Western European Journal of Medicine and Medical Science
Volume 2, Issue 6, June, 2024
https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

FEATURES OF SOCIAL AND BIOLOGICAL HISTORY OF CHILDREN DURING THE FORMATION OF LTBI AND ITS PROGRESSION TO ACTIVE TUBERCULOSIS

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ABSRTACT
According to the WHO, a quarter of the world's population are carriers of latent tuberculosis and the risk of progression of latent tuberculosis to an active form throughout a person's life is in the range of 5-15%. It is well known that children living in foci of tuberculosis infection are more at risk of infection and tuberculosis. It is important to establish the prognostic significance of risk factors that must be taken into account when planning further treatment measures for this cohort of the population. **Purpose of the study**: conduct analysis social risk factors and characteristics of the antenatal and intranatal periods of children's development during the development of latent tuberculosis infection and its progression to active tuberculosis. **Materials and methods:** A retrospective-prospective cohort study was conducted in accordance with the international STROBE standard. 60 children were selected and divided into three groups: Group 1 included 40 children with latent tuberculosis infection, Group 2 included 20 children with active tuberculosis. **Research methods.** Medical histories and outpatient records of patients of all groups were analyzed, data from general clinical, instrumental, laboratory and immunological examination methods were studied. **Results.** Among the reasons for the activation of the tuberculosis process in children with the presence of a latent ongoing process, the leading factors turned out to be social factors. Today, the presence of unsatisfactory living conditions, large families and low-income families, lack of higher education among parents, alcoholism, smoking or drug addiction in the family, as well as the development of a child in a single-parent family must be considered as risk factors for the development of active forms of tuberculosis among children. **Conclusion.** Thus, in our opinion, such ranking is necessary and relevant, since the influence of any of the risk factors on the activation or persistence of tuberculosis infection in an inactive form is unequal.
Keywords: latent tuberculosis infection, risk factors, active tuberculosis, children, focus of tuberculosis infection

Introduction. According to the WHO definition, latent tuberculosis infection (LTBI) is the presence of a persistent immune response to the introduction of pathogenic strains of Mycobacterium tuberculosis into the human body in the absence of clinical symptoms of tuberculosis process activity [10, 17]. A quarter of the world's population are carriers of latent tuberculosis, according to a global WHO report [10, 16]. The risk of progression of latent tuberculosis to an active form throughout a person's life is in the range of 5-15%, with the maximum peak risk of activation occurring in the first five years from the moment the pathogen enters the human body, most often a child or adolescent [1, 3, 9, 15].

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The priority objective of the "Global strategy to combat tuberculosis after 2015" is the paradigm of personalized medicine, which has a preventive direction. As part of the strategy, attention is focused on working with the LTBI reservoir, which will lead to a reduction in new cases of tuberculosis, which, in tandem with adequate treatment measures for all patients with active tuberculosis, will guarantee the elimination of this infectious disease in the world by 2050 [2, 4, 14]. From today's perspective, despite numerous studies in phthisiopediatrics, the study of risk factors for activation of the latent tuberculosis process continues [3, 5, 8, 13], and there are also no gold standards for the early detection of LTBI and differential diagnosis between latent and active tuberculosis infection in the child's body [2, 6, 12]. Children infected with Mycobacterium tuberculosis represent a risk group; the realization of such a risk, according to a number of authors, occurs when risk factors of a different nature are combined. In recent years, there has been a need to clarify the contribution and assessment of each risk factor in the activation of the latent tuberculosis process.

It is well known that children living in foci of tuberculosis infection are more at risk of infection and tuberculosis. Scientists are searching for biomarkers of activation and progression of a latent ongoing process into an active specific process [4, 5, 7, 9]. It is important to establish the prognostic significance of risk factors that must be taken into account when planning further treatment measures for this cohort of the population.

Purpose of the study: conduct analysis social risk factors and characteristics of the antenatal and intranatal periods of children's development during the development of latent tuberculosis infection and its progression to active tuberculosis.

Materials and methods: The study was carried out at Samarkand State Medical University, at the Department of Phthisiology and Pulmonology. The clinical part of the work began in 2024 on the basis of the Samarkand Center for Phthisiology and Pulmonology, the city TB dispensary. The study is carried out on the basis of permission from the ethical committee of Samarkand State Medical University (protocol No. 51 of 12/10/2023). The children and their parents who took part in the study signed voluntary informed consent. A retrospective-prospective cohort study was conducted in accordance with the international STROBE standard. 60 children were selected and divided into three groups: Group 1 included 40 children with latent tuberculosis infection, Group 2 included 20 children with active tuberculosis.

