs is in demand in clinical practice. The prospective part of the study is focused at solving this problem.

50 children participating receiving intensive phase of chemotherapy in 2022-2023 were diagnosed with the following clinical forms of tuberculosis: uncomplicated intrathoracic lymph node tuberculosis (ITNT) — 17 (34.0%), complicated ITNT — 13 (26.0%), primary tuberculosis complex (PTC) — 9 (18.0%), infiltrative TB — 2 (4.0%), focal TB — 3 (6.0%), disseminated TB — 4 (8.0%), tuberculous pleurisy — 2 (4.0%). The structure of complicated ITNT (26.0%) included: foci of dropouts in the lung tissue — 10 (20.0%), bronchial tuberculosis 2 (4.0%) and bronchopulmonary lesions — 1 (2.0%). The vast majority of children — 45 (90.0%) — received I/III ChTR, which included the main 1st-line TB drugs (isoniazid, rifampicin, ethambutol, pyrazinamide). In isolated cases, II ChTR (in case MBT was resistant to isoniazid, 2 children), and IV ChTR (in case of multidrug-resistant MBT, 3 children) were prescribed; these regimens included reserve TB drugs prescription in accordance with the current clinical recommendations.

Analysis of chemotherapy tolerance showed that only 18 (36.0%) children had no UARs. 7 (14.0%) children developed allergic UARs, 11 (22.0%) had toxic-allergic UARs and 14 (28.0%) suffered from toxic UARs. Other reasons for allergic reactions (except TB drugs) were excluded according to the anamnesis, clinical and laboratory data obtained by the moment of the research. Thus, the ratio of UARs types in the prospective study coincided with the retrospective one. 50 children were divided into three groups according to the presence or absence of UARs.

- Group I (18 (36.0%)) — children with allergic and toxic-allergic reactions to the drugs administered;
- Group II (14 (28.0%)) - children with toxic reactions without allergic manifestations;
- Group III (18 (36.0%)) - children without undesirable adverse reactions to the drugs.

Clinical and laboratory manifestations of UARs in children of groups I and II are presented in Figures 2 and 3.

The number of BATs performed as well as their results are presented in Table 1. A total of 196 tests were performed, mainly for 1st-line drugs — 178 (90.8%), in isolated cases for 2nd-line drugs — 18 (9.2%) (for children receiving II and IV RCTs). Positive results of BAT (presence of sensitization to drugs) were obtained in 38 tests out of 196 (19.4%). The most frequent positive BAT results were for rifampicin (23.9%) and ethambutol (23.4%), while isoniazid (9.3%) was the least frequent (Table 1).

20 patients (40.0%) out of 50 children tested had negative BATs for all drugs taken. There were

