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Case report

Disseminated tuberculosis with hydrocephalus and cerebral salt wasting syndrome: the importance of early diagnosis

Ana Raquel Mendes[1], Ana Lúcia Cardoso[2], Daniel Meireles[2], Alzira Sarmento[2], Alexandre Fernandes[3]

[1]Pediatrics Department, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto, Porto, Portugal

[2]Pediatric Intensive Care Unit, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto, Porto, Portugal

[3]Pediatric Infectious Diseases and Immunodeficiencies Unit, Pediatrics Department, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto, Porto, Portugal

Abstract

Background: Tuberculosis (TB) remains an important global health problem. Children have greater risk than adults for developing severe disease manifestations, such as tuberculous meningitis (TM). Because TM usually presents with non-specific symptoms in the early stages of the disease, early diagnosis and management are important to prevent adverse outcomes.

Case presentation: A previously healthy 2-year-old boy without history of Bacillus Calmette-Guérin vaccination was admitted to a Pediatric Ward due to fever that persisted for 11 days and altered consciousness. On day 1 of admission, his consciousness worsened and he developed symptomatic seizures. Emergent head computed tomography revealed hydrocephalus. He was intubated and ventilated, and subsequently transferred to a Pediatric Intensive Care Unit, where an external ventricular drain was inserted. Head magnetic resonance imaging confirmed the presence of meningitis concentrated on the base of his brain, together with vasculitic phenomena and ischemic lesions. We decided to initiate oral quadruple anti-bacillary drug therapy and intravenous adjuvant corticosteroids. The culture and molecular analysis of the cerebrospinal fluid and respiratory secretions were positive for *Mycobacterium tuberculosis* complex. Because his hyponatremia persisted, despite increasing sodium supplementation and hypovolemia, we suspected cerebral salt wasting syndrome. He was

therefore treated with oral fludrocortisone, which progressively improved his laboratory test results. The patient remained afebrile after day 4 and was extubated on day 10. He preferentially looked to his left, and other findings included right hemiparesis with increased muscular tone, right hand rhythmic finger movements, generalized hyperreflexia, bilateral hypertonia, and bilateral striatal hallux.

Conclusions: This case report emphasizes the importance of considering TB and TM in the differential diagnosis of a child with a fever of unknown origin to reduce the risk of short-term complications, such as seizures and hydrocephalus, and long-term complications, such as hemiplegia and cognitive impairment.

Keywords

Anti-bacillary drug therapy, cerebral salt wasting syndrome, fever of unknown origin, hydrocephalus, seizures, tuberculous meningitis.

Corresponding author

Ana Raquel Mendes, Pediatrics Department, Centro Materno-Infantil do Norte, Centro Hospitalar Universitário do Porto, Porto, Portugal; email: ana.mendes1890@gmail.com.

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Background

Tuberculosis (TB) remains an important global health problem even through its incidence is steadily declining. In the World Health Organization *Global Tuberculosis Report 2020*, it was estimated that 10.0 million people were infected with TB in 2019 [1]. Of these, 12% were children (aged < 15 years). Furthermore, it was estimated that TB caused 205,000 deaths in children aged < 15 years old in 2019 (32,000 in HIV-infected children), representing 13.8% of all TB deaths [1]. In Portugal, 34 cases of TB were reported in children aged < 6 years in 2018, corresponding to an incidence of 6.59 cases per 100,000 children aged < 6 years. Of those pediatric cases, 4 had severe disease [2].

Children have greater risk than adults of developing severe disease manifestations, such as disseminated TB or tuberculous meningitis (TM) following infection [3]. TM usually presents with non-specific symptoms in the early stages and is often only diagnosed at a late stage of the disease following brain damage. Patients with TM may also present with symptoms characteristic of complications, such as hydrocephalus and hyponatremia, due to cerebral salt wasting syndrome (CSWS) [4, 5]. Early diagnosis and management of TM is particularly important because a delay in diagnosis and treatment may lead to adverse outcomes, such as death, or neurologic and cognitive sequelae [6].

In this case report, we present a previously healthy 2-year-old boy without history of Bacillus Calmette-Guérin (BCG) vaccination, who suffered from prolonged fever lasting 11 days together with an altered level of consciousness and symptomatic seizures. He was later diagnosed with disseminated (pulmonary and meningeal) TB complicated with hydrocephalus and CSWS.

Case presentation

A previously healthy 2-year-old boy without history of BCG vaccination presented at a Pediatric Emergency Department due to fever persisting for 11 days, anorexia, and progressive prostration. On arrival, he was sleepy, but his physical examination was unremarkable and his blood tests were normal. The cytomegalovirus and Epstein-Barr virus serological tests and SARS-CoV-2 antigen test were negative. His chest X-ray scan was normal.

