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Z.I. Piskur[1], L.I. Pylypiv[1], O.M. Shvets[2], O.P. Kostyk[1], M.I. Sakhelashvili[1]

The profile of drug resistance of *Mycobacterium tuberculosis* and clinical features of extrapulmonary resistant tuberculosis among children living in Lviv region, Ukraine

[1]Danylo Halytsky Lviv National Medical University, Ukraine
[2]Kharkiv National Medical University, Ukraine

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Pediatric tuberculosis (TB) is a serious infectious disease that affects many children worldwide and is more likely to be extrapulmonary than adult TB.

The purpose — to analyze the profile of drug resistance of *Mycobacterium tuberculosis* and clinical features of extrapulmonary resistant (EPR) TB among children from Lviv region, Ukraine.

Materials and methods. We analyzed all cases of EPR TB (n=23) and extrapulmonary sensitive (EPS) TB (n=24) among 478 medical charts of children, who were hospitalized in the Lviv Anti-TB hospital during 2013–2020.

Results. It was found out that EPR TB was diagnosed significantly more often at the age of 1 year and up to 3 years old than EPS TB and significantly less often — among children aged 4–7 years. The children with EPR TB were significantly more likely to live in rural areas and they were significantly more likely to be from families with less than 2 children, compared to EPS TB. The children with EPR TB were more often diagnosed with meningeal and central nervous system (CNS) TB, less often — with TB of the bones and joints, only they had TB of the intestine, compared to EPS TB. Miliary pulmonary TB and the predominance of bilateral process were more common at EPR TB. Among children with EPR TB, rifampicin-resistant TB was significantly more common found than the risk of multidrug-resistant TB (MDR-TB) and monoresistant TB. The resistance profile of MDR-TB showed that 17.4% are resistant to the combination of HR (H-isoniazid, R-rifampicin), 8.6% — to HRES (E-ethambutol, S-streptomycin), 4.3% — to HRS. Among 43.5% of children with EPR TB the contact with a TB patient was not established. At the same time, only a third of children who had came into contact with bacterial excretors were under dispensary observation and only about 9% received chemoprophylaxis.

Conclusions. In order to prevent the development of EPR TB, it is necessary to improve TB prevention measures among the most vulnerable segments of the population.

The research was carried out in accordance with the principles of the Helsinki Declaration. The study protocol was approved by the Local Ethics Committee of all participating institutions. The informed consent of the patient was obtained for conducting the studies.

No conflict of interests was declared by the authors.

Keywords: extrapulmonary tuberculosis, resistant/sensitive tuberculosis, pulmonary tuberculosis, children, contact.

Профіль медикаментозної резистентності *Mycobacterium tuberculosis* і клінічні особливості позалегеневого резистентного туберкульозу в дітей Львівської області, Україна

З.І. Піскур[1], Л.І. Пилипів[1], О.М. Швець[2], О.П. Костик[1], М.І. Сахелашвілі[1]
[1]Львівський національний медичний університет імені Данила Галицького, Україна
[2]Харківський національний медичний університет, Україна

Туберкульоз (ТБ) є серйозним інфекційним захворюванням у дітей у всьому світі і частіше, ніж у дорослих, має здатність до позалегеневої локалізації.

Мета — проаналізувати профіль медикаментозної резистентності *Mycobacterium tuberculosis* і клінічні особливості позалегеневого резистентного (ПР) ТБ в дітей Львівської області (Україна).

Матеріали та методи. Серед 478 історій хвороб дітей, госпіталізованих до Львівського протитуберкульозного стаціонару впродовж 2013–2020 рр., проаналізовано всі випадки ПР ТБ (n=23) та позалегеневого чутливого (ПЧ) ТБ (n=24).

