TUBERCULOSIS IN ADOLESCENTS AND YOUNG PATIENTS IN HIGH PREVALENCE REGION

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The study aims to determine what forms of tuberculosis (TB) are the most common in high prevalence region, establishes the drug sensitivity of *Mycobacterium tuberculosis* in the region, and reveals the key risk factors of the disease as well as assesses the health status of adolescents with tuberculosis. For 10 years, regional anti-tuberculosis hospital in Smolensk has been collecting data from all TB patients aged 14–34 years. Diagnosis of tuberculosis was based on specific radiological data and detection of *M. tuberculosis* in sputum or bronchial lavage fluid. In total, the study involved 129 TB cases in adolescents aged 14–17 and 420 TB cases in young people. Sixty-five adolescents had close family or periodic contact with TB patients (50.6%), but only eight out of 65 (12%) had received complete course of chemotherapy prevention. Sixty-two adolescents had social risk factors (48%). Those patients significantly more often had extended pulmonary TB (28.3% versus 16.7%), complicated (36.7% versus 16.9%), and destructive (41.7% versus 26.2%) cases. Eighty out of the 129 (62%) had one or more concomitant diseases; they had significantly higher rate of extended and complicated TB cases. Two hundred and fourteen out of the 420 young patients had drug resistance of *M. tuberculosis*. Resistant TB cases significantly more often developed in unemployed (83.2% versus 71.8%), heavy drinkers and smokers (59.3% versus 43.7%), and in ex-prisoners (26.6% versus 15%). In conclusion, a comprehensive approach to examination and treatment of adolescents with TB should be performed. History and clinical data can be beneficially used to predict of drug resistance before results of cultural investigation.

Keywords: infectious lung diseases, tuberculosis control, tuberculosis epidemiology, tuberculosis in adolescence, drug-resistant tuberculosis

Introduction

For the last two decades, epidemiological tuberculosis situation in the Russian Federation is considered to be unfavorable and progressing [1–3]. Activities of the medical community to combat tuberculosis in Russia have been supported by the Russian Government. Fight against tuberculosis involves evidence-based techniques as well as achievements of Russian and European experts [4–6].

Recent years have been characterized by significant changes in the organization of TB management in Russia. Russian Public Health Ministry has already committed significant funds to fight tuberculosis according to the basic concepts of the national project ‘Public Health Modernization’ and the Federal Program ‘Prevention and Controlling of Community Diseases’ (2007–2012). In 2010, a special public health regulation for tuberculosis services in the Russian Federation was approved and implemented into health care practice. The regulation is aimed at intensification of the fight against tuberculosis in the Russian regions. Due to the activities performed over the past 5 years, the death rate because of tuberculosis has decreased [7, 8].

But in some Russian regions, including the Smolensk one, these figures are still higher compared to the aver-

age national data. In the last 7 years, the incidence of TB in the adult population ranged from 76.4 to 66.3 per 100,000. In 2010, the TB rate in Russia was 62.3, and in the Smolensk region, it was noted as high as 73.6 cases per 100,000 population. The situation is aggravated by unidentified contacts with sputum-positive patients, so increase of opportunity for TB infection has actively spread. A proportion of acute progressive, drug-resistant forms of tuberculosis is also increasing [9].

The problem of TB in children as well as adult population in the Smolensk region is also considered to be an issue of the day because of high morbidity and mortality rates in the adult population, high incidence in groups at risk, unidentified contacts with infected persons, failure to identify TB particularly in the distant regional areas, lack of efficient preventive measures in regional pediatric and TB services.

The Smolensk State Medical Academy initiated an extensive study to discover causes of the poor epidemiological situation. The study demonstrated that the contributing factors are as follows: lack of unified regional database of all infected patients and patients who have had tuberculosis in childhood, information from obstetricians and pediatricians since the first year of infants’ life, and certain

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national law regulations connected with confidentiality of medical information as well as poor cooperation between various health care units

TB has been determined to be almost twice more common in men than in women, the maximum incidence being observed in women aged 25–34, and in women peaks of tuberculosis are reported 18–24 and 25–34 years of age, occurring mostly at the fertile period [10]. Children born in these families come into contact with the sources of tuberculosis infection. However, the fact is not always taken into account when infants are discharged from the hospital.

