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Clinical case of rifampicin-resistant tuberculous meningitis in a child: features of diagnosis, management and outcomes

Yu. V. Myronchuk[1,A–F], **O. O. Pushnova**[2,A,B,C,D], **L. V. Taran**[2,A,B,C], **L. I. Chernyshova**[2,A,C], **O. V. Dvizov**[2,B,C]

[1]Zaporizhzhia State Medical and Pharmaceutical University, Ukraine, [2]Public Non-Profit Enterprise "Zaporizhzhia Regional Clinical and Diagnostic Center of Phthysiatry and Pulmonology" of Zaporizhzhia Regional Council, Ukraine

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

Aim: to demonstrate, based on an original clinical observation, the features of diagnosis, clinical management, and outcomes of rifampicin-resistant tuberculous meningitis in a child.

Materials and methods. A clinical case of rifampicin-resistant tuberculous meningitis in a child treated in the Pediatric Unit at the clinical base of the Department of Phthisiology and Pulmonology of Zaporizhzhia State Medical and Pharmaceutical University, located at the Public Non-Profit Enterprise "Zaporizhzhia Regional Clinical and Diagnostic Center of Phthisiology and Pulmonology" of the Zaporizhzhia Regional Council.

Results. A child was admitted to the Pediatric Unit from the pediatric intensive care unit (ICU) with a diagnosis of acute tuberculous meningitis. The diagnosis was confirmed by cerebrospinal fluid analysis using the Xpert MTB/RIF Ultra assay, which detected *Mycobacterium tuberculosis* resistant to the first-line antituberculous medication rifampicin. At the time of transfer, chest radiography revealed no pulmonary abnormalities. Brain magnetic resonance imaging showed no focal pathology. During further evaluation, the child's mother was diagnosed with chemoresistant tuberculosis. The child received antituberculous and symptomatic therapy prescribed by a neurologist in the ICU for more than four months. During follow-up, chest computed tomography revealed disseminated pulmonary involvement. Following completion of treatment, the child was cured; however, epileptic syndrome developed, requiring lifelong therapy.

Conclusions. Delayed diagnosis of tuberculous meningitis in children is a major risk factor for disability. The clinical presentation is nonspecific, with manifestations typically occurring at later stages of the disease. Management requires combined antituberculous, hormonal, and symptomatic therapy and close cooperation among physicians of various specialties. Rapid and timely diagnosis, screening of at-risk groups, and effective treatment significantly improve prognosis and reduce mortality and disability.

Keywords: tuberculosis, meningitis, children, drug resistance, diagnosis, outcomes.

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Клінічний випадок рифампіцин-стійкого туберкульозного менінгіту у дитини: особливості діагностики, клінічного ведення та наслідки

Ю. В. Мирончук, О. О. Пушнова, Л. В. Таран, Л. І. Чернишова, О. В. Двізов

Мета роботи – на прикладі власного клінічного спостереження навести особливості діагностики, клінічного ведення та описати наслідки рифампіцин-стійкого туберкульозного менінгіту у дитини.

Матеріали і методи. Наведено клінічний випадок власного спостереження діагностики, клінічного ведення та наслідків рифампіцин-стійкого туберкульозного менінгіту у дитини, яка перебувала на лікуванні у дитячому відділенні Комунального некомерційного підприємства «Запорізький регіональний фтизіопульмонологічний клінічний лікувально-діагностичний центр» Запорізької обласної ради – на клінічній базі кафедри фтизіатрії і пульмонології Запорізького державного медико-фармацевтичного університету.

Результати. До дитячого відділення дитина надійшла з відділення анестезіології та інтенсивної терапії дитячої лікарні. Діагноз гострого туберкульозного менінгіту підтверджено результатом дослідження спинномозкової рідини, що здійснене методом Xpert MTB/RIF Ultra, виявлено мікобактерії туберкульозу, стійкі до протитуберкульозного препарату першого ряду – рифампіцину. На час переведення пацієнта, за даними рентгенологічного дослідження органів грудної порожнини, змін у легенях не виявлено. За даними магнітно-резонансної томографії головного мозку, осередкової патології також не виявлено. У процесі дообстеження в матері виявили туберкульоз, стійкий до ізоніазиду та рифампіцину. Понад 4 місяці дитина отримувала протитуберкульозну та симптоматичну терапію, призначену неврологом, в умовах відділення анестезіології та інтенсивної терапії. Після контрольного обстеження, за даними комп'ютерної томографії, в дитини виявлено дисемінований процес у легенях. Після завершення лікування дитина одужала, однак сформувалися епілептичний статус і когнітивний дефіцит, що потребують пожиттєвої терапії.

Висновки. Несвоєчасна діагностика туберкульозного менінгіту є фактором ризику інвалідизації дитячого населення. Клінічна картина неспецифічна, маніфестація зазвичай відбувається на останніх стадіях захворювання. Ведення таких пацієнтів передбачає протитуберкульозну, гормональну та симптоматичну терапію, а також залучення лікарів різних спеціальностей. Швидка та своєчасна діагностика, робота з дітьми із груп ризику та ефективне лікування сприяють покращенню прогнозу, зниженню показників смертності та інвалідизації.

Ключові слова: туберкульоз, менінгіт, діти, резистентість до препаратів, діагностика, наслідки.

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Every year, approximately one million children and adolescents develop active tuberculosis (TB), with most cases occurring in low-income countries. Ukraine remains a country with a high burden of drug-resistant TB, including among children [1].

Tuberculous meningitis (TBM) is a form of extrapulmonary TB caused by *Mycobacterium tuberculosis* (MTB) affecting the meninges. Although relatively rare, it is the most severe form of TB [2]. Despite advances in treatment, TBM, particularly drug-resistant forms, is associated with high mortality and severe neurological sequelae [3]. Rahimi B. A. et al. reported that at hospital admission, 53.9 % and 15.2 % of children had stage II and III TBM, respectively; 23.2 % presented with focal neurological deficits. Mortality reached 20.2 %, and 30.6 % of survivors had persistent neurological impairment. Evidence suggests that independent risk factors for mortality included lack of BCG vaccination, male sex, absence of dexamethasone at treatment initiation, recent weight loss, and stage III TBM [4].