Результати. Встановлено, що ПР ТБ достовірно частіше діагностували в дітей першого року життя і від 3 років, ніж ПЧ ТБ, однак значно рідше — у дітей віком 4–7 років. Діти з ПР ТБ порівняно з ПЧ ТБ значно частіше проживали в сільській місцевості та були з малодітних сімей. У дітей з ПР ТБ частіше діагностували ТБ мозкових оболонок і центральної нервової системи, рідше — ТБ кісток і суглобів, і лише в цій групі констатували ТБ кишечника. При ПР ТБ частіше спостерігали міліарний ТБ легень, переважало двобічне ураження. Серед дітей з ПР ТБ резистентність до рифампіцину констатували значно частіше за ризик мультирезистентного ТБ (МР-ТБ) і монорезистентний ТБ. Профіль резистентності МР-ТБ показав, що у 17,4% констатували резистентність до комбінації HR (H — ізоніазид, R — рифампіцин), у 8,6% — до HRES (E — етамбутол, S — стрептоміцин), у 4,3% — до HRS. У 43,5% дітей з ПР ТБ контакт з хворим на ТБ не був встановленим. При цьому лише третина дітей, які контактували з бактеріовиділювачами, перебувала на диспансерному спостереженні, і лише близько 9% отримували хіміопрофілактику.

Висновки. Для запобігання розвитку ПР ТБ слід удосконалювати профілактичні протитуберкульозні заходи серед найбільш вразливих верств населення.

Дослідження виконано відповідно до принципів Гельсінської декларації. Протокол дослідження ухвалено Локальним етичним комітетом зазначених у роботі установ. На проведення досліджень отримано інформовану згоду батьків дітей.

Автори заявляють про відсутність конфлікту інтересів.

Ключові слова: позалегеневий туберкульоз, резистентний туберкульоз, чутливий туберкульоз, туберкульоз легень, діти, контакт.

Tuberculosis (TB) remains a well-known and one of the five most common causes of death worldwide. The problem of TB has not lost its relevance in the XXI century. About 10 million new cases of TB are diagnosed worldwide each year and about 12% of them are children [17].

Diagnosing of TB among children is more difficult than among adults [14]. Leading experts in the field point to the frequently low or asymptomatic course of the disease in children, with the symptoms of TB being disguised with clinical manifestations of concomitant pathology, and is resulting in the late diagnosis of the disease [5,13].

Decreased adaptive capacity of the child's body and an increase in the number of patients with resistant forms of TB [4,12], which are a source of infection with *Mycobacterium tuberculosis* (MTB), led to a new problem — MTB chemoresistance [15,18]. According to the World Health Organization (WHO), in 2014 Ukraine was included into the top five countries in the world with the burden of multidrug-resistant TB (MDR-TB). Experts estimate that the increase in chemodrug-resistant TB (CDR-TB) will be 300,000 new cases annually [16]. The simulation of the consequences of the COVID-19 pandemic for Ukraine [2] has shown that the largest increase in TB mortality is expected in 2021, and the largest increase in morbidity, including resistant forms — in 2022 [10].

Pediatric TB is more likely to be extrapulmonary than in adults [3]. Due to the tense epidemiological situation with regard to TB, there is an increase in the number of children with extrapulmonary TB with severe clinical course and with the presence of resistant strains of MTB [1], which is difficult to treat and has unpredictable consequences.

Thus, the growing prevalence of TB in Ukraine, often asymptomatic disease in children [9] and insufficient information provided in scientific sources, indicate the relevance of this study. In today's conditions, the analysis of profile of drug resistance of MTB and clinical features of extrapulmonary resistant TB among children is relevant and promising in order to optimize the tactics to prevent the spread of a specific process due to timely diagnosis and prescription of specific treatment and chemoprophylaxis.

The purpose of the work — to analyze the profile of drug resistance of MTB and clinical features of extrapulmonary resistant TB among children and to identify possible causes of its development.

Materials and methods of the study

This is a retrospective research in which we analyzed medical files to examine TB-related characteristics among the total number of hospitalized children. All medical files of children, aged zero to fifteen years who were hospitalized with any local form of TB from January 2013 to January 2020, which were available during the data collection period, have been included. No medical records were excluded from the database.

From 478 medical charts of children we selected medical files of 47 patients with extrapulmonary TB who were hospitalized in the pediatric department of the Lviv Anti-TB Hospital. The studied patients with extrapulmonary TB were divided into two groups: with extrapulmonary resistant TB (EPR TB) (n=23; the Group 1) and extrapulmonary sensitive TB (EPS TB) (n=24; the Group 2). To compare some clinical and laboratory parameters the control group consisted of 49 children with pulmonary forms of TB who secreted the MTB sensitive to anti-TB drugs (ATD).

