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Application of Modern Immunological Tests and X-Ray Methods in the Diagnosis of Tuberculosis of the Intrathoracic Lymph Nodes in Children

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Abstract

This study helped to ascertain the superiority of Diaskintest® (DST) with respect to the wealth of information it provides when compared with the Mantoux test with PPD 2 TU (M2) in determining the activity of tuberculosis infection in children. The evaluation parameters of diagnostic value with DST (DE=77.5%, NPV=72.4%, PPV=91.1%) were significantly higher than with M2x test 2TU (DE=57.2%, NPV=47.6%, PPV=53.2%). On positive testing with Diaskintest®, Tuberculosis of Intrathoracic Lymph Nodes (TITLN) showed nodes larger than 0.5 cm, which was determined in 80.4% and could be estimated as minor manifestations of intrathoracic lymphadenopathy against the background of the high activity of tuberculosis infection. Diaskintest® and X-ray methods are mandatory in the diagnosis of tuberculosis in children. This is absolutely necessary to adequately assess the child's condition and provide timely administration of disease specific therapy. IJBM 2012; 2(3):204-210.
Key words: *tuberculosis, children, Diaskintest®, QuantiFERON-TB test, computed tomography, diagnostic.*

Introduction

Intrathoracic lymph nodes lesions indicate the main clinical form of tuberculosis (TB) in children, commonly found in 74% of all cases [1, 2].

The diagnosis of tuberculosis of the intrathoracic lymph nodes (TITLN) is a little more difficult. Diagnosis of this form of TB in children includes the clinical symptoms, tuberculin diagnosis (M2, graded tuberculin skin test (TSE)) and standard X-ray examination with plain roentgenograms and linear tomograms. However, the frequent absence of the intoxication symptoms of tuberculosis in children along with the increasing comorbidity in modern scenarios significantly impedes the assessment of the intoxication symptoms and nature of sensitivity to tuberculin, which has a normoergic response in 60% of the patients showing the presence of a specific process [3-5]. The assessment of the intrathoracic lymph nodes (LNs) based on X-ray examination by «circumstantial evidence» leads to hypodiagnosis in 10% of the cases and hyperdiagnosis of the specific process in 40% [6]. Currently, computed tomography (CT) is found to detect a specific process on the reverse phase of development in more than half of the cases of children with suspected TINLN [7,8]. This indicates late detection of the disease; therefore, there is an urgent need for the introduction of new immunological tests for early detection and determination of the activity of

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the tuberculosis infection. To create new approaches for the diagnosis of tuberculosis of the intrathoracic lymph nodes in children and for the prompt use of adequate therapy, the results of employing new immunological tests (Diaskintest®) necessitate a comparison with the disorders identified on the CT scan.

The aim of this study is to determine the effectiveness of the modern immunological tests in the diagnosis of TITLN in children.

Material and Methods

Between 2001 and 2012, a prospective study of the information by employing Diaskintest® in a complex diagnosis of tuberculosis in children was conducted in the Department of Pediatric Phthisiology. A total of 120 children were examined, of whom 50 (41.7%) were between 3 to 6 years of age (m=4.5±0.2), and 70 (58.3%) were between 7 and 14 years of age (m=12.3±0.3).

To achieve correct diagnosis of the disease, a standard set of phthisiatric surveys supplemented by a complex battery of serological tests was conducted in the hospital. These tests include the indirect hemagglutination reaction (IHAR), passive hemolysis reaction (PHR), complement fixation test (CFT) and enzyme immunoassay (EIA) [9, 10]. Apart from these X-ray method diagnosis ((multislice spiral computed tomography (MSCT) and MSCT angiography (MSCT-AG)) and X-ray examination were done using a spiral CT scanner with a multirow detector (multislice) «Aquilion-32» (Toshiba Medical Systems Corporation, Japan), with intravenous bolus contrast administration using an automatic injector «CT 9000 ADV» (Liebel-Flarshein (Mallincrodt Inc.).

An analysis of the results of the tuberculin skin test M2 (administration of the purified tuberculin in standard dilution (ready form)) and DST (tests with recombinant TB allergens in standard dilution) was conducted [11, 12].