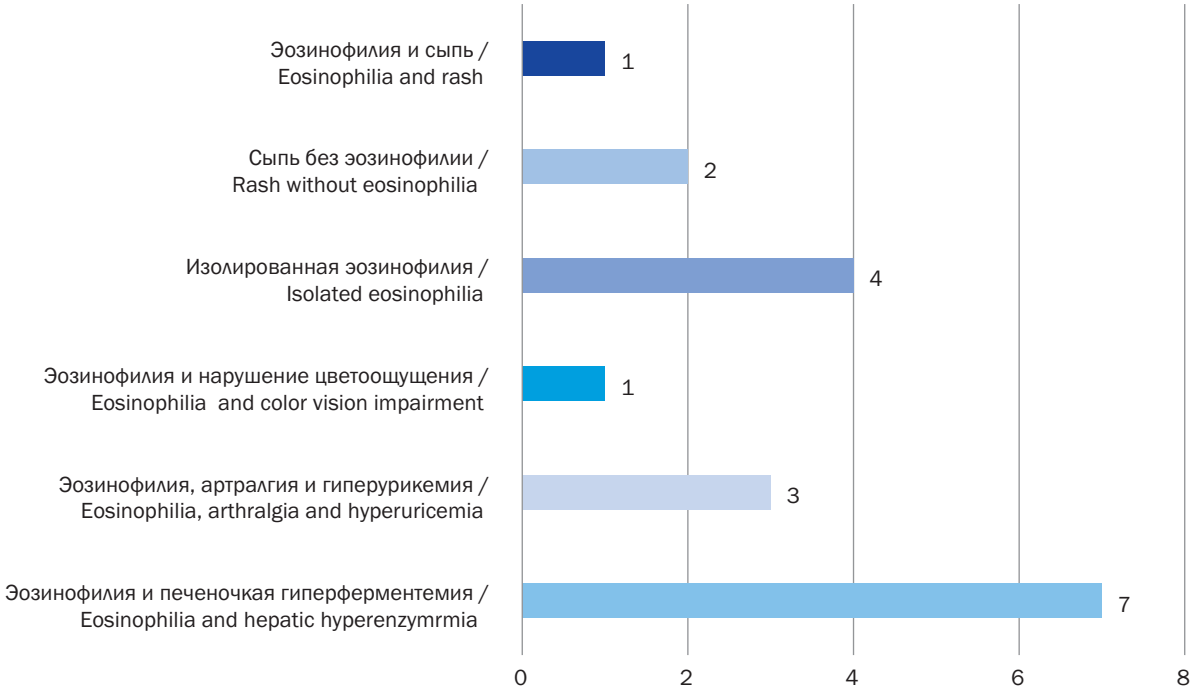

Fig. 2. Manifestations of allergic and toxic-allergic advers reactions to antituberculosis drugs, I group of children (n=18)

Рис. 2. Проявления аллергических и токсико-аллергических побочных реакций на противотуберкулезные препараты, I группа детей (n=18)

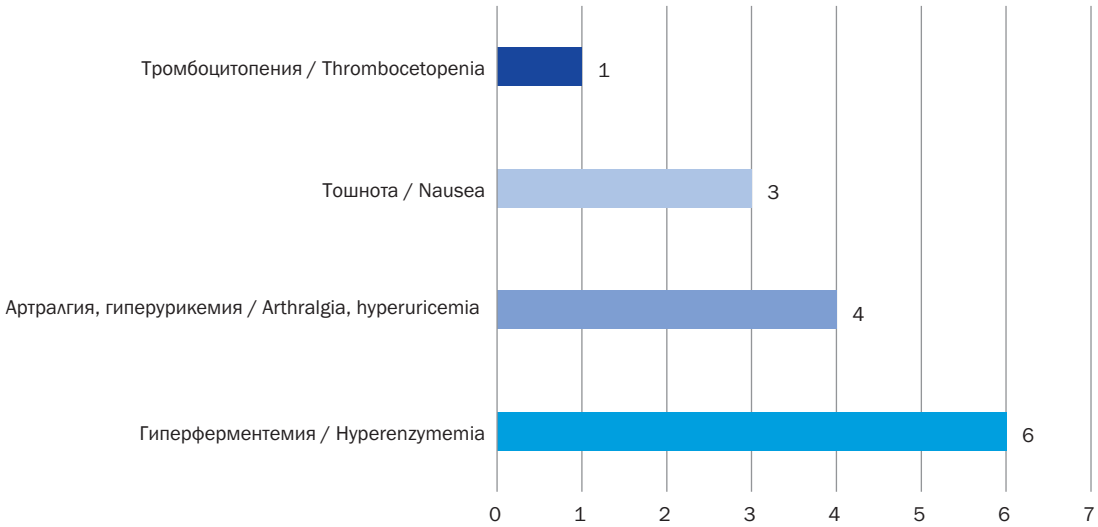

Fig. 3. Manifestations of toxic advers reactions to antituberculosis drugs, II group of children (n=14)

Рис. 3. Проявления токсических побочных реакций на противотуберкулезные препараты, II группа детей (n=14)

30 (60.0%) children with positive BAT results, including BAT positive to one drug in 22 cases (44.0%) and positive to two drugs (8, or 16.0%).

