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TUBERCULOSIS MENINGITIS IN CHILDREN

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Tuberculosis meningitis in children
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Infection of the central nervous system (CNS) caused by Mycobacterium tuberculosis is rare yet highly devastating and potentially lethal manifestation of tuberculosis (TB). In spite of a current global decrease of incident cases, TB persists a prominent cause of death on a worldwide scale.
On account of its rarity (1-2% of active TB) and variable nature of symptoms, TB with CNS involvement remains a diagnostic challenge while any delay in implementation of specific treatment may result in worsening the prognosis. Despite the availability of effective treatment, there are still numerous cases of deaths among patients as an effect of late diagnosis.
Early diagnosis is essential for the result of treatment, yet tricky because patients tend to present subacute course with nonspecific symptoms. Significant proportion of patients may suffer from sever neurologic disability. The review describes clinical features and diagnostic procedures regarding TBM in children as well as the method of treatment.
Provision of adequate multi-drug anti-tuberculosis treatment in conjunction with adjunctive corticosteroids is likely to achieve a good prognosis in patients with TMB. TBM should be kept in mind this diagnosis when encountering patients with meningitis of unknown origin and uncertain history. Main concerns should include the advancement of diagnostic testing strategies and the optimization of anti-tuberculosis therapies.
Keywords: *infection, central nervous system, tuberculosis, treatment, outcome, complications.*

Балалардағы туберкулез минингиті
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Микобактерия туберкулезінен туындаған орталық жүйке жүйесінің инфекциясы сирек кездесетін, бірақ өте жойқын және туберкулездің өлімге әкелетін көрінісі болып табылады. Қазіргі уақытта туберкулездің жаһандық төмендеуіне қарамастан, ол бүкіл әлемде өлімнің басты себептерінің бірі болып қала береді.
Сирек кездесетініне (белсенді туберкулездің 1-2%) және белгілердің өзгергіштігіне байланысты орталық жүйке жүйесінің зақымдануы бар туберкулез диагностикалық мәселе болып қала береді және нақты емдеудегі кешеуілдеу болжамның нашарлауына әкелуі мүмкін. Тиімді емнің қол жетімділігіне қарамастан, пациенттер арасында кеш диагностикалау салдарынан қайтыс болғандар көп.
Туберкулездік менингиттің ерте диагнозы емнің нәтижесі үшін маңызды, бірақ пациенттер әдетте спецификалық емес белгілері бар субакутты курсты өткізетіндіктен қиын. Науқастардың едәуір бөлігі ауыр неврологиялық кемістіктен зардап шегуі мүмкін. Шолуда балалардағы туберкулезді менингиттің клиникалық ерекшеліктері мен диагностикалық процедуралары, емдеу әдісі сипатталған.
Қосымша кортикостероидтармен үйлесімді түрде туберкулезге қарсы дәрілерді жеткілікті мөлшерде емдеу туберкулезді менингиттің бар науқастарда жақсы болжамға қол жеткізуі мүмкін.

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туберкулезді менингит белгісіз шығу тарихы және белгісіз тарихы бар менингитпен емделушілермен кездескенде, бұл диагнозды есте ұстауы керек. Негізгі міндеттер диагностикалық тестілеу стратегиясын және туберкулезге қарсы емдеуді оңтайландыруды қамтуы керек.
Негізгі сөздер: *инфекция, орталық жүйке жүйесі, туберкулез, емдеу, нәтиже, асқынулар.*

Туберкулезный менингит у детей

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Инфекция центральной нервной системы, вызванная микобактериями туберкулеза, является редким, но крайне разрушительным и потенциально смертельным проявлением туберкулеза. Несмотря на нынешнее глобальное сокращение числа случаев заболевания туберкулезом, он по-прежнему является одной из основных причин смертности во всем мире.

В силу своей редкости (1-2% активного туберкулеза) и вариабельности симптомов, туберкулез с поражением центральной нервной системы остается диагностической проблемой, а любая задержка в проведении специфического лечения может привести к ухудшению прогноза. Несмотря на доступность эффективного лечения, все еще имеются многочисленные случаи смерти среди пациентов в результате поздней диагностики.

Ранняя диагностика туберкулезного менингита имеет важное значение для результата лечения, но сложна, потому что пациенты, как правило, представляют подострое течение с неспецифическими симптомами. Значительная доля пациентов может страдать от тяжелой неврологической инвалидности. В обзоре описаны клинические особенности и диагностические процедуры в отношении туберкулезного менингита у детей, а также метод лечения.