In the 1st group of children with latent tuberculosis infection, the average age was 7.5±0.5 years; there were 11 (55.0%) boys and 9 (45.0%) girls in the group. However, in this group of patients no significant differences by gender were identified ($p>0.05$). Diagnosis LTBI is diagnosed when a child is examined for contact with a patient with an active form of tuberculosis, as well as based on the results of immunodiagnostics. The size of the papule with the Mantoux test with 2TE PPD-L was on average 12.1±0.4 mm (95% CI 10.2-13.9 mm), and with the test with the recombinant tuberculosis allergen "Diaskintest" - 2.2± 0.5 mm (95% CI 1.6-2.87 mm). In this group of examined children, the Mantoux test with 2TE PPD-L in most cases showed positive results (n=40; 90.0%), and the test with the drug Diaskintest - negative results (n=20; 80.0%). BCG vaccination was performed in 39 children (95.0%) and was assessed as effective in 27 (69.3%) children.

In the 2nd group of patients with active forms of tuberculosis, 20 children were examined; the average age was 9.8 ± 0.3 years. By gender, there were 11 (55.0%) boys and 9 (45.0%) girls in the group examined. In this group of patients with active forms of tuberculosis, there was also no significant difference by gender ($p>0.05$). Methods for detecting patients in

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ISSN (E): 2942-1918 Open Access| Peer Reviewed

this group: 6 children (30.0%) were identified during examination regarding contact with patients with an active form of respiratory tuberculosis; when seeking medical help, 14 (70.0%) children were identified, while in 5 cases (35 .7%) a focus of tuberculosis infection with the presence of massive bacterial discharge was identified. Thus, the presence of contact was established in 11 examined children (55.0%), with a predominance of close family and residential contact in 10 (n=11; 90.0%) children. The epidemiological history of 4 children (n=11; 36.3%) established the presence of deaths from tuberculosis, that is, these lesions were regarded as "focuses of death." 9 children from the 2nd group we examined (n=11; 81.8%) were in contact with patients with pulmonary tuberculosis with massive bacterial excretion, of which in 4 cases (n=9; 44.4%) the source was found to have multiple drug resistance of the pathogen to anti-tuberculosis drugs.

The size of the papule with the Mantoux test with 2TE PPD-L was on average 12.8±0.7 mm (95% CI 12.9-13.4 mm), and with the test with the recombinant tuberculosis allergen "Diaskintest" - 14.66± 0.4 mm (95% CI 14.1-15.9 mm). In this group of examined children, the Mantoux test with 2TE PPD-L in most cases showed positive results (n=20; 65.0%), and the test with the drug Diaskintest – hyperergic results (n=20; 85.0%). BCG vaccination was performed in 39 children (95.0%) and was assessed as effective in 27 (69.3%) children.

The diagnosis of the active form of tuberculosis was approved by the central medical control commission (CMCC) based on data from a comprehensive clinical, radiological laboratory examination and immunodiagnostics of patients. In this group of patients, primary forms of tuberculosis predominated: 6 (30.0%) patients had a primary tuberculosis complex, 7 (35.0%) had tuberculosis of the intrathoracic lymph nodes, however, 4 patients (20.0%) had diagnosed with infiltrative pulmonary tuberculosis, 2 (10.0%) with disseminated pulmonary tuberculosis, 1 (5.0%) with tuberculous pleurisy. 95.0% of patients (n=19) had an isolated course of tuberculosis, only 1 patient (5.0%) had a combined tuberculous lesion of the lungs and femur, 2 patients (10.0%) had a complication of the main process in the lungs with a right-sided exudative pleurisy. The infiltration stage of the tuberculosis process was established in 12 (60.0%) respondents, the stage of disintegration and contamination - in 1 (5.0%), the resorption stage - in 1 (5.0%), the petrification stage - in 2 (10.0 %) of children in the study group. Isolation of Mycobacterium tuberculosis with sputum was detected in 3 cases (15.0%), while two of these children isolated a multidrug-resistant pathogen, while another had multiple drug resistance of the pathogen to anti-tuberculosis drugs of the main group. Primary forms of tuberculosis (primary tuberculosis complex and tuberculosis of intrathoracic lymph nodes) were more often registered in the cohort of children 0-13 years old - 12 patients (n=13; 92.3%). In the cohort of children 13-17 years old, infiltrative tuberculosis was more often observed - 4 cases (n=7; 57.1%). PostBCG sign was found in all children of this group, but its effectiveness was established only in 7 children (n=20, 35.0%).

