MAIN FORMS AND CLINICAL PROGRESSION OF PRIMARY TUBERCULOSIS IN CHILDREN AND ADOLESCENTS

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Introduction. The rise of tuberculosis incidence among pediatric population of Yakutia was first registered in the beginning of the 90s. In 1990 pediatric incidence was 11.7 per 100 000, in 1997 it has reached its maximum and was as high as 59.9 per 100 000. Since then and until 2006 inclusive, pediatric incidence over republic never fell lower than 41.0 to 44.0 per 100 000. But for the last years, apparent decline of the incidence rate had been observed (31.0 in 2007, 29.9 in 2008, 22.8 in 2009, 21.8 in 2010). One of the reasons for noticeable decrease in pediatric tuberculosis incidence was the implementation of modern digital examination techniques, namely computed tomography (CT), to the field of pediatric phthisiatry in Yakutia. CT-based diagnosis has started to be widely used in the republic since 2007, and has been a major step towards improvement of primary tuberculosis infection diagnosis.

Aim: To analyze CT-based semiotics of primary tuberculosis, we studied X-ray data of children and adolescents who had tuberculosis of intrathoracic lymph nodes (n=270) or various phases of primary tuberculosis complex (n=88), treated in the "Phthisiatry" Research-Practice Center. Children and adolescents were divided to 4 age groups (Table 1).

Table 1

Children and adolescents with tuberculosis of intrathoracic lymph nodes at various disease stages

No.	Age group	Infiltration phase	Early consolidation and calcification phase	Calcification phase	Total:
1	0-3 years	25 (37.3%)	11(16.4%)	31 (46.3%)	67 (24.8%)
2	4-6 years	25 (28.7%)	10 (11.5%)	52 (59.8%)	87 (32.2%)
3	7-13 years	20 (20.6%)	4 (4.1%)	73 (75.3%)	97 (36.0%)
4	14-17 years	4 (21.0%)	-	15 (79.0%)	19 (7.0%)
	Total:	74 (27.4%)*	25 (9.3%)	171 (63.3%)**	270 (100%)

Note: $p<0.01$ when comparing between * and **;
$p<0.05$ when comparing between calcification phases in groups 1 and 4.

The following groups of children and adolescents were referred to CT examination: patients with early phase of primary tuberculosis infection (with tuberculin test conversion) who developed hyperergic reaction, patients with infection in the past who showed a gradual increase of susceptibility to tuberculin, patients exposed to a person with tuberculosis disease, and patients whose alterations on both plain chest X-ray pictures and linear CT-scans required differential diagnosis of tuberculosis.

Results and discussion. Analysis of the patterns of radiological alterations showed, that, among 270 children and adolescents, presence of tuberculosis process in lymph nodes was detected: at infiltration phase in 27.4%, at early reverse development phase in 9.3%, and at calcification phase in 54.9%. Timeliness of tuberculosis detection clearly correlated with age: the younger was the age, the more was the percentage of cases detected at infiltration phase, while the elder age correlated with more percentage of cases detected at calcification phase. These findings demonstrate the untimely detection of local tuberculosis in children and adolescents, which is a source for development of chronic and secondary disease.

Tuberculosis of intrathoracic lymph nodes affects 1 to 6 or more lymph node groups (Table 2). When many groups are involved, the extent of involvement is chiefly age-dependent. Involvement of 3 and more lymph node groups on average, along with their marked enlargement is more often seen in newborns and infants (0 to 3 year old). Predominant involvement of less then 3 lymph node groups, i.e. minor form of bronchadenitis, is observed more often in preschool and school children. Extensive primary process with involvement of 6 and more lymph node groups is observed more often in adolescents (in 75% of cases).