The patients underwent microscopic (according to Ziel-Nielsen), molecular genetics (GeneXpert MTB/RIF), culture studies on solid (Levenstein—Jensen), liquid (BACTEC MGIT 960) nutrient media and line-probe assay (Hain Lifesciences, including sensitivity of the MTB to ATD I line (isoniazid — H and rifampicin — R) using kits for hybridization GenoType MTBDRplus) sputum, biopsy, resection materials, cerebrospinal fluid and other fluids in accordance with current standards. Upon receipt of a positive result of molecular genetics or cultural studies, a test of drug sensitivity to ATD was performed. In addition, we used radiography of thoracic cavity, computed tomography of the chest and other areas, radiography of bones and joints, the intestines, ultrasound examination of internal organs, magnetic resonance imaging of central nervous system (CNS), musculoskeletal system, spinal tap, morphological examination of biopsy, resection materials and other examinations according to the lesion organ.

It has been analyzed age and gender characteristics of the researched groups, place of residence, frequency of detection of clinical forms of TB, profile of resistance of the MTB to ATD, the presence of contact with a patient with TB and conducting preventive measures.

The research was carried out in accordance with the principles of the Declaration of Helsinki. The research protocol was approved by the Institution's Local Ethics Committee.

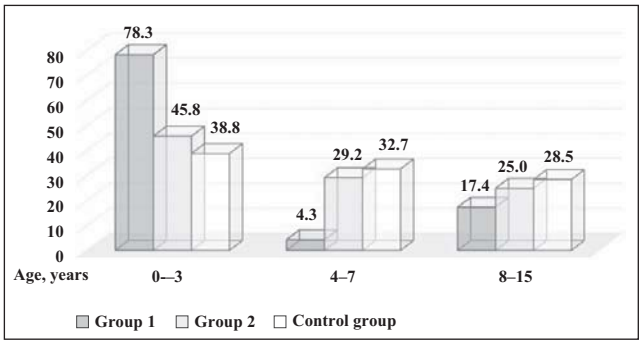

Fig. 1. Distribution of children among the researched groups by age (%)

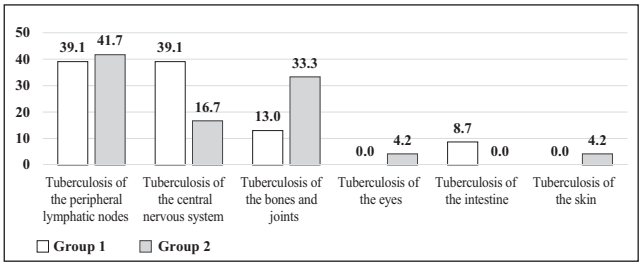

Fig. 2. The structure of the clinical forms of extrapulmonary tuberculosis among children of the Group 1 and the Group 2 (%)

The obtained digital results were processed by the methods of variation statistics using Student's t-test, the results were considered significant at $p<0.05$. The results are given in the form of mean values and standard error of mean values (M±m). Statistical processing of materials was performed using the computer program Statistica 10.0.

Results and discussion of the study

It was estimated that among all local forms (478) of TB the extrapulmonary forms accounted for 47 (9.8%) patients during the period from 2013 to 2020. EPR TB was diagnosed among 23 (48.9%) children and EPS TB — among 24 (51.1%) children out of 47 cases of extrapulmonary lesions.

Children under 3 years of age predominated among patients of the Group 1 and the Group 2 (78.3±8.6% and 45.8±10.2%; among the control group — 38.8±6.9%), (Fig. 1). At the same time, children of this age group occurred significantly more often among the Group 1 compared to the Group 2 ($p<0.05$) and control ones ($p<0.01$). It should be noted that more than the half of the Group 1 were children under one year of age, compared with the Group 2 and control (56.5±10.3% vs. 20.8±8.3% and 10.2±4.3%; $p_{1-2}<0.05$; $p_{1-3}<0.01$) groups. Children aged 4–7 years old were significantly less likely to be detected among the Group 1 than among the Group 2 (4.3±4.2% vs. 29.2±9.3%; $p<0.05$) as well as among the control (4.3±4.2% vs. 32.7±6.7%; $p<0.01$). As can be seen in the Figure 1, children aged 8–15 years old were slightly less likely to be found among the patients of the Group 1 than among the Group 2 (17.4±7.9% vs. 25.0±8.8%; $p>0.05$).