Another prospective cohort study of 80 children with TBM aged 9 months to 12 years reported a mortality rate of 42.5 %. Only 20 % achieved full recovery, while 36.25 % survived with disabilities. Reported sequelae included motor impairment (33.3 %), hearing loss (4 %), cognitive impairment (33.3 %), and visual impairment (48.9 %). Intracranial hypertension and stage III disease were significantly associated with mortality [5].

Diagnosis of TBM remains challenging for physicians of various specialties, due to the nonspecific clinical presentation and the oligobacillary nature of cerebrospinal fluid (CSF), which limits the sensitivity of conventional diagnostic methods to compare between meningitis of other etiologies [6,7]. The diagnosis of TBM is mostly clinical and relies on a combination of epidemiological history, clinical findings, laboratory data, neuroimaging, CSF biochemical and cytological analysis, and microbiological confirmation. Undoubtedly, the principal anamnestic criterion for suspecting TB is prior exposure to a patient with active TB disease. Typical CSF findings include clear appearance, lymphocytic pleocytosis, elevated protein levels, and low glucose concentration or a reduced CSF-to-serum glucose ratio. When left standing, CSF may form a delicate fibrinous coagulum resembling a spider web primarily attributable to high protein concentration [7]. The identification of MTB retains diagnostic importance in TBM; however, microbiological confirmation is infrequently obtained in the majority of pediatric TBM cases [8].

Since 2017, the World Health Organization has recommended the Xpert MTB/RIF Ultra assay as the primary diagnostic molecular genetic (MG) test for detecting multidrug-resistant TB (MDR-TB) and rifampicin resistance in CSF. The Xpert Ultra cartridge has a larger reaction space to isolate more samples and therefore more DNA for testing, and contains 2 additional target genes for multiplex amplification, which increases the diagnostic sensitivity and reliability of rifampicin resistance detection [6]. Neuroimaging commonly reveals basal meningeal enhancement, hydrocephalus, infarctions, and/or tuberculomas [8].

Children frequently present at advanced stages of disease. Mortality rates average approximately 19 %, and more than 50 % of survivors develop neurological disability despite treatment [9]. Naveed Anjum et al. in a prospective study reported that all 40 children in their cohort presented with stage III central nervous system TB and 26 of them were younger than 5 years. Mortality was 5 % (2 children) and nearly all survivors had significant neurological deficits, including motor disorders in 38 (95 %), low Glasgow Coma Scale (GCS) scores in 35 (92 %), epilepsy in 29 (76.3 %), hydrocephalus in 32 (84.2 %), cranial nerve palsy in 9 (23.5 %), and 32 (84.2 %) were discharged on nasogastric feeding [10]. Due to severe hydrocephalus, 11 (28.9 %) patients underwent neurosurgical intervention with ventriculo-peritoneal shunting. The third clinical stage was also characterized by optic disc atrophy in 47.5 % and optic nerve edema in 20 % of children [10]. Thus, children remain the most vulnerable group to severe TBM.

In recent years, an increasing number of drug-resistant TB cases has been reported, leading to the development of new treatment protocols with high success rates. However, a review of the literature reveals that data on drug-resistant TBM in the pediatric population remain scarce. Specifically, we examine a case of resistant TBM in a 14-year-old female admitted with fever, headache, and blurred vision. CSF analysis showed lymphocytic pleocytosis, elevated protein, and decreased chloride levels. The Xpert MTB/RIF assay detected MTB in the CSF, though rifampin resistance remained undetermined at that stage. Subsequent cultures confirmed resistance to isoniazid, rifampin, and fluoroquinolones.

Chest computed tomography (CT) demonstrated diffuse miliary nodules in both lungs, while magnetic resonance imaging (MRI) revealed multiple contrast-enhancing lesions within the brain parenchyma, cisterns, and meninges. A diagnosis of pre-extensively drug-resistant (pre-XDR) miliary TB was established. The patient was prescribed a tailored anti-TB regimen and symptomatic therapy for 19 months. By the end of treatment, pulmonary and cerebral lesions had completely resolved. No neurological sequelae were observed, although peripheral neuropathy developed as an adverse effect of linezolid. This highlights the critical importance of rapid, accurate diagnosis and timely, effective intervention to improve prognosis and reduce mortality and disability [11].

In this clinical case, we present the diagnostic features, clinical course, and treatment of TBM in a school-age child. Furthermore, we analyze the consequences of delayed diagnosis and evaluate clinical challenges encountered at various stages of medical care.

Aim

To present a clinical case study focusing on the diagnostic challenges, clinical management, and therapeutic outcomes of rifampicin-resistant tuberculous meningitis in a pediatric patient.

Materials and methods

The study describes a clinical observation of the child diagnosed with rifampicin-resistant TBM. The patient received treatment in the Pediatric Unit at the clinical base of the Department of Phthisiology and Pulmonology of Zaporizhzhia State Medical and Pharmaceutical University, located at the Public Non-Profit Enterprise “Zaporizhzhia

Table 1. Dynamics of the complete blood count in the intensive care unit

Parameter, units of measurement	December 8, 2021	December 10, 2021	December 12, 2021	December 14, 2021	December 17, 2021	December 18, 2021	December 20, 2021
Hemoglobin, g/L	117	119	121	131	129	134	131
Red blood cells, 10^{12}/L	4.5	4.5	4.6	4.9	4.8	4.9	4.9
White blood cells, 10^9/L	13.6	9.8	8.7	15.0	12.7	26.2	21.6
Platelets, 10^9/L	430	420	380	490	390	425	430
Erythrocyte sedimentation rate, mm/h	25	27	20	30	16	25	20
Band neutrophils, %	25	15	14	8	20	25	18
Segmented neutrophils, %	52	64	66	73	61	57	62
Eosinophils, %	1	0	0	0	0	0	0
Lymphocytes, %	16	15	12	12	12	13	12
Monocytes, %	7	6	8	7	7	5	8

Table 2. Dynamics of urinalysis parameters

Parameter, units of measurement	December 8, 2021	December 9, 2021	December 11, 2021	December 18, 2021
Color	yellow	yellow	yellow	yellow
Clarity	clear	turbid	clear	clear
Ph	neutral	acidic	neutral	alkaline
Protein, g/L	negative	negative	negative	negative
Ketones, mmol/L	1+	1+	negative	negative
Glucose, mmol/L	negative	negative	negative	negative
Erythrocytes, hpf	0	45–50 dysmorphic	0	0–1
Leukocytes, hpf	0–3	1–3	1–2	2–3
Squamous epithelium, cell	single	single	single	moderate amount

Regional Clinical and Diagnostic Center of Phthisiology and Pulmonology" of the Zaporizhzhia Regional Council (PNE "ZRCDCPP" ZRC).

