Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 05/13/2020
Approved on: 06/24/2020

CASE REPORT

An infant with central nervous system tuberculosis and miliary tuberculosis

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Keywords:
tuberculosis,
central nervous system,
infant.

Abstract

Introduction: Tuberculosis is a serious infectious disease and a great problem for public health, in all the world. Its incidence has grown, according World Health Organization (WHO). **Objective:** The authors describe a success case of neurotuberculosis, demonstrating the importance of early diagnosis and treatment. **Case Report:** Male infant, 3 months of life. During the course of a treatment for miliary tuberculosis, the liver enzymes have risen, being necessary to suspend rifampicin, isoniazid, and pyrazinamide. The medicines were gradually reintroduced, but neurological symptoms have been observed, deviation of labial commissure and strabismus. Immediate hospitalization, neurological evaluation, computed tomography (CT), investigation for immunodeficiency and prescription of pyridoxine and dexamethasone. The contrast tomography revealed focal hypodense images and a ring enhancement, compatible with neurotuberculosis. The drugs against tuberculosis were reintroduced and the motor physiotherapy led to the clinical improvement. The discharge ocurred after 10 days. **Conclusion:** Neurotuberculosis requires a long treatment. Early diagnosis and multidisciplinary treatment were important for the favorable evolution of this patient. Cases like that are unusual, contributing to greater knowledge about this disease.

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Residência Pediátrica; 2022: Ahead of Print.
DOI: 10.25060/residpediatr-2022.v12n2-311

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INTRODUCTION

Tuberculosis (TB) is a severe infectious disease with growing incidence in recent years[1]. Data published by the World Health Organization (WHO) in 2018 showed that approximately 10 million cases of TB are recorded every year globally, accompanied by one death every 21 seconds by the disease, which places it as the deadliest infectious disease among young people and adults[2]. On that same year, approximately 76,000 new cases of TB and 4,500 deaths by the disease were reported in Brazil, a country among the 20 nations with the highest incidence of TB globally[3].

In addition to the lungs, other sites may be involved, such as the central nervous system (CNS). The most common form of involvement seen in children with central nervous system tuberculosis (CNS-TB) is tuberculous meningoencephalitis, the most severe complication of the disease[4], responsible for nearly half of the deaths by neurological involvement in Brazil[5]. This is one of the most feared complications in children, due to its significant morbimortality and the neurological sequelae it may cause[6].

In pediatrics, diagnosing TB can be challenging, since children may present with non-specific signs, symptoms, and X-ray imaging alterations. Besides, since it is not easy to isolate Mycobacterium tuberculosis from patients in this age range[7], score-based diagnosis takes precedence over lab workup[8]. However, this contributes to the underreporting of cases of TB in children[9], which, nevertheless, account for 10% of all cases of the disease[10]. Additionally, little attention is given to TB in child health programs[9], a factor that leads to delayed diagnosis and potentially irreversible neurological involvement[11].

CASE REPORT

On July 16, 2017, a previously healthy male infant aged three months and 16 days with a BCG scar was admitted for coughing and fever lasting for 10 days not responsive to treatment with amoxicillin/clavulanic acid. On July 19, 2017, he had nocturnal fever and sweated profusely. Chest X-ray images showed a bilateral miliary pattern. The infant's caregiver was being treated for TB. His tuberculin skin test produced a weakly positive response, while gastric lavage search for acid-alcohol resistant bacilli (AARB) and tests for anti-HIV I and II were negative. He was given 40 points in the diagnostic scoring system published by the Ministry of Health[12]. Triple therapy (2RHZ/4RH) with rifampicin, isoniazid, and pyrazinamide was prescribed. On July 28, 2017, the patient was discharged after symptoms improved. He was referred to an outpatient clinic for follow-up care.

On August 21, 2017, according to the infant's mother, a physician ordered the suspension of treatment with antitubercular drugs due to liver toxicity (GOT:191/GPT:179). As liver enzyme levels decreased (GOT:43.3/GPT:27), the patient was restarted on rifampicin. New tests were performed (GOT:33.9/GPT:14.7/GGT:33.6) and, on August 22, 2017, isoniazid was reintroduced. A week later, after another set of tests, pyrazinamide was added back to treatment.

