CASE REPORT

Tuberculous Meningitis: The Important Role of Imaging

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Abstract

Tuberculous meningitis is the most severe form of tuberculosis, and the diagnosis continues to be challenging for clinicians. Indeed, many cases of tuberculous meningitis cannot be confirmed based on clinical findings, and laboratory techniques are largely insensitive or slow. Clinical presentation can be nonspecific and suggest alternative conditions. The difficulty in diagnosis often leads to a delay in treatment and subsequent morbidity and mortality. We present the case of a 4-year-old Indian girl with meningitis that presented neurological deterioration while taking antibiotics. The epidemiological history and neuroimaging findings of incipient hydrocephalus, infarcts, and probable tuberculomas were essential to evoking the diagnosis of tuberculous meningitis. Diagnosis of tuberculous meningitis is difficult mainly in these rare cases with acute presentation that clinically present similarly to other forms of meningitis. The recognition of this entity involves a high index of suspicion based on the previous referred findings and is essential to prevent morbidity and mortality.

Keywords: Antitubercular Agents/therapeutic use; Child, Preschool; Mycobacterium tuberculosis; Treatment Outcome; Tuberculosis, Meningeal/diagnostic imaging; Tuberculosis, Meningeal/drug therapy

Introduction

Tuberculosis is an airborne disease caused by the bacteria *Mycobacterium tuberculosis*. Despite mainly affecting the lungs, causing pulmonary disease, it has a protean presentation, and may act as a multi-systemic disease.[1] Tuberculous meningitis, caused by the seeding of the meninges with the bacilli, is the most severe form of extra-pulmonary tuberculosis. It accounts for 1% of all cases of extra-pulmonary tuberculosis and in the developed world 6% of all causes of meningitis.[2]

Definitive diagnosis requires the detection of *Mycobacterium tuberculosis* in the cerebrospinal fluid, either by the detection of acid-fast bacilli or culture. As the sensitivity of these laboratory tests can be low, the assumption of a diagnosis is frequently made based on the signs and symptoms, the cerebrospinal fluid characteristics, and the imaging findings, in association with the exclusion of the most likely alternative diagnosis. The early recognition and timely treatment of tuberculous meningitis is critical to prevent the considerable mortality and morbidity associated with this condition.[3] The difficulty in diagnosis often leads to a delay in treatment and subsequent mortality. Those who survive are left with long-term sequelae leading to lifelong disability.

We report a clinical case of a 4-year-old girl with tuberculous meningitis in which the epidemiological context and the imaging findings had an essential role in the diagnosis and enabled an early treatment. We also discuss the difficulties in establishing a diagnosis in the absence of the standardized diagnostic criteria.

Case Report

A previously healthy 4-year-old girl, born in India and living in Portugal for two years, presented to the emergency department with a 12 day history of fever, cough, headache, and vomiting, evolving to an episode of loss of consciousness and generalized tonic-clonic movements. She was immunized according to the Indian national immunization schedule that included the bacillus Calmette-Guérin vaccine (BCG) but did not have anti-pneumococcal or meningococcal immunization. On admission, her blood pressure was 135/68 mmHg (systolic > 95th + 12 mmHg), heart rate of 95 beats/min., and regular breathing of 24 breaths/minute. She

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presented meningeal signs, photophobia, and mydriatic but with reactive pupils. Regarding the laboratorial results, there was a microcytic hypochromic anemia (hemoglobin 12 g/dL, mean corpuscular volume 67.1 fL, mean corpuscular hemoglobin 21.8 pg, red cell distribution width 14.9%), serum electrolytes, C reactive protein, aminotransferases, glucose, coagulation, and ammonia were normal and blood cultures were negative. The polymerase chain reaction performed on a nasopharyngeal swab was positive for coronavirus HKU1, rhinovirus, and bocavirus. A head computed tomography (CT) scan showed a mild enlargement of the temporal horns without other signs of hydrocephalus and without brain parenchymal changes. A lumbar puncture revealed clear cerebrospinal fluid, pleocytosis of 113 lymphocytes/µL, raised protein (1.9 g/L), and low glucose (24 mg/dL, 20% of the blood level), with sterile cerebrospinal fluid culture. A polymerase chain reaction from cerebrospinal fluid was negative for herpesvirus, enterovirus, and *Mycoplasma pneumoniae*. A stool polymerase chain reaction was also negative for enterovirus. Pneumococcal meningitis could not be excluded, and vancomycin was associated to ceftriaxone until a negative result of the polymerase chain reaction for *Pneumococcus*. The amplification of bacterial 16S ribosomal deoxyribonucleic acid (DNA) with a polymerase chain reaction in cerebrospinal fluid was also negative.

