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Vaccination of Children with Tuberculosis Infection by Pneumococcal Polysaccharide 23-Valent Vaccine

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ABSTRACT

Importance: Vaccination against pneumococcal infection is an important method to reduce the morbidity caused by respiratory diseases in patients with chronic diseases. Children with tuberculosis infection are in the group of risk due to their susceptibility to pneumococcal infections. Tuberculosis in children and adolescents is an urgent challenge for public health service in Russia, but these children are not vaccinated against pneumococcus.

Objective. To widen the indications for vaccination of children with various manifestations of tuberculosis infection by pneumococcal polysaccharide 23-valent vaccine (PPV-23) according to the evaluation of its safety and efficiency.

Methods: There were analyzed the data taken from medical histories of 96 children with various manifestations of tuberculosis (Mycobacterium tuberculosis infection - 48 children; local forms of tuberculosis in the stage of involution - 48 children). In 63 patients tuberculosis infection was associated with frequent respiratory infections (one case every 1-2 months) with administration of antibacterial therapy treatment. 35 patients of these 63 children were vaccinated by PPV-23 (24 - in the first group, 11 - in the second one). None of them had had the vaccination against pneumococcus before that. The children were under clinical observation within 12 months, and the frequency of respiratory infection cases was evaluated. Before the vaccination, and on the 14th and 45th days after the vaccination there were determined subpopulations of lymphocytes by the method of flow cytometry, functional activity of lymphocytes by the reaction of blast-transformation with phytohemagglutinin (RBLT with PHA); level of TNF-a, IL-1β, IL-6, INF-γ, IgE cytokines in blood serum by the method of immunofluorescence analysis; concentration of Ig A, M, G, circulating immune complex common pool.

Results: The vaccinated patients did not manifest any side effects in the postvaccinal period, the course of the main disease did not worsen, the frequency of respiratory infections decreased by 2.1 times in children of the first group and by 2.5 times in the second one. Vaccination against pneumococcal infection by PPV-23 was suggested to be included in the standard of medical service for patients with tuberculosis infection.

INTRODUCTION

Vaccination against pneumococcal infection is recommended worldwide for patients with respiratory system chronic pathology [1]. Tuberculosis of the lungs is one of the most severe chronic diseases of the lungs in children and adolescents. According to

WHO data the Russian Federation is included in the group of the countries with the most threatening tuberculosis situation [2,3]. In 2019 the morbidity indicator in our country was 41.08 per 100 thousand population, the mean year indicator of the disease was 64.26 per 100 thousand population. A special attention was given to the increase of the number of children under two years of age in the general structure of pediatric morbidity: from 10-11% in 2009-2013 to 13-15% in 2015-2019. The pediatric morbidity indicator in Russia among children under 17 years of age was on the average 9.13 per 100 thousand population in 2019 [4]. The necessity of vaccination of patients with tuberculosis infection was considered in the world long time ago, however in routine practice these patients have not been vaccinated for a long time period, considering that a current chronic infection and furthermore the presence of immunologic changes, make the efficiency of the vaccination quite debatable. A number of studies prove that the immune status of patients with tuberculosis is characterized by the depression of immunity cell chain with the decrease of general level of lymphocytes, T-lymphocytes, and inhibition of their functional activity [5-7]. In Russia vaccination by pneumococcal vaccine is not included in medical service standards for patients with tuberculosis. An important factor of the absence of vaccination in patients with chronic diseases is also the decrease in the trust to vaccination among parents and medical staff that leads to vaccination refusal or time-limit medical failure of vaccination [8,9].

OBJECTIVE

To study clinical and immunologic safety and clinical efficiency of vaccination by pneumococcal polysaccharide 23-valent vaccine of children with various manifestations of tuberculosis infection.

MATERIALS AND METHODS

Pediatric Research and Clinical Center for Infectious Diseases performed an observation of over 96 children aged 3-14 years old with various manifestations of tuberculosis infection: 48 children infected by Mycobacterium tuberculosis with different degree of manifestation of specific sensitization to tuberculin (according to ICD-19 R76.1 Abnormal reaction to tuberculin test; Z03.0 supervision caused by tuberculosis suspicion). The second group included 48 patients with local forms of tuberculosis, involution stage: 27 children with tuberculosis of intrathoracic lymph nodes, involution stage (resolutions, consolidations); 6 patients with a primary tuberculosis complex; 15 children with a risk of recurrent tuberculosis (Ghon's tubercle) (A16.3 Tuberculosis of intrathoracic lymph nodes without bacteriological or histological confirmation; A16.1. Tuberculosis of the lungs without bacteriological and histological investigations; A16.9 Tuberculosis of respiratory organs of unknown localization without bacteriological or histological confirmation; B90.9 Long-term effects of tuberculosis of respiratory organs and unspecified tuberculosis). The diagnosis was confirmed by phthisiatricians of Scientific Research Institute of Phthisiopulmanology by standard complex of phthisiatric examination (Mantoux test, skin prick test, Diaskin test, chest X-ray examination and/or tomogram) with extra multispiral computer tomography and computer tomographic angiography. Diaskintest is a recombinant protein produced by a genetically modified Escherichia coli culture. When administered intradermally, it causes a specific reaction in people with tuberculosis infection, which is a manifestation of delayed hypersensitivity [10].