Results

An 8-year-old girl was born to a primigravida mother with a birth weight of 3,200 g and was breastfed for two months. Her medical history included infrequent acute respiratory viral infections (twice yearly) and varicella in 2018. She had an allergy to grapes (presenting as erythema). Her physical and psycho-emotional development was age-appropriate. BCG-m vaccination was administered in the maternity hospital on April 18, 2014, resulting in a 7 mm scar. Tuberculin surveillance data (Mantoux test, 2 TU) for the period 2015–2020 were unavailable due to the family's difficult social circumstances. No known TB contacts were identified, and the mother reported no illness. The child had no prior history of TB and was not previously registered with specialized health services.

According to the mother, the illness onset was on December 1, 2021, presenting with a fever of 38.5 °C, headache, and vomiting. A pediatrician initially diagnosed an acute respiratory infection and prescribed symptomatic therapy. By December 7, 2021, the child's condition deteriorated significantly, leading to emergency hospitalization at the Infectious Diseases Hospital. The diagnosis of COVID-19 was ruled out. Due to increasing severity, the patient was transferred to the Department of Anesthesiology and Intensive Care of the City Children's Hospital on December 8, 2021, with a diagnosis of severe acute meningitis.

The patient was in critical condition due to severe neurological symptoms and endotoxemia. Mental status was characterized by contact sopor; the child was drowsy, asthenic, disoriented in time and space, and responded sluggishly to questions. She exhibited irritability and aggression during examinations by screaming and crying. Meningeal signs were positive, including nuchal rigidity and Kernig's sign. Generalized muscular hypotonia and hyperesthesia were noted. The skin was pale but clear; mucous membranes were dry with reduced turgor. Respirations were spontaneous and effective, harsh breath sounds on auscultation bilaterally and no rales. Hemodynamics were stable with a tendency toward bradycardia and muffled heart tones. A systolic murmur was audible at the apex. The abdomen was soft; the liver was at the costal margin, and the spleen was non-palpable.

Diagnostic procedures performed included a complete blood count, urinalysis, biochemical blood profile, coagulogram *(Tables 1, 2, 3, 4)*, microbiological testing, neuroimaging, specialist consultations, and lumbar puncture.

Blood culture (December 8, 2021) showed no growth. Pharyngeal swab (December 8, 2021) revealed growth of Staphylococcus aureus. Nasal swab (December 8, 2021) showed scanty growth of S. aureus. Procalcitonin level (December 8, 2021) was <0.07 ng/mL (reference range: <0.1 ng/mL). SARS-CoV-2 PCR (December 8, 2021) was negative for viral RNA.

Electrocardiography (ECG) (December 8, 2021): adequate voltage; high amplitude in left precordial leads. Sinus arrhythmia with episodes of bradycardia (HR: 63–90 bpm). Normal cardiac axis. Non-specific metabolic changes in the ventricular myocardium. Left ventricular dominance was noted.

Ophthalmological consultation (December 8, 2021): optic disc – margins were distinct, veins slightly dilated, and arteries unremarkable. The peripheral retina was unremarkable.

The patient was admitted to the Intensive Care and Anesthesiology Department, where a lumbar puncture (LP)

Table 3. Dynamics of biochemical serum parameters

Parameter, units of measurement	December 8, 2021	December 9, 2021	December 13, 2021	December 18, 2021	December 20, 2021
Glucose, mmol/L	6.1	5.6	6.4	6.2	7.0
Total bilirubin, μmol/L	77	73	74	69	68
Potassium, mmol/L	3.50	3.83	3.50	3.65	3.86
Sodium, mmol/L	135	134	134	134	138
Chloride, mmol/L	102	103	101	97	106
Urea, mmol/L	2.6	4.5	3.3	3.6	3.3
Creatinine, μmol/L	78	75	98	86	65
Alanine aminotransferase, U/L	0.29	0.25	0.39	0.18	0.28
Aspartate aminotransferase, U/L	0.18	0.21	0.24	0.16	0.19

Table 4. Dynamics of coagulation parameters

Parameter, units of measurement	December 8, 2021	December 13, 2021	December 18, 2021	December 20, 2021
Prothrombin index, %	90	97	84	86
Activated partial thromboplastin time, s	27	40	24	25
Thrombin time, s	20	23	22	18
Soluble fibrin-monomer complexes, mcg/ml	10	5	9	7
International normalized ratio	1.09	1.03	1.16	1.11
Fibrinogen, g/L	3.0	3.6	3.5	4.66

was performed on December 8, 2021. PCR testing for HSV-1/2, HHV-6, and CMV in the CSF was negative. CSF Analysis (December 8, 2021): pre-centrifugation: red and turbid; post-centrifugation: colorless and slightly turbid; protein: 0.33 g/L. Pandy's test: negative. Nonne-Apelt test: 2+. Pleocytosis: 150 cells/μL (80 neutrophils (53 %), 70 lymphocytes (47 %)). Single crenated erythrocytes were observed.

From December 8, 2021 to December 12, 2021, the patient received ceftriaxone, dexamethasone (3 mg/kg/day), intravenous (IV) heparin (350 U, 6 times daily), pentoxifylline, and infusion therapy (saline and Ringer's solution). Diuretics included furosemide, acetazolamide, and magnesium sulfate.

During this period, the child's condition deteriorated due to progressive endotoxemia, worsening neurological deficits, and the onset of hemodynamic instability.

Follow-up LP (December 13, 2021): CSF was colorless and transparent. Protein – trace amounts. Pleocytosis – 130 cells/μL (40 neutrophils (31 %), 90 lymphocytes (69 %)). Erythrocytes – dysmorphic.