Before performing these tests, a venous blood sample was drawn for QuantiFERON-TB test (QFT), which is the reference method and allows a qualitative assessment of the information content. The QuantiFERON®-TB Gold In-Tube is a diagnostic tool designed for the diagnosis of tuberculosis in vitro. This method is based on using a peptide cocktail simulating ESAT-6, CFP-10 and TB7.7 (p4) proteins to stimulate the cells in heparinized whole blood. Test-system «Tubinferon» is a set of reagents used for the immunological detection of interferon-γ (IFN-γ) by Enzyme-Linked Immunosorbent Assay (ELISA). Determination of the quantification of IFN-γ by ELISA was performed to identify in vitro the cellular response to the stimulation of these peptide antigens associated with Mycobacterium tuberculosis infection.

Totally 80 (66.7%) children were identified and sent for examination based on the increasing sensitivity to tuberculin; 35 (29.2%) based on contact with TB patients; and 5 (4.1%) based on clinical complaints. More than half the children examined were found to be infected with MBT for two to five years, 21.7% were found to be infected for more than 5 years, and 13.3% patients were detected to be in the early period of MBT infection (Table 1). According to patient history, all the children had been vaccinated with BCG in the maternity hospital, 65 of them effectively (54.2%), as evident from the presence of a vaccination scar (more than 4mm). Manifestations of intoxication syndrome were absent in 17.5%, were moderate in 39.2%, and more pronounced in 43.3%.

Table 1
Characteristic of the general observation group

Detection methods			BCG vaccination		Time of infection		
Mantoux probe (M2)	**Contact with TB patients**	**By complaints**	**efficiently**	**inefficiently**	**early stage**	**2-5 years**	**more than 5 years**
66.7 (80)	29.2 (35)	4.1 (5)	54.2 (65)	45.8 (55)	13.3 (16)	65.0 (78)	21.7 (26)
120			120		120		

An analysis of the standard X-ray complex on plain roentgenograms showed a disturbance in the roots of the lungs in 58 (48.3) patients. The reaction caused by the intrathoracic LNs by «circumstantial evidence» was bronchopulmonary in nature in 57.5% of the cases, paraaortic in 32.5%, paratracheal in 10.0%, and the bifurcation group in 5.0%. Lime deposition in the projections of the intrathoracic LNs was suspected in 17.5% of the children, while focal changes were noted in the lung tissue in 18.3% of the cases. The results from X-ray, clinical, and laboratory investigations (indicating moderate and marked signs of active tuberculosis infection) and a suspicion due to the enlargement of ITLN served as the basis for the diagnosis of MSCT, and MSCT-AG (suspected enlargement of the nodes of the bronchopulmonary group).

Assessment of intrathoracic LNs in children using X-ray methods was performed in line with the recommendations, according to which the transverse dimension of the lymph nodes in children (from 3 to 14 years) should not exceed 10 cm depending on the group and the age of the child; however, that did not exclude the presence of pathological changes, including specific changes, in the smaller nodes [13]. According to Ya.V. Lazoreva [14], F. E. Gegeeva [15], and Ya. A. Dauletova [16], all LNs between 5 and 10 mm should be treated as «small» manifestations

of intrathoracic adenopathy, although, the standard CT imaging studies can be the limit for visualization of the LNs according to criteria of «imaging». In complex X-ray studies, single LNs (from 0.2 to 0.4 cm in transverse dimension, of conventional structure and density) were visualized in 16.7% of the cases, while single and multiple LNs (from 0.5 to 1.2 cm, of conventional structure and density) were visualized in 50.0% of the cases. Lime deposition in the intrathoracic LNs was detected in 39 (32.5%) patients, which is twice as high as the standard study. Subpleural located foci (up to 0.3 cm in diameter) in the lung tissue were identified in 27.5% of the cases.

