

Unusual Case of Childhood Tuberculosis: Clinical Report and Literature Review.

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Abstract

Introduction: Tuberculosis of the central Nervous system occurs more frequently in children under three years of age and in immunodeficient populations, in which it is usual that it manifests as a disseminated disease, the frequency is usually higher in countries with a high prevalence of tuberculosis, and its presentation is related to a period of rapid dissemination of the germ that can occur during the first year, with the first infection. **Case:** 3-year-old girl with a history of latent tuberculosis who presented acute symptoms of eyelid ptosis, impossibility to adduct, and pupillary hyperactivity, with neuroimaging findings of a lesion suggestive of tuberculous granuloma, as well as bilateral mesencephalic and thalamic vascular lesions, which allowed concluding a tuberculosis involvement of the CNS. He received antituberculosis treatment with tetra conjugate, achieving clinical stability. **Conclusions:** The case presented describes a rare presentation of childhood tuberculosis with the finding of tuberculoma without meningitis of unusual location in the subarachnoid space and vasculitis. The diagnosis and management of this pathology, as well as a correct adherence to treatment, will have an impact on the morbidity and mortality of the patients, considering the variable clinical spectrum.

Keywords: tuberculosis, tuberculoma, pediatrics, vasculitis, central nervous system.

INTRODUCTION

Tuberculosis is a disease whose incidence has been declining for many years. It is difficult to recognize it, especially in the form of atypical presentations; for this reason, we should always have it as a differential diagnosis of nervous system involvement in children. Clinical suspicion and neuroimaging, when there are no other data or specific paraclinical findings, are essential for early management and better prognosis of patients.

Mycobacteria involve the central nervous system (CNS) in 1% of patients with active infection; this is generated by hematogenous dissemination of the germ and the presence of subependymal and subpial foci formations. However, this phenomenon does not always occur, and the mycobacterial focus can spread through the meningeal structures without rupture, in which case tuberculomas occur without associated meningitis. The appearance of these lesions will depend on the age of the patient and the patient's immunological response capacity (1) (2) (3).

The frequency is usually higher in countries with a high prevalence of tuberculosis (TB). Its presentation is related to a period of rapid germ dissemination that may occur during the first year after primary infection. It occurs more frequently in children under three years of age and in immunodeficient population, in which it usually manifests as a disseminated disease with CNS involvement; antecedents such as diabetes, neoplastic disease, prolonged use of corticosteroids, anti-tumor necrosis factor (TNF) medications, malnutrition, and HIV infection can generate a decrease in the immune response and are considered important risk factors for the appearance of neurological involvement by TB (4) (5) (6).

PRESENTATION OF THE CASE

3-year-old female infant, with a history of latent TB, diagnosed by contact with the mother, managed for pulmonary TB, associated with positive tuberculin test (greater than 5 mm), treated with isoniazid, with no other history and normal neurodevelopment; she consults for a sudden episode of blurred vision, associated with vertigo.

The neurological examination on admission revealed palpebral ptosis in the right eye, difficulty in adduction, pupillary hyporeactivity of the eye, fundus, and the rest of the physical exam were normal. Hematological and biochemical examinations were without alterations. Normal sedimentation rate. Positive C - reactive protein-positive, not significant. Cerebrospinal fluid study, leukocytes 2, differential count with lymphocytes 100%, proteins 28.2 mg/dL, CRP for mycobacteria gene-Xpert negative, Ziehl Nielsen staining negative, ADA 5.39 U/L (levels compatible with TB >5 U/L at 37°C), the rest without alterations.

T1-weighted Brain Magnetic Resonance Imaging with contrast showed a hyperintense nodular lesion in the interpeduncular (subarachnoid) region suggestive of tuberculous granuloma. Axial T2weighted image showed a well-defined rounded hyper signal at the foot of the cerebral peduncle on the right side; in addition, At the level of the nucleus of the third cranial nerve, a hypointense lesion in the midbrain suggested an old lesion (Figure 1). Angioresonance imaging was performed, which was within normal limits.

With these findings, a diagnosis of tuberculosis disease was made, and management with prednisolone and tetraconjugate (rifampicin, isoniazid, pyrazinamide, and ethambutol) was started. The patient was readmitted one week later due to instability in walking with frequent falls, associated with left hemicranial headache and projectile vomit, with findings of facial asymmetry and deviation of the labial commissure to the right. A control brain MRI showed a new lesion visualized in axial T2 FLAIR with an increased signal at the left medial thalamus, diffusion restriction, which generates a slight mass effect at that level (Figure 2).

