Case Report/Relato de Caso

Neurological involvement in visceral leishmaniasis: case report

Envolvimento neurológico na leishmaniose visceral: relato de caso

Lílian Martins Oliveira Diniz[1], Helena Duani[2], Camila Rodrigues Freitas[3], Rosângela Maria Figueiredo[4] and Christovão Castro Xavier[5]

ABSTRACT

Visceral leishmaniasis is a severe and potentially fatal vector-borne disease. The most typical symptoms are fever, hepatosplenomegaly, weight loss, bleeding and bacterial infections. Neurological changes are rarely reported. This paper describes a child who presented with neurological signs as the first symptoms of leishmaniasis; tone was diminished and tremors in the extremities were observed. A diagnosis of visceral leishmaniasis was confirmed by parasite detection in the bone marrow. Symptoms were reversed by specific treatment. The nature of a possible mechanism of neurological involvement in visceral leishmaniasis remains unexplained.

Key-words: Neurological symptoms. Visceral leishmaniasis. Kala-azar. Children.

RESUMO

A leishmaniose visceral é uma doença severa e potencialmente fatal transmitida pela picada de flebótomos infectados pelo parasita. Os sintomas mais comuns incluem febre, hepatoesplenomegalia, perda de peso, sangramentos e infecções bacterianas. Alterações neurológicas têm sido raramente descritas nesses pacientes. Descrevemos aqui o caso de uma criança que desenvolveu um quadro de infecção pela *Leishmania*, tendo como principal sintoma tremor de extremidades. O diagnóstico da doença foi confirmado pela demonstração do parasita no aspirado de medula. Os sintomas foram revertidos pelo tratamento específico. A natureza do possível mecanismo do envolvimento neurológico na leishmaniose visceral permanece duvidoso.

Palavras-chaves: Sintomas neurológicos. Leishmaniose visceral. Calazar. Crianças.

INTRODUCTION

Visceral leishmaniasis, also known as kala-azar, is the most severe form of leishmaniasis. The disease is caused by protozoan parasites of the *Leishmania* genus and is the second-largest parasitic killer in the world[1,2]. The most typical symptoms are fever, splenomegaly and hepatomegaly. Other signs and symptoms include weight loss, fatigue, anemia, bleeding and bacterial infections related to neutropenia[2]. Reports of neurological changes in visceral leishmaniasis are rare. Misdiagnosis is dangerous, since without proper treatment, the case-fatality rate for kala-azar is close to 100%[2]. Traditional treatment is the administration of pentavalent antimonial compounds or amphotericin B[1,2]. The gold standard for diagnosis is visualization of the amastigotes in splenic aspirate or bone marrow.

This paper describes the case of a child who presented with neurological signs as the first symptoms of leishmaniasis. The clinical profile and possible mechanisms for the pathogenesis of neurological leishmaniasis are discussed.

CASE REPORT

A 16 month-old boy presented at the Emergency Room with a 3-day history of coughing and wheezing followed by fever. On day 3, he developed tremors of the extremities that were most visible in the hands, head and tongue. His parents did not have a regular house and had been living with the child in a homeless shelter for the previous four months. His mother had been using anticonvulsant drugs for the several years. The patient was on an inadequate diet consisting of fast and staple foods. He had two previous hospitalizations due to asthma and was up to date with all immunizations. The patient's growth curves were ascendant for weight and height until he was 13 months-old, when both stopped increasing.

On examination in the Emergency Room, he weighed 9kg, still within normal range. He looked pale, with moderate enlargement of the liver (4cm) and spleen (3cm). Observation verified that he was slightly hypotonic, with primitive reflexes present. His developmental milestones had been delayed. By At one year-old, he presented an axial and peripheral hypotonic syndrome and was unable to roll over prone to supine, could sit erect only with support and was unable to stand alone. Intellectual and speech development were also delayed. Cranial nerves were normal, with no difficulties present in the sensory examination or in coordination. Tone was diminished throughout the body and abnormal movements characterized by tremors of the extremities were observed, even when sleeping. Myoclonic movements were also observed on his face. No other abnormalities were detected during the neurological examination. He was admitted to the hospital for further investigation of his neurological disorders.

A complete blood count revealed a hemoglobin level of 6.8g/dl and a white cell count of 2,500/mm^3. He showed normal levels of aspartate aminotransferase, alanine aminotransferase and creatinine. Albumin levels were decreased to 2.1g/dl and total protein level was approximately 6.5g/dl (**Table 1**). An increase in