Table 2

Number of lymph nodes groups involved in tuberculosis of intrathoracic lymph nodes, by age groups

No.	Age groups	Lymph node groups involved (absolute number / %)						Total:
		1 group	2 groups	3 groups	4 groups	5 groups	6 groups >	
1	0-3 year	4 (11.1%)	6 (16.7%)	14 (38.9%)	6 (16.7%)	4 (11.1%)	2 (5.5%)	36 (100%)*
2	4-6 year	8 (22.9%)	8 (22.9%)	8 (22.9%)	5 (14.2%)	4 (11.4%)	2 (5.7%)	35 (100%)*
3	7-13 year	9 (37.5%)	5 (20.8%)	4 (16.7%)	5 (20.8%)	-	1 (4.2%)	24 (100%)**
4	14-17 year	-	-	1 (25%)	-	-	3 (75%)	4 (100%)**
	Total:	23 (23.2%)	18 (18.2%)	26 (26.3%)	17 (17.3%)	7 (7%)	8 (8%)	99 (100%)

Note: p>0.05 in age groups 1 and 2 with involvement of 3 and more lymph node groups,
p<0.05 when comparing between age groups: 1 and 3, 3 and 4.

The following lymph node groups are involved in tuberculosis most often: bronchopulmonary, subcarinal and retrocaval (Table 3). Enlargement of hilar lymph nodes leads to dilatation of the lung hilum. The margins become uneven and wavy. Enhancement and deformation of the hilar pattern caused by thickening of interlobular intersticium in the surrounding lung, and abnormality of anatomical organization of the hilum are detected on CT. Tuberculosis of intrathoracic lymph nodes rarely affects hilar nodes alone without involvement of mediastinal lymph nodes.

Table 3

Lymph node groups involved in tuberculosis of intrathoracic lymph nodes, by age groups

Lymph node groups	Age				Total:
	0-3 year	4-6 year	7-13 year	14-17 year	
Right bronchopulmonary	38 (23.0%)	50 (26.5%)	42 (20.1%)	13 (18.3%)	143 (22.6%)*
Left bronchopulmonary	49 (29.7%)	50 (26.5%)	55 (26.3%)	14 (19.7%)	168 (26.5%)*
Subcarinal	27 (16.4%)	31 (16.4%)	40 (19.2%)	17 (24.0%)	115 (18.1%)*
Retrocaval	17 (10.3%)	19 (10.0%)	24 (11.5%)	10 (14.1%)	70 (11.0%)
Паравазальная	10 (6.1%)	16 (8.5%)	13 (6.2%)	3 (4.2%)	42 (6.6%)
Paratracheal	11 (6.7%)	11 (5.8%)	10 (4.8%)	6 (8.5%)	38 (6.0%)
Para-aortic	8 (4.8%)	8 (4.2%)	8 (3.8%)	5 (7.0%)	29 (4.6%)
Tracheobronchial	2 (1.2%)	1 (0.5%)	9 (4.3%)	0	12 (1.9%)
Aortic window lymph nodes	1 (0.6%)	2 (1.0%)	5 (2.4%)	1 (1.4%)	9 (1.4 %)**
Paraesophageal	2 (1.2%)	1 (0.5%)	3 (1.4%)	2 (2.8%)	8 (1.3%)**
Total:	165 (100 %)	189 (100 %)	209 (100 %)	71 (100 %)	634 (100 %)

Note: p<0.01 when comparing between * and **

CT-based angiography enables to reliably differentiate between the enlarged lymph nodes and the large mediastinal and hilar vessels. Contrasting agent is accumulated within the capsule of an affected lymph node, marking the limits of caseous-necrotic matter contained within the capsule. It should be noted, that this is not a feature in tuberculosis alone. The same response to contrast enhancement is seen in other diseases as well, e.g. in metastatic involvement of lymph nodes, sarcoidosis, or lymphomas.

Primary pulmonary complex is a triad formed by a specific lesion at the site of penetration of mycobacteria, lymphangitis and involvement of regional lymph nodes. Classical primary complex with marked pulmonary process and an extensive perifocal response develops when the following unfavorable factors meet: heavy bacterial excretion, virulence of tuberculosis infection, and impaired immune and biological capabilities of the host.