The following month she consults for drowsiness and unsteady gait, associated with poor adherence to corticosteroid treatment. In addition to the findings previously described in the neurological examination, left endotrophic, left hemiplegia, gait with a slight increase in the polygon of sustentation and lateropulsion to the left. Brain MRI with axial T2 image documented a new right thalamic hyperintense lesion with heterogeneous enhancement and mass effect that restricts diffusion, not evidenced in previous studies; the granulomatous lesion in axial T1 image with contrast, compared to previous study, showed a significant decrease in size and inflammation (Figure 3). Spectroscopy was performed, which showed no significant changes considering evolution towards improvement.

The neuroimaging findings of a lesion suggestive of tuberculous granuloma, as well as the bilateral mesencephalic and thalamic vascular lesions, explained the clinical picture manifested by the patient and allowed concluding a tuberculosis involvement of the central nervous system due to TB granuloma and vasculitis. Therefore, she received antituberculosis treatment with tetraconjugate rifampicin, isoniazid, pyrazinamide, and ethambutol (56 doses), with the second phase of rifampicin and isoniazid, completing ten months of treatment together with prednisolone for one month and subsequent progressive decrease, with which clinical stability was achieved.

Symptoms of tuberculosis with CNS involvement can be nonspecific. However, headaches, vomiting, anorexia, and fever are most commonly associated. It is estimated that 50-90% of those affected have positive contact with a person with active TB, as in this patient's case (1) (6).

In preschool age, the clinical presentation may include weight loss, irritability, hyporexia, sleep disorders, persistent emesis, or abdominal pain. However, there are more dramatic presentations in which patients may present febrile crises or not associated with fever and focal neurological deficit given by paresis or paralysis of cranial pairs and hemiplegia (7). In this case, signs of neurological focalization secondary to the rapidly evolving CNS vasculitic process were evidenced.

Concerning tuberculomas without meningitis, it should be considered that a large percentage of these patients may not have such a clear clinical manifestation and that the appearance of the clinical findings will depend on the location of these lesions; Among those, headache, weight loss, fever, focal or generalized crises (more common in children and older adults), cerebellar symptoms, papilledema (adolescents and adults), unusual symptoms such as hypopituitarism, chorea and brain stem symptoms can be found; at the paraclinical level, it is usual to have proteinuria but with pleocytosis of 10-100 cells per mm only in 50% of the cases (5)(1).

CSF adenosine deaminase activity can be a helpful test for diagnosis; however, it can be affected by false-positive results such as in the presence of brucellosis, malaria, lymphomas, and pionic meningitis; in HIV immunodeficiency, 57% of the tests can have a false positive reaction to cytomegalovirus, cryptococcus and cerebral lymphomas (7). A meta-analysis showed that the sensitivity and specificity of ADA for diagnosing tuberculous meningitis depends on the range established as standard; for an ADA threshold of 4 U/L, sensitivity was > 93% and specificity <80% (8). In the case described, taking into account that the patient did not have any risk factor that contributed to a false positive, the result-oriented towards the diagnostic suspicion of TB.

In brain magnetic resonance imaging, the differences are usually related to the location of the lesions; most of them present meningeal enhancement with hyperintense exudates. In the case of a large tuberculoma, it may cause compression of the nerve roots. It is unusual, but vascular involvement has been described in the spinal presentation when it is pachymeningitis. When the meninges involvement involves the dura mater, meningeal enhancement is usually a sign that helps to make the diagnosis (9).

There are presentations with tuberculoma without associated meningitis, in which ring enhancement and edema related to the perilesional region are observed; it can be solitary or multiple (10). Its differential diagnoses should always include neurocysticercosis, metastasis, neoplasms, toxoplasmosis, and pyogenic abscesses (9, 11). Different locations in the pediatric population have been described in the literature, including supratentorial and infratentorial, cerebellar, intraventricular, and frontal, among others (12, 13). In the case described the lesion suggestive of tuberculous granuloma had an unusual location at the interpeduncular, subarachnoid level, with an excellent clinical and imaging response to treatment.

