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Drug-Resistant Tuberculosis in Children and Adolescents in the Republic of Sakha (Yakutia)

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Abstract

The aim of the study was to determine the prevalence of drug-resistant tuberculosis among children and adolescents in the Republic of Sakha (Yakutia) (RS(Y)) and the features of its clinical manifestation, in order to improve the prevention and treatment of the disease.

We monitored a total of 250 children and adolescents with tuberculosis (TB) who underwent inpatient treatment in the Yakut NPZ in 2012-2016: The patients included 34(13.6%) children in the 0-2 age group, 80(32%) in the 3-6 age group, 74(29.6%) in the 7-14 age group, and 62(24.8%) adolescents between 15 and 17 years. The timing of the development of the disease from the time of primary infection with *Mycobacterium tuberculosis* differed significantly depending on the age of children. In young children, compared with older children, signs of the disease appeared at an earlier time. In the structure of clinical forms of TB, the differences were observed depending on the age of the children:

- In children under 2 years, the lesion of intrathoracic lymph node tuberculosis (ITLN) was most common, as well as generalized TB
- For children aged between 3 and 6 years, the lesion of ITLN was characteristic
- For older children, the different clinical forms of TB were characteristic.

The expression of immunological tests depended on the age of the patients and the number of ITLN lesions. Drug resistance to anti-tuberculosis drugs was found in 21(36.8%) patients; *m*ultidrug-resistant TB was mainly registered in adolescents and multidrug resistance was mainly primary. Drug resistance to isoniazid, rifampicin, and streptomycin was the most frequent.

Thus, it has been established that the outcome of the disease and the timing of the onset of clinical involution of the disease depend on many factors, including the timeliness of disease detection, the age of the patient, the dissemination of TB process, and others. **(International Journal of Biomedicine. 2018;8(1):51-55.)**

Key Words: children • adolescents • drug-resistant tuberculosis • anti-tuberculosis drugs

Abbreviations

ATD, anti-tuberculosis drugs; **DR**, drug resistance; **DRT**, drug-resistance test; **DR-TB**, drug-resistant tuberculosis; **ITLN**, intrathoracic lymph nodes; **ITLNTB**, intrathoracic lymph node tuberculosis; **MTB**, *Mycobacterium tuberculosis*; **MDR**, multidrug resistance; **MDR-TB**, multidrug-resistant TB; **MT**, Mantoux test; **PTC**, primary tuberculosis complex; **RA**, recombinant allergen; **TB**, tuberculosis.

Introduction

Tuberculosis (TB) is one of the top 10 causes of death worldwide. In 2016, 10.4 million people fell ill with TB, and 1.7 million died from the disease (including 0.4 million among people with HIV).[1] Children represent about 10-11% of all TB cases.

At least 1 million children become ill with TB each year.[2] In 2016, 250 000 children died of TB.[1] The actual burden of TB in children is likely higher given the challenge in diagnosing childhood TB.

Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. MDR-TB is TB that does not respond to at least isoniazid and rifampicin, the 2

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most powerful anti-TB drugs. In 2015, an estimated 480 000 people worldwide developed MDR-TB, and an additional 100 000 people with rifampicin-resistant TB were also newly eligible for MDR-TB treatment. India, China, and the Russian Federation accounted for 45% of the 580 000 cases.[3] In 2016, WHO estimates that there were 600,000 new cases with resistance to rifampicin - the most effective first-line drug, of which 490,000 had MDR-TB.[1]

Globally,[1] TB incidence is falling at about 2% per year. However, in Russia, the prevalence of MDR-TB of the respiratory organs continues to grow. Whereas in 1999 this indicator was 8.6, in 2015 it was 25.5 per 100 thousand of the population. In the Republic of Sakha (Yakutia) (RS(Y)), according to the official statistical reporting, there has been a clear growth trend in the proportion of patients with MDR-TB among newly diagnosed pulmonary TB patients with bacterial excretion: 23.0% in 2011, 25.8% in 2013, 30.0% in 2015, and 34.6% in 2016. M.K.Vimokurova et al.[4] have observed in RS(Y) a growth in the incidence of TB cases presenting with destructions in lung tissue and a bacillary-positive state, a persistent trend towards an increase in TB cases caused by MDR MTB, and a high proportion of deaths during the first year of outpatient follow-up for TB.