On day 1 of admission to the Pediatric Ward, the patient showed a decreased response to stimuli and fluctuating conscience. He also suffered symptomatic seizures characterized by generalized spasticity and conjugate eye deviation with chewing motions. A physical examination indicated neck stiffness and left hemiparalysis. An emergent head computed tomography (CT) scan revealed dilatation of the ventricular system with greater symmetrical supratentorial expression. The patient was therefore started on broad-spectrum intravenous (IV) antibiotics, together with acyclovir and levetiracetam. Due to a persistent Glasgow Coma Scale score of 7, he was intubated, ventilated, and transferred to a Pediatric Intensive Care Unit (PICU).

On admission to the PICU, the patient's blood pressure was 134/70 mmHg (systolic

value > 95th percentile), heart rate was 85 beats/min, peripheral oxygen saturation was 97% (FiO_2 0.4), and respiratory rate was 37 breaths/minute. An external ventricular drain was inserted immediately upon admission. Laboratory tests of cerebrospinal fluid (CSF) revealed an erythrocyte count of 1,300/μL, leukocyte count of 21/μL (polymorphonuclear cells 6/μL, mononuclear cells 15/μL), glucose concentration of 57 mg/dL, and protein concentration of 19 mg/dL. The adenosine deaminase (ADA) level was 2.7 U/L.

A head CT scan on day 3 showed a decreased amplitude of the ventricular system and non-specific inflammation on the base of the brain. Head MRI confirmed the presence of meningitis on the base of the brain with vasculitic phenomena and ischemic lesions (**Fig. 1**). On suspicion of TM, the antibiotics and acyclovir were stopped, and the patient was started on oral quadruple anti-bacillary drug therapy (isoniazid, rifampicin, pyrazinamide, and ethambutol) and IV dexamethasone for 2 weeks, which was then tapered over 2 weeks. The culture and molecular analysis of CSF and the molecular analysis of respiratory secretions were positive for *Mycobacterium tuberculosis* complex. HIV infection was excluded.

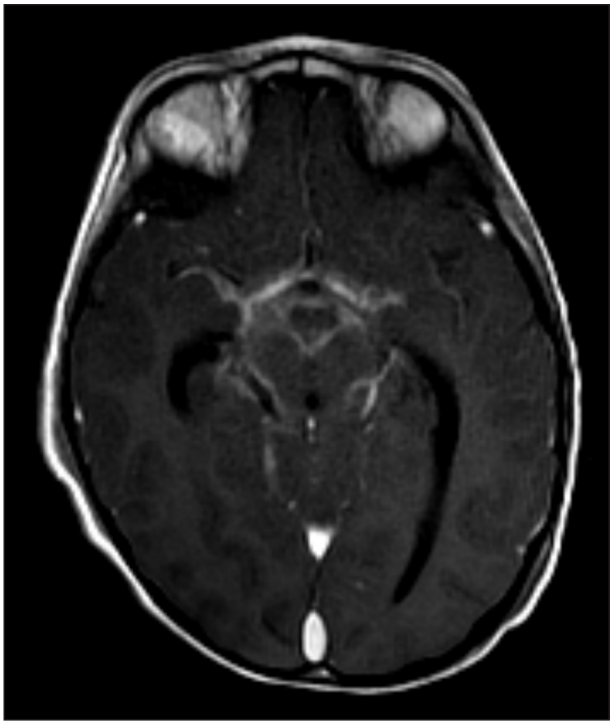

Figure 1. Contrast-enhanced T1 weighted axial MRI image. MRI image of the brain shows extensive leptomeningeal enhancement in the basal cisterns and sylvian fissures. Dilation of the temporal horns of the lateral ventricles due to hydrocephalus can also be seen.

Hyponatremia (minimum value of 132 mEq/L) persisted from day 6, despite increasing sodium supplementation up to 15 mEq/kg/day via total parenteral nutrition. Because the other clinical findings included dry skin and mucous membranes, a negative water balance, polyuria with a maximum value of 3.5 mL/kg/h, and a hematocrit value in the upper limit of normal (39.7%), we suspected CSWS (**Tab. 1**). Serum and urinary uric acid tests indicated hypouricemia (**Tab. 1**) and an increased fractional excretion of uric acid (12.05%). The patient was therefore treated with oral fludrocortisone for 3 months, which progressively improved the laboratory test results.

The patient remained afebrile after day 4 and was extubated on day 10. Clinical findings included a preferential look to the left, right hemiparesis with increased muscular tone, right hand rhythmic finger movements, generalized hyperreflexia, bilateral hypertonia, and bilateral striatal hallux. Ophthalmological evaluation excluded visual deficits.

One and a half months after admission, the patient was discharged to a regional Rehabilitation Center. He continued treatment with anti-bacillary drugs, levetiracetam, and a 1-month course of oral prednisolone and fludrocortisone. His expressive language remained impaired and he kept his left upper limb flexed, while keeping his left hand closed for most of the time, and limped on his left side. After 3 months, he was discharged home, while continuing multidisciplinary follow-up at the hospital Outpatient Clinic.

Contact tracing identified an intrafamily case of TB.

Table 1. Clinical and laboratory findings in cerebral salt wasting syndrome (CSWS) versus patient's results.