In the spinal presentation, the thoracic location is usually the most common; it is accompanied by meningeal enhancement and spinal edema; there may be involvement of the posterior elements, canal stenosis, and nerve root compressions up to vertebral collapse.

If the patient presents with involvement of several vertebral bodies, it is more common that the etiology is tuberculous since it is one of the few conditions with this pattern of involvement; up to 90% of patients with positive findings in CNS imaging present lesions in another location, some may present hyper intense fusiform lesions of the cord (9, 11). Table 1 summarizes each subtype of CNS

TB PRESENTATION'S CLINICAL, IMAGING, AND MICROBIOLOGICAL FINDINGS.

The management of TB with CNS involvement consists of two phases: the first is the intensive phase, in which the number of mycobacteria is dramatically reduced, and the second is the so-called continuation phase, in which the growth rate of mycobacteria is controlled, and bacteriostatic activity is generated (7). During the beginning of the treatment, clinical deterioration may occur.

Corticosteroids are another pharmacological resource within the treatment plan, although evidence regarding their routine use is insufficient. However, in cases of poor control or deterioration of symptomatology, they can be administered (7). Evidence supports their benefit in mortality reduction, with no significant effect on the secondary neurological deficit (14,15). In the case presented, irregular corticosteroid intake was associated with acute deterioration, probably secondary to the inflammatory reaction provoked by the antituberculosis treatment. The corticosteroid was essential for stabilization.

CONCLUSION

CNS involvement by tuberculosis has a broad spectrum of clinical presentation, whose diagnosis can sometimes represent a challenge in the pediatric population. The described case describes the presentation of tuberculoma without meningitis, whose unusual location and difficult access without causing damage to brain tissue made it difficult to perform a complementary biopsy, requiring the use of different tools to establish the diagnosis and early

initiation of treatment. When this pathology is suspected, the significant clinical variability, the progressive and severe course, and the establishment of an interdisciplinary team for acute management and the complications that may arise should be considered since timely management, as well as good adherence, will have an impact on patient morbidity and mortality.

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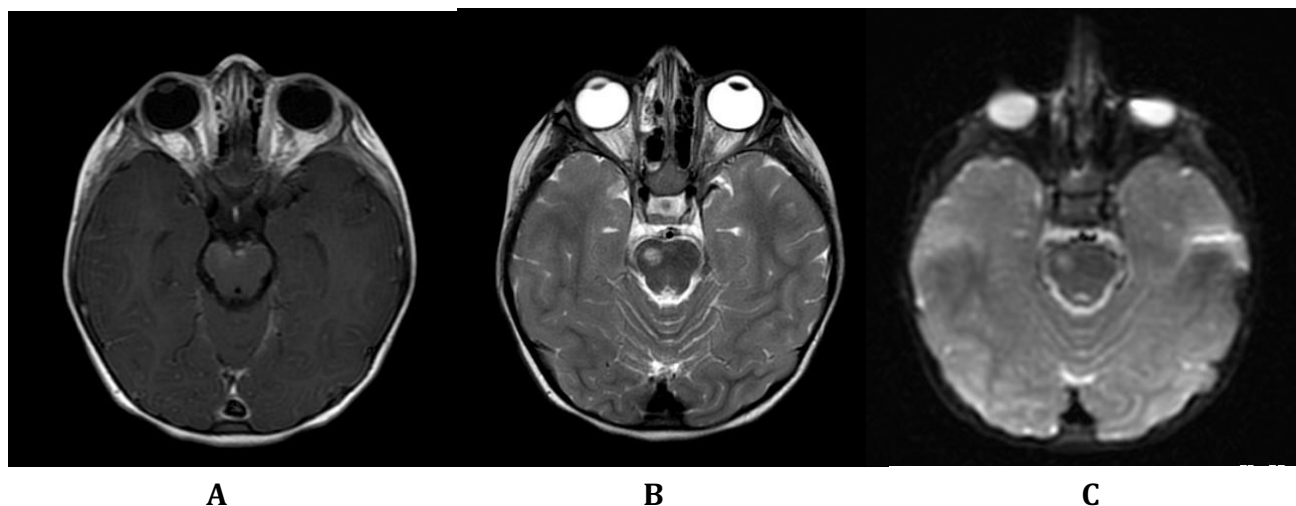


Figure 1. Initial brain MRI. A) Axial T1 with contrast: micronodular enhancement in the interhemispheric region, cisternal. B) Axial T2: well-defined round hyper signal at the right side's foot of the cerebral peduncle. C) Axial DWI, diffusion restriction at the level of the right cerebral peduncle.