All the data was processed employing the variation statistics methods using the software Microsoft Office Word Excel 2007, Statistica 8. The difference was considered reliable when $p<0.05$. The Mann-Whitney (U Test) was used to compare the differences between two independent groups (for nonparametric data). The mean (M) and standard error of the mean (m) were deduced. Pearson's Correlation Coefficient (r) was used to determine the strength of the relationship between two continuous variables. P value less than 0.05 was considered significant. Spearman's rank correlation coefficient was also used. The diagnostic accuracy of the tests employed was analyzed as well as the method used to calculate the operating characteristics: diagnostic sensitivity (DSS), the diagnostic specificity (DSC), positive predictive value (PPV) and negative predictive value (NPV), and diagnostic efficiency (DE).

Results and discussion

Clinical manifestations of the intoxication syndrome were mild in 39.2% of cases, pronounced in 43.3%, and not significant in 17.5%. At the same time, the normergic sensitivity to tuberculin in M2 was detected in 62.5% of the cases, a low level of specific sensitization was marked in 17.5% of the cases, and hyperergic sensitivity was evident in 20% (Table 2).

Table 2
The results of immunological reactions in the general observation group

Mantoux (M2)			**DST**			**QFT**		
low	medium	high	negative	doubtful	positive	negative	doubtful	positive
17.5 (21)	62.5 (75)	20.0 (24)	48.3 (58)	5.0 (6)	46.7 (56)	57.5 (69)	0.8 (1)	41.7 (50)

DST was negative in 48.3%, doubtful in 5% (m=3.2±0.1 mm), and positive 46.7% (m=18.0±0.3 mm). QFT showed a negative result in 57.5%, a positive response in 41.7%, and a doubtful one in 0.8%, which confirms the positive results of DST in 87.5% and allows us to define a differentiated approach to the administration of QFT.

The titer of specific antibodies in all the serological reactions was lower than the diagnostic reference level in 56.7%; however a positive titer noted in reactions one and two was seen in 30.8% of cases, which was possible because of the presence of infection with MBT. The positive titer noted in reactions three and four was seen in 12.5% of the cases, which indicated the activity of tuberculosis infection.

An analysis of the clinical manifestations, the results of the immunological tests and X-ray methods (MSCT and MSCT-AG), and changes in the intrathoracic LNs were done in the children examined. The direct dependence of the severity of the intoxication syndrome in both negative and positive DST/QFT was detected. Therefore, significantly, often negative DST (66.7%) and QFT (80.9%) were marked by the absence of clinical manifestations; however, the presence of positive DST (67.3%) and QFT (59.6%) was associated with significantly pronounced intoxication symptoms. At the same time, manifestations of the intoxication syndrome did not significantly differ in children possessing a different type of sensitivity to tuberculin (Table 3).

Results of the QFT study confirmed the dependence obtained during DST. Clinical symptoms were often absent with negative QFT (80.9%, $p<0.001$, $\chi^2=10.8$), whereas pronounced intoxication syndrome was marked on positive testing (59.6%, $p<0.01$, $\chi^2=9.86$), which confirmed the presence of the activity of tuberculosis infection.

Significantly, often negative and positive DST results were detected in 75 (62.5%) children with moderate sensitivity in M2, which indicated the presence of the activity of tuberculosis infection in half the cases. Here, LNs (larger than 0.5 cm) were visualized in 52.0% of the cases. Patients with low sensitivity to tuberculin in M2 frequently showed significantly negative results of DST (66.7%, $p<0.01$, $\chi^2=9.6$) with the absence of intrathoracic LNs in 71.4% ($p<0.001$, $\chi^2=10.5$) of cases (Table 4).

The positive results of DST in children (42.7%) with moderate sensitivity confirmed the presence of frequent changes in the intrathoracic LNs determined by MSCT, which already exist, but were not detected by M2, as the sensitivity remained normergic.

A comparison of the results of the X-ray examinations (MSCT and MSCT-AG) revealed the frequent absence of changes in the intrathoracic LNs at low sensitivity (71.4%, $p<0.001$, $\chi^2=13.2$), the presence of the LNs (larger than 0.5 cm) at moderate sensitivity (in 52.0%, $p<0.001$, $\chi^2=11.5$), and changes in the intrathoracic LNs (often significantly, in 75.0%, $p<0.001$, $\chi^2=12.2$) at high sensitivity, in 85.5% with lime deposition.