The researched groups did not differ significantly by gender ($p>0.05$): the number of boys and girls among the researched groups (47.8±10.4% and 52.2±10.4% among the Group 1, 45.8±10.2% and 54.8±10.2% among the Group 2, 55.1±7.1% and 44.9±7.1% among the control one) was almost the same.

It was found out that children of the Group 1 have lived significantly more often in rural areas (69.6±9.6% vs. 30.4±9.6%; $p<0.05$), while children of the Group 2 — slightly more often in the city (54.2±10.2% vs. 45.8±10.2%; $p>0.05$). Among the control group, the frequency of living in rural and urban areas did not differ significantly (49.0±7.1% vs. 51.0±7.1%; $p>0.05$). The frequency of living in the village of children of the Group 1 was 1.3 times higher and in the city — 1.5 times lower than of the Group 2, but the difference between these indicators did not reach the level of essentiality ($p>0.05$).

We analyzed the marital status of patients among the researched groups and found out that EPR TB was significantly more common among children from families with less than 2 children than EPS TB (78.3±8.6% vs. 16.7±7.6%; $p<0.01$) and significantly less common among children from large families (21.7±8.6% vs. 83.3±7.6%; $p<0.01$).

The structure of the specific lesions in the children of the Group 1 and the Group 2 is shown in Figure 2. It was found that TB of the meninges and CNS was 2.3 times more common among children of the Group 1 than the Group 2 and specific process of bones and joints — 2.6 times more often among patients of the Group 2 than the Group 1 (both $p>0.05$). Importantly, only the Group 1 was diagnosed with intestinal TB in two (8.7±5.9%) cases and at the same time no case TB of eye and skin was detected, in contrast to the Group 2 (0 vs. 4.2±4.1% in both cases; all $p>0.05$).

In a comparative analysis of the structure of clinical forms of pulmonary TB (PTB) (Fig. 3), we found out that among the patients of the Group 1 and the Group 2 miliary PTB was dominated (60.9±10.2% and 42.1±11.3%, respectively), while among EPR TB it occurred in 1.5 times more often. At the same time, the control group was dominated with the detection of primary tuberculous complex (PTC), (61.2±7.0%).

It should be noted that among children of the Group 1 miliary PTB was observed probably more often than other clinical forms (60.9±10.2%

vs. 17.4±7.9% of detected TB of intrathoracic lymphatic nodes (ITLN); p<0.01 and 21.7±8.6% of detected PTC; p<0.05). At the same time, TB of ITLN among the Group 1 was detected 1.2 and 2.2 times less often than among the Group 2 and control one (17.4±7.9% vs. 21.0±9.3% and 38.8±7.0%; p_{1-3}<0.05). Patients of the Group 1 were also 1.7 and 2.8 times less likely to had PTC compared to the Group 2 and control (21.7±8.6% vs. 36.8±11.1% and 61.2±7.0%; p_{1-3}<0.05).

It is important to note that among EPR TB bilateral lesions were found probably more often than unilateral (65.2±9.9% vs. 34.8±9.9%; p<0.05). At the same time, children of the Group 2 (57.9±11.3% vs. 42.1±11.3%; p>0.05) and control (98.0±2.0% vs. 2.0±2.0%; p<0.01) group were more likely to show unilateral lesions. Bilateral localization was statistically more frequent among the Group 1 and the Group 2, compared to the control (65.2±9.9% and 42.1±11.3% vs. 2.0±2.0%; $p_{1-3,2-3}$<0.01) and unilateral — among control compared to the Group 1 and the Group 2 (98.0±2.0% vs. 34.8±9.9% and 57.9±11.3%; all p<0.01).