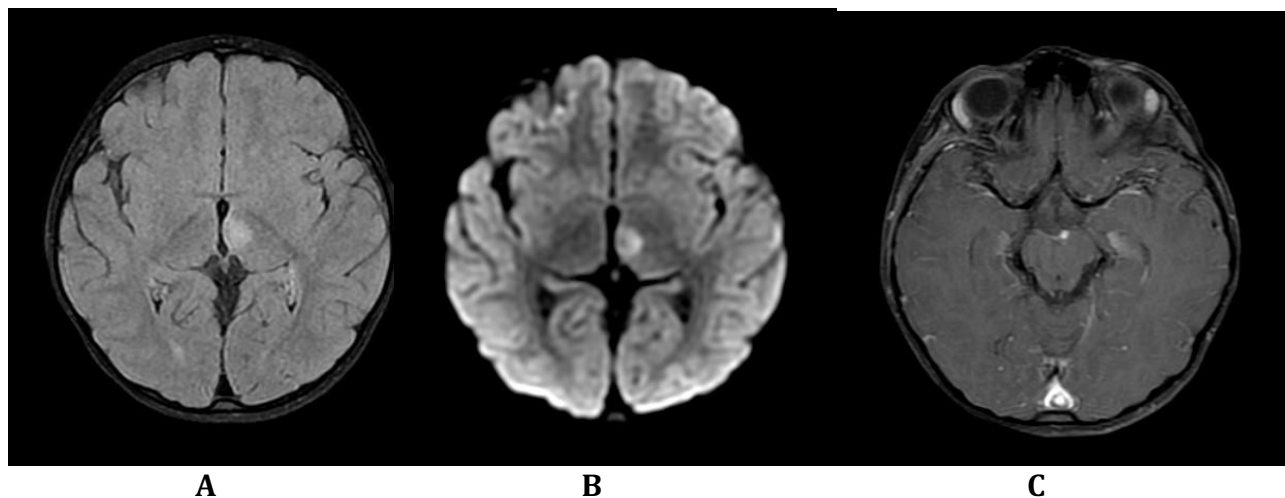


Figure 2. Brain NMR No.2. A) FLAIR, a new axial lesion with an increased signal at the level of the left medial thalamus. B) Axial DWI: diffusion restriction generates a slight mass effect at that level. C) Axial T1 with contrast: micronodular enhancement in the interhemispheric region, cisternal corresponding to tuberculoma.

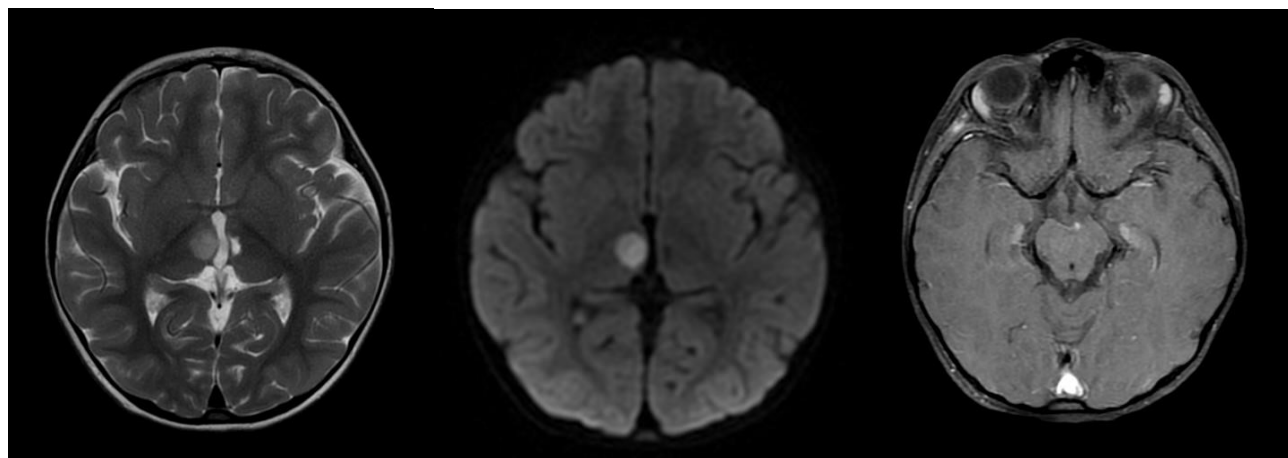


Figure 3. Brain NMR No.3, A) Axial T2, hyperintense right thalamic lesion. B) Axial DXI, heterogeneous enhancement, and mass effect that restricts diffusion, not evidenced in previous studies. C) Axial T1 with contrast, compared with a previous study, showed a significant decrease in an interpeduncular cistern.