The incidence of TB in children in 2004–2011 ranged from 11 to 29.1 per 100,000 population. Starting from 2005, the rate consistently exceeded the average national data, and only in 2010–2011, there was a slight decrease in 11–12. Six per 100,000 children population were reported. The incidence of tuberculosis in adolescents, 14–17 years of age, still remains high enough. The trend for decrease in 2006 was replaced by a sharp morbidity in 2010 (54.6 per 100,000 of population), much higher than the average national data.

So features of TB in young people in high prevalence region, frequency of drug resistant TB in the region, key risk factors, and assessment of the health status of adolescents with tuberculosis have been investigated.

Materials and Methods

Study subjects

A comprehensive regional study and analysis of all pulmonary tuberculosis cases in adolescents identified in the area over the decade between January 2000 and December 2009 ($n = 129$) and 420 TB cases in 18–34 years old patients have been performed. The study was ethically approved by the ethical committee of The Smolensk State Medical Academy. One of the criteria was active tuberculosis and being an inhabitant of the Smolensk region. Exclusion criteria were inactive and extrapulmonary tuberculosis.

Study design

All patients included in the study received the chest roentgenography, bacteriological sputum investigation and clinical examination including blood and urine analyses. All adolescents received tuberculin skin test (TST) with 2 TU purified protein derivate (PPD). These procedures are included into standard examination of TB patients. Psychological testing was performed for 24 TB patients and 20 healthy adolescents. These patients were asked for informed consent.

Methods

Staff of the regional anti-tuberculosis dispensary and tuberculosis department of the Smolensk State Medical

Academy asked each patient for history data. They registered the following information: date of birth, sex, occupation, household member of patient, contact with TB patient, BCG-vaccination, prior TST results, concomitant diseases, and bad habits. Received data were linked to the medical documentation. Radiological investigation was step-by-step: fluorography, plain chest roentgenography, multiple view roentgenography and tomography, and, in proper indications, computed tomography. Sputum examination included Ziehl–Neelsen staining and culture on the Lowenstein–Yensen medium. In case of positive growth, we perform drug resistance investigation by indirect method.

Statistical analysis of the results involved methods of nonparametric methods using the Mann–Whitney *U*-test, odds ratio, confidence intervals, and Fisher's test.

Analysis

In the structure of morbidity, the highest incidence (85.3%) involved secondary forms with dominating infiltrative pulmonary tuberculosis (53.5%). Primary forms of tuberculosis in adolescents were only in 14.7% of newly diagnosed cases. Complications were observed in 44.9%, destructive processes in 33.3% of TB cases. Bacterial excretion was found in 23% of drug-resistant strains, 6.7% of patients had multiple-drug resistance TB.

It was noted that 57.6% of TB cases were in adolescents having a history of contact with a source of TB infection. In most cases (87.8%), it was the intra-family contact, and only in some case, the contact was periodic. According to the TST, in 19.3%, there was a conversion of tuberculin sensitivity, other patients had positive TST for more than 2 years. However, only 50.6% of cases were registered by a TB doctor, only 12% had a full course of preventive chemotherapy. Neglecting tuberculin dispensary examination for teenagers also indicates a low percentage of cases of disease detection with this method (12.4%). X-ray examination to be still a method of choice for early detection of tuberculosis in adolescents [11, 12] was a method revealing only in 18.6% of patients. Most cases (41.9%) were detected only when there are clear clinical symptoms. However, in 16.7% of the patients, the diagnosis of tuberculosis was made by pediatricians at an out-patient department within 10 days.