As a result, the treatment regimen was adjusted: ceftriaxone was replaced with meropenem (800 mg TID) and IV fluconazole (250 mg). Vancomycin (200 mg QID) was added on December 15, 2021, followed by benzylpenicillin (1 million IU 6 times daily) starting December 19, 2021.

Conclusion of neurological consultation (December 14, 2021): acute purulent meningitis.

Follow-up ECG (December 14, 2021): sinus arrhythmia. Findings remained stable without negative dynamics compared to the previous study.

Brain MRI (December 16, 2021): MRI findings were consistent with cerebral meningitis. No focal brain pathology or intracranial lesions were identified at the time of examination.

During this period, the patient's condition remained severe, characterized by manifestations of endotoxemia, along with neurological and hemodynamic instability. Recurrent high-grade fever (up to febrile levels) was noted. The level of consciousness was classified as sopor, with a GCS score of 10–11 points. The pupillary light reflex was preserved and symmetric. The patient was drowsy, showed no response to verbal commands, and maintained minimal meaningful contact. Physical examination and medical manipulations elicited pronounced distress (irritability, screaming). No acute focal neurological deficits were observed. Meningeal signs were positive, including nuchal rigidity and Kernig's and Brudzinski's signs. Muscle tone was globally reduced, and significant hyperesthesia was present.

The skin and visible mucous membranes were pale pink and dry; skin turgor was preserved. Respiration was spontaneous, supported by humidified oxygen via face mask. Dyspnea was mild, and oxygen dependence was moderate. Auscultation revealed harsh breath sounds bilaterally, with no rales or wheezing. Hemodynamics were compensated with inotropic support (4 % dopamine at 5 μg/kg/min). Clinical findings included a tendency toward bradycardia, muffled heart sounds, and a systolic murmur at the apex. The abdomen was soft; the liver was palpable at the costal margin, and the spleen was not enlarged. Urinary output was monitored via catheter, requiring pharmacological stimulation.

Due to clinical deterioration and brain MRI findings, the patient was re-evaluated by a neurologist, who recommended a LP for CSF biochemistry (including glucose and chlorides) and PCR for MTB.

CSF analysis (December 20, 2021): the fluid was clear and colorless both before and after centrifugation. Findings included: protein 0.19 g/L, Pandy reaction (1+), Nonne-Apelt reaction (2+), pleocytosis 77 cells/μL (neutrophils 45 (58 %), lymphocytes 32 (42 %)), glucose 1.0 mmol/L, and chlorides 108 mmol/L.

MG testing of CSF (December 20, 2021): MTB was detected; results indicated rifampicin resistance.

Bronchoscopy (December 20, 2021): mild bilateral endobronchitis was observed. Bronchial lavage was collected for MTB analysis. Molecular testing of the bronchoalveolar lavage (BAL) fluid did not detect MTB.

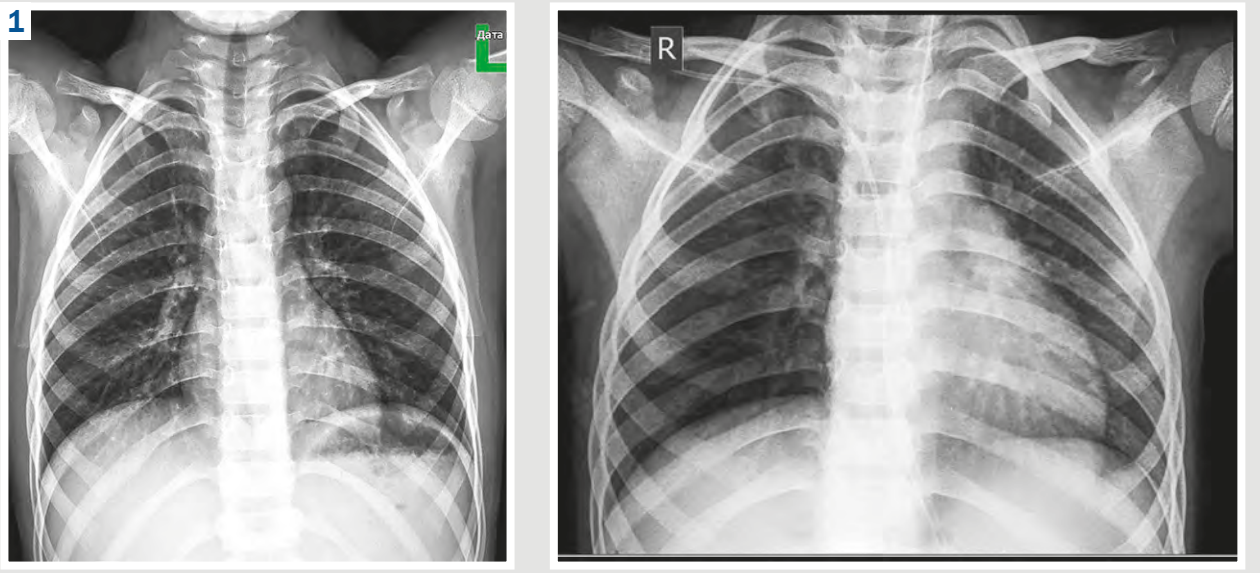


Fig. 1. Chest X-ray upon admission to the Pediatric ICU of the PNE "ZRCDCPP" ZRC.

Chest X-ray (December 20, 2021): no focal infiltrative shadows were observed in the lung parenchyma. The pulmonary vascular markings were diffusely prominent bilaterally. The hila were well-defined, and the costophrenic angles were clear *(Fig. 1)*.

Neurological consultation (December 20, 2021): the patient's condition was critical. The child showed an inappropriate response to examination due to severe hyperesthesia; patient engagement was diminished; she was disoriented to time and place and unable to track objects. Pupillary light reflexes were brisk and preserved. Muscle tone was increased (hypertonia). Deep tendon reflexes were symmetrical in both upper and lower extremities. Marked nuchal rigidity and positive meningeal signs were present. Conclusion: Tuberculous meningitis, acute phase. Recommendations: continue daily dexamethasone; acetazolamide 125 mg/day; citicoline 500 mg/day (course up to 45 days); vitamin B complex; vinpocetine 5 mg/day. Serial clinical monitoring was required.

Ophthalmological consultation (December 20, 2021): partial optic disc atrophy, bilateral.

Surgical Procedure (December 20, 2021): insertion of a central venous access device (Centrofix Mono No. 320).