Table 1. CNS involvement in TB.			
	Meningeal TB.	Tuberculoma without meningitis.	Spinal TB.
Clinical findings	Age-dependent: Schoolchildren and adolescents (>5 years): Headache, vomiting, and anorexia. Preschoolers and children (<5 years): weight loss, constant irritability, hyporexia, sleep disturbances, continuous vomiting, and abdominal pain. Atypical presentation: Crises: Febrile and nonfebrile. Focal neurological deficit: cranial nerve paresis, hemiplegia.	Clinical manifestation depends on location. (Impossible to distinguish from other types of space-occupying lesions by clinic) Most are asymptomatic. Common symptoms: Headache, weight loss, fever. Seizures: focal or generalized (more common in adults and children.) Cerebellar symptoms and papilledema (adults and adolescents) Unusual symptoms: Hypopituitarism, chorea, brainstem syndromes (Compression)	It is related to nerve root compression. Upper or lower motor neuron involvement. (up to 10% with tuberculous meningitis) Pott's disease (vertebral bone involvement due to TB): Signs of extrinsic compression of the cord; these extra-dural lesions are responsible for up to 60% of non-bone paresis. Radicle myelitis (unusual): for subacute paresis, radicular pain, and bladder dysfunction. Syringomyelia is recorded in some cases, but its presentation is exceptional.

CSF characteristic.	Leukocytosis: 1×10^3/ml. lymphocyte predominance. Proteinorachia: 0.53gr/lt. Glycorrachia: <50% concerning serum. Atypical findings: Patients with immunodeficiencies. Sample without leukocytosis or presence of predominantly neutrophilic.	Proteinorachia in most patients. Pleocytosis of 10-100 cells/mm in 50% of patients.	It can be expected. The presence of proteinorachia is variable. Pleocytosis is dependent on stage and level of involvement.
Imaging.	Chest X-ray: About 50% of cases have changes in chest X-rays. Patient with miliary disease (extra pulmonary) > risk of CNS involvement. Skull CT: Hydrocephalus or exudates with basal contrast. (+/- 80%) Infarcts secondary to vasculitis or tuberculoma: 20% in the striatum's basal ganglia and medial perforating arteries. 70% of patients may develop a tuberculoma during or after treatment, but most are asymptomatic	CT and MRI: typical characteristics of ring enhancement with perilesional edema. A distinction from other causes is impossible: Neurocysticercosis, metastasis or neoplasia, toxoplasmosis, pyogenic abscess. Infratentorial tuberculomas are usual; always carry out an active search.	Compromise of posterior elements. Canal stenosis. Root or canal compression. Spinal collapse. (Thoracic spine is the most affected) Affectation of several vertebral bodies: usual in TB, uncommon in other dx. MRI: >90% of cases have an extra CNS focus. Hyperintense fusiform cord lesions.
Microbiology.	CSF study: Positive in up to 80% of patients (adults). Dependent volume: > volume greater probability of finding the germ.	Tissue biopsy is the ideal method for diagnosing: Tuberculomas without meningitis and spinal TB. • Stereotaxy should be considered for sampling to avoid injury or complications.	

	(Repeating the puncture is recommended in patients with high risk and clinical suspicion of meningeal TB) Repeat LP and CSF examination: They increase the possibility of making the diagnosis. Acid-alcohol resistant strain (GS). 80% effective in adult patients. 15-20% effective in pediatric patients. Crops: They are sample volume dependent (>6ml): Liquid media recover more colonies of <i>M. tuberculosis</i> than solid media. More sensitive, very slow. (2 weeks for result) Useful to determine germ susceptibility. It is more common to find positive findings in HIV patients than in immunocompetent ones.	
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