63 patients out of 96 patients (45 children from the first group and 18 from the second one) had in their medical histories tuberculosis infection combined with frequent respiratory infections (one case every 1-2 months) with the administration of antibacterial therapy treatment. None of them had had the vaccination against pneumococcus before that. After receiving the informed voluntary consent from their parents for vaccination and in agreement with the phthisiatricians 35 children from the risk group were vaccinated by PPV-23 (24 patients from the first group and 11 children from the second one).

The children from the 1st group were vaccinated on the background of both preventive chemotherapy and without specific treatment. The children of the 2nd group were vaccinated under the following conditions: the therapy basic course was being performed for 4 and more months (the stage of therapy continuation); positive clinical and laboratory and radiological dynamics of tuberculosis process (decrease of manifestations of intoxication syndrome, improvement of radiological imaging, decrease of tuberculosis activity determined by the dynamics of biological tests (Mantoux test,

Diaskin test) and serologic reactions to tuberculosis mycobacterium antigenes). To check serologic indicators confirming low activity of tuberculosis infection there were used the indicators of the reaction of indirect hemagglutination not higher than 1:4, of complement consumption reaction - not higher than 12, of hemolysis reaction - not higher than 5 standard units, and of immune-enzyme analysis - not higher than 0.2 IU/ml.

All vaccinated children were under clinical observation during the postvaccinal period, with everyday measurement of body temperature within the first two weeks and medical examination on the 14th and 45th days after the vaccination. In 1, 3 and 12 months after the vaccination all children were examined by the doctor.

According to the international protocols there were evaluated general and local unfavourable manifestations, as well as the absence of severe unfavourable manifestations. Laboratory investigation was made before the vaccination, on the 14th and 45th days and included the following parameters: phenotyping of lymphocytes by the method of flow cytometry (CD3+, CD4+, CD8+, CD16+, CD20+, CD25+, CD95+) by Backton Dickenson FACS Calibur (USA) cytometer; determination of functional activity of lymphocytes in RBLT with PHA; the level of cytokines TNF-a, IL-1β, IL-6, INF-γ, IgE in blood serum by the method of immunofluorescence analysis with the usage of commercial immunofluorescence test systems produced by Limited Liability Company "Cytokine" (Saint Petersburg); concentration of IgA, M, G by turbodiametrical method with a kit of reagents produced by "SENTINEL" company (Italy), circulating immune complex common pool by the method of polyethylene glycol precipitation (PEG) with 3.5% PEG solution of "Sigma".

The statistical analysis of the received results was made with the use of StatisticaStatSoft program, version 8 for Windows. Calculation of mean values was made by the methods of descriptive statistics. The data were presented in the form of median (Me) and confidence interval (95% CI), mean geometric value with an average error. To compare the groups there were applied nonparametric criteria (Mann-Whitney, Kolmogorov-Smirnov, Wilcoxon tests). The differences were considered statistically relevant in case of $p<0.05$.

RESULTS AND THEIR DISCUSSION

2 children out of 24 patients (8.3%) from the 1st group had fever up to 38°C. 1 child out of 11 patients (9.1%) from the 2nd group had fever up to 39.5°C on the first day after the vaccination. The reactions in the introduction place in the form of hyperemia up to 5 cm were in 2 children from the 1st group (8.3%) and in 1 child from the 2nd group (9.1%). The frequency of development of unfavourable manifestations was not different in the groups and did not exceed the indicators specified in the instruction for the drug. Catarrhal manifestations (cough, rhinitis) were in 2 children from the 1st group (8.3%). Both children appeared to have a family contact with respiratory infection and became ill on the 3rd and 7th days after the vaccination. 27 children (77.1%) did not develop any unfavourable manifestations.

All children were observed after the vaccination by a phthisiatrician with carrying out the basic methods of examination (clinical condition, tuberculin skin tests, X-ray examination control, specific serologic reactions). Supervision in dynamics did not reveal any deterioration of tuberculosis infection course.

All children vaccinated by PPV-23 had clinical supervision within 12 months that allowed to evaluate the influence of vaccination on the morbidity caused by pneumococcal infection. To evaluate clinical and epidemiological efficiency there were analyzed anamnestic data: the number of cases of respiratory infections, acute otitis media and community-acquired pneumonia, being the most widely spread forms of pneumococcal infection in pediatric population, during the year before the vaccination and within the year after the vaccination. It was revealed that within the year after the vaccination the number of respiratory infections, otitis media and community-acquired pneumonia of any aetiology reduced in both groups: in the 1st group - by 2.1 times (from 6.8 cases to 3.2 ones), in the 2nd group - by 2.5 times (from 6.1 cases to 2.4 ones).