Otolaryngological consultation (December 20, 2021): acute rhinopharyngitis.

Given the positive CSF PCR result for MTB, the child was transferred to the intensive care unit (ICU) of the Specialized Children's Clinical Center on December 21, 2021. Upon admission to the ICU, the patient's general condition was severe. The child was of regular constitution. The skin and visible mucous membranes were pale and dry; skin turgor was reduced. Cervical lymph node enlargement (micropolyadenopathy) was noted. The chest was normosthenic. Percussion revealed resonance (pulmonary sound). Auscultation: harsh breath sounds with isolated dry crackles in the upper lobes. Cardiac activity was rhythmic with muffled heart sounds and a systolic murmur at the apex. The heart rate was 30 beats per minute. Cardiac borders were within age-appropriate limits. On palpation, the abdomen was soft and non-tender; the liver was at the costal margin, and the spleen was not palpable. Diuresis was maintained via pharmacological stimulation.

Clinical and laboratory findings at admission. Complete blood count (December 21, 2021): Hb 80 g/L, RBC 2.69 × 10^{12}/L, PLT 218×10^{9}/L, WBC 9.2 × 10^{9}/L. Differential count: eosinophils 5 %, band neutrophils 9 %, segmented neutrophils 66 %, lymphocytes 20 %, and monocytes 5 %. Erythrocyte sedimentation rate – 17 mm/h.

Biochemical blood analysis (December 21, 2021): total bilirubin 9.48 μmol/L, thymol test 4.81 U, ALT – 0.53 U/L, AST – 0.63 U/L, total protein – 59.0 g/L, glucose – 5.63 mmol/L, β-lipoproteins – 52 U, creatinine 137.2 μmol/L, urea – 10.1 mmol/L, urea nitrogen – 4.73 mmol/L, and potassium – 3.57 mmol/L. Serum α-amylase was 5.31 U/L.

Proteinogram (December 23, 2021): seromucoids – 26.3 U, total protein – 68.7 g/L, C-reactive protein – 4+ (24 mg/L). Antistreptolysin O and rheumatoid factor were negative. Albumin / globulin ratio – 1.4. Protein fractions: albumin – 57.8 %, α1-globulins – 6.7 %, α2-globulins – 5.3 %, β-globulins – 14.5 %, and γ-globulins – 15.7 %.

Urinalysis (December 21, 2021): color – light yellow; transparency – moderate; specific gravity – 1.012; pH – alkaline. Protein – 0.066 g/L; glucose and ketone bodies were absent. Microscopic examination: erythrocytes – 5–6/hpf, leukocytes – 4–6/hpf, occasional squamous and renal epithelial cells, and 1+ phosphate crystals.

ECG (December 23, 2021): sinus tachycardia – 109 bpm. Normal QRS voltage. Normal electrical axis (no deviation); intermediate electrical position. Shortened PR interval. Diffuse changes in the ventricular myocardium. QTcF = 368 ms.

TB screening on admission: the Mantoux test (2 TU, December 21, 2021) was negative.

Based on clinical history and laboratory data, the patient was diagnosed on December 22, 2021, with rifampicin-resistant extrapulmonary tuberculosis (Rif-RR TB): tuberculous meningitis, acute phase. Bacterial status: MTB+ (microscopy positive, GeneXpert positive (CSF), culture positive, rifampicin-resistant).

Table 5. Dynamics of cerebrospinal fluid analysis results in the ICU of PNE "ZRCDCPP" ZRC

Parameter, units of measurement	December 29, 2021	January 10, 2022	January 24, 2022	February 23, 2022
Volume, ml	2.5	1.2	2.0	1.8
Color	colourless	colourless	colourless	colourless
Clarity	clear	clear	clear	clear
Protein, g/L	0.99	0.66	0.66	0.33
Nonne-Apelt Test	++	++	++	+
Pandy Test	+++	+++	++	+++
Pleocytosis, cells/μL	151	55	28	7
Differential Count – Neut/Lymp, %	71/29	20/35	3/26	2/5
Glucose, mmol/L	1.68	2.62	3.43	3.19
Chloride, mmol/L	106.7	121.7	117.7	107.3

The prescribed treatment regimen included: bedaquiline (initial course), levofloxacin, linezolid, and cycloserine for 12–15 months, supplemented with meropenem and amoxicillin / clavulanate (Amx/Clv) for 5 months. CSF culture confirmed rifampicin resistance, while BAL culture was negative. The regimen required no further adjustment.

Epidemiological examination revealed that the child's mother had MDR-TB, resistant to first-line drugs (isoniazid and rifampicin). Three siblings were screened, diagnosed with latent TB infection, and prescribed preventive therapy.

In the ICU, the child underwent serial LPs to monitor CSF parameters *(Table 5)*.

While in the ICU, the patient was evaluated by a pediatric neurologist and an ophthalmologist.

Neurological evaluation (January 27, 2022): the patient's condition remained critical. She responded to the examination with mild agitation and exhibited selective tracking of objects. Mild nuchal rigidity persisted. Generalized muscular hypotonia was noted, characterized by poor axial stability (weak verticalization of the back and neck). Deep tendon reflexes of the upper and lower extremities were symmetrical (D = S). No pathological pyramidal signs were elicited. Recommendations: continue citicoline (total duration 45–60 days), B-complex vitamins, vinpocetine (5 mg/day), and acetazolamide (125 mg/day). Follow-up scheduled.

Neurological evaluation (March 10, 2022): the patient showed significant clinical improvement. She responded appropriately to questions and was oriented to time and place. Neurological status: palpebral fissures were symmetrical (D = S). Object tracking was intact. Mild bilateral convergence insufficiency was noted. No facial asymmetry was present. Muscle tone was near normal. Deep tendon reflexes were diminished in both upper and lower extremities. Coordination tests were performed successfully. No pathological pyramidal or meningeal signs were observed. The patient was unable to sit independently (required support) due to weakened spinal verticalization. Recommendations: general massage (focusing on the back), physical therapy, B-complex vitamins. Continued monitoring.