When analyzing the results in three groups (Fig. 4), it turned out that negative BATs were significantly more frequent in Group III (without UARs). It amounted to 15 children (83.3%, P <0.05), Group I demonstrated a negative BAT test in 1 child (5.6%) and Group II — in 4 (28.6%) children. Accordingly, group III was significantly less likely to have positive BATs to both one and two ATDs (P <0.05). Group I which consisted of children with allergic and toxic-allergic reactions to antituberculosis drugs, included 94.4% children with positive BATs (to one or two drugs), which was higher than in group II

Table 1. Results of testing sensitization to antituberculosis drugs using the basophil activation test

Таблица 1. Результаты тестирования сенсибилизации к противотуберкулезным препаратам методом теста активации базофилов

Препарат / Drugs	Количество тестирований / Number of tests	Число положительных результатов / Number of positive results	Доля положительных результатов, % / Percentage of positive results, %
Изониазид / Isoniazid	43	4	9,3
Рифампицин / Rifampicin	46	11	23,9
Пиразинамид / Pyrazinamide	48	10	20,8
Этамбутол / Ethambutol	41	10	23,4
Амикацин / Amikacin	7	2	28,6
Левофлоксацин / Levofloxacin	4	1	25,0
Циклосерин / Cycloserine	2	0	0
Парааминосалициловая кислота / Para-aminosalicylic acid	2	0	0
Линезолид / Linezolid	2	0	0
Протионамид / Prothionamide	1	0	0
Всего / Total	**196**	**38**	**19,4**

(toxic UARs only) with 71.1% of positive BATs (P=0.07; χ^2=3.3) and significantly higher than in group III (without UARs) where positive BAT was observed in 16.7% of children (P <0.05; χ^2=54.9).

When comparing the number of positive tests for individual drugs, it was found (Table 2) that group I had the most frequent positive tests for ethambutol 42.9% (6 out of 14 tests were positive) and rifampicin 35.3% (6 out of 17 tests were positive). Positive BAT for pyrazinamide was the most frequent (46.2%) in group II. It should be noted that positive BAT results in group with no UARs were observed in 5.6% (4 positive tests out of 70), which is significantly rarer compared to both group I (31.4%, P <0.05) and group II (21.4%, P <0.05).

Odds ratio (OR) of UAR development was calculated in group I (18 children) (reactions presented) and group III (18 children) (no UAR) in order to study the prognostic value of BAT for allergic (allergic and toxic-allergic) UAR development. Calculation of the odds ratio (Table 3) showed that a positive BAT test in a child resulted in an 85-fold higher chance of clinical and laboratory manifestations of allergy (confidence interval 7.9–906.8). Since the lower limit of the 95% confidence interval is greater than 1, this result is reliable.

The sensitivity and specificity calculation of the test in predicting allergic manifestations showed the following results. Group I (18 children) which consisted of children with clinical manifestations of allergic and toxic-allergic reactions to TB drugs had positive basophil activation test in 17/18 children, i.e. 94.4% sensitivity of the test. Group III (18 children) did not have clinical manifestations of allergic reactions to TB drugs. The basophil activation test in the 3rd Group was negative in 15/18 children, or 83.3% specificity.