On the first day after hospital admission, despite spontaneously opening her eyes and following the instructions given, the patient's neurological state deteriorated with intermittent drowsiness and episodes of bradypnea that motivated her admission to the intensive care unit for mechanical ventilation. She required hyperosmolar therapy with hypertonic saline and intravenous levetiracetam to prevent further seizures. The electroencephalogram performed under sedation with midazolam and fentanyl showed slow and poorly reactive activity.

Brain magnetic resonance (MRI) revealed multiple focal intra-axial lesions with ring or miliary enhancement after contrast, most likely compatible with tuberculomas due to her age and clinical signs and symptoms, and cortical lesions, presumably ischemic (Figs. 1 and 2A). The epidemiological history was investigated and it was discovered that she lived in an area with a high incidence of tuberculosis (100 cases per 100,000 habitants[4]) and in precarious living conditions. This epidemiologic context, the signs and symptoms of the disease, cerebrospinal fluid findings as well as the cerebral imaging findings were enough to evoke the diagnosis of tuberculous meningitis without repeating lumbar puncture, and anti-bacillary drugs – isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and levofloxacin – and prednisolone were prescribed.

Chest radiography was unremarkable, but a thoracic CT revealed a pulmonary nodule and pleural effusion as well as a mediastinal adenopathy. An abdominal ultrasound did not have any typical imaging findings of tuberculosis. Three morning gastric aspirates examined by microscopy (Ziehl-Neelsen stain) were negative for acid-fast bacilli and gastric aspirates and cerebrospinal fluid nucleic acid amplification tests and solid and liquid cultures were negative for *Mycobacterium tuberculosis*. Interferon-gamma release assay (IGRA) T-SPOT (enzyme-linked immunospot assay on peripheral blood mononuclear cells) was positive and, although not confirming active tuberculosis, made it possible to diagnose latent tuberculosis infection. A human immunodeficiency virus (HIV) infection was excluded. On the ninth day in the hospital, she developed a convergent strabismus compatible with a left *abducens* palsy, papilledema and reinitiated headache, and vomiting. She was tachycardic (139 beats/min. and her blood pressure was 118/57 mmHg (systolic $\geq 95^{th}$ percentile to $< 95^{th}$ percentile + 12 mmHg). A head CT scan revealed similar findings, and a lumbar puncture elevated opening pressure of 44 mmHg, with a cerebrospinal fluid pleocytosis of 128 lymphocytes/µL, raised protein (1.5 g/L), and a low glucose (41 mg/dL, 42% of the blood level). Acetazolamide was initiated as a treatment for intracranial hypertension and maintained for one month, with the clinical improvement of the headache and vomiting and the total regression of the papilledema. Metabolic acidosis and hypokalemia occurred due to carbonic anhydrase inhibitor therapy and were treated appropriately.

She had another brain MRI in the following month with the dimensional improvement of the multiple small intra-axial lesions (Figs. 1 and 2B). She was kept on steroid therapy for one month, withdrawing on the second month and was discharged under treatment with anti-bacillary drugs. She completed two months of HRZE and levofloxacin and ten months of isoniazid and rifampicin. A follow-up showed clinical improvement, without headache or vomiting, and the regression of the convergent strabismus. She maintained a mild asymmetry of the lower face presumably due to hypomobility on the right side and no other motor deficits. The brain MRI that was performed one year later was unremarkable (Figs. 1, 2C, and 3) and ophthalmological and ear, nose, and throat evaluations excluded visual or hearing deficits. Screening of all close contacts was negative and the next-generation sequencing gene panel for susceptibility to mycobacterial infections excluded immunodeficiencies.

Discussion

Tuberculosis is an ancient disease that continues to be a modern-day public health problem.[5] Even though nowadays it can be preventable and curable, a considerable number of cases are misdiagnosed, especially in countries with a low incidence of the disease.