Neurological evaluation (April 20, 2022): continued positive dynamics. The patient followed complex instructions. However, she developed recurrent generalized seizures occurring once weekly, lasting up to 10 minutes. Neurological status: palpebral fissures were symmetrical (D = S). Object tracking was preserved; pupillary light reflex was intact. Convergence insufficiency was more pronounced on the left. No facial asymmetry. Muscle tone was satisfactory. Deep tendon reflexes were brisk, with left-sided predominance. No meningeal or pyramidal signs. Recommendations: initiation of antiepileptic drugs and B-complex vitamins. Brain MRI and detailed ophthalmological assessment were indicated to clarify the seizure etiology.

Ophthalmological evaluation (April 26, 2022): diagnosis – bilateral compound hyperopic with-the-rule astigmatism; mild amblyopia of the left eye; suspected bilateral partial optic nerve atrophy. Recommended: continuous corrective lens wear, right eye occlusion (2–3 hours/day), and left eye visual stimulation.

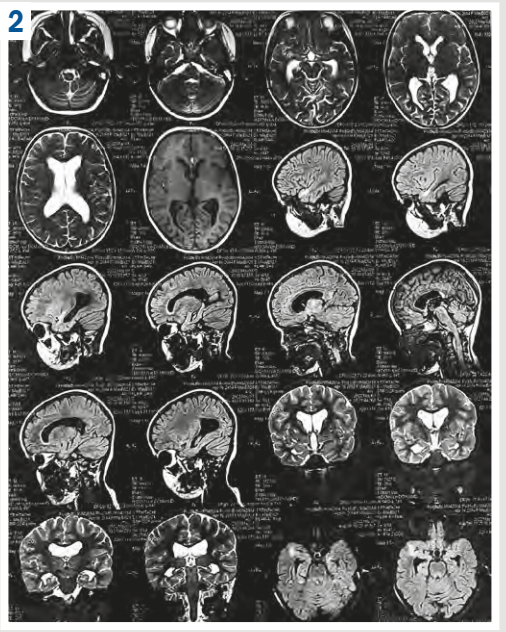
Brain MRI (May 3, 2022): the periventricular white matter of both hemispheres exhibited scattered hyperintense foci (1.5–2.0 mm in diameter) without perifocal edema or diffusion restriction. A zone of abnormal signal intensity (13 × 12 × 8 mm) was identified in the subcortical white matter of the right superior temporal gyrus, showing no diffusion restriction. Abnormal signal intensity was also noted in the white matter tracts of the superior cerebellar peduncles and dentate nuclei, with minimal diffusion restriction. Ventriculomegaly was observed, with the lateral ventricles and temporal horns measuring up to 18 × 11 mm in the frontal plane. Mild periventricular leukoaraiosis was present. Conclusion: MRI findings of compensated triventricular hydrocephalus and non-specific polyfocal leukoencephalopathy involving the right temporal lobe, superior cerebellar peduncles, and cerebellar nuclei *(Fig. 2)*.

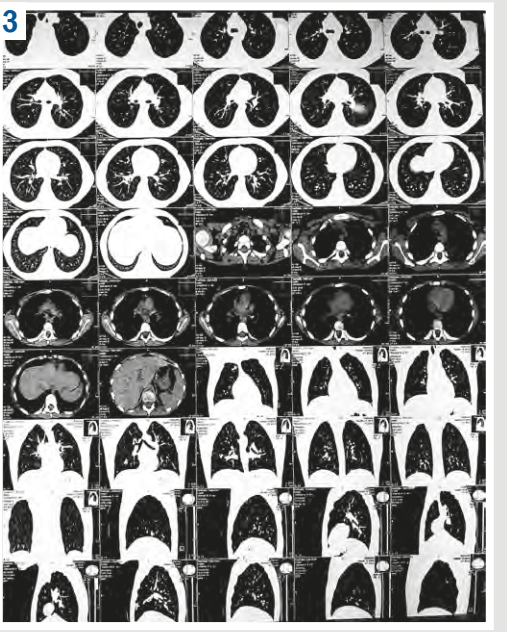
A follow-up examination was performed at the end of the intensive phase of treatment (after 150 doses). A thoracic CT examination was performed.

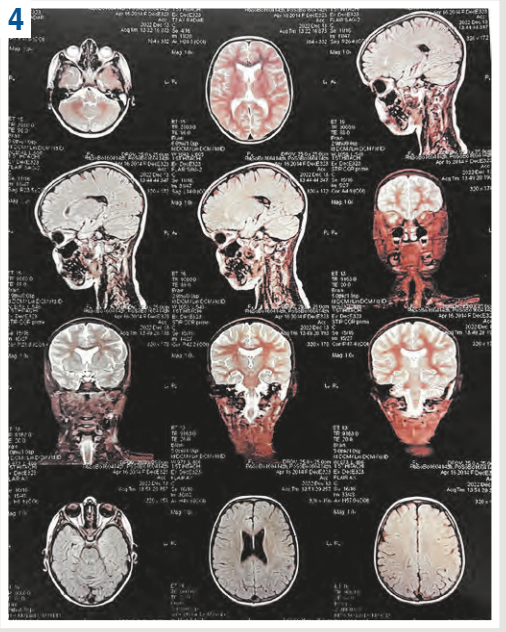
Chest CT scan (May 2, 2022): the thoracic cage was symmetric and normal in configuration. Axillary lymph nodes were not enlarged on either side. Lung parenchyma: fully expanded, with uniform aeration and normal transparency. "Soft" and "conventionally soft" foci were detected: 6.6 × 4.2 mm in S3 on the right, 2.6 mm in S8 paravasally, 3.5 mm in S8/9, 7 mm on the left, and 2.2 × 4.5 mm in S10. No infiltrative shadows were observed in any lung fields. Linear fibrosis was noted in S5 on the right. Hilar and mediastinal lymph nodes were not enlarged. Conclusion: CT signs of multiple soft and conventionally soft lung foci. Linear fibrosis in S5 of the right lung. No infiltrative changes or extensive mediastinal pathology detected *(Fig. 3)*.

Mantoux test (2 TU, May 31, 2022): 12 mm infiltrate.