It was found out that among all children of the Group 1 the tuberculous process was in stages of progression. The infiltration and seeding phases were significantly more often observed among the Group 1 and the Group 2 compared to the control (60.9±10.2% and 54.1±10.2% vs. 2.0±2.0%; all p<0.01). At the same time, the infiltration phase was probably more often detected among the control group (75.5±6.1% vs. 21.7±8.6% and 33.3±9.6%; all p<0.01). It should be noted that the decay phase was 4 times more often observed among children of the Group 1 compared with the Group 2 and control group (17.4±7.9% vs. 4.2±4.1% and 4.1±2.8%). Among 18.4±5.0% of control cases and among 8.4±5.6% of cases of the Group 2, the specific process was in the initial compaction phase.

When determining the type of resistance of the MTB to ATD (Fig. 4) it was found out that almost the half (43.5±10.3%) of children among the Group 1 was found with the resistance to rifampicin (RifTB), among 30.4±9.6% cases — the multiple drug resistance in the form of multidrug resistance TB (MDR-TB) and only two cases (8.6±5.8%) had monoresistant TB. It is important to note that in 17.4±7.9% of cases the risk of developing MDR-TB was diagnosed because these children were in the foci of MDR-TB infection.

In addition, RifTB among children was found significantly more often compared to the risk of MDR-TB (43.5±10.3% vs. 17.4±7.9%; p<0.05) and monoresistant TB (43.5±10.3% vs. 8.6±5.8%; p<0.01).

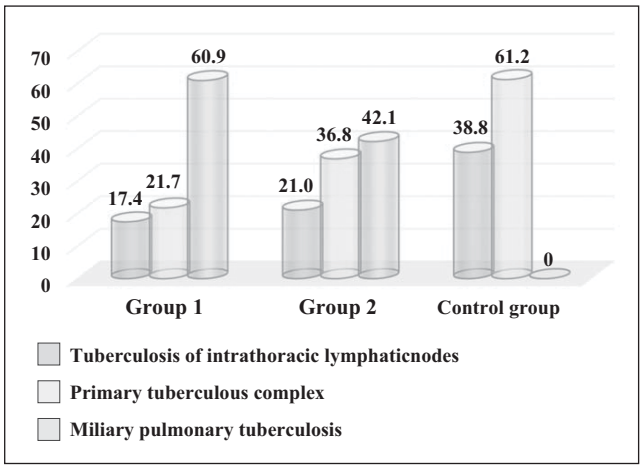

Fig. 3. The structure of the detected clinical forms of pulmonary tuberculosis among the researched groups (%)

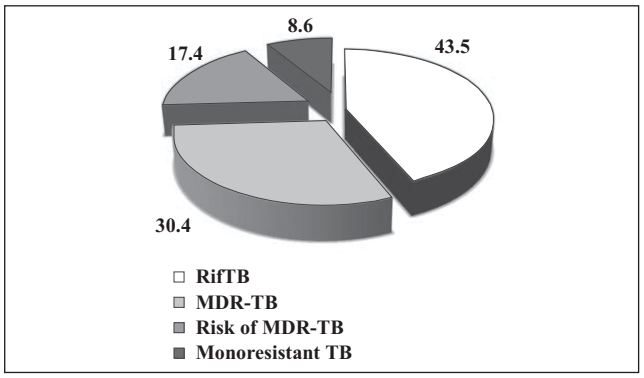

Fig. 4. Results of the detecting the drug resistance of MTB strains for anti-TB drugs among children of the main group (%)

The resistance profile of MDR-TB cases shown that in 17.4±7.9% are resistance to the combination of HR (H-isoniazid, R-rifampicin), in 4.3±4.2% — to the combination of HRS (S-streptomycin), in 8.6±5.8% — to HRES (E-ethambutol), (all p>0.05). Monoresistant TB was presented in one case (4.3±4.2%) with resistance to H and Z (Z-pyrazinamide).

It is proved that one of the most important factors of TB is epidemiological, in particular the contact with a patient with TB. It was found that children of the Group 1 were in contact with bacterial excretors 1.4 and 1.8 times more often than children of the Group 2 and control group (52.2±10.4% vs. 37.5±9.9% and 28.6±6.4%; all p>0.05), (Table). At the same time, the Group 1 and the Group 2 were probably less likely to have contacts with a person with non-bacterial discharging compared to the control group (4.3±4.2% and 16.7±7.6% vs. 51.0±7.1%; p<0.01). It is important that almost half of the children of the Group 1 and the Group 2, the contact with a patient with TB was not established (43.5±10.3% and 45.8±10.2%, respectively).