The effectiveness of treatment of patients with drug-resistant strains of MTB is much lower than in patients with drug-susceptible MTB. In this regard, in these patients there is a persistent bacteria discharge.[5-8] The increase in the number of patients with DR-TB leads to an increased risk of a further spread of infection and the emergence of new cases of disease with primary DR.[9] For children and adolescents, DR-TB represents the greatest danger.[10,11]

The aim of the study was to determine the prevalence of DR-TB among children and adolescents in RS(Y) and the features of its clinical manifestation, in order to improve the prevention and treatment of the disease.

Material and Methods

We monitored a total of 250 children and adolescents with TB who underwent inpatient treatment in the Yakut NPZ "Ftiziatriia" in 2012-2016: The patients included 34(13.6%) children in the 0-2 age group, 80(32%) in the 3-6 age group, 74(29.6%) in the 7-14 age group, and 62(24.8%) adolescents between 15 and 17 years. TB contacts were identified in 78.7% of cases (including 98% cases among children in the 0-2 age group, in 86.7% cases among children in the 3-6 age group, in 74.6% among children in the 7-14 age group, and 64.3% of cases among adolescents between 15 and 17 years).

All patients underwent clinical, laboratory, and radiation study methods according to the Federal Clinical Recommendations for Diagnosis and Treatment of Respiratory Tuberculosis in Children.[8]

In the diagnosis of TB, we used chest X-ray, sputum examination on MTB by fluorescence microscopy, culture in both liquid and solid media, and bronchial washing for AFB staining. Immunological tests included the 2 tuberculin unit MT and a skin test with MTB-RA. PCR was used for detecting drug resistance. Patients were treated according to standard regimens in accordance with the Federal Clinical Recommendations for Diagnosis and Treatment of Respiratory Tuberculosis in Children, taking into account the results of drug-susceptibility testing.

Results were statistically processed using Microsoft Office Excel 2007. Baseline characteristics were summarized as frequencies and percentages for categorical variables and as means and SDs for continuous variables. For data with normal distribution, inter-group comparisons were performed using Student's t-test. The Mann-Whitney U Test was used to compare the differences between the two independent groups (for nonparametric data). A probability value of $P<0.05$ was considered statistically significant.

Results

In the structure of clinical forms of TB in children under 2 years of age, ITLNTB was identified in 67.6% of cases, PTC in 26.4%, and generalized TB in 6.0% of cases. In children aged between 3 and 6 years, ITLNTB was detected most frequently (66.2%), and PTC in 33.7% of cases. In children of school age and adolescents, there were different clinical forms of TB. Thus, in children aged between 7 and 14 years, ITLNTB was detected in 48.6% of cases, PTC in 28.4%, infiltrative pulmonary TB in 10.8%, focal pulmonary TB in 8.1% of cases, disseminated TB in one case, and caseous pneumonia and generalized TB in one case. In adolescents (between 15 and 17 years), infiltrative (40.3%) and focal (33.9%) pulmonary TB were most often recorded, but we also diagnosed disseminated TB(11.3%), ITLNTB(6.5%), and PTC(3.2%). In addition, in this age group, one case of caseous pneumonia, one case of tuberculoma and one case of generalized TB were identified.

Thus, in the structure of clinical forms of TB, the differences were observed depending on the age of the children. Thus, in children under 2 years, the lesion of ITLN was most common, as well as generalized TB. For children aged between 3 and 6 years, the lesion of ITLN was characteristic; For older children, the different clinical forms of TB were characteristic.

The average time of onset of the disease manifestations after the appearance of signs of primary infection in children (for the first time a positive MT, not related to vaccination and revaccination of BCG) differed significantly depending on the age. The earliest terms for the appearance of signs of TB from the time of primary infection were observed in young children: 1.5±0.1 months for children aged between 0 and 2 years, and 4.1±0.7 months for children aged between 3 and 6 years. In older children, signs of the disease appeared in later terms: 11.4±1.6 months and 34.1±7.1 months for the 7-14 and 15-17 age groups, respectively.

We also found that in the 15-17 age group the timing of the onset of the disease from the first positive MT differed significantly depending on the clinical forms of TB. Thus, primary forms of TB developed after 17.5±1.7 months since the appearance of primary TB infection, and secondary forms after 38.8±8.4 months ($P<0.05$).

Thus, the timing of the development of the disease from the time of primary infection with MTB differed significantly depending on the age of children. In young children, compared

with older children, signs of the disease appeared at an earlier time.