Предоставление адекватного мультилекарственного противотуберкулезного лечения в сочетании с дополнительными кортикостероидами, вероятно, позволит достичь хорошего прогноза у пациентов с туберкулезным менингитом.

При встрече с пациентами с менингитом неизвестного происхождения и неопределенным анамнезом следует иметь в виду диагноз «туберкулезный менингит». Основные проблемы должны включать в себя продвижение диагностических стратегий тестирования и оптимизацию противотуберкулезной терапии.
Ключевые слова: *инфекция, центральная нервная система, туберкулез, лечение, исход, осложнения.*

Introduction

Infection of the central nervous system (CNS) caused by *Mycobacterium tuberculosis* is rare yet highly devastating and potentially lethal manifestation of tuberculosis (TB). Before the modern chemotherapy era, TB with CNS involvement was usually of fatal outcome. In spite of a current global decrease of incident cases, TB persists a prominent cause of death on a worldwide scale.

According to WHO data in 2015, there were approximately 10.4 million new cases of active tuberculosis and 1.5 million deaths caused by TB reported worldwide. In children, 1 million new cases and 140 thousand deaths were noticed mostly in Asia and Africa [1]. In 2015 there were nearly 6.5 thousand cases of TB in the Polish population, which is a number smaller than in previous years. The incidence rate of 16.8/100,000 for 2014 qualified Poland to countries with a low incidence of TB in Europe. In 2015 66 cases of TB were registered in children below 14 years of age. There were only 7 cases of tuberculosis meningitis (TBM) in Poland in 2013, none of which was diagnosed in children [2,3].

On account of its rarity (1-2% of active TB) and variable nature of symptoms, TB with CNS involvement remains a diagnostic challenge while any delay in implementation of specific treatment may result in worsening the prognosis. Despite the availability of effective treatment, there are still numerous cases of deaths among patients as an effect of late diagnosis.

TB infections, irrespective of clinical manifestation, start with the inhalation of bacilli into distal airways, in the form of droplet nuclei. Subsequently evading the airspace into the interstitial tissue, *M. tuberculosis* reaches initially the local draining lymph nodes in the lung and then spreads towards distant locations on hematogenous way. The TBM is a consequence of a hematogenous spread from the primary foci – most commonly located in the lungs, to the highly oxygenated regions of the body, including the brain. TB with CNS involvement begins with forming the small tuberculous foci (Rich foci) in the brain, spinal cord and meninges. The most common form of CNS tuberculosis is TBM, however less common forms include tubercular encephalitis, intracranial tuberculoma, and tuberculous brain abscess. Capability to control the Rich foci combined with its location determine which form of CNS TB is developed [4]. The significant conse-

quence of TBM is a vasculitis of Willis circle and the perforating branches of the middle cerebral artery, resulting in abnormal blood distribution and brain infarctions in the regions of these vessels supply [4].

Clinical presentation

TBM usually has a subacute course with initially unspecific symptoms. Children with TBM often present with fever, nuchal rigidity, seizures and abdominal complaints (nausea, vomiting). A headache occurs more frequently in adults. The severity of clinical signs can be assessed with the use of British Medical Research Council staging system which has a considerable prognostic value (Table 1) [5,6]. Patients may present altered consciousness and neurological deficits. In selected cases initial symptoms may be located in in the ear in the absence of pulmonary lesions [7].

Diagnosis

The diagnosis of TBM is difficult and can be based only on clinical presentation and preliminary cerebrospinal fluid (CSF) findings without unequivocal microbiologic confirmation. The probability of TBM increases when certain clinical characteristics are present, such as longer duration of symptoms (>six days), the presence of focal deficits and moderate CSF pleocytosis [8,9]. Characteristic CSF findings of TBM include lymphocytic-predominant pleocytosis, elevated protein levels, (usually: 100–500 mg/dL) and low glucose, (typically less than 45 mg/dL). Isolation of the bacillus in the CSF from the culture or on smear remains the gold standard for the diagnosis. The cultures are, however, slow-growing, and the results obtained from the CSF are very often negative. Various reviews have reported positive results on CSF smear or cultures in 33% to 64% of cases [10,11]. Acid-fast bacilli (AFB) microscopy has a low sensitivity [12,13]. Culture can take several weeks and also is of low sensitivity (40–80%), though it should be performed to determine drug susceptibility [14].

Interferon-γ release assays (IGRAs) such as QuantiFERON-TB Gold test that detect *M.tuberculosis*-specific interferon-γ–producing lymphocytes in the peripheral blood are more accurate than skin testing at diagnosing of latent TB. These tests do not distinguish between active disease and latent infection, and a negative result does not rule out disease in symptomatic patient. Currently, IGRA tests are only recommended for diagnosing latent TB [15].