Thus, the conducted study confirmed safety and clinical and epidemiological efficiency of vaccination by PPV-23 of children with various manifestations of tuberculosis infection.

Also there was made an immunologic description of vaccinal process after the vaccination by PPV-23. The results are given in Table 1.

Table 1: Dynamics of some immunologic indicators before, on the 14th and 45th days after the vaccination against pneumococcal infection (by PPV-23 vaccine).

Indicators	Groups	Time of examination		
		before vaccination	14th day	45th day
IL-1 β, (pg/ml)	1st	144.5 (37.5-250.5)	191.3 (25-379)	103 (16-148)
	2nd	282 (0-415)*	261 (168-264)	27 (16-148)*
INF - γ, (pg/ml)	1st	125.3 (21.5-171.5)*	78.1 (0-161)*	20.0 (0-60)*
	2nd	65.7 (0-136)*	22 (0-44)	3.7 (0-26)*
Ig G, (g/l)	1st	7.6 (6.4-10.8)*	10.0 (7.0-13.5)*	11.8 (7.8-15.6)*
	2nd	9.6 (9.4-10.8)*	13.2 (11.4-142)*	11.8 (10.2-14.9)*

*p<0.05 – relevant differences on 0 and 14 and 45 days of examination.

The study of immunologic indicators in postvaccinal period did not reveal any statistically significant changes in subpopulation of lymphocytes. In both groups there was a statistically significant increase of IgG level by the 14-45th days after the vaccination, in the 1st group from 7.6 mg/ml (95% CI 6.4-10.8) to 10.0 mg/ml (95% CI 7.0-13.5) (p=0.03) by the 14th day and to 11.8 mg/ml (95% CI 7.8-15.6) by the 45th day, in the 2nd group from 9.6 mg/ml (95% CI 9.4-10.8) to 13.2 mg/ml (95% CI 11.4-14.2) by the 14th day and to 11.8 mg/ml (95% CI 10.2-14.9) by the 45th day.

There was a decrease of the level of INF-γ and IL-1β in both groups. In the 1st group there was a statistically significant decrease of IFN-γ by the 14-45th days from 125.3 pg/ml (95% CI 21.5-171.5) to 78.1 pg/ml (95% CI 0-161) (p=0.01) and 20.0 pg/ml (95% CI 0-60) (p=0.002) accordingly, and a tendency to the decrease of the level of IL-1 from 144.5 pg/ml (95% CI 37.5-250.5) to 103 pg/ml (95% CI 16-148) by the 45th day. In the 2nd group IFN-γ level decreased from 65.7 pg/ml (95% CI 0-136) to 3.7 pg/ml (95% CI 0-26) (p=0.03), IL-1 level from 282 pg/ml (95% CI 0-415) to 27 pg/ml (95% CI 16-148) (p=0.02) by the 45th day.

DISCUSSION

Competitive interactions between viruses and bacteria in microbiota of respiratory ways influence over the types which can colonize mucous membranes and potentially contribute to the development of the infection of upper and lower respiratory ways [11]. According to the literature data the frequency and load of acute respiratory infections are associated with an abundant growth of pneumococcus in the nasopharynx of patients. Colonization of mucous membranes of upper respiratory ways by Streptococcus pneumoniae can increase replication of respiratory syncytial virus (RSV), and in this connection there are suggestions about a more severe course of RSV-infection in patients [12,13]. The results of Fan R.R. et al. demonstrate a dynamic change of pneumococcus density before, during and after the cases of respiratory infections in children of early age. There was observed a gradual increase of pneumococcus density leading to a case of respiratory infection with the most abundant growth at the peak of the disease and a decrease in density during the recovery. The received data once more illustrate an important role of pneumococcus in the pathogenesis of respiratory infections [14]. Estrada J. et al. described in their study a clinical efficiency of PPV-23 in the form of decrease of frequency of respiratory infections in 96% of the vaccinated ones [15]. Thus, the results received by us correlate with the literature data and prove the importance of vaccinal prevention of pneumococcus infection including the decrease of frequency of respiratory infections in children.

CONCLUSIONS

1. Vaccination by PPV-23 is clinically safe. The frequency of the development of unfavourable manifestations did not exceed the one specified in the recommendations for vaccines. In 77.1% of patients there were not registered any unfavourable manifestations.
2. Vaccination by PPV-23 is imminologically safe and has a nonspecific positive effect in the form of IgG increase by the 14-45th days of the vaccination.
3. Vaccination by PPV-23 contributes to the decrease in frequency of respiratory infections, otitis media, and pneumonia by 2.1-2.5 times in paedriatic patients infected by M. tuberculosis.
4. During the observation within 12 months after the vaccination there was no any deterioration of tuberculosis infection course.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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