Based on the chest CT findings and clinical progression, the diagnosis was revised: Rifampicin-resistant tuberculosis (initially diagnosed December 22, 2021). Extrapulmonary tuberculosis: meningitis, acute period, without destruction (Dest-), MTB+ (GeneXpert+), Culture+ (CSF), Rifampic-







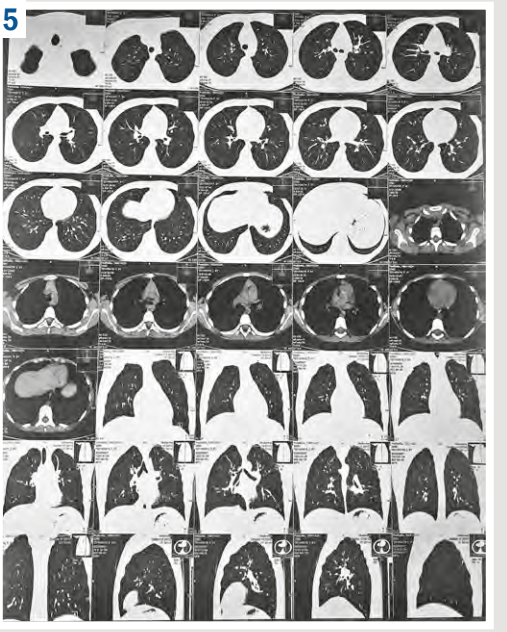


Fig. 2. Brain MRI performed in the ICU of the PNE "ZRCDCPP" ZRC.

Fig. 3. Chest CT scan performed in the Pediatric Unit following intensive care treatment at the PNE "ZRCDCPP" ZRC.

Fig. 4. Brain MRI performed in the Pediatric Unit of the PNE "ZRCDCPP" ZRC.

Fig. 5. Chest CT scan obtained at the completion of treatment in the Pediatric Unit.

in-resistant. Disseminated pulmonary tuberculosis: Dest-, MTB-negative (Microscopy-, Culture-). Ophthalmic findings: complex hyperopic astigmatism (direct type) and partial optic nerve atrophy in both eyes.

The patient remained in the ICU until May 23, 2022. Neurologist evaluation (June 2, 2022): tuberculous meningitis, early recovery period with severe brain damage (triventricular hydrocephalus, multifocal leukoencephalopathy involving the right temporal lobe, superior cerebellar peduncle, and corpus callosum nuclei). Cognitive deficit, mild left-sided motor deficit, and epileptic syndrome. Recommended treatment: antiepileptic drugs, B-group vitamins, Phenibut (250 mg/day for 1 month), and Acetazolamide (125 mg/day).

Ophthalmologist evaluation (June 28, 2022): severe hyperopic astigmatism (direct type) in both eyes. Recommendation: gradual discontinuation of occlusion therapy. Follow-up scheduled for Dec 2022.

Brain MRI (December 13, 2022): comparison with the results from May 3, 2022 showed positive dynamics.

Minimal signs of compensated triventricular hydrocephalus. Signs of non-specific multifocal leukoencephalopathy with gliosis formation in the right temporal lobe; involvement of the superior cerebellar peduncles and cerebellar nuclei. Potential residual inflammatory changes in the left mastoid air cells *(Fig. 4)*.

Neurological consultation (December 26, 2022): no focal neurological deficits identified. Diagnosis: Sequelae of tuberculous meningitis; epilepsy with personality changes; cognitive impairment. Recommendations: psychiatric consultation, follow-up brain MRI, and psychological counseling sessions. Treatment guidelines were provided.

Ophthalmological examination (January 13, 2023): bilateral complex hyperopic with-the-rule astigmatism. Recommendations: consistent use of corrective lenses, visual hygiene, and continued neurological monitoring.

Prior to treatment completion, a follow-up chest CT was performed. Chest CT (March 07, 2023): fully expanded lung parenchyma, uniformly aerated, with normal transparency. No focal or infiltrative opacities detected. Linear fibrosis observed in S5 and S10 of the left lung; paravertebral fibrosis in the S6 segment of the right lung. Localized fibrosis (up to 5.5 mm) noted at the sites of previous foci. Lymphatic system: hilar and mediastinal lymph nodes were not enlarged. Conclusion: no CT evidence of focal, infiltrative, or space-occupying lesions in the lungs or mediastinum. Identified linear fibrosis in S5 (right) and S10 (left), and localized fibrosis in S6 (right). Over the observation period, significant radiological improvement was noted, characterized by the complete resolution of all previously identified pulmonary lesions *(Fig. 5)*.

The patient tolerated the entire course of therapy without adverse reactions. Upon discharge from the Pediatric Unit, the final diagnosis was: rifampicin-resistant extrapulmonary tuberculosis (confirmed December 22, 2021); specifically, tuberculous meningitis in the early recovery period with severe neurological sequelae (triventricular hydrocephalus, multifocal leukoencephalopathy with involvement of the right temporal lobe, superior cerebellar peduncle, and the corpus callosum). The concurrent diagnosis included disseminated pulmonary tuberculosis in the phase of complete resolution (non-destructive, smear-negative, culture-negative, Rif-resistant). Additional comorbidities included cognitive impairment, epilepsy with personality changes, and bilateral complex hyperopic with-the-rule astigmatism. Long-term outpatient follow-up by a pediatric pulmonologist (phthisiologist), neurologist, and ophthalmologist was recommended.

Discussion

TBM is the most severe manifestation of central nervous system involvement caused by MTB. As the most devastating form of TB, TBM imposes a persistent long-term burden not only on the patient's family but also on clinicians across various disciplines. This is primarily due to diagnostic complexities; TBM remains a significant clinical challenge, often leading to delayed initiation of anti-TB therapy. Consequently, timely prevention and early detection are critical predictors for improving clinical outcomes [8].

One major hurdle in the management of TBM is a potential lack of clinical suspicion among physicians. In its early stages, TBM lacks pathognomonic features and is frequently misdiagnosed as other febrile illnesses. Literature analysis reveals that initial symptoms often mimic flu-like syndromes. Clinically, TBM is classified into three stages. The first stage typically lasts 1–2 weeks and is characterized by non-specific symptoms such as low-grade fever, headache, irritability, drowsiness, vomiting, photophobia, lethargy, and weight loss, which often complicates early diagnosis. Most patients are diagnosed during the second stage, presenting with lethargy, nuchal rigidity, positive meningeal signs, convulsions, and focal neurological deficits. Features of hydrocephalus, increased intracranial pressure, and encephalitis, manifesting as disorientation, movement or speech disorders, and cranial nerve palsies (most commonly the VI nerve) may also emerge. The third stage is associated with decerebrate or decorticate posturing, hemiplegia, coma, and, ultimately, high mortality rates.