Analysis of the results of QFT in patients with different parameters of DST (Fig. 1) showed the predominance of negative results (98.3%, $p<0.001$, $\chi^2=88.5$) in QFT at a negative DST and positive results (87.5%) in QFT at a positive DST.

Table 3

The results of immunological reactions in children with various forms of intoxication syndrome (n=120)

Manifestations of the intoxication syndrome	Methods								
	Mantoux (M2)			DST			QFT		
	low	moderate	high	negative	doubtful	positive	negative	doubtful	positive
absent (n=21)	4 (19.1)	13 (61.8)	4 (19.1)	14* (66.7)	1 (4.8)	6 (28.6)	17* (80.9)	0	4 (19.1)
moderate (n=47)	9 (19.1)	32 (68.1)	6 (12.8)	29 (61.7)	3 (6.4)	15 (31.9)	32 (68.1)	0	15 (31.9)
manifest (n=52)	8 (15.4)	30 (57.7)	14 (26.9)	15 (28.9)	2 (3.8)	35** (67.3)	20 (38.5)	1 (1.9)	31** (59.6)
Total	21 (17.5)	75 (62.5)	24 (20.0)	58 (48.3)	6 (5.0)	56 (46.7)	69 (57.5)	1 (0.8)	50 (41.7)

Note: ** - significant differences between the groups with low and moderate sensitivity to tuberculin;*
*** - significant differences between the groups with low and high sensitivity to tuberculin*

Table 4

The results of immunological tests and changes in the intrathoracic LNs during X-ray examination (MSCT-AG and MSCT) in children with different sensitivity to tuberculin (n=120)

Mantoux probe (M2)	Methods						
	DST			Radiation complex			
	negative	doubtful	positive	no change	0.2-0.5	> 0.5	calcifications
Low (n=21)	14* (66.7) p<0.01	2 (9.5)	5 (23.8)	15* (71.4) p<0.001	3 (14.3)	3 (14.3)	0
					6		
Moderate (n=75)	39** (52.0) p<0.01	4 (5.3)	32** (42.7) p<0.01	21 (28.0)	15 (20.0)	39* (52.0) p<0.001	22 (40.7)
					54		
High (n=24)	5 (20.8)	0	19*** (79.2) p<0.01	4 (16.7)	2 (8.3)	18*** (75.0) p<0.001	17** (85.0) p<0.01
					20		
Total	58 (48.3)	6 (5.0)	56 (46.7)	40 (33.3)	20 (16.7)	60 (50.0)	39 (32.5)
					80		

Note: ** significant differences between the groups with low and moderate sensitivity to tuberculin*
*** significant differences between the groups with moderate and high sensitivity to tuberculin*
**** significant differences between the groups with low and high sensitivity to tuberculin*

Thus, QFTs confirm the results of DST in 85% of the cases, which makes it possible to limit applying the QFT and recommend it only in the case of contraindications to the use of DST.

Changes of the intrathoracic LNs during X-ray examination (MSCT and MSCT-AG) were not marked in 43.1% ($p<0.01$, $\chi^2=8.53$) patients with no activity of tuberculosis infection according to the results of DST (negative), and LNs (smaller than 0.5 cm) were visualized in 31.1% cases, which is the norm. LNs larger than 0.5 cm were found significantly frequently (80.4%, $p<0.001$, $\chi^2=33.93$) with positive DST, with lime deposition 73.9% ($p<0.001$) of cases (Table 5).

The results obtained imply that LNs larger than 0.5 cm, against the background of a positive DST result (QFT) are typical of a specific process. During a standard phthisiatric complex examination with MSCT and MSCT-AG, the data for specific changes was not received in 51 (42.5%) children (1st group - Infected by MBT), and the local forms of tuberculosis were diagnosed in 69 (57.5%) children (2nd group). The comparison of these groups allowed the calculation of indices of diagnostic accuracy of the tests employed. According to M2, in the comparison groups significant differences of sensitivity in patients and healthy children were not marked. Normergic sensitivity equally frequently was marked in the 2nd (73.8%) and 1st (88.2%) groups (Fig. 2).