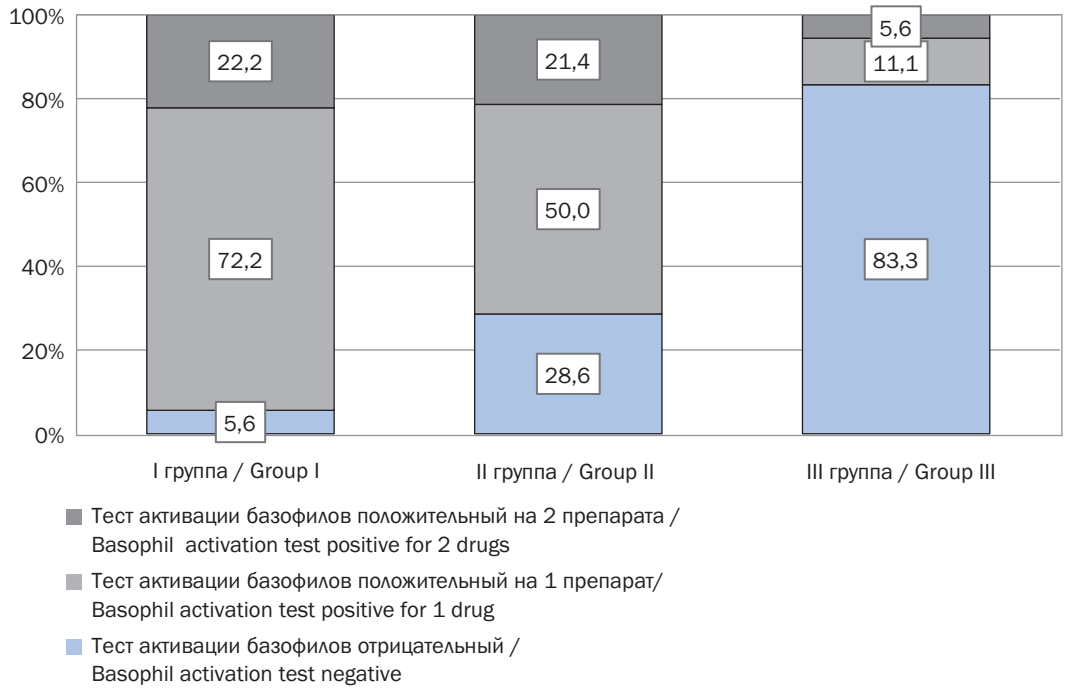

Fig. 4. Proportion of children with positive and negative basophil activation test results in three patient groups

Рис. 4. Доля детей с положительными и отрицательными результатами теста активации базофилов в трех группах пациентов

Table 2. The proportion of positive results of the basophil activation test in groups of children

Таблица 2. Доля положительных результатов теста активации базофилов в группах детей

Препарат / Drugs	I группа / I group	II группа / II group	III группа / III group
Изониазид / Isoniazid	3/14 (21,4%)	1/13 (7,7%)	0/16 (0%)
Рифампицин / Rifampicin	6/17 (35,3%)	4/13 (30,8%)	1/16 (6,3%)
Пиразинамид / Pyrazinamide	4/17 (23,5%)	6/13 (46,2%)	0/18 (0%)
Этамбутол / Ethambutol	6/14 (42,9%)	1/13 (7,7%)	3/14 (21,4%)
Амикацин / Amikacin	2/3	0/2	0/2
Левофлоксацин / Levofloxacin	1/2	0/1	0/1
Циклосерин / Cycloserine	0/1	–	0/1
Парааминосалициловая Кислота / Para-aminosalicylic acid	0/1	–	0/1
Линезолид / Linezolid	0/1	–	0/1
Протионамид / Prothionamide	–	0/1	–
Всего /Total	22/70 (31,4%)	12/56 (21,4%) P_{II-III}= 0,17; χ^2=1,89	4/70 5,6% P_{I-III}= 0,00008; χ^2=15,5

Table 3. The odds ratio of developing allergic and toxic-allergic reactions depending on the results of the basophil activation test

Таблица 3. Отношение шансов развития аллергических и токсико-аллергических реакций в зависимости от результатов теста активации базофилов

Группа пациентов / Patient group	Результаты теста активации базофилов (число детей) / Basophil activation test results (number of children)		Всего / Total	Отношение шансов (95% доверительный интервал) / Odds ratio (95% confidence interval)
	положительный / positive	отрицательный negative		
I группа (аллергические и токсико-аллергические реакции) / I group (allergic and toxic-allergic reactions)	17	1	18	85,0 (7,9–906,8)
III группа (нежелательные побочные реакции отсутствуют) / III group (advers reactions are absent)	3	15	18	

However, specificity may increase with extended follow-up time, as sensitization does not always manifest itself with allergic reactions.

CASE HISTORY 1

Girl S., 13 years old. She was treated as an inpatient at the St. Petersburg State Budgetary Healthcare Institution “Children's Infectious Diseases Hospital No. 3” in 2023 with the diagnosis “Right-sided exudative pleurisy of tuberculous etiology, MBT (–)”. Allergological anamnesis was calm. She was treated according to III chemotherapy regimen with a standard set of first-line antituberculosis drugs (isoniazid, rifampicin, ethambutol, pyrazinamide). At the start of tuberculosis chemotherapy, there were no clinical and laboratory manifestations of allergy, as well as liver function abnormalities. One month after the start of anti-tuberculosis chemotherapy, the appearance of eosinophilia up to 10% (650 cells in 1 μl) in the clinical blood test (initial index 3% (195 cells in 1 μl)) was noted during routine control examination. Simultaneously blood biochemical analysis showed an increase of ALT up to 227 units/l (more than 4 times higher than normal) and AST up to 292 units/l (more than 5 times higher than normal), which is an indication for cancellation of antituberculosis treatment.TB drugs were cancelled, detoxification therapy, antihistamine therapy, sorbents were prescribed to the child. A basophil activation test was performed, which was positive for two anti-TB drugs. The basophil activation index for isoniazid was 1.4 (N 0-1.1), basophil activation index for ethambutol 3.6 (N 0-1.1). Basophil activation index was negative for the rest of the drugs. According to the results of the research, the culprits that caused toxic-allergic reactions were identified, and chemotherapy was resumed by replacing ethambutol with amikacin. It was decided to preserve isoniazid since it was highly important in the treatment regimen. The antibiotic therapy was covered by courses of desensitizing therapy. The course of anti-tuberculosis therapy ended effectively with the clinical recovery of the child.