On September 9, 2017, the patient was hospitalized after his mother sought care for what she described as a "deviated glance". Physical examination showed the infant was in good general condition, hemodynamically stable, with rough respiration and audible vesicular breath sounds, without adventitious sounds. Anterior fontanelle tension was normal and no signs of nuchal rigidity were found. His pupils were isochoric and responsive to light. Neurology examination found bilateral convergent strabismus and right facial palsy. Suspicion revolved around neurological involvement by TB or isoniazid neuropathy. Contrast-enhanced skull computed tomography (CT) scans showed focal hypodense ring enhancing lesions with parenchymal edema consistent with CNS-TB (Figure 1). In addition to antitubercular drugs, the patient was prescribed intravenous dexamethasone (0.4 mg/kg/day) and pyridoxine (50 mg/day), both for seven days, and was started on early motor physiotherapy. The infant remained in a stable condition, with liver enzyme levels under control, and improved from facial palsy and the miliary pattern seen in chest X-ray images. On September 19, 2017, he was discharged and referred to an outpatient clinic for follow-up care. The patient was kept on triple therapy + Prednisolone and time of treatment was extended to nine months, as stipulated for tuberculous meningoencephalitis (2RHZ/7RH) in the guidelines in effect in 2017. In a follow-up visit a month later, the infant was asymptomatic and imaging findings had significantly improved. He was sent home without complications and was kept on follow-up care with a Pediatrician, an Ophthalmologist, a Neurologist, and a Physiotherapist.

DISCUSSION

Miliary TB is a severe disease seen more often in immunocompromised individuals[12]. Involvement of the CNS is more common in children between the ages of six months and six years. Granulomas – particularly submeningeal ones – formed via hematogenous dissemination from the primary site of involvement in the lungs are observed in most cases[4,6]. These granulomas may cause the discharge of caseous content into the meninges, potentially causing the following: 1) obstruction of the passage of cerebrospinal fluid through the cisterns, causing hydrocephalus; 2) involvement of the cranial nerves and optic chiasm, causing paresis, palsy, and amaurosis; and 3) involvement of the internal carotid and middle cerebral arteries, causing impaired parenchymal irrigation. Other signs

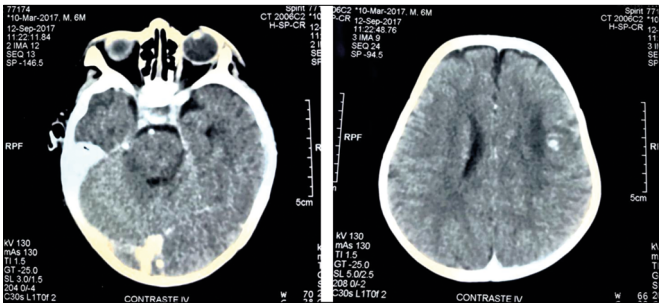


Figura 1. Skull Computed Tomography Scan CT scans consistent with CVS-TB.

of disease include tissue edema and vasculitis by hypersensitivity reaction to the antigen, contributing to the occurrence of neurological sequelae[6].

The signs and symptoms of neurological involvement may be non-specific, and diagnosis is often reached in later stages of the disease, a factor that hinders treatment and has been associated with poor outcomes[6]. Symptomatic patients may develop fever and intracranial hypertension syndrome, which may include headaches, nausea, vomiting, mental confusion, and coma. Diagnosis relies mainly on the analysis of cerebrospinal fluid (CSF) and imaging[13]. Computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) should be ordered first. The most common findings are hydrocephalus, basilar meningeal thickening, and brain parenchyma infarction[12].