The calculated data of the diagnostic value of M2 (DSS-84.1%, DSC-19.6%, PPV-53.2%, NPV-47.6%, DE-57.2%) gives evidence of its low degree of information and

Figure 1
QFT results in children with different rates of Diaskin test.

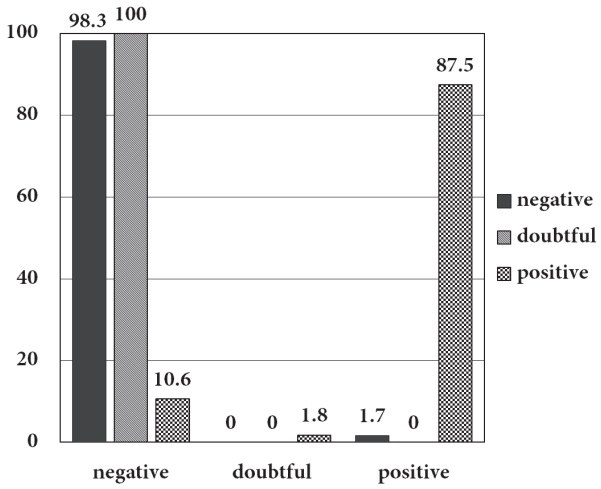


Figure 2
Indicators of tuberculin sensitivity in Mantoux test (M2).

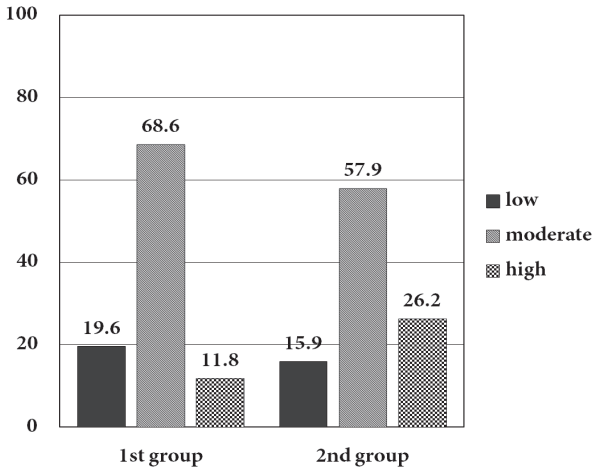


Table 5
QFT results and changes in X-ray examination of children with different indices of DST (n=120)

DST	Methods				
	MSCT and MSCT-AG				
	no change	0.2-0.5	>0.5 cm	calcifications	foci
negative (n=58)	25* (43.1) p<0.01	18 (31.1)	15 (25.9)	5 (15.2)	15 (25.9)
		33			
doubtful (n=6)	5 (83.3)	1 (2.7)	0	0	2 (33.3)
		1			
positive (n=56)	10 (17.8)	1 (1.8)	45* (80.4) p<0.001	34* (73.9) p<0.001	16 (28.6)
		46			
Total	40 (33.3)	20 (16.7)	60 (50.0)	39 (32.5)	33 (27.5)

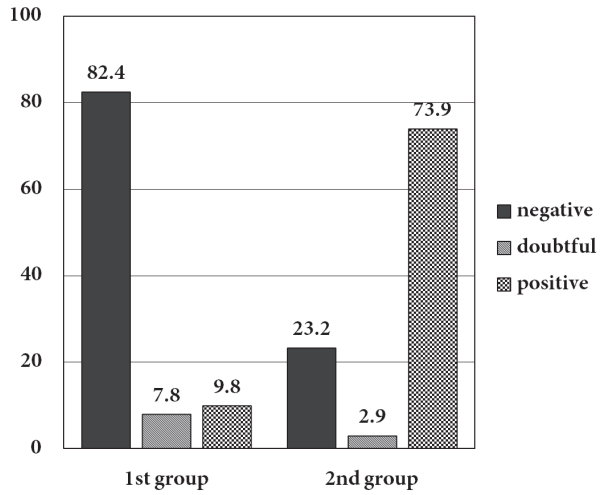
Note: ** - significant difference between the negative and positive results of DST*

the pressing need for the introduction of new methods to determine tuberculosis activity.

