

## Diagnosis and clinical-radiological characteristics of pulmonary tuberculosis among adolescents (15-18 years old) in North-Western region of Russia

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### Abstract

The article presents clinical and radiographic features of pulmonary tuberculosis (TB) in North-Western region of Russia. The main method of detection of tuberculosis in adolescents is X-ray. Use of Diaskintest in the diagnosis of tuberculosis infection in adolescents (15-18 years old) confirmed its high information value. Diaskintest was positive in 96.7% cases of patients with TB in the study. In 29.2% cases latent TB infection was diagnosed. Tuberculosis of respiratory organs in adolescents was characterized by prevalence of destructive forms with bacterial excretion; among which multidrug-resistant strains of MBT were observed in 64.0% in 18 patients with bacterial excretion that indicates late verification of diagnosis and adverse epidemic situation.

**KEYWORDS:** pulmonary tuberculosis, adolescents, diagnosis, Diaskintest®, multidrug resistant TB

### Introduction

Current epidemiological situation in Russian Federation is characterized by the decrease of tuberculosis morbidity and mortality [5, 6].

However, increase of tuberculosis cases with multi-drug resistance (MDR-TB) is observing nowadays. Within the period from 2002 to 2012 in Russia the rate of MDR among all patients with respiratory TB increased twice - from 14.5% to 24.3% (Nechaeva O., 2012). Russian Federation still remains among the countries with the highest rate of MDR-TB [8, 9, 10].

The incidence of tuberculosis in adolescents depends on: TB prevalence, the number of smear-positive patients, the quality and effectiveness of specific prevention, introduction of methods for early detection of tuberculosis [1, 2, 3, 4, 11, 12, 13].

In 2012, the incidence of tuberculosis adolescents in Russia was 32.1 per 100 thousand of overall population. In St. -Petersburg and in the North-Western region of Russia, the incidence was accordingly 21.8 and 26.8 per 100 thousand adolescent population [7].

Objectives of the study were to reveal clinical-radiological characteristics of pulmonary tuberculosis in adolescents 15-18 years old and to evaluate diagnostic value of new immunologic methods.

### Materials and methods.

At St-Petersburg Phthisiopulmonology Institute the cohort prospective study was performed in 2011-2014. In 112 adolescents with suspected tuberculosis were examined. Diagnosis complex included: tuberculin skin test (TST), Diaskintest (Generium) and X-ray (spiral computed tomography of the chest).

Bacteriological research of wash water bronchi and sputum included: fluorescent bacterioscopy, the culture results on nutrient dense Lowenstein-Jensen, sowing on liquid nutrient medium with the use of the automated system of WASTES MGIT 960. Determination of DNA of MBT was carried out by usage of a polymerase chain reaction (PCR) in real time. By PCR diagnostic DNA was isolated with the use of system "AmpliTube-RV and amplification of the nucleotide sequence IS6110-marker Mycobacterium tuberculosis complex with the use of test systems: CJSC "Synthol" (Russia), "AmpliTube-RV-Screen" by PCR in real time at analyzer iCycler iQ5, BioRad, USA.

Statistical data processing was performed by SPSS.16.0. Quantitative data was estimated as  $M \pm SD$ , where M is the mean, SD - standard deviation. The degree of correlation between the examined characteristics were determined with the use of correlation coefficient in the formula Pearson (r) for quantitative indicators. Differences or indicators ties were considered significant in the level of  $p < 0.05$ . The following indicators of diagnostic value were calculated: diagnostic sensitivity (DSS), diagnostic specificity (DSP), the diagnostic efficiency (DEF).

Based on comprehensive survey in 48(42.8%) patients the diagnosis of pulmonary tuberculosis was not confirmed (group I); in 64 (57.2%) patients respiratory tuberculosis was diagnosed (group II).

### Results and discussion.

In Igroup (n=48) Diaskintest was negative significantly more often in comparison with group II (70.8% against 3.2% of cases, which  $p > 0.001$ ,  $\chi^2 = 34.01$ ) (Fig.1.).