When a primary complex is caused by aerogenic infection, the lungs are the common site where disease develops – by A.I. Strukov's data, the percentage of such cases is 95% [2]. And most often the disease affects peripheral subpleural parts of predominantly well-aerated segments and quite frequently, these are right segments II and III. Initially, several alveoli are involved in the process, this is followed by development of alveolitis, and later, when the bronchioles become involved, bronchiolitis develops. Thus, the primary affect initially appears as pneumonia. The size of pneumonic focus depends on the number of alveoli involved: if a small number of alveoli are affected, pneumonic focus can be the size of a millet seed, in other cases acinar, lobular, or even lobar focus may develop.

Radiological diagnostics of primary complex is based on recognition of basic features of the disease. We studied the local manifestations of primary tuberculosis complex in 88 children and adolescents. Primary complex occurs in different age groups.

Because of the presence of alterations in the lungs and the large extent of the process, the percent of cases detected in infiltration phase is higher in age group 1, than in other age groups (Table 4).

Table 4

Children and adolescents with primary tuberculosis complex detected at different disease phases

Age groups	Infiltration phase:	Early consolidation and calcification phase:	Calcification phase:	Total:
0-3 year	11 (61.1%)*	5 (27.8%)	2 (11.1%)*	18 (20.5%)
4-6 year	11 (40.8%)	4 (14.8%)	12 (44.4%)	27 (30.7%)
7-13 year	19 (47.5%)	5 (12.5%)	16 (40.0%)	40 (45.4%)
14-17 year	1 (33.3%)	-	2 (66.7%)	3 (3.4%)
Total:	42 (47.7%)	14 (15.9%)	32 (36.4 %)	88 (100%)

Note: * $p<0.01$

Today, with the help of high resolution CT-imaging, most cases of primary affect are detected as acinar (sized 0.2 to 0.9 sm.) or lobular pneumonic focus (sized 1.0 to 1.5 sm.), which always has a subpleural localization. As our data show, in 61.9% of cases the primary affect is a lesion of less than 1 sm. in size, while in 21.4% of cases the size of primary affect is 1 to 1.5 sm., and in 16.7% of cases an entire segment or two are affected by primary tuberculous pneumonia. Small acinar and lobular lesions are round-shaped, with low or medium density and relatively well-defined margins. With the growth of the extent of infiltration, the shape of dense areas tends to assume the anatomic shape of the affected part of the lung, its subsegment or segment. Bronchial lumina may be visible in the zone of specific pneumonia.

Primary affect can be localized in various sites, but is found predominantly in well-aerated regions of lung tissue. In 65.9% of cases primary affect develops in the right lung, usually in segments S6 (25.8%), S1 (19.0%), S2 (10.3%), S3 (10.3%), and S4 (10.3%). In 34.1% of cases the left lung is affected, with segment S6 affected in 40.0% and segments S1-S2 affected in 20% of them.

A simultaneous involvement of a number of intrathoracic lymph nodes is one of the most important distinguishing features of primary tuberculosis complex (Table 5). In contrast to tuberculosis of intrathoracic lymph nodes, right-sided hilar bronchopulmonary lymph nodes enlarge more often (22.6%), while involvement of left-sided hilar bronchopulmonary nodes occurs in 19.0%, subcarinal lymph nodes become involved in 18.1%, and retrocaval lymph nodes – in 14.5% of cases.