CSF analysis (not performed) shows pleocytosis, predominantly lymphocytic leukocytosis, high protein and low glucose levels. Tests for AARB are positive in 5-20% of the cases. Culture is positive in about half of the cases[14]. PCR is currently one of the main methods used in the detection of tuberculous meningoencephalitis[13]. Therefore, diagnosis is reached based on the assessment of clinical and imaging data with the aid of bacilloscopy, sputum culture, and molecular biology tests whenever possible. Differential diagnosis must include bacterial, fungal, and viral infections of the CNS, and other causes of meningitis. Differential imaging diagnosis includes cryptococcosis, sarcoidosis, lymphoma, metastases, and cytomegalovirus encephalitis[12].

The treatment of CNS-TB for children below the age of ten years currently recommended by the Ministry of Health is based on the 2RHZ/10RH scheme. Treatment is divided into intensive and maintenance stages, and the schemes described in the Manuals published in 2011 and 2019 differ only in the length of the maintenance stage (Table 1). Thus, in the case presented herein, the infant was treated with the 2RHZ/7RH scheme (total of nine months) recommended in the Manual in effect in 2017[16,17]. Corticosteroids are added in the intensive care stage to attenuate the inflammatory response to the antigen and assist in the treatment of complications[15]. Although rare in children, the main adverse events must be reported to the family. Advice must also be given about follow-up care.

Table 1. Comparison between protocols stipulated in the 2011 and 2019 Manuals of the Ministry of Health.

Stage	Ministry of Health's 2011 Manual (2RHZ/7RH)	Ministry of Health's 2019 Manual (2RHZ/10RH)
Intensive	2 months on RHZ + Prednisone or IV Dexamethasone	2 months on RHZ + Prednisone or IV Dexamethasone
Maintenance	7 months on RH	10 months on RH

R – rifampicin; H – isoniazid; Z – pyrazinamide. Doses: Rifampicin (10-20 mg/kg/day), isoniazid (7-15 mg/kg/day), pyrazinamide (30-40 mg/kg/day), prednisone (1-2 mg/kg/day), dexamethasone (0.3-0.4 mg/kg/day).

Liver toxicity is a frequent adverse event in individuals with severe TB. Liver function must be tested before the start of treatment and monitored periodically (every 3-7 days). If an increase ≥ 5 times the upper limit of normal (ULN) is seen in asymptomatic patients or of 3 times the ULN in patients with symptoms of dyspepsia or if jaundice is present, treatment must be suspended. Reintroduction of medication must be performed gradually after the assessment of liver function, in the following order: first RE, followed by H, and then Z[12]. Other concerns include neurological sequelae such as motor deficit, developmental delays or dementia, seizures, and hydrocephalus[15].

The earlier drug therapy and physiotherapy are introduced, the better are the outcome and recovery of the patient. In lung TB, many factors may affect clinical improvement, such as age, presence of extrameningeal TB, BCG vaccination, CSF alterations, intracranial hypertension, alterations in consciousness, neurological deficit, type of treatment scheme, use of corticosteroids, and other comorbidities[12,15].

Treatment must encompass monthly multidisciplinary follow-up care, along with testing for bacterial disease whenever possible. Particularly in pediatric patients, medication doses must be adjusted based on weight gain. Imaging examination must be performed on the second month of treatment if the patient is developing well or on the first month of the patient is not developing well, and at the end of treatment. Improvement in signs and symptoms and imaging findings are the main criteria in the assessment of cure[12].

CONCLUSION

Miliary TB is a severe disease grave for pediatric patients that may include meningeal involvement via hematogenous dissemination. Patients with neurological involvement require lengthy hospitalization and treatment and multidisciplinary follow-up care. Given the high prevalence of TB in Brazil, CNS involvement must always be considered in diagnostic evaluation. Early diagnosis and treatment, along with prevention, are required to decrease the occurrence of severe forms of the disease and the morbimortality that affects involved children.

ACKNOWLEDGEMENTS

The authors would like to thank the "Quality of Life and Epidemiology" research group at the Federal University of São João Del Rei (UFSJ) – Dom Bosco Campus, advised by Professor Jacqueline Domingues Tibúrcio, PhD, with the assistance of Professor Márcia Reimol de Andrade.

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