We conducted a comparative analysis of the degree of involvement of ITLN by the number of groups of lymph nodes involved in the tuberculosis process in children of different ages. For example, ITLNTB was observed in 23(67.6%), 53(66.2%) and 36(48.6%) cases among children between 0-2 years, 3-6 years, and 7-14 years, respectively. Thus, TB of one group of ITLN was observed in 6(26.1%), 10(18.8%), and 7(19.4%) cases among children from 0-2 years, 3-6 years, and 7-14 years, respectively. TB of 2 groups of ITLN was observed in 6(26.1%), 18(34%), and 15(41.7%) cases among children from 0-2 years, 3-6 years, and 7-14 years, respectively. TB of 3 groups and more than 4 groups of ITLN was observed in 7(30.4%) and 4(17.4%), 18(34%) and 7(13.2%), 5(13.9%) and 9(25%) cases among children from 0-2 years, 3-6 years, and 7-14 years, respectively.

Thus, the above data indicate that in children at different ages with TB, 2-3 groups of ITLN are mainly affected. The lesion of more than 4 groups of ITLN was observed more often in children aged from 0-2 and 7-14 years: 17.4 and 25%, respectively.

The expression of immunological tests, depending on the number of ITLN lesions in different age groups, is presented in Table 1. In children aged between 0 and 2 years with a lesion of more than 4 groups of ITLN, there was a high immune response simultaneously in MT and MTB-RA. In children between 3 and 6 years, the immune response in MT and MTB-RA did not differ significantly and did not have a clear dependence on the severity of ITLNTB, but with the lesion of 4 or more groups of ITLNT, both immunological tests had a hyperergic character. In children aged between 7 and 14 years with ITLNTB of any degree, the test with MTB-RA had a hyperergic response, and the severity of reaction to MT was less pronounced with a lesion of one group of ITLN.

In the 15-17 age group, we examined the severity of immunological tests depending on the clinical forms of TB. It was found that in patients with primary forms of TB (ITLNTB and PTC), the average size of the papule in MT was 16.9±1.6 mm; in the skin test with MTB-RA it was 17.7±2.0 mm ($P>0.05$). In patients with secondary forms of TB (focal, infiltrative, and disseminated TB), the average size of the papule in MT was 13.0±0.8 mm; In the skin test with MTB-RA it was 16.9±0.7 mm ($P<0.05$). Data for immune response in MT and the skin test with MTB-RA, depending on the clinical forms of secondary TB in patients aged between 15 and 17 years, are presented in Table 2. The immune response in the test with MTB-RA was more pronounced than in MT. It should be noted that in the primary forms of TB, in contrast to secondary forms, a hyperergic reaction was simultaneously observed in MT and the test with MTB-RA. In the infiltrative and disseminated forms of TB, the degree of immune response in the test with MTB-RA was significantly higher than in MT. The average time of appearance of the first signs of the disease from the time of primary TB infection in patients aged between 15 and 17 years with primary forms of TB was 17.5±1.7 months, with secondary forms it was 38.8± 8.4 months ($P<0.05$).

Patients with MTB discharge accounted for 24.4%. Among children between 0 and 2 years, 3 and 6 years, 7 and 14 years, and 15 and 17 years, MTB discharge was determined in 2(3.3%), 1(1.6%), 12(19.7%), and 46(75.4%) cases, respectively.

DRT was performed in 57(93.4%) patients. It was found that drug sensitivity to all ATD was preserved in 36(63.2%) patients. DR to ATD was found in 21(36.8%) patients: 2(10%) in the 0-2 age group, 4(19%) in the 7-14 age group, and 15(71.4%) in the 15-17 age group. Monoresistance was noted only in 1(4.7%), MDR in 95.2%.

Table 1.

The expression of immunological tests depending on the number of ITLN lesions in different age groups

Immunological tests	Number of ITLN lesions			
	Children aged between 0 and 2 years (n=23)			
	1 group of ITLN (n=6)	2 groups of ITLN (n=6)	3 groups of ITLN (n=7)	4 or more groups of ITLN (n=4)
MT (mm)	11.9±1.7	13.0±0.9	14.4±1.3	10.5±1.2*
Skin test with MTB-RA (mm)	10.7±2.9	14.2±0.8	15.1±1.4	14.7±2.1
Children aged between 3 and 6 years (n=53)				
Immunological tests	1 group of ITLN (n=10)	2 groups of ITLN (n=18)	3 groups of ITLN (n=18)	4 or more groups of ITLN (n=7)
MT (mm)	13.9±1.1*	13.4±0.8	13.4±0.9	17.0±4.0
Skin test with MTB-RA (mm)	16.7±0.1	16.6±1.6	15.3±1.3	18.0±2.0
Children aged between 7 and 14 лет (n=36)				
Immunological tests	1 group of ITLN (n=7)	2 groups of ITLN (n=15)	3 groups of ITLN (n=5)	4 or more groups of ITLN (n=9)
MT (mm)	10.3±1.6*	16.6±1.6	16.8±1.7	14.7±1.0
Skin test with MTB-RA (mm)	17.5±1.8	17.5±1.5	20.8±1.1	17.3±3.6