Table 5

Lymph node groups involved in primary tuberculosis complex, by age groups

Lymph node groups	Age				Total:
	0-3 year	4-6 year	7-13 year	14-17 year	
Right bronchopulmonary	14 (26.4%)	16 (24.6%)	20 (20.0%)	-	50 (22.6%)*
Left bronchopulmonary	9 (16.9%)	12 (18.4%)	18 (18.0%)	3 (100%)	42 (19.0%)*
Subcarinal	10 (18.9%)	11 (16.9%)	19 (19.0%)	-	40 (18.1%)*
Retrocaval	8 (15.0%)	12 (18.5%)	12 (12.0%)	-	32 (14.5%)
Paravasal	3 (5.7%)	4 (6.2%)	13 (13.%)	-	20 (9.0%)
Paratracheal	3 (5.7%)	4 (6.2%)	6 (6.0%)	-	13 (5.9%)
Para-aortic	2 (3.8%)	-	8 (8.0%)	-	10 (4.5%)
Tracheobronchial	2 (3.8%)	3 (4.6%)	2 (2.0%)	-	7 (3.2%)
Aortic window lymph nodes	-	3 (4.6%)	1 (1.0%)	-	4 (1.8%)**
Paraesophageal	2 (3.8%)	-	1 (1.0%)	-	3 (1.4%)**
Total:	53 (100%)	65 (100%)	100 (100%)	3 (100%)	221 (100%)

Note: $p<0.05$ when comparing between * and **.

Distinction between complicated and non-complicated forms of pediatric primary tuberculosis was offered as far back as in 1930-40s by M.P. Pokhitonova and A.I. Kudryavtseva [1]. In non-complicated disease, the specific process is limited to bronchoadenitis and primary complex. The infiltration phase lasting for 4 to 6 months, is followed by the phase of resolution (5-6 months long) and consolidation, and finally by calcification phase. During consolidation phase, both the primary lesion and the lymph node become smaller and better defined, and their borders become more sharply marginated. Early calcification in this phase can be seen as multiple “lumps” and “crumbs” along the periphery of the lesion or lymph node. The phase of scarring and calcification begins in 8 to 10 months, on average.

CT is one of the basic methods for diagnosis of complicated primary tuberculosis (Table 6).

Table 6

Complications of primary tuberculosis in children and adolescents

Complications of primary tuberculosis:	Age groups (n)				Total (n=155)
	0-3 year (n=52)	4-6 year (n=50)	7-13 year (n=48)	14-17 year (n=5)	
Total number of children with complications:	*13 (25%)*	*13 (26%)*	*16 (33%)*	*3 (40%)*	*45 (29.0%)*
Bronchopulmonary involvement	5	4	2	1	12 (18.2%)
Bronchonodular fistula	-	1	-	-	1 (1.5%)
Bronchogenic seeding	1	2	3	1	7 (10.6%)
Lymphogenic seeding	8	9	12	1	30 (45.4%)
Hematogenic seeding	2	-	-	1	3 (4.6%)
Pleurisy	-	1	3	-	4 (6.0%)
Destruction	1	-	1	1	3 (4.6%)
Chronic tuberculosis	-	1	2	-	3 (4.6%)
Infiltrative exacerbation	-	1	-	-	1 (1.5%)
Generalized tuberculosis, including:	2	-	-	-	2 (3.0%)
Meningitis	-	-	-	-	-
Involvement of bones	1	-	-	-	1
Involvement of vertebrae	1	-	-	-	1
Enlargement of intra-abdominal lymph nodes	-	-	-	-	1
Involvement of adrenal gland	1	-	-	-	-
Number of complications:	*19 (28.8%)*	*19 (28.8%)*	*23 (34.8%)*	*5 (7.6%)*	*66 (100%)*

Based on incidence structure of newly identified primary tuberculosis, 29.0% children and adolescents had complicated disease forms. We observed 45 patients with complicated tuberculosis forms. Half of patients had two and more complications along with the specific process. Lymphogenic seeding (45.4%) and bronchopulmonary involvement (18.2%) were the leading types of complications.