All patients of the first group have no pathology in lung tissue and intrathoracic lymph nodes by x-ray examination. In this group patients have TST positive with normal sensitivity ( $m = 12.3 \pm 4.5$  mm in 68.5%-78.9% 95CI%). This group of patients did not need preventive treatment. In 29.2% (14) of cases Diaskintest was positive. All patients were examined by computer tomography of chest and molecular-genetic sputum determination of DNA (deoxyribonucleic acid) of MBT by polymerase chain reaction (PCR).

In patients of the first group with positive Diaskintest latent TB infection was concluded by the presence of symptoms of intoxication (sweats, low grade fever, fatigue, decreased body weight), which even in the absence of x-ray changes demanded administration of preventive therapy.

In IIgroup (n=64) secondary forms of tuberculosis prevailed (95.3%). The main method of detection of tuberculosis was X-ray- 64.8%; by contact with TB patients - 20.4%; by clinical signs - 12.4 %; and in 2.4% case - by positive TST. Diaskintest was positive in 96.8% (62) cases that was significantly more frequently in comparison with the first group (29.2%).

The calculation of diagnostic values showed the high relevance of Diaskintest (DDS-96.7%; DDP-70.8%; DEF-83.8%).

On admission, the patients of the second group had symptoms of intoxication and local manifestations of the disease. Symptoms of intoxication varied in severity in 54 (84.3%) patients: severe - in 24.1% (13) cases, moderate manifestations in 37.1% (20), mild - in 38.8% (21) cases (tabl.1).

The leading complaints were weakness, fatigue, weight loss, cough, including sputum, shortness of breath during physical activity, pain in the chest, coughing up blood, low grade fever is revealed in 24 (44.4%) patients. 13 patients (24.1%) complained on febrile temperature, severe weakness, night sweats and chills. 42

patients (65.6%) identified various hematologic disorders, including increased sedimentation rate more than 31 mm/H. 16 patients (38.0%) have leukocytosis over  $10 \times 10^9$  (19.0%), stab shift ( $>6$ ) – in 27 (64.2%) patients. Lymphopenia less than 15.0% was observed in 42.8% (18) cases.

By X-ray examination in 82.8% cases (53) single or multiple, mostly cheesy, foci of up to 2-4cm in diameter, often with destruction of lung tissue were identified. Infiltrative tuberculosis was characterized by lobitin 39.0% (25) cases and in 45.3% (29) cases - by polysegmental processes. Additional information was collected by CT in 96.6% of its use: in 43.6% (28) destructive changes in the lung tissue were revealed, which was not determined by conventional X-ray, in 5.7% of patients enlarged lymph nodes of mediastinum were found out, and in 50% cases - focal changes in the nearby segments. Pulmonary TB is characterized by polysegmental (more than 3 segments) and lobular processes in 85.1% (57) cases, 10.9% (7) patients demonstrated mono - and bi-segmental defects with the presence of both formed cavities and the destruction of the lung tissue (73.0%). The metastatic focus to the surrounding lung tissue and opposite lung were registered in 65.9% of cases. In 85.1% exudative and caseous pattern of inflammation was observed.

Thus, infiltrative pulmonary tuberculosis was diagnosed in 79.7% (51) cases, disseminated TB - in 5.7% (3), in 6.2% (4) - focal tuberculosis of lungs, in single cases - caseous pneumonia (1) and cavernous TB (2). Primary tuberculosis complex was revealed only in 5.7% (3).

The use of molecular genetic methods allowed in the short term (4-5 days) to get data on drug resistance to the most active anti-TB drugs (H and R). Molecular-genetic methods performed in all 64 patients. PCR (polymerase chain reaction) revealed DNA (deoxyribonucleic acid) of Mycobacterium tuberculosis (MBT) in 28 samples (43.8%). In all these cases smear-positive confirmation was provided by culture liquid and solid mediums, while fluorescent microscopy determined MBT only in half of these cases (16).