Risk factors of TB in adolescents

Tuberculosis is clear to be a socially determined disease [13]. However, the social risk factors (poor housing, low income, single-parent family, migrants) were detected only in 48% of adolescents of the main group; the remaining patients were socially advantaged. According to the received data, social risk factors do not influence a clinical form of the disease in adolescents, but increase the risk of complicated tuberculosis, 36.7% versus 16.9% for social affluent teenagers ($p < 0.005$) and the effect on the basic

characteristics of tuberculosis process – the length and the presence of degradation and bacteria. The incidence of large processes (more than 2 lung segments) was 28.3% (versus 16.7%, $p < 0.05$), bacterial – 36.7% (versus 15.4%, $p < 0.005$), the destruction of the lungs – 41.7% (versus 26.2%, $p < 0.05$).

In TB adolescents, chronic somatic diseases commonly become clear and diagnosed having a negative impact on the immune system [14–16]. Co-morbidities were diagnosed in 62% of TB adolescents. All children were screened for diabetes, but this disease was not confirmed. Only one case of TB had HIV-positive results.

Anemia (27.5%), chronic gastrointestinal diseases (26.3%), and recurrent respiratory viral infections (17.5%) were commonly diagnosed. The course of tuberculosis in adolescents with a history of somatic diseases was characterized by extensive processes – 45% (versus 30.6%, $p < 0.05$) complications (52.5% versus 32.7% ($p < 0.005$)) and sputum – 28.8% (compared to 14, 3%, $p < 0.05$). Clinical symptoms in these cases were often accompanied by febrile temperature (32.5% versus 18.3%, $p < 0.05$) and weight loss (35% versus 8.2%, $p < 0.001$).

One of the poor-discovered aspects of the TB problem in adolescents is autonomic dysfunction. Parameters of vegetative status were studied in 24 patients demonstrating that autonomic regulation in adolescents with pulmonary tuberculosis was more commonly sympathicotonic (54.2%) and in the majority of patients (95.8%) insufficient vegetative activities with a wedge-orthostatic test were diagnosed. Stress and failure of adaptation were common enough in TB adolescents. The second study of autonomic parameters in 2–3 months after the start of TB treatment showed normal vegetative support of one third of the adolescents, the deficit was observed in only 61.6%.

Psychological features of adolescents with TB

The study involved 24 teenagers to determine their mental and emotional status (general, social anxiety, and character of accentuation). The results were compared with 20 healthy adolescents. Most of the patients demonstrated a high level of anxiety (60.8%) (Taylor's test), while in healthy adolescents, anxiety was marked in 35% ($p < 0.05$). Data of social anxiety (Kondash's scale) in adolescents with pulmonary tuberculosis in 34.8% were high enough.

Healthy patients showed normal levels of social anxiety, suggesting a good adaptation to the social environment and high stress resistance. In patients with tuberculosis teens revealed a high frequency of character accentuation (66%), and 60.8% were paranoiac, epileptoid and hysteroid psycho, which are characterized by a tendency to aggression and, in adverse conditions, pose a threat of social conflict. In 30.4%, adolescents have conformal, unstable, labile, or cycloid psycho. The health status of these patients depended on their peace of mind, yet they often fell into apathy and dejection. Our data are in accordance with some other investigations [17]. Obviously,

in these cases, a psychologist is of great significance for a favorable outcome of the disease.

Thus, this study revealed a close link between the different aspects of adolescent health and importance of a comprehensive approach to diagnostics and treatment. It also demonstrated the necessity to strengthen the cooperation between pediatric, gynecological, and TB services.

Tuberculosis in young people

The problem of tuberculosis in young patients (18–34 years) in the Smolensk region is associated with an increase in the number of cases caused by strains of *Mycobacterium tuberculosis* drug resistance. The study involved 420 cases of sputum-positive pulmonary tuberculosis patients 18–35 years of age (2000–2009). In 214 of them, drug resistance was revealed. Incidence of drug-resistant TB is higher in the Smolensk region compared to other world regions [18–21]. About 25.7% of patients had multidrug resistance, 36.0% of patients was monoresistant, and 38.3% was polyresistance. Resistance to isoniazid in combination with other drugs is the most common (26.4%). Resistance to rifampicin in combination with other drugs was detected in 15.9% of patients.