Diagnosis is multifaceted, integrating epidemiological, clinical, laboratory, and neuroimaging data. In this clinical case, the child was initially suspected of having acute bacterial meningitis; TBM was not considered due to the non-specific nature of the initial presentation. This underscores the necessity of prioritizing epidemiological factors, such as contact with known TB patients, BCG vaccination status, and socio-economic conditions. Notably, in our case, the social environment, a large family living in substandard conditions, was initially overlooked.

Critical diagnostic delays were also observed. Scientific guidelines emphasize the urgency of CSF analysis (evaluating protein, glucose, and chloride levels) to identify MTB etiology, followed by microbiological confirmation. In our patient, these parameters were only assessed two weeks after admission, following neurological deterioration and a failure to respond to empirical treatment for acute bacterial meningitis. During this delay, the lack of targeted anti-TB therapy resulted in significant neurological decline. Diagnostic confirmation was finally achieved after a third lumbar puncture using the GeneXpert MTB/RIF Ultra assay. This test not only identified MTB but also detected rifampicin resistance, enabling the timely adjustment of the treatment regimen. Thus, the application of modern molecular tests like GeneXpert Ultra is essential for rapid TBM confirmation and serves as a vital alternative to traditional culture methods [12].

Based on the analysis of the literature, researchers emphasize the importance of chest imaging for identifying primary pulmonary localization. Although the initial chest X-ray was unremarkable, a subsequent CT scan revealed characteristic tubercular changes. The negative Mantoux test upon admission is also typical for severe forms of TB, often reflecting a state of secondary immunodeficiency or anergy.

Contact investigation revealed that the mother had pulmonary TB resistant to first-line drugs (isoniazid and rifampicin). Following this discovery, the family was screened, and the remaining three children received preventive therapy. This highlights the vital role of contact tracing in identifying the index patient. Finally, the management of such patients requires a multidisciplinary approach, including the timely administration of corticosteroids, anticonvulsants, and symptomatic therapy to mitigate long-term sequelae [13,14].

Thus, drug-resistant TBM presents the most significant diagnostic and therapeutic challenges. The scarcity of research on drug-resistant TB in pediatric populations results in a lack of standardized management algorithms, necessitating further study.

Conclusions

1. Central nervous system tuberculosis remains a major cause of significant disability and mortality in children, particularly in high-burden countries.

2. The clinical course of tuberculous meningitis in children is characterized by specific features, with initial symptoms frequently manifesting as severe disease.

3. Early diagnosis necessitates a high index of clinical suspicion among physicians across various specialties. This is facilitated by the implementation of modern molecular diagnostic tools, such as Xpert MTB/RIF Ultra, integrated with comprehensive clinical, laboratory, and imaging investigations.

4. Prompt initiation of comprehensive anti-tuberculosis therapy and adjunctive treatments, specifically corticosteroids and psychosocial support, reduces mortality rates and improves long-term neurological outcomes.

5. Systematic screening of high-risk groups and the administration of preventive treatment are crucial for reducing the incidence of this severe condition.

Prospects for further research. Future studies should focus on optimizing diagnostic algorithms for pediatric tuberculous meningitis to ensure earlier detection and improved clinical management.

Ethical approval
Written informed consent was obtained from the (parents for the child's participation in the study and for all treatment procedures, including surgical interventions. The study protocol was reviewed and approved by the Bioethics Committee of Zaporizhzhia State Medical and Pharmaceutical University (Protocol No. 4, dated April 3, 2025). The study was conducted in strict accordance with the principles of the Declaration of Helsinki (1964, as revised), ICH-GCP guidelines, the Council of Europe Convention on Human Rights and Biomedicine (1997), the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Advances in Biology and Medicine, other regulatory documents, and current national legislation of Ukraine.

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Information about the authors:
Myronchuk Yu. V., MD, PhD, Assistant of the Department of Phthisiology and Pulmonology, Zaporizhzhia State Medical and Pharmaceutical University, Ukraine.
ORCID ID: 0000-0002-4608-2991
Pushnova O. O., MD, pediatric phthisiatrician, PNE "Zaporizhzhia Regional Clinical and Diagnostic Center of Phthysiatry and Pulmonology ZRC", Ukraine.
ORCID ID: 0009-0004-4302-961X
Taran L. V., MD, pediatric phthisiatrician, PNE "Zaporizhzhia Regional Clinical and Diagnostic Center of Phthysiatry and Pulmonology ZRC", Ukraine.
ORCID ID: 0009-0009-3926-5966
Chernyshova L. I., MD, Head of the Pediatric Department, PNE "Zaporizhzhia Regional Clinical and Diagnostic Center of Phthysiatry and Pulmonology" ZRC, Ukraine.
ORCID ID: 0009-0003-3955-2064
Dvizov O. V., MD, radiologist, PNE "Zaporizhzhia Regional Clinical and Diagnostic Center of Phthysiatry and Pulmonology" ZRC, Ukraine.
ORCID ID: 0009-0001-3264-3313

Відомості про авторів:
Мирончук Ю. В., д-р філософії, асистент каф. фтизіатрії та пульмонології, Запорізький державний медико-фармацевтичний університет, Україна.
Пушнова О. О., лікар-фтизіатр дитячий, КНП «Запорізький регіональний фтизіопульмонологічний клінічний лікувально-діагностичний центр» ЗОР, Україна.
Таран Л.В., лікар-фтизіатр дитячий, КНП «Запорізький регіональний фтизіопульмонологічний клінічний лікувально-діагностичний центр» ЗОР, Україна.
Чернишова Л. І., зав. дитячого відділення, КНП «Запорізький регіональний фтизіопульмонологічний клінічний лікувально-діагностичний центр» ЗОР, Україна.
Двізов О. В., лікар-рентгенолог, КНП «Запорізький регіональний фтизіопульмонологічний клінічний лікувально-діагностичний центр» ЗОР, Україна.

Yuliia Myronchuk (Юлія Мирончук)
yashmayulya92@gmail.com

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