The drug resistance by biochip method was determined in 32.4% (9) cases. Multidrug resistance (resistance to Isoniazid and Rifampicin) by classical culture method of absolute concentration was found out in 64.3% cases in 18 strains, among them - extensive drug resistance (XDR) was detected in 7.1% (2 cultures). Results of express-diagnosis of MBT drug-resistance, including MDR, with the help of test-systems "TB-Biochip", were received in early terms (5-7 days). To these patients treatment was administered taking into account data on MBT drug-resistance. However, for majority of patients confirmation of MBT strains resistance was obtained only in 2-3 months by cultural method.

Drug-resistant TB in common group of adolescents with bacterial exertion was identified in 64.2% (18) cases that is 28.1% of all patients with TB. The majority of patients with newly diagnosed tuberculosis did not receive treatment before. (43.4%) patients with TB was diagnosed when referring to the clinic, the other 10 (56.6%) patients - in the survey due to contact with sick relatives, every fourth of them "focal point of death."

Example № 1. The patient I.P., 16 years. The expressed intoxication syndrome, positive Diaskintest (p-17mm), hemoptysis, radiological changes with the defeat of the left lung, expressed changes in hematological parameters, excessive sputum smear-positive. Diagnosis: caseous pneumonia of left lung in a phase of contamination, MBT (+) by culture liquid and dense substance MDR (Fig.2).

Example № 2. The patient I.P., 16 years .The patient with symptoms of intoxication,positive result of Diaskintest(22mm), defeat of one segment with focal changes of various sizes, some of them inhomogeneous structure. MBT excretion was confirmed by culture after 2 months from starting treatment. The diagnosis of disseminated tuberculosis of both lungs in the phase of infiltration and destruction. TB(+),MDR (Fig.3)

### Conclusions.

The main method of detection of tuberculosis in adolescents in North-Western region of Russia is X-ray. The use of Diaskintest in diagnosis of TB has high diagnostic value. In 96.7% of TB cases Diaskintest was positive. In 29.2% of cases Diaskintest allowed to reveal latent TB infection.

Pulmonary TB was diagnosed in 57.1% cases with positive result of bacterial excretion in 43.8% cases. In 64.3% multi-drug resistance was determined. The use of PCR with "TB-Biochip" test-systems helped in diagnosis of MDR within 3-5 days (rapid diagnostic method), while standard culture method presented results of drug resistance in 2-3 months after start of treatment that allowed to adjust treatment.

### References

1. V.A.Aksenova Diaskintest when assessing the activity of tuberculosis in children and adolescents/ J. Tuberculosis and lung disease- 2009- 10:13-16. [in Russian]
2. I.F.Dovgalyuk,N.V.Korneva Clinical and epidemiological features of tuberculosis in children of the North-West of the Russian Federation/ J. J. Tuberculosis and lung disease - 2011-3:12-16. [in Russian]
3. Y.S.Ovsiyankina, M.F. Gubkina, I.U.Petrakova and other. Experience of application of the new skin test (Diaskintest®) for diagnostics of tuberculosis of the respiratory system of children and teenagers in the tuberculosis unit/ J. Tuberculosis and lung disease.-2009- 1:16-19.[in Russian]
4. Pediatrics: a textbook for students/ edited/ N. Shabalov.-St.-Petersburg:Spec lit, 2007.-442s.[in Russian]
5. Tuberculosis in the Russian Federation 2011/Analytical review.-Moscow-2013.-280s. [in Russian]
6. M.V. Shilova Organization of TB care in Russia and the ways of modernization of the organizational-methodical management of dispensary observation of TB patients in the current epidemic and the socio-economic conditions/J. Tuberculosis and lung diseases-2011-5:236.[in Russian]
7. P.K. Yablonskii Russian Phthisiology today - the choice of development path/Picaresque// Medical Alliance - 2013. -3:5-24.[in Russian]
- 8.Amita Jain, Pratima Dixit, Rajendra Prasad Pre-XDR & XDR in MDR and Ofloxacin and Kanamycin resistance in non-MDR Mycobacterium tuberculosis isolates/J.Tuberculosis - 2012- 92-5: 404-406.
- 9.WHO Global tuberculosis report, 2013.
- 10.Guidelines for Using the QuantiFERON®-TB Gold Test for Detecting Mycobacterium tuberculosis Infection, United States/Recommendations and Reports.-2005-54:15.
- 11.J.A.Streeton, N.Desem, S.L. Jones Sensitivity and specificity of a gamma interferon blood test for tuberculosis infection/Int J Tuberc Lung Dis.- 1998;2:443-50.