Tuberculous meningitis is the most lethal and disabling disease form.[6] Several presentations, considering the clinical signs and symptoms, cerebrospinal fluid analysis, and cerebral imaging, have been described, but diagnosis remains a challenge. In children, given the young age and the nonspecific symptoms, other diagnosis is often considered in the first instance. To overcome these problems and allow an early recognition of the disease before permanent neurologic damage, it was published in 2010 a personal view proposing a case definition[7]: definite diagnosis when acid-fast bacilli are detected and/or *Mycobacterium tuberculosis* is cultured or detected by a reliable molecular method from cerebrospinal fluid in someone with symptoms and signs suggestive of the disease, and probable or possible diagnosis based on clinical, cerebrospinal fluid and cerebral imaging criteria, evidence of tuberculosis elsewhere and exclusion of alternative diagnosis.

In this case report, the usual nonspecific clinical features of tuberculous meningitis like fever, headache, and vomiting were present and lasted more than five days, latter evolving to neck stiffness and neurological signs such as convulsions, abnormal mental state, and cranial nerve palsy. Routine analysis of cerebrospinal

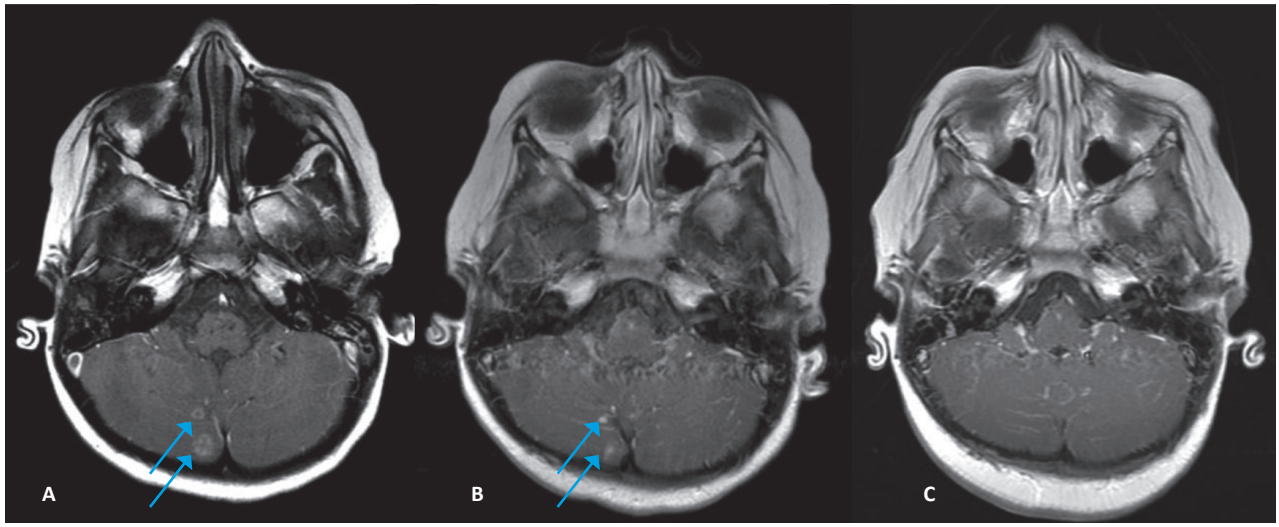

Figure 1. Brain magnetic resonance. Axial T1 with gadolinium. Initial study (A) and follow up after one month (B) and one year (C). Right cerebellar lesions initially with ring enhancement (A), posterior improvement with reduced size and miliary enhancement (B), and total regression (C).