Risk factors for drug-resistant TB development

Risk factors for pulmonary drug-resistant *M. tuberculosis* were studied with involvement of clinical, laboratory, and radiological data of patients with drug resistance ($n = 214$ – Group 1) and with stable sensitivity to anti-tuberculosis drugs ($n = 206$ – Group 2).

The study showed that in tuberculosis caused by drug-resistant pathogens, there is an increased risk of caseous pneumonia development (14.5% versus 4.4%) and disseminated pulmonary tuberculosis (25.2% versus 18.9%) compared to other forms of pulmonary tuberculosis.

Drug-resistant forms of TB in the study were significantly more common in lung TB (37.3% versus 22.8% in other groups, $p < 0.001$). Significant differences in the severity of destructive changes in the pulmonary tissue were also detected. Incidence of small cavities up to 2 cm in diameter significantly was higher (47.6%), and they were detected in patients in group 2 and in patients of group 1 only in 31.8% of cases ($p < 0.05$). Cavity diameter of 2 to 4 cm, in contrast, were more common in patients with drug-resistant *M. tuberculosis* (40.7 versus 24.8%, $p < 0.05$).

History of potential risk factors involved unemployment, two or more bad habits, alcohol and smoking.

Features of drug-resistant pulmonary TB in young people

Drug-resistant TB is characterized by severe course and poor treatment efficacy [22–24]. In our study, in pulmonary drug-resistant tuberculosis, the more severe conditions characterized by severe intoxication reported were

(28.0% versus 11.2%, $p < 0.001$), febrile temperature (48.6% versus 32.5%, $p < 0.05$), dyspnea (63.6 % versus 48.0%, $p < 0.05$), changes in percussion (22.4% versus 11.7% ($p < 0.05$), weak or bronchial respiration (71.5% versus 58.3%, $p < 0.05$), and pulmonary exudation (39.7 versus 20.9%, $p < 0.001$).

In examination of the pulmonary function in patients with drug-resistant tuberculosis, significant reduction in vital capacity (38.5% versus 23.5%, $p < 0.05$) and ventilation capacity of the lung (41.7% versus 23.4%, $p < 0.005$), as well as bronchial obstruction (61.4% versus 44.4%, $p < 0.05$) were noted.

Discussion

The study showed the validity of some history and clinical facts to predict drug-resistant tuberculosis in patients with primarily diagnosed pulmonary tuberculosis even before the results of laboratory confirmation. It can contribute to the treatment efficacy of newly diagnosed TB patients.

The results formed the basis of the Regional Program on Tuberculosis in the Smolensk region in 2011–2015. The program was developed jointly by the Smolensk Regional Department of Public Health and the Smolensk State Medical Academy. It includes the following areas: educational, organizational, methodological, theoretical and practical, and research activities on the fight against tuberculosis in the Smolensk region.

Educational activities involve education of the regional medical community and population through website of the SSMA, Regional Health Care Department, TV and radio programs devoted to TB problem. Scientific and practical activities include guidelines and manuals in comprehensive examination of children and adolescents; joint meetings of the Smolensk Regional TB Association with the involvement of pediatricians, obstetricians and gynecologists, infectious disease experts and health care managers to monitor current epidemiological situation and activities of TB services of the Smolensk region; consultations of EU and WHO experts to improve organizational and methodological activities of the TB laboratory, as well as bacteriological and radiological services of TB hospitals.

Research program regulates TB studies in children and adolescents; participation in international conferences organized by the Koch–Metschnikow-Forum and other TB organizations as well as scientific reports at the Pediatric National Congress, international, national, regional symposiums and meetings.

To implement the comprehensive program to combat tuberculosis, it is also essential to create a unified database for pediatric, gynecological, and TB services; to perform compulsory TB examination of an expected mother's family; to organize transfer of TB information to the obstetric (birth certificate) and pediatric (history of the child) services; to perform simultaneous treatment of tuberculosis and somatic diseases in children; and to educate population on preventive methods in tuberculosis.

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