In complicated development of primary tuberculosis, the clinical and radiological manifestations of intrathoracic processes show some age-specific features. This is true primarily for early age. In children aged 0 to 3, the more severe forms of complications – such as generalization of tuberculosis infection to other organs or bronchopulmonary involvement – are found more often than in other age groups. Primary pneumonic alterations in children from this age group often occupy a large part of the lung or an entire lobe. Patients from this age group are detected mainly on visit to a hospital. The most frequent diagnosis is pneumonia, and inefficiency of nonspecific antibacterial therapy requires differential diagnosis of tuberculosis. A caseous process in mediastinal lymph nodes which manifests in the form of tumor-like

bronchadenitis is especially pronounced in early age, when tuberculosis is characterized by a predominant presence of large parcels of caseation-alterated lymph nodes.

Direct signs of bronchial involvement are bronchial obstruction, altered diameter and deformed walls of the bronchi. Indirect symptoms are various degrees of impaired bronchial lumen patency ranging from hypoventilation to atelectasis, which appear on CT as well-defined areas of diminished and thickened lung tissue.

If a bronchonodular fistula develops, it is a precondition for the invasion of caseous-necrotic matter from the molten lymph nodes to bronchial lumina, causing a bronchogenous dissemination.

Tendency to generalization and to hematogenous dissemination of the process is one of the most noticeable features of primary tuberculosis in infants. A characteristic feature in acute microfocal and miliary disseminations is the presence of multiple monomorphous foci distributed over the lungs from apices to diaphragm. These focal alterations are accompanied by a mild response of interstitial structures, which manifests as a diffuse thickening of interlobular intersticium. A characteristic feature in subacute hematogenous disseminations is that numerous homogeneous or polymorphous foci develop in the lungs. And the upper lobes are predominant sites, where alterations take place.

Lymphogenous tuberculosis dissemination is seen more often in preschool and school children and is marked by highly irregular pattern of involvements. The alterations have predominantly subpleural localization and appear as productive foci of medium density with relatively well-defined margins, 0.3 to 0.5 sm. large. These foci are found more often in anterior and posterior segments of the upper lung lobes, in apical segments of lower lobes, in lingular segments and in middle lobes.

A slower progression of primary tuberculosis is more common in children of elder age (second half of preschool age and school age). A pulmonary process with acute onset, later followed by a prolonged disease course, is the reason to consider chronic process. Lymphotropic nature of *M.tuberculosis* is manifested as a tendency of the disease towards lympho-glandular progression with involvement of new groups of lymph nodes.

Involvement of pleura in primary tuberculosis rarely occurs (6%) in preschool and school children. Pleurisy in primary tuberculosis is certainly a complication, which is attributable to a special sensitivity of serous membranes to inflammatory responses that develop during the first phase of infection. Besides, because the lymphatics of hilum and pleura are directly interconnected, an inflammatory process can easily spread on pleura.

Destruction of pulmonary tissue is the rarest complication in a primary tuberculosis complex. Such alterations may take place in an affected lymph node as well. In this case a “glandular cavity” is diagnosed on CT.

Progressive disease is observed more often in adolescence, compared to early preschool and preschool age, along with clinically favorable forms of tuberculosis that also develop in this age. In the presence of underlying primary tuberculosis that started to develop in the past but stopped in early phase, adolescents develop pulmonary alterations that are indicative of secondary forms of tuberculosis. Almost all intrathoracic lymph node groups (6 and more groups) can be involved in the process. Along with this involvement of lymph nodes, miliary, acinar and exudative lobular foci are found, as a byproduct of either hematogenous and lymphogenous generalization, or bronchogenous spread of infection, associated with marked exudative response, necrosis, molten foci and development of cavities, all of which are signs of a progressive disease.

Conclusion. To summarize the analysis, it must be stated once more, that in adolescents and infants, a complicated clinical progression of the primary tuberculosis complex occurred more often, manifesting as a disease with bronchopulmonary involvement, accompanied by a generalization of the process onto other organs and systems. In preschool and junior school age, an unfavorable clinical progression of tuberculosis is a rare exclusion and occurs predominantly in the form of a lymphogenous seeding.