Given the relatively low sensitivity of acid-fast smear and inherent delay in culture, newer diagnostic methods for TBM have been developed. Polymerase chain reaction (PCR) method has an important role, with high sensitivity (85-95%) and specificity (95-100%) in newer nucleic acid amplification test that amplifies several target genes simultaneously [16-18]. Neuroimaging can be a massive

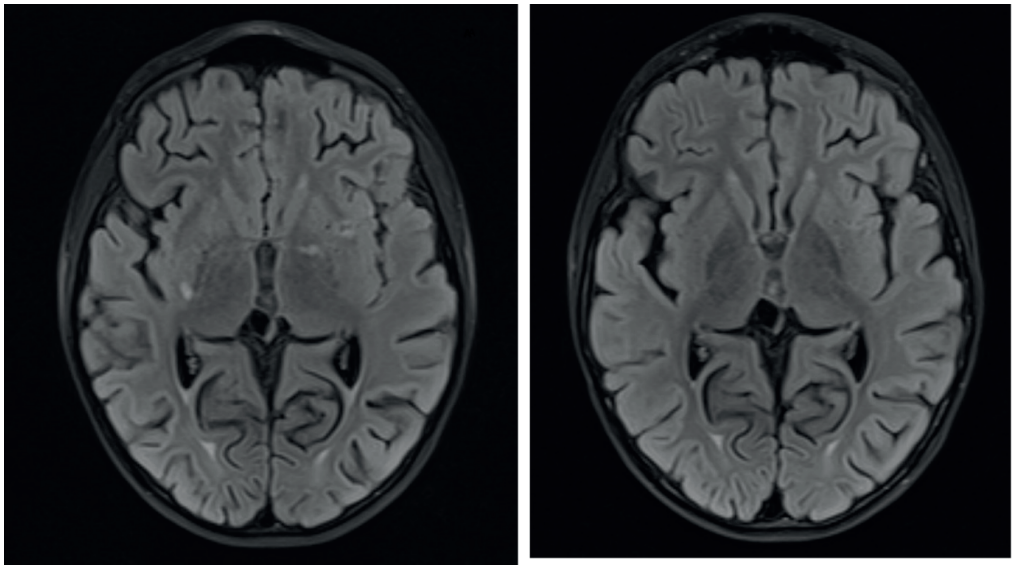

Figure 1.

Head MRI – T1 weighing, transverse cut (A) hypertensive foci visible bilaterally in globus pallidus; image suggestive for hemorrhage within ischemic lesions and inflammation of the small vessels, (B) partial regression of lesions.

Table 1. The British Medical Research Council (BMRC) Clinical Stages for TBM

CLASSICAL				MODIFIED
Level of Consciousness	***Focal Neurological Deficits***	***Other Findings***	***Stage***	***Glasgow Coma Score***
normal	none	none	I	15 without focal neurological defects
lethargy	minor (cranial nerve palsy)	altered behavior, meningismus	II	15 with focal neurological defects; 11-14
stupor or coma	major (hemiparesis)	seizures, abnormal movements	III	1-10

help in diagnosis. Magnetic resonance imaging (MRI) is the test of choice for visualizing abnormalities in TBM, as it is superior to computed tomography (CT) for evaluating the brainstem and spine. Standard radiologic features of TBM are basal meningeal enhancement and hydrocephalus. Other parts of the CNS may be involved as well (Figure 1). Cerebral infarcts with hypodensities, cerebral oedema, and nodular enhancing lesions may also be seen [19,20].

Management

Once the TBM is suspected, early implementation of treatment dramatically improves the outcome as death, or long-term sequelae are more often seen in patients in stage III BMRC at the time of admission [9]. Therefore, empiric treatment is warranted when both CSF findings and clinical features are suggestive of TBM. In published reports, the decision to start specific treatment was empirical [9, 21]. The dosing of tuberculosis drugs for treating TBM has been generally extrapolated from adult populations. The initial regimen for presumed drug-susceptible TBM should include two-months of daily isoniazid, rifampin, pyrazinamide and either streptomycin or ethambutol. The Polish Respiratory Society, as many others currently recommend antituberculous therapy of TBM for 12 months [15, 21-25]. Multidrug-resistant TBM, characterized as resistance to equally isoniazid and rifampin with or without resistance to other agents, results in poor prognosis. The significant rise in mortality of TBM when rifampin and isoniazid resistance is present establishes the importance of the first in the treatment regimen. Thus rifampin displays relatively limited penetration into CSF contrasted to isoniazid.