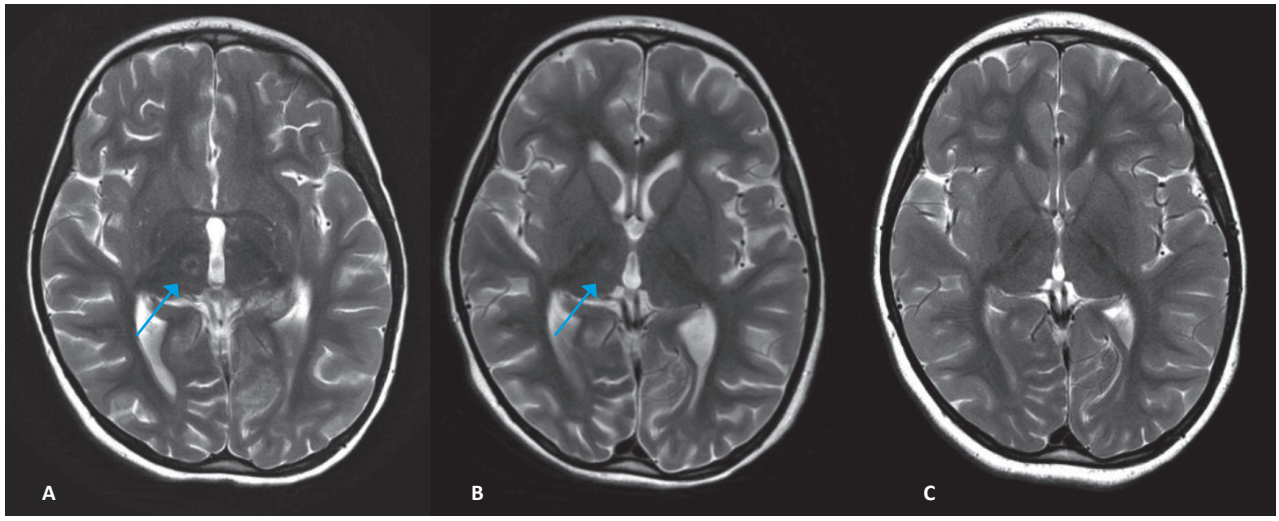

Figure 2. Brain magnetic resonance. Axial T2. Initial study (A) and follow up after one month (B) and one year (C). Right thalamic and left posterior hippocampal lesions with central hyposignal and peripheral hypersignal and some millimetric hypersignals in the left thalamus (A), posterior improvement with reduced size (B), and total regression (C).

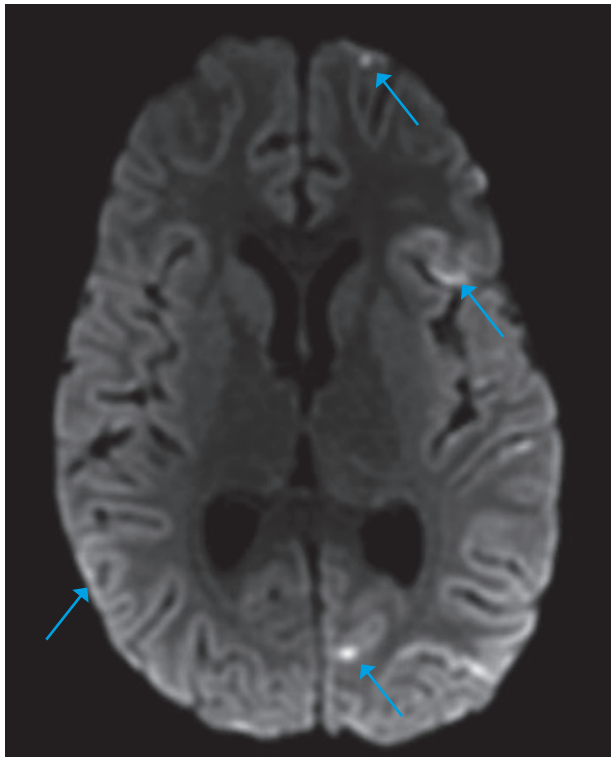

Figure 3. Brain magnetic resonance. Axial DWI. Millimetric cortical lesions with restricted diffusion in both cerebral hemispheres and left cerebellum.

fluid showed the typical clear appearance, pleocytosis with lymphocyte predominance, raised protein levels greater than 1 g/dL, and profound hypoglycorrhachia with cerebrospinal fluid to plasma ratio < 50%. Cerebral imaging revealed incipient hydrocephalus, infarcts, and probable tuberculomas that are typical neuroradiologic findings of tuberculous meningitis.[7-10] Evidence of a pulmonary node, pleural effusion, and a mediastinal adenopathy in the thoracic CT scan made it possible to identify lung involvement. Cerebrospinal fluid bacteriological exams, however, did not detect *Mycobacterium tuberculosis*, leaving us with a probable diagnosis of tuberculous meningitis, according to the referred case definition criteria.[7]

In fact, several studies[11-12] have reported low diagnostic yields of *Mycobacterium tuberculosis* due to its low bacillary loads in cerebrospinal fluid, stating that smears, although diagnostic, are positive in only 3% of children, cultures in about 60% and nucleic acid amplification tests in 80%. Greater volumes of cerebrospinal fluid (10-15 mL) have, therefore, been suggested to improve the positivity of the bacteriological diagnosis, but as these quantities are highly impractical to obtain in children, they often make the detection of the bacteria in the cerebrospinal fluid unfeasible.