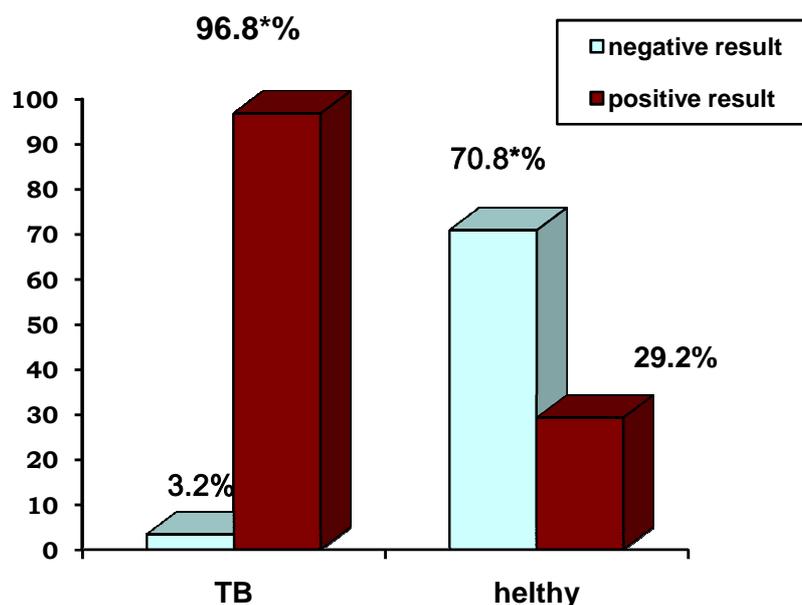
12.T. Meier Sensitivity of a new commercial enzyme-linked immunospot assay (T SPOT-TB) for diagnosis of tuberculosis in clinical practice/Eur. J ClinMicrobiol Infect Dis.-2005;24:529–36.

13.R.Palazzo Use of whole-blood samples in in-house bulk and single-cell antigen-specific gamma interferon assays for surveillance of *Mycobacterium tuberculosis* infections/J.Clin Vaccine Immunol.- 2008;15:327–37.

Table 1.  
The severity of intoxication syndrome in patients with tuberculosis of respiratory organs

Numero fpatients	The severity of intoxication syndrome						Symptoms of intoxication are missing	
	Severe		Moderate manifestations		Mild			
	Abs	%	Abs.	%	Abs.	%	Abs.	%
64	13	24.1	20	37.1	21	38.8	10	15.6