Positive DST was marked in 73.9% (m=17.2±0.2 mm) in the 2nd group, which was significantly higher compared with the 1st group (9.8% , χ^2=34.8, p<0.001). At the same time, negative DST was detected significantly more frequently among healthy children in the 1st group (82.4% vs. 23.2%, χ^2=46.7, p<0.001) (Fig. 3).

As QFT is the reference method for DST, it confirms the results in 95% of the cases. Positive results were obtained

Figure 3
DST results in the comparison groups.



in 69.6% of the cases in the 2nd group, and in only 3.9% in the 1st group. The test was negative in 94.1% of the cases among healthy children (1st group), which is significantly higher than in 2nd group (30.4%, χ^2=10.6, p<0.01).

According to MSCT and MSCT-AG single and multiple LNs of different sizes (from 0.3 to 1.5 cm) with altered structure and density (from +25 to +73 HU) were visualized in patients of the 2nd group. Lime deposition in the intrathoracic LNs was determined in 56.5% children, whereas multiple calcifications were found in 11 children. The lesion LNs of one group was diagnosed in 33.3% cases; specific changes in two or more groups were marked in.68.1%.

The negative results of the DST and the QFT were observed in the phases of reverse development of the specific processes, which indicated the absence of activity of tuberculosis infection and required observation of the child in a certain type of dispensary. As the results of QFT are almost equal to the results of DST, this test can be recommended only for a narrow group of children, who have contraindications to undergoing DST.

The data of the diagnostic value of DST (DSS-77.3%, DSC-89.4%, PPV-91.1%, NPV-72.4%, DE-77.5%) and the QFT (DSS-69.6%, DSC-96.0%, PPV-96.0%, NPV-69.6%, DE-80.0%) do not exhibit significant differences among themselves. However, the degree of information provided by DST is twice as high as the data from M2, which are confirmed during QFT.

Thus, M2 does not provide sufficient information to determine the activity of tuberculosis infection in children infected with MBT, which leads to a late diagnosis of the disease and identification of the specific process involved in the phase of reverse development. The data of the diagnostic value of DST (DSS-77.3%, DSC-89.4%, PPV-91.1%, NPV-72.4%, DE-77.5%) is two-fold higher than the data of the diagnostic value of M2 (DSS-84.1%, DSC-19.6%, PPV-53.2%, NPV-47.6%, DE-57.2%). The high degree of informational content of DST to determine the true activity of the tuberculosis infection is confirmed during the reference QFT, which in 95% of cases confirms the results of DST. Children with a positive DST have pronounced symptoms of intoxication in 67.3% of the cases, and LNs (larger than 0.5 cm on MSCT and MSCT-AG) are visualized in 80.4%, and in 73.9% of the cases in the reverse phases of development. Thus, the data obtained requires mandatory testing using DST in the complex of the phthisiatric survey to determine the activity of tuberculosis infection, and conducting MSCT and MSCT-AG to verify the specific changes in the intrathoracic LNs and lung tissue to administer adequate and timely treatment.

Conclusion

Thus, this study demonstrates highly informative data with DST vs M2 in determining the activity of tuberculosis infection in children. The data of the diagnostic values of DST (DSS-77.3%, DSC-89.4%, PPV-91.1%, NPV-72.4%, DE-77.5%) are significantly higher than the data of the diagnostic value of M2 (DSS-84.1%, DSC-19.6%, PPV- 53.2%, NPV-47.6%, DE-57.2%). With a positive DST the intrathoracic LNs (larger than 0.5 cm) are determined in 80.4%, which against background of high activity of tuberculosis infection may be regarded as evidence of small manifestations of intrathoracic adenopathy. Currently, DST and X-ray examinations (MSCT and MSCT-AG) must be conducted to diagnose tuberculosis, and adequately assess children infected with MBT, and provide timely and specific therapy.

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