*- $P<0.05$

Table 2

The expression of immunological tests depending on the clinical forms of TB in the 15-17 age group

Immunological tests	Focal TB (n=21)	Infiltrative TB (n=25)	Disseminated TB (n=7)	Primary forms of TB (n=6)
MT (mm)	14.1±1.2	13.1±1.3*	9.9±1.1*	16.9±1.6
Skin test with MTB-RA (mm)	16.7±1.0	18.0±1.2	15.3±1.2	17.6±2.0

**-P<0.05*

DR to isoniazid, rifampicin, and streptomycin was the most frequent: 95.2%, 81% and 76.2% of cases, respectively. DR to kanamycin, capreomycin and ethionamide was found in 2(10%), 1(4.7%), and 2(10%) cases, respectively. DR to the combination of isoniazid with streptomycin was found in 31.2% of cases, isoniazid with streptomycin and isoniazid with rifampicin in 8.3% of cases; other combinations of ATD were more rare. It should be noted that only 3(15%) out of 20 children with DR to isoniazid previously received this drug for preventive purposes. Other drugs have not been received by any child, which indicates that the children had primary DR to ATD, associated with drug-resistant strains of MTB.

MDR to ATD was observed in 17(27.8%) patients with MTB discharge, including 2(11.8%) children under the age of 2 years, 1(5.9%) in the 7-14 age group, and 14(82.3%) in the 15-17 age group. Thus, MDR-TB was mainly registered in adolescents and MDR was mainly primary.

It has been established that the outcome of the disease and the timing of the onset of clinical involution of the disease depend on many factors, including the timeliness of disease detection, the age of the patient, the dissemination of TB process, and others.

In patients with the multidrug-resistant strains of MTB, there were some features of the clinical course of the disease: the rapid onset of the disease (68%); the severity of symptoms of tuberculous intoxication(43%); a slow rate of decreasing the severity of the reaction to MT and MTB-RA; a decrease in the rate of resorption of the infiltrative changes, sputum negativization and elimination of destructive changes in the lungs; a high rate of pronounced residual changes (39%); a greater need for surgical treatment; and a high risk of recurrence of the disease (5.6%).

The duration of activity and the inadequacy of the healing process in MDR-TB were indicated by the presence of MTB growth in the biopsy material and the histological picture of the resected part of the lung in 5 postoperative patients. In 4 out of 5 postoperative patients, we noted the growth of drug-resistant strains of MTB. In all 5 patients, in a lung biopsy during surgery, MTB was found by fluorescence microscopy. In a histological examination of the resected regions of the lungs in 3 of the patients, we found the morphological picture of active TB: the presence of tuberculosis granulomas, large zones of productive tissue, and extensive areas of caseous necrosis. To reduce the risk of recurrence of the disease in the postoperative period, we performed a correction of chemotherapy, taking into account the drug resistance of MTB.

Conclusion

The timing of the development of the disease from the time of primary infection with MTB differed significantly depending on the age of children. In young children, compared with older children, signs of the disease appeared at an earlier time. In the structure of clinical forms of TB, the differences were observed depending on the age of the children:

- In children under 2 years, the lesion of ITLN was most common, as well as generalized TB
- For children aged between 3 and 6 years, the lesion of ITLN was characteristic
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The expression of immunological tests depended on the age of the patients and the number of ITLN lesions. DR to ATD was found in 21(36.8%) patients; MDR-TB was mainly registered in adolescents and MDR was mainly primary. DR to isoniazid, rifampicin, and streptomycin was the most frequent.

Thus, it has been established that the outcome of the disease and the timing of the onset of clinical involution of the disease depend on many factors, including the timeliness of disease detection, the age of the patient, the dissemination of TB process, and others.

Worldwide, only 54% of MDR-TB patients are currently successfully treated. In 2016,[1] WHO approved the use of a short, standardized regimen for MDR-TB patients who do not have strains that are resistant to second-line TB medicines. Improving the prevention and treatment of tuberculosis in children and adolescents requires a joint effort by all stakeholders involved in TB control.

Competing interests

The authors declare that they have no competing interests.

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