In this case, a positive IGRA T-SPOT documented latent infection, but it was the MRI multiple intra-axial infra and supra-tentorial lesions, presumably tuberculomas, that raised the suspicion of underlying tuberculosis, even in the absence of meningeal enhancement, and enabled an early diagnosis and appropriate treatment. It is important to mention, however, that regardless of a normal head CT, which is estimated to occur in 30% of all cases, it is a useful exam in the suspicion of tuberculous meningitis, as an MRI is not widely available. Hydrocephalus and meningeal enhancement are important CT findings that can be found in 80% and 75% of children with tuberculous meningitis,[13] respectively, and infarcts, tuberculomas, and pre-contrast basal hyperdensities can also be seen.

Regarding the treatment, according to the World Health Organization guidelines[14] for pediatric tuberculous meningitis, a four-drug regimen (HRZE) of two months followed by a two-drug regimen (isoniazid and rifampicin) of ten months, including high-dose rifampicin (15 mg/kg/day) and the association with levofloxacin (17 mg/kg/day) on the initial two months was defined. Rifampicin is an essential drug to treat tuberculous meningitis and, despite its poor cerebrospinal fluid penetration, these higher doses aimed to improve its effectiveness. Levofloxacin, with good cerebrospinal fluid penetration, was associated with improving the prognosis, considering the severity of the disease. Standard isoniazid (7.5 mg/kg/day), pyrazinamide (35 mg/kg/day), and ethambutol (20 mg/kg/day) were used according to the recommendations. As for adjuvant steroids, as it is recommended in all cases of tuberculous meningitis to improve survival and reduce morbidity, prednisolone was initiated in a dosage of 2 mg/kg/day.

Concerning the disease transmission vehicle, it should be noted that, even though this child was born and lived in India until 2 years of age, the evolution from the primo infection to tuberculous meningitis is usually fast, taking up to six months. Her current living area, with a high incidence of the disease, and the close contact with Indians seemed to us as the most important factor in developing the disease.

In addition, although one of the benefits of BCG vaccination is protection against disseminated forms of childhood tuberculosis in immunocompetent patients, especially meningitis,[14] in this case BCG immunization did not prevent this severe form of tuberculosis. The real effectiveness of the vaccine to prevent these severe forms of the disease has been questioned, but it seems that even in these situations the outcomes of these children are better than in unvaccinated ones.[13] Against all odds, this child almost totally recovered and had a great evolution.

In conclusion, we present a case report that did not

meet the known criteria for a definite diagnosis of tuberculous meningitis, in which the epidemiological and socioeconomic context, clinical presentation, cerebrospinal fluid characteristics and mainly the typical findings of the MRI that were distinctive, raised a high index of suspicion for the disease and helped in achieving a diagnosis.

This case intends to raise awareness for the importance of considering tuberculous meningitis as a differential diagnosis of meningoencephalopathy in countries without a high burden of tuberculosis, while bacterial, viral, or fungal causes are being excluded, and for the challenges of this diagnosis. Key risk factors for severe tuberculosis in children such as this child's age should be noted. In the absence of a microbiological confirmation, as in this case, the combination of the defined criteria for probable or possible diagnosis that include unspecific signs and symptoms, cerebrospinal fluid characteristics, and typical imaging findings, associated with the epidemiological context should evoke the diagnosis of tuberculous meningitis.

Appropriate screening and strengthening healthcare networks should not be neglected as they are the key to combating this public health problem.

WHAT THIS CASE REPORT ADDS

- Tuberculous meningitis should be included in the differential diagnosis of meningoencephalopathy and a high index of suspicion with an emphasis on the epidemiological context is required.
- Identifying tubercle bacilli in the cerebrospinal fluid is difficult and time consuming and, therefore, the diagnosis of tuberculous meningitis usually relies on clinical evidence, combined with laboratory and cerebral imaging findings.
- This case report aims to raise awareness for the importance of imaging and the magnetic resonance distinctive features that should raise suspicion of underlying tuberculous meningitis.
- Even though the immunization with BCG is defined, we question its role.
- Early treatment of tuberculous meningitis may prevent serious complications and decrease the rates of morbidity and mortality.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Consent for publication

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Confidentiality of data

The authors declare that they have followed the protocols of their work centre on the publication of patient data.