CASE HISTORY 2

A girl Ch., 4 years old. She was hospitalized at the St. Petersburg State Budgetary Healthcare Institution “Children's Infectious Diseases Hospital No. 3” in 2023 with the diagnosis “Tuberculosis of intrathoracic lymph nodes of the bronchopulmonary group on the left side in the phase of incomplete calcification, MBT (–)”. The patient had a allergic reactions to nuts, which manifested as skin rash and itching. There were no allergic

manifestations at the time of admission to the hospital. She underwent a standard examination by specialists, including an ophthalmologist; no visual disturbances were detected. She was treated according to the III regime of chemotherapy (isoniazid, rifampicin, ethambutol, pyrazinamide). One month after the start of treatment, the clinical blood test showed 9% (450 cells in 1 μl) eosinophils, other parameters were normal. Biochemical blood test showed ALT up to 69 units/l (slight increase) and AST up to 51 units/l (upper limit of norm). The child was tested for all TB drugs taken. A positive result was obtained for two drugs: basophil activation index for rifampicin 1.4 (N 0-1.1), basophil activation index for ethambutol 2.0 (N 0-1.1). At the same time ophthalmologist revealed a typical toxic reaction to ethambutol in the form of impaired color perception. Taking into account high sensitization to ethambutol in combination with its characteristic toxic effect on vision, this undesirable adverse reaction was considered as toxic-allergic effect of ethambutol. The drug was cancelled for the whole period of treatment. Taking into account the positive BAT for rifampicin, hepatoprotective therapy and courses of antihistamines were intensified, and its use was continued. Further treatment was completed successfully without UARs.

Thus, the high-tech basophil activation test is a minimally invasive, safe, informative method in determining undesirable adverse reactions by detecting hidden sensitization to antituberculosis drugs. It allows to effectively predict undesirable adverse reactions and identify the culprit drug. The use of minimally invasive and safe diagnostic methods is especially relevant in pediatric practice. Such laboratory diagnostics is available for any specialists, it does not require a large number of additional laboratory and instrumental studies.

Comprehensive diagnosis of allergic conditions, including the use of pathogenetically determined laboratory methods, will contribute to adequate treatment and, consequently, to the improvement of public health.

CONCLUSION

1. A cohort retrospective study including 146 children undergoing the intensive phase of tuberculosis chemotherapy in 2018–2021 found that undesirable adverse reactions with an allergic component were observed in 37.0% of children, including allergic ones in 21.9% of children and toxic-allergic ones in 15.1% of patients.

2. The basophil activation test makes it possible to determine sensitization to the main TB drugs. Allergic and toxic-allergic reactions were most often sensitized to rifampicin (35.3%) and ethambutol (42.9%). In toxic reactions, sensitization to pyrazinamide was more common (46.2%).

3. Calculation of the odds ratio of allergic and toxic-allergic reactions showed that a positive basophil activation test increases the chance of their occurrence by 85 times.

4. The basophil activation test has high sensitivity (94.4%) and specificity (at least 83.3%), it is a valuable and promising method of determining the sensitization to antituberculosis drugs, allowing to prevent the development of undesirable adverse reactions caused by allergy. It is particularly useful in difficult cases when there is poor tolerance to chemotherapy and it is hard to identify the culprit drug causing undesirable adverse reactions.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Competing interests. The authors declare that they have no competing interests.

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

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