1. Department of Pediatric Infectious Diseases, Hospital Infantil João Paulo II, Fundação Hospitalar do Estado de Minas Gerais, Belo Horizonte, MG, Brazil. 2. Academic Division of Child Health, Federal University of Minas Gerais, Belo Horizonte, MG, Brazil. 3. Pediatric Residency Program, Hospital Infantil João Paulo II, Fundação Hospitalar do Estado de Minas Gerais, Belo Horizonte, MG, Brazil. 4. Department of Pediatric Hematology, Hospital Infantil João Paulo II, Fundação Hospitalar do Estado de Minas Gerais, Belo Horizonte, MG, Brazil. 5. Department of Pediatric Neurology, Hospital Infantil João Paulo II, Fundação Hospitalar do Estado de Minas Gerais, Belo Horizonte, MG, Brazil.
Address to: Dra. Lílian Diniz. Deptº Doenças Infecciosas Pediátricas/HIJPII/FHEMIG. Al Ezequiel Dias 345, Santa Efigênia, 30130-110 Belo Horizonte, MG, Brazil.
Phone: 55 31 3239-9091; 55 31 9237-3076
e-mail: lmodiniz@medicina.ufmg.br
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TABLE 1 - Laboratorial findings at admission and after treatment with amphotericin B.

	Laboratorial findings	
	at admission	after treatment
Hemoglobin (g/dl)	6.8	8.4
Platelet count (/mm³)	212,000	335,000
Leukocyte count (cells/mm³)	2,500	7,800
Neutrophils (cells/mm³)	625	3,510
AST (U/L)	55	51
ALT (U/L)	30	40
Albumin (g/dl)	2.1	2.8
Protein, total (g/dl)	6.5	6.6
Creatinine (mg/dl)	0.3	0.5

AST: aspartate aminotransferase, ALT: alanine aminotransferase.

C-reactive protein was observed, suggesting an acute infection or an inflammatory disease. Urine analysis was normal. A negative HIV antibody test result was also obtained. Blood and urine cultures all yielded no microorganism growth. A lumbar puncture was performed and the cerebrospinal fluid demonstrated no abnormalities. A Gram stain produced negative results, as did bacterial, viral and fungal cerebrospinal fluid cultures. The level of serum B12 vitamin dosage was normal (399pg/ml; reference value 211-911pg/ml). Carbamazepine, phenobarbital and phenytoin plasma levels were also examined and produced negative results.

A computed tomography (CT) scan of the brain revealed diffuse reduction of brain volume. Areas that were particularly affected were the frontal lobes, especially on right side (**Figure 1**). Brain imaging using conventional magnetic resonance imaging (MRI) revealed cerebral atrophy in white matter and an increase in the third ventricle (**Figure 2**). Nerve conduction studies were not performed.

A bone marrow aspirate was performed in order to explain the child's anemia. The diagnosis of visceral leishmaniasis was confirmed by the visualization of a hyper cellular marrow and isolation of numerous *Leishmania* amastigotes, showing the patient was heavily parasitized. He was treated with a course of amphotericin B based upon a regimen of 22 days.

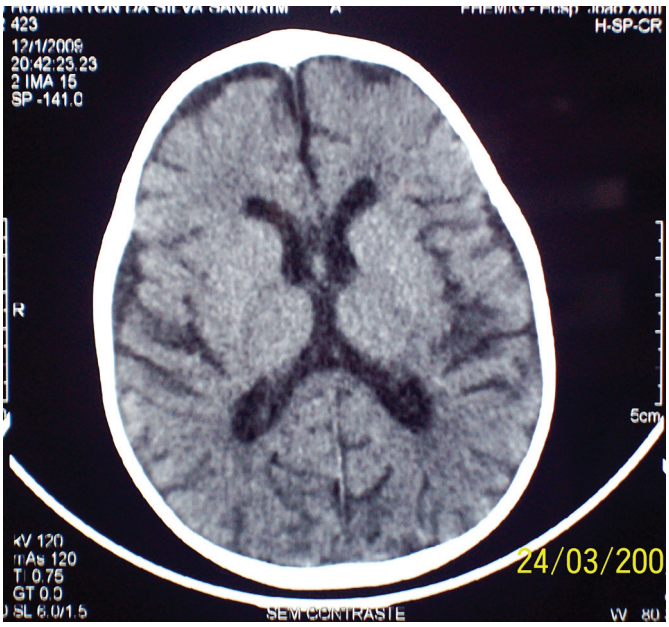

FIGURE 1 - Computed tomography scan of the brain showing diffuse reduction of brain volume.