References

1. Adigun R, Singh R. Tuberculosis. 2020. In: StatPearls. Treasure Island: StatPearls Publishing; 2021.
2. Slane VH, Unakal CG. Tuberculous meningitis. 2021. In: StatPearls. Treasure Island: StatPearls Publishing; 2021.
3. Cherian A, Thomas SV. Central nervous system tuberculosis. Afr Health Sci 2011;11:116-27.
4. Direção Geral de Saúde. Tuberculose em Portugal 2018 (dados provisórios). Lisboa: DGS; 2019.
5. Zaman K. Tuberculosis: A global health problem. J Health Popul Nutr 2010;28:111-3. doi: 10.3329/jhpn.v28i2.4879.
6. Méchaï F, Bouchaud O. Tuberculous meningitis: Challenges in diagnosis and management. Rev Neurol 2019;175:451-7. doi: 10.1016/j.neurol.2019.07.007.
7. Marais S, Thwaites G, Schoeman JF, Török ME, Misra UK, Prasad K, et al. Tuberculous meningitis: A uniform case definition for use in clinical research. Lancet Infect Dis 2010;10:803-12. doi: 10.1016/S1473-3099(10)70138-9.
8. Mezochow A, Thakur K, Vinnard C. Tuberculous meningitis in children and adults: New insights for an ancient foe. Curr Neurol Neurosci Rep 2017;17:85. doi: 10.1007/s11910-017-0796-0.
9. Thwaites GE, van Toorn R, Schoeman J. Tuberculous meningitis: More questions, still too few answers. Lancet Neurol 2013;12:999-1010. doi: 10.1016/S1474-4422(13)70168-6.
10. Ramachandran T. Tuberculous meningitis workup [accessed 31 March 2021]. Available at: https://emedicine.medscape.com
11. Walter N, Daley C. Tuberculosis and nontuberculous mycobacterial infections. In: Siro S, Silvestri G, Agustí A, editors. Clinical Respiratory Medicine. 4th ed. Philadelphia: Saunders; 2012.p.383-405.
12. Daniel BD, Grace GA, Natrajan M. Tuberculous meningitis in children: Clinical management & outcome. Indian J Med Res 2019;150:117-30. doi: 10.4103/ijmr.IJMR_786_17.
13. World Health Organization. Guidelines for treatment of drug-susceptible tuberculosis and patient care. Geneva: WHO; 2017
14. SAGE working group on BCG vaccines, World Health Organization secretariat. Report on BCG vaccine use for protection against mycobacterial infections, including tuberculosis, leprosy, and other nontuberculous mycobacteria infections [accessed 21 December 2020]. Available at: https://www.who.int

Meningite Tuberculosa: O Papel Importante da Imagem

Resumo

A meningite tuberculosa é a forma mais grave de tuberculose e o seu diagnóstico continua a ser um desafio. De facto, a maioria dos casos de meningite tuberculosa não pode ser diagnosticada com base nos achados clínicos e as técnicas laboratoriais são pouco sensíveis e morosas. A apresentação clínica pode ser inespecífica e sugerir outros diagnósticos. A dificuldade no diagnóstico frequentemente condiciona um atraso no tratamento e morbilidade e mortalidade subsequente. Apresentamos o caso de uma criança indiana de 4 anos com o diagnóstico de meningite que, sob antibioterapia, apresentou agravamento neurológico. A história epidemiológica e os achados de neuroimagem compatíveis com hidrocefalia incipiente, enfartes e prováveis tuberculomas, foram essenciais para evocar o diagnóstico de meningite tuberculosa. O diagnóstico de meningite tuberculosa é difícil, principalmente em casos raros de rápida evolução como este, em que a apresentação clínica é semelhante à de outras formas de meningite. O reconhecimento desta entidade envolve um elevado índice de suspeição com base nos achados anteriormente referidos e é essencial na prevenção de morbilidade e mortalidade.

Palavras-Chave: Antituberculosos/uso terapêutico; Mycobacterium tuberculosis; Pré-Escolar; Resultado do Tratamento; Tuberculose Meníngea/diagnóstico por imagem; Tuberculose Meníngea/tratamento farmacológico