Published reports showed that adjuvant treatment with corticosteroids, such as dexamethasone, improved outcome in HIV-negative children with TBM, as many of the neurologic sequelae of TBM is considered to be an effect of an excessive host-inflammatory response that results in brain oedema [26-27]. The most prominent benefits of adjuvant therapy are yet observed in early diagnosed patients.

The most common complication of TBM is hydrocephalus with particularly high risk in children [28]. It has been shown that in children with significant hydrocephalus, early ventriculoperitoneal shunting reduces morbidity and mortality, and is a predictor of functional outcome [11]. Other neurological complications are cranial nerve palsies due to adhesions (particularly II-IV, VI-VIII), stroke as a result of constriction of the internal carotid and seizures as an effect of hydrocephalus, oedema or hyponatremia (inappropriate ADH secretion).

Prognosis and outcome

Certain factors predisposing for TB are widely known such as malnutrition, recent infections (measles, varicella, pertussis, HIV, and other viral illnesses), immunosuppressive therapies, stress and hormonal changes. Another critical relation reported in multiple studies is a history of an adult source of contact that was found in 42 – 70% of patients [11,12]. Statistically, every adult with pulmonary TB infects up to 15 people before receiving a diagnosis and starting treatment [12,29]. Many significant variables for predicting the outcome of TBM were proposed, among them the age of the patient (young worsens the prognosis) and stage of disease combined with the existence of neurological complications (focal weakness, cranial nerve palsy, hydrocephalus) are of most significant value. Children with stage I TBM disease are likely to have a *good* outcome, whereas children with stage III disease have a high risk of mortality [21,24].

Published cases describing TBM cases in children were presented in Table 2 [31-36]. Only two cases were present in children with a proven history of BCG vaccination. A significant proportion of described cases had no apparent contact with an infected family member. Children developed typical abnormalities in the CSF, and various lesions were found in brain imaging. No residual deficits were noticed in some patients, but hydrocephalus was the most common complication.

Conclusion. As diagnostic tests of TBM still have suboptimal performance, diagnosis relies on a thorough history, clinical examination, and relevant investigations. Distinguishing tuberculous meningitis from acute bacterial meningitis is very important. Prompt diagnosis and adequate treatment are lifesaving. In the presented case, the disease proceeded in typical three phases, and as patient's condition deteriorated the final result of the therapy was dependent on the time of inclusion of specific treatment. It is worth stressing the long interval between boy's exposure with a probable source (biological mother) ant the onset of the disease. The inverse relation between the delay in the start of adequate treatment and the clinical outcome makes early diagnosis of TBM essential.

Conflict of interest: The authors declare no conflict of interest.

Table 2. Review of published cases with TBM in children

Author, year	Age and GENDER	BCG	Family history	Symptoms	GCS and BMRC ON admission
Neele A et al., 2014	4 years-old, girl	yes	unremarkable	fever, periorbital oedema, vomiting for 3 weeks; followed by drowsiness, neck stiffness, left hemiparesis; relapse (3 weeks after 1st course): headache, abdominal distension, hepatosplenomegaly, aphasia, left hemiparesis	GCS unknown, BRCM III
Birnbaum G. D. et al., 2014	22 months-old, girl	UNK	mother - cavitary pulmonary TB	primary symptoms - not given; secondary - difficulty walking, left-sided tremor and leaning to the left while, right eye ptosis, 3 generalized tonic-clonic seizures	GCS 10 pts, BRCM III
Chow E.J. et al., 2015	2 years-old, girl	UNK	unremarkable	fever (38-39) for 5 weeks, ear pain, nonproductive cough, followed by left-sided muscle weakness; after admission letargic	UNK
Wood K., 2012	6 years-old, boy	no	aunt with chronic cough of unknown etiology	2-week history of headache, vomiting, and fever with progression to diplopia (right sixth cranial nerve palsy)	UNK
Wen L.S. et al., 2011	16-minths-old, girl	no	unremarkable	cough and fatigue for 6 weeks, fever (38,5-39,5ºC) for 2 weeks, anorexia, lethargy; the day of admission: 20 min. generalised seizure, anisocoria	GCS 3 pts
Radmanesh F. et al., 2010	14-months-ld, boy	UNK	UNK	right-sided hemiparesis and repeated generalized tonic-colonic seizures; 2 months later: drowsiness, bilateral sixth nerve palsies, bilateral papilledema, right-sided hemiplegia and severe spasticity of all limbs; followed by: severe abdominal pain and distention and low-grade fever;	UNK
Frąszczak-Wojańska J. et al.	8-years old boy	Yes	Mother- died of TB	Fever, fatigue, right middle-ear cholesteatoma, Kernig sign and diminished patellar reflex on the right side, nuchal rigidity, bradycardia and generalized seizures, altered consiousness	GCS 10