Research methods. Medical histories and outpatient records of patients of all groups were analyzed, data from general clinical, instrumental, laboratory and immunological examination methods were studied. Vaccination was considered effective if there was a post-vaccination mark measuring 4-10 mm.

Statistical research methods: Statistical data processing was performed using the Statistica 6.0 program. The arithmetic mean (M), confidence interval with a level of p=0.95, standard error of the mean (±SEM), median (ME) were calculated. The significance of differences was calculated using Student's test (t).

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https://westerneuropeanstudies.com/index.php/3
ISSN (E): 2942-1918 Open Access| Peer Reviewed

Results and its discussion: To establish the prognostic significance of risk factors for the development of latent or active tuberculosis infection in children, an analysis of data from 40 patients of the 1st group and 20 patients of the 2nd group of examination was performed.

When analyzing social history It was found that in the manifestation of the active tuberculosis process, the decisive risk factors were the child's residence in a low-income (RR 5,000), large (RR4,667), or single-parent family (RR3,200), unsatisfactory living conditions of the child and his family (RR4.857), lack of a permanent job for the father (RR3,467), secondary or secondary specialized level of education of parents (RR 3,000), mother's unemployment (RR2,308), alcoholism, smoking abuse and drug addiction of parents (RR 2,000), and also in our study the social factor of "disorganization" of the child was often present (RR 2,000).

The results of the social history allowed us to identify social risk factors, which are presented in Table 1.

Table 1. Social risk factors in groups I and II of those examined

Social history data	**ACT TB n=20**	**LTI n=40**	**RRTB-LTI, 95%CI**	**χ2TB-LTBI criterion, p**
	Abs (%)	Abs (%)		
Living in a single-parent family	8 (40.0)	5 (12.5)	3,200; 8.526-1.201	5.941; 0.015
Living with a child in a large family	7 (35.0)	3 (7.5)	4.667; 15,150-1,348	7.260; 0.008
Living with a child in a low-income family	11 (55.0)	4 (10.0)	5,500; 15.111-2.002	14,400;<0.001
Secondary or secondary specialized level of education for parents	18 (90.0)	12 (30.0)	3,000; 4.924-1.828	19,200;<0.001
Mother lacks a permanent job	15 (75.0)	13 (37.5)	2.308; 3.856-1.381	9.676; 0.002
Father does not have a permanent job	10 (66.7) n=15	5 (19.2) n=26	3.467; 8.235-1.459	8.077; 0.005
Alcoholism, smoking abuse and drug addiction of parents	11 (55.0)	11 (27.5)	2,000; 3.795-1.054	4.342; 0.038
Unsatisfactory living conditions for the child and his family	17 (85.0)	7 (17.5)	4.857; 9.758-2.418	25.313;<0.001

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ISSN (E): 2942-1918 Open Access| Peer Reviewed

The child is not organized	5 (25.0)	5 (12.5)	2,000; 6.114-0.654	1.500; 0.221

Analysis of the biological history showed the need for separate consideration of risk factors affecting during the intrauterine period of the child's development and during the child's extrauterine life. Intrauterine risk factors for tuberculosis were maternal smoking during pregnancy with this child (RR 5,000), the presence of chronic extragenital pathology during pregnancy (RR 2, 615), as well as the presence of anemia, ARVI, toxicosis of pregnancy (RR 1,440, RR 1,600, and RR 2,400 respectively). The main risk factors were pathology during childbirth in the form of premature or prolonged labor (RR1.833 and R.R.3,500 respectively). The fact of operative delivery in the woman's biological history was also significant (RR2.727).

Biological antenatal risk factors in groups I and II of those examined are presented in Table 2.