Table

Distribution of researched groups according to the presence of contact with a patient with tuberculosis

Researched groups / Presence of contact	Group 1 (n=23)		Group 2 (n=24)		Control group (n=49)		p
	n	M±m, %	n	M±m, %	n	M±m, %	
Contact with bacterial excretor	**12**	**52.2±10.4**	**9**	**37.5±9.9**	**14**	**28.6±6.4**	**all p>0.05**
Contact with a person with non-bacterial discharging	1	4.3±4.2	4	16.7±7.6	25	51.0±7.1	$p_{1-3}<0.01$ $p_{2-3}<0.01$
Contact with a patient with tuberculosis was not established	10	43.5±10.3	11	45.8±10.2	10	20.4±5.8	$p_{2-3}<0.05$

When analyzing the resistance profile of the foci TB, it was found out that among the 12 children of the Group 1, only six (50.0%) had a contact with bacterial excretors with resistant forms of TB. In addition, these children had the contact with family members; in one case double contact was established (simultaneous contact with two bacterial excretors with resistant forms of TB). Almost complete coincidence of the resistance profiles of these children with theirs sources of infection was revealed. Thus, four bacterial excretors were diagnosed with MDR-TB/extended TB resistance, and the contacted children were diagnosed with the risk of MDR-TB, two people with discharging bacteria — RifTB, and also these children were diagnosed with rifampicin-resistant TB.

However, antiepidemic preventive measures have not been fully implemented. It was found that children of the Group 1 and the Group 2 were at the dispensary observation probably less often than among the control (34.8±9.9% vs. 61.2±7.0%; p<0.05; 25.0±8.8% vs. 61.2±7.0%; p<0.01). At the same time, only two children from the Group 1 and the Group 2 and three children of control one received chemoprophylaxis.

Scientists from around the world point to the lack of attention to the study of childhood TB. In the analysis of scientometric databases, we found isolated literature sources, which present the data on the resistance of MTB strains in children [9]. The vast majority of studies focuses on adults [6,7,8], which is associated with difficulties in diagnosing a specific process in children, rare cases of bacterial excretion, and a variety of clinical manifestations of the disease.

In the 12-year retrospective study M.B. Stosic et al. [14] described the trend of TB associated with risk factors among children and adolescents in Serbia. The researchers report that among all 596 children and adolescents, 305 (51.2%) cases were bacteriologically confirmed, 60% of which (n=284) were diagnosed with PTB and 17.1% (n=21) with extrapulmonary TB. At the same time, MDR-TB was recorded in only 3 out of 225 cases (37.8%) covered by the test for sensitivity to ATD. In our study, the attention is focused on the most difficult to diagnosing extrapulmonary forms of TB with basic clinical and microbiological data.

According to O.I. Bielogortseva et al., the structure of clinical forms of TB among children in Ukraine has shifted towards severe and widespread, the percentage of bacterial excretors has increased from 11.7% to 27.8% (p<0.05) [1]. The authors also noted a gradual increase in the share of patients with chemoresistant TB, so in the general group of children (under 17 years) the cases of the risk of MDR-TB (46.4%) prevailed, in the second place — MDR-TB (30.4%). Our study showed that in 43.5±10.3% of children with extrapulmonary lesions RifTB was found, in the same amount (17.4±7.9%) — MDR-TB and risk of MDR-TB. We described the resistance profile of MTB strains to ATD, which was observed among the majority of children with the resistance to the combination of HR, which coincides with the data of other researchers [11].

M.I. Sakhelashvili et al. conducted a study of clinical and microbiological parameters in children and adolescents with pulmonary specific process, who were from MDR-TB focies [11]. The data of our work and M.I. Sakhelashvili et al. indicate the almost complete coincidence of the resistance profile of the identified children with the resistance profiles of the bacterial excretors, who the sick children were in contact with. It should be noted that in determining the resistance of the MTB to ATD were revealed the combinations that included streptomycin. This drug is no longer included in the TB treatment regimen, so it is possible to think of undetected adult patients with chronic long-term course of the process, as in 43.5±10.3% of children the source of TB infection was not identified and among 52.2±10.4% of children who came into contact with bacterial excretors, only half of the

bacterial excretors had resistant TB. In addition, only a third of children in contact with bacterial excretors were registered at the dispensary, and only in isolated cases received chemoprophylaxis. In order to prevent the development of an extrapulmonary resistant specific process, it is necessary to improve TB prevention measures among the most vulnerable segments of the population.