Fig.1. Results of Diaskintest



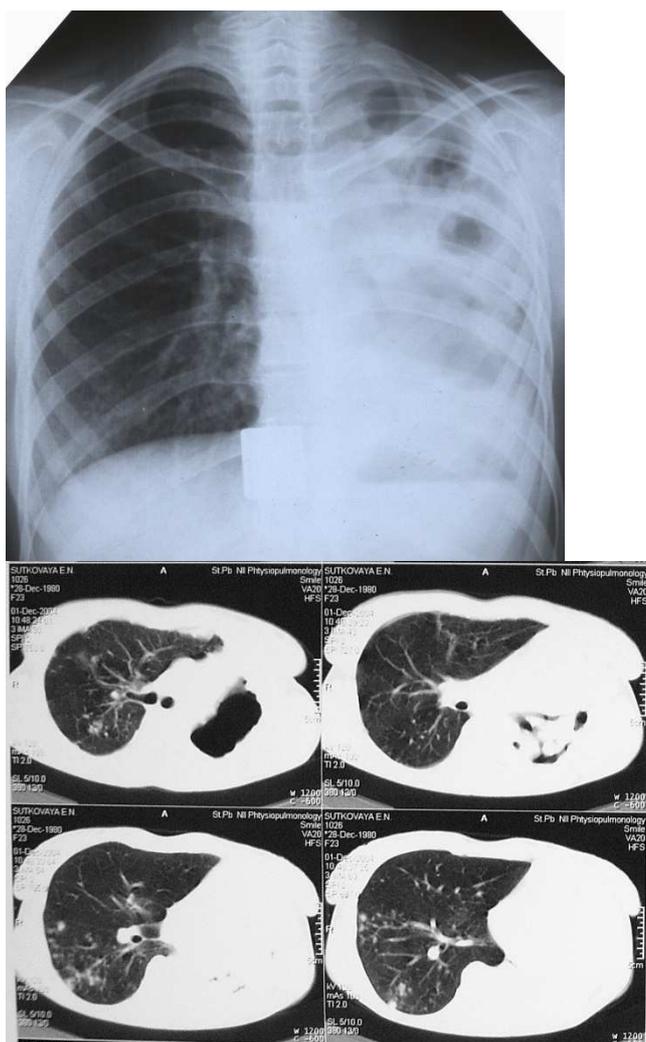


Fig. 2. Sightseeing x-ray of the patient I.P., 16 years old. DS: caseous pneumonia left lung in a phase of disintegration and contamination, TB (+) MDR. Is determined by the total defeat of the left lung with multiple cavernous.

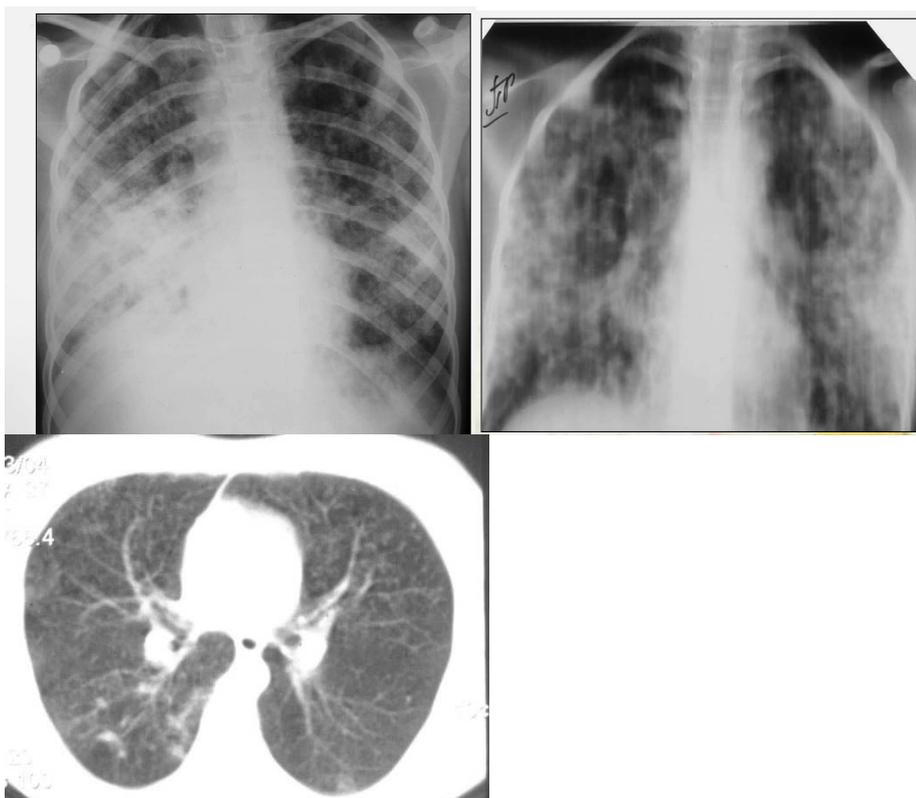


Fig. 3. Overview radiograph and linear tomography patient S.O. (16 years). DZ: disseminated tuberculosis of both lungs in the phase of infiltration and degradation. ILO (+) by culture, drug-resistant. Determined bilateral total of dissemination in the lungs.