	Clinical and laboratory findings in CSWS	Patient's results
Hypovolemia/dehydration	Yes	Yes
Serum sodium	< 135 mEq/L	132 mEq/L
Plasma osmolality	Low (< 275 mOsm/kg)	269 mOsm/kg
Urine osmolality	High (> 100 mOsm/kg)	699 mOsm/kg
Urine sodium	High (> 40 mEq/L)	295 mEq/L
Serum uric acid	Low (< 2 mg/dL)	1.1 mg/dL

CSWS: cerebral salt wasting syndrome.

Discussion

Despite being one of the most common infectious causes of fever of unknown origin in children, many cases of TB remain misdiagnosed or the diagnosis is delayed. In the present case, the non-specific features led to a significant delay between the onset of symptoms and diagnosis of TB. Disseminated TB is a severe form of the disease that affects more than one organ system. It is more common in young children (< 5 years) and immunocompromised hosts [7]. TM is the most severe form of extrapulmonary TB, and carries a high rate of disability and death [8]. Seizures, cranial nerve palsy, hemiparesis, and coma are common in children with advanced TM. Severe manifestations include pyramidal and cerebellar signs, spasticity, and posturing [9].

The diagnosis of TB is based on a combination of clinical signs and symptoms, recent contact with a case of TB, a positive tuberculin skin test, and radiological findings [7]. However, the diagnosis and management of TM in children are challenging because of its non-specific initial symptoms, the difficulty in obtaining diagnostic samples, and the low yields of mycobacteria [8]. Additionally, routine laboratory test results are non-specific. Chest X-ray images should be examined for the presence of hilar adenopathy, an interstitial miliary pattern, parenchymal infiltrates, or apical scarring [9, 10], but these were absent in our case.

CSF alterations suggestive of TM include pleocytosis, lymphocytic predominance, protein concentration > 100 mg/dL, glucose concentration < 40 mg/dL, and a low ratio of CSF to blood glucose, which were absent in this case. Cellular reactions are often atypical early in the disease course, with few cells or a predominance of polymorphonuclear leukocytes, which usually change to a lymphocytic response [9]. Measuring the CSF ADA concentration may be useful as an additional parameter to support the diagnosis of TM, although its sensitivity is low [10].

Aside from the clinical progression, imaging studies were fundamental to the suspicion of TM in the present case. MRI is considered to show greater sensitivity than CT. The typical neuroimaging findings of TM are hydrocephalus and basilar enhancement, and common findings include infarction involving the basal ganglia and internal capsule, or solitary or multiple tuberculomas. Meningeal enhancement together with hydrocephalus are strongly suggestive of TM [9, 10].

Identification of acid-fast bacilli in CSF by smear or culture confirms central nervous system TB infection. Mycobacterial confirmation in children with presumed TM is difficult due to the small CSF samples that can be obtained in infants and young children, and the paucibacillary aspect of TM [8, 10]. Tests of solid culture media, such as Lowenstein-Jensen, typically take 4-6 weeks to yield a positive result [10].

Hydrocephalus is one of the most common complications of TM and has an unfavorable prognosis. Worsening consciousness is a sign of hydrocephalus and requires urgent neuroimaging [4].

Hyponatremia is also common in TM and is more frequently caused by CSWS than syndrome of inappropriate antidiuretic hormone secretion. The onset and progression of hyponatremia may be insidious and its manifestations include non-specific symptoms, such as nausea, confusion, delirium, and seizure [10]. Persistent hyponatremia, despite progressively increasing sodium supplementation and hypovolemia in the context of a cerebral lesion, raised our suspicion of CSWS in this case.

A 12-month treatment regimen is recommended for children aged 0-10 years with TM, consisting of isoniazid, rifampicin, pyrazinamide and ethambutol given daily for the first 2 months, and isoniazid and rifampicin given daily for the next 10 months [11]. Corticosteroids are recommended for all cases of TM because they can improve survival and reduce mortality, although they do not alter the neurologic outcomes [8, 11]. More severe disease and young age at diagnosis seem to be associated with worse neurological sequelae. Long-term adverse outcomes in children with TM include hemiplegia, vision impairment, hearing loss, cognitive impairment, epilepsy, behavioral disturbance, and developmental disability [8].

The difficulty of diagnosing TM in its early stage and its poor outcome highlight the importance of BCG vaccination, which confers effective protection against severe forms of TB and can prevent death [12].

The COVID-19 pandemic greatly affected the global health response to TB. This potentially contributed to the delayed diagnosis of TB in the intrafamilial case identified by contact tracing. If the diagnosis had been made earlier, our case could have received appropriate therapeutic measures to avoid the severe manifestations that occurred.

In conclusion, this case report highlights the importance of considering TB and TM in the differential diagnosis of a child presenting with

fever of unknown origin, to minimize the short- and long-term complications.

Informed consent

Written informed consent was obtained from the parent of the patient.

Declaration of interest

The Authors declare no conflicts of interest. No funding was obtained for this work.

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