Conclusions

Extrapulmonary specific process with the resistance of the MTB was significantly more often diagnosed at the age under 3 years than extrapulmonary sensitive TB (78.3% vs. 45.8%; $p<0.05$). The same trend was observed among children under 1 year of age who constituted more than a half in the Group 1 (56.5% vs. 20.8%; $p<0.05$). At the same time, significantly less extrapulmonary resistant TB was observed among children aged 4–7 years old (4.3% vs. 29.2%; $p<0.05$).

It was found that children with extrapulmonary resistant TB were significantly more likely to live in rural areas than in urban areas (69.6% vs. 30.4%; $p<0.05$) and compared to extrapulmonary sensitive TB were more often from families with less than 2 children (78.3% vs. 16.7%; $p<0.01$).

Children with extrapulmonary resistant TB were 2.3 times more likely diagnosed with meningeal and CNS TB, than those with extrapulmonary sensitive TB, and 2.5 times less likely to have bone and joint TB. In addition, only in this group, intestinal TB was detected in two cases (8.7%) and at the same time no case of eye and skin TB was detected, in contrast to extrapulmonary sensitive TB (0 vs. 4.2% in both cases).

Miliary lung damage was found 1.5 times more often among children with extrapulmonary resistant TB than extrapulmonary sensitive TB (60.9% vs. 42.1%). Bilateral lesions also predominated among this group (65.2%), while among patients with extrapulmonary sensitive TB — unilateral (57.9%).

Among children of the Group 1 RifTB was found significantly more often than the risk of MDR-TB and monoresistant TB (43.5% vs. 17.4% and 8.6%; $p_{1-2}<0.05$; $p_{1-3}<0.01$). The resistance profile of MDR-TB showed that 17.4% were resistant to the combination of HR, 8.6% — to HRES, 4.3% — to HRS.

Almost the half of children with extrapulmonary resistant TB had no contact with a patient with TB (43.5%). At the same time, only the third of children who came into contact with bacterial excretor were under dispensary observation (34.8% vs. 61.2% in control; $p<0.05$) and only 8.6% of children received chemoprophylaxis.

The results prove the importance of work to further improvement of measures to detection, diagnosing, treatment and TB prevention not only among children, but also among adults. As an increase in the incidence of adults with chemoresistant TB, and therefore children, is predicted, because children are an indicator of the prevalence of TB in the population and their incidence depends on the incidence of adults.

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Відомості про авторів:
Піскур Зоряна Іванівна — к.мед.н., доц. каф. фтизіатрії і пульмонології Львівського НМУ імені Д. Галицького. Адреса: м. Львів, вул. Пекарська, 69; тел.: +38 (032) 275-76-32. https://orcid.org/0000-0001-9920-2291.
Пилипів Леся Ігорівна — к.мед.н., асистент каф. внутрішньої медицини № 2 Львівського НМУ імені Д. Галицького. Адреса: м. Львів, вул. Пекарська, 69; тел.: +38 (032) 275-76-32. https://orcid.org/0000-0003-1143-1626.
Швець Ольга Миколаївна — к.мед.н., асистент каф. фтизіатрії та пульмонології Харківського НМУ. Адреса: м. Харків, просп. Науки, 4; тел.: +38 (057) 707-73-80. https://orcid.org/0000-0002-8371-8258.
Костик Ольга Петрівна — д.мед.н., проф., зав. каф. фтизіатрії і пульмонології Львівського НМУ імені Д. Галицького. Адреса: м. Львів, вул. Пекарська, 69; тел.: +38 (032) 275-76-32. https://orcid.org/0000-0001-5606-7931.
Сахелашвілі Манана Іванівна — д.мед.н., проф. каф. фтизіатрії і пульмонології Львівського НМУ імені Д. Галицького. Адреса: м. Львів, вул. Пекарська, 69; тел.: +38 (032) 275-76-32. https://orcid.org/0000-0002-2503-5440.

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