Table 2. Biological antenatal risk factors in groups I and II of those examined

Risk factors	TB Act n=20	LTI n=40	RRTB-LTI, 95%CI	χ2TB-LTBI criterion, p
	Abs (%)	Abs (%)		
Mother's age less than 18 years, more than 25 years	9 (45.0)	26 (65.0)	0.692; 1.182-	2.194;0.139
Maternal smoking during pregnancy:	5 (25.0)	2 (5.0)	5,000; 23.546-0.791	5.175; 0.023
The presence of chronic extragenital pathology in a woman during pregnancy	17 (85.0)	13 (32.5)	2.615; 4,240-1,613	14,700;<0.001
Availabilitytoxicoses of pregnancy	12 (60.0)	10 (25.0)	2,400; 4.575-1.259	7.033; 0.008
Having anemia during pregnancy	18 (90.0)	25 (62.5)	1.440; 1.907-1.087	4.966; 0.026
Presence of ARVI during pregnancy	16 (80.0)	20 (50.0)	1,600; 2.339-1.095	4.484; 0.033
Preterm labor	11 (55.0)	12 (30.0)	1.833; 3.399-0.989	3.525; 0.061
Prolonged labor	7 (35.0)	4 (10.0)	3,500; 10.568-1.159	5.566; 0.019

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Surgical delivery	15 (75.0)	11 (27.5)	2.727; 4.790-1.533	12.251; <0.001
Previous history of tuberculosis in the family	13 (65.0)	2(5.0)	9.750; 38,640-2,460	24.995; <0.001

The antenatal risk factor for active tuberculosis was the presence of cases of tuberculosis in the family in the past (RR 9.750). However, the Federal Clinical Guidelines for LTBI of the Russian Federation do not take this risk factor into account [4].

According to the Federal Clinical Guidelines of the Russian Federation on LTBI, biological extrauterine risk factors for active tuberculosis infection are not presented as reliably possible [4]. However, we have established the following risk factors for active tuberculosis: prematurity (RR 1.600), such as birth weight less than 2500 g (RR 4.677), perinatal damage to the central nervous system at birth (RR 1.753), history artificial nutrition after birth (RR 2.545),frequent episodes of ARVI in the 1st year of life (RR 3.429), the presence of iron deficiency anemia in the 1st year of life (RR 4.286), a burdened allergic history (RR 4.400), ineffective BCG vaccination (RR 2.182), childhood infections (RR 2.000).

Biological postnatal risk factors in groups I and II of those examined are presented in Table 3.

Table 3. Biological antenatal risk factors in groups I and II of those examined

Risk factors	**TB Act n=20**	**LTI n=40**	**RRTB-LTI, 95%CI**	**χ2TB-LTBI criterion, p**
	Abs (%)	Abs (%)		
Presence of congenital malformations	2 (10.0)	5 (12.5)	0.800; 3.767-0.170	0.081; 0.777
Prematurity	4 (20.0)	5 (12.5)	1,600; 5.314-0.482	0.588; 0.444
Presence of hypoxic damage to the central nervous system	6 (15.0)	10 (25.0)	1,200; 2.830-0.509	0.170; 0.680
Birth weight less than 2500 g	7 (35.0)	3 (7.5)	4.667; 16,150-1,348	7.260; 0.008
History of artificial nutrition	14 (70.0)	11 (27.5)	2.545; 4.543-1.426	9.909; 0.002
Frequent episodes of ARVI in 1 year of life	12 (60.0)	7 (17.5)	3.429; 7,347-1,600	11,130;<0.001
Presence of iron deficiency anemia at 1 year of age	15 (75.0)	7 (17.5)	4.286; 8.795-2.088	18.401;<0.001

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Physical and neuropsychic development by 1 year of life with delay	5 (25.0)	11 (27.5)	0.909; 2.260-0.366	0.043; 0.837
Ineffective BCG vaccination	12 (60.0)	11 (27.5)	2.182; 4.046-1.177	5.958; 0.015
Childhood infections	14 (70.0)	8 (20.0)	2,000; 3,332-1,200	14.353;<0.001
Aggravated allergy history	11 (55.0)	5 (12.5)	4,400; 10,939-1,770	12.315;<0.001

Conclusions: Thus, among the reasons for the activation of the tuberculosis process in children with the presence of a latent ongoing process, the leading factors turned out to be social factors. Today, the presence of unsatisfactory living conditions, large families and low-income families, lack of higher education among parents, alcoholism, smoking or drug addiction in the family, as well as the development of a child in a single-parent family must be considered as risk factors for the development of active forms of tuberculosis among children.

In the literature, there is no division of risk factors, separately for active and latent tuberculosis infection. In our opinion, such ranking is necessary and relevant, since the influence of any of the risk factors on the activation or persistence of tuberculosis infection in an inactive form is unequal.

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