GA - gastric aspirate, CSF – cerebrospinal fluid, MDR-TBM – multidrug resistant TBM, INH – isoniazid, RIF – rifampin, PZA – pyrazinamide, ETO – ethionamide, AMK – amikacin, OFX – floxacin, TZD – terizidone, PAS - para-aminosalicylic acid, STP- streptomycin.

MicrobioloGy RESULTS	CSF general exam	Imagning	Treatment, additional therapy	Complication and outcome
CSF and GA AFB and culture negative, PCR not available; relapse: ascitic fluid AFB-positive and culture-positive	L: 100/ucl P: 2,2 g/l G: 1,8mmol/L; relapse: L: 15/mm3, P: 3 g/L, and G: 2.3 mmol/L	CT scan: meningeal enhancement, multiple lesions, multiple infarcts in basal ganglia, hydrocephalus; 2nd CT: progressive meningeal enhancement and worsening hydrocephalus;	1st course INH, RIF, PZA, ETO, prednisolone (6 wk) followed by INH, RIF, ETO, TZD (7 mo.); relapse (MDR-TBM): PZA, EMB, ETO, AMK, OFX, TZD, PAS	hydrocephalus (ventriculoperitoneal shunt); tuberculomas in the brain stem and ascites during anti-TB therapy; no residual deficits
pan-susceptible Mycobacterium tuberculosis from CSF and GA	UNK	hydrocephalus (ventriculoperitoneal shunt), basilar meningitis, right basal ganglia infarct;	INH, RIF, PZA, ETO plus two courses of corticosteroids 2 + 3 months	hydrocephalus (ventriculoperitoneal shunt); tuberculoma during effective anti-TB therapy; no residual deficits
AFB negative; culture negative; QuantiFERON-TB Gold positive	L: 233/ucl, protein 103 mg/100mL (N:15-60 mg/100mL), glucose 20 mg /100mL (N: 50-80 mg/100mL)	CT: ventriculomegaly (lateral, third, fourth ventricles); MRI: basilar meningeal enhancement, acute infarcts of the corpus callosum and bilateral basal ganglia	azithromycin; ceftriaxone; cefdinir; isoniazid, rifampin, ethambutol, pyrazinamide	no residual deficits
serum QuantiFERON-TB Gold test + CSF PCR - positive; CSF culture - pansensitive *M tuberculosis* (4 weeks)	lymphocytic pleocytosis with 376 white blood cells, low glucose, elevated protein	MRI: basal enhancement	empirical parenteral antibiotics; after progression: INH, RIF, PZA, ETO, and prednisone	no residual deficits
Mycobacterium tuberculosis from CSF and GA	UNK	MRI: ischemic infarct in the left basal ganglia, right MCA distribution, left gyrus rectus and decreased perfusion in multiple areas (widespread vasculitis); CXR: diffuse micronodular pattern throughout both lung fields	six-drug anti-TB regimen and steroids	minimal neurologic function with withdraw to pain and no response to voice; no track to noise or light
PPD skin test negative; culture of GA negative for tuberculosis, PCR of the CSF positive for Mycobacterium tuberculosis; peritoneal biopsy: granuloma formation with caseous necrosis;	CSF: protein level of 150 mg/dL, rest NG; peritoneal fluid: protein 1,500 mg/dL, WBC 1,400/dL with 60% lymphocytes, glucose 30 mg/dL	CT: severe tri-ventricular hydrocephalus, periventricular edema	four-drug regimen for the first 2 months, continued with a two-drug regimen, for a total course of 1 year	hydrocephalus (ventriculoperitoneal shunt); ascites
serum QuantiFERON-TB Gold test + CSF PCR - positive; GA CSF culture - pansensitive *M tuberculosis (18 day)*	L: 350/ucl P: 1,26 g/l G: 37 mg/dl; chloride 114,4 mmol/l	numerous hyperintense foci in T2 and FLAIR with areas of cerebral edema in the occipital lobes and generalized leptomeningeal enhancement suggestive for initial phase of inflammatory process	INH, RIF, PZA, STP (2 weeks), dexamethazone (6 weeks) followed by INH, RIF, ETO, PZA (2 mo.); RIF, INH (10 mo)	no residual deficits

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