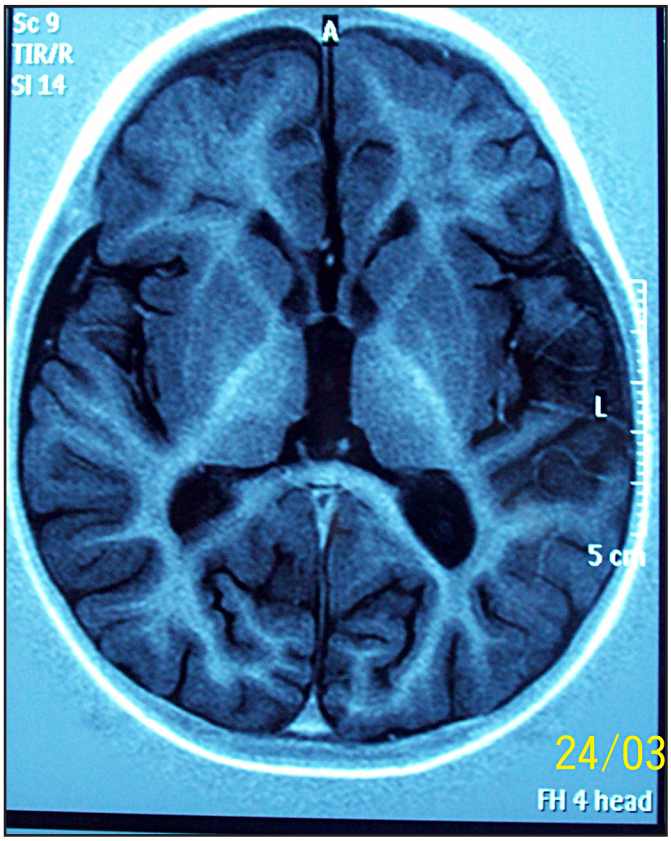

FIGURE 2 - Magnetic resonance imaging showing cerebral atrophy in white matter.

Symptoms improved soon after the onset of treatment. During the first week, the regression of neurological symptoms was observed. At the end of treatment, the tremors were almost invisible, spleen size had decreased to 1.5cm and laboratorial exams had also improved (**Table 1**). A review of bone marrow aspirate was not performed. He has been followed in the outpatient clinic and no symptoms have recurred one year after being discharged. After six months, his weight had increased to 11kg. The acquisition of developmental functions and motor milestones occurred gradually during the following months.

DISCUSSION

Visceral leishmaniasis is a severe and potentially fatal vector-borne disease. The estimated number of people at risk of infection is approximately 350 million, with approximately 550,000 new cases annually[2]. More than 90% of cases worldwide occur in Bangladesh, India, Nepal, Sudan and in northeastern Brazil[3].

Visceral leishmaniasis has assumed an increasing importance in Brazil due to its high incidence and wide geographical distribution. A notable increase in transmission rates related to urbanization has been observed in the past 20 years. Current control measures are unable to eliminate and prevent new outbreaks[1,4].

Following inoculation of parasites, protozoa of the genus *Leishmania* spread throughout the mononuclear macrophage system to the spleen, liver and bone marrow[1]. The symptomatology of visceral leishmaniasis is well documented and neurological changes are rarely reported[5].

Signs suggestive of peripheral neuropathy of varying grades have been reported previously by Mustafa in 13 patients[6]. The chief neurological abnormalities were confined to the lower limbs.

Hyperalgesia of the soles, calf tenderness and vibration disturbance were observed. It has been suggested that the cause of these symptoms was probably a deficiency of one or more members of the B group of vitamins. The factors responsible for the production of the deficiency were deficient intake and interference with absorption[6]. Whether or not other mechanisms are responsible, such as the use of the vitamin by *Leishmania*, has yet to be proven either way.

Another study described the sensation of burning feet and hyperesthesia as the most common symptoms. Axonal degeneration and demyelination were revealed by nerve conduction studies. The changes were reversed by specific treatment with antileishmanial drugs[7].

This is the first case of neurological tremor described in a child with visceral leishmaniasis in Brazil. The only reference to this complication was reported in another child in Kenya[8]. She had a five-month history of progressively worsening tremors throughout the body. Neurological investigations yielded no diagnosis and splenic aspirate smear showed infection by *Leishmania.* The patient was treated with sodium stibogluconate and allopurinol with improvement of symptoms. It is possible that the tremors were associated with malnutrition; however, the nature of a possible mechanism of neurological involvement remains unexplained

Our patient was resident in an area highly endemic for visceral leishmaniasis. Presentation of symptoms began with neurological tremors of the extremities, which has never been described as a common feature of this infection. Peripheral neuropathy seems to be more common as a neurological manifestation of visceral leishmaniasis, as reported by previous studies[6,7].

Neuropathological abnormalities resulting from malnutrition have been observed in severely undernourished children[9]. According to World Health Organization Growth Charts, at first presentation the child was only at risk of under nutrition, as his weight was still within normal range[10]. The rapid weight gain observed after treatment was initiated also indicated a good catch-up grown.

Clinical manifestations affecting the central and peripheral nervous system can also occur in vitamin deficiency states. Diagnosis of vitamin deficiency was considered primarily on suspicions raised by the dietary history. Tremors have been observed mainly in vitamin B12 and thiamine deficiency[9]. Serological levels of vitamin B12 were normal and no obvious signs of this deficiency were observed in this patient. An infantile form of thiamine deficiency (beri-beri) has been reported in breast-fed infants of thiamine-deficient mothers and is characterized by vomiting, aphonia, abdominal distention, diarrhea, cyanosis, tachycardia and convulsions. More prolonged deficiency can be associated with signs of peripheral neuropathy and cardiomiopathy[9]. Clinical response to the administration of thiamine is the best confirmatory test[9]. Deficiency of thiamine as a possible cause of neurological symptoms seems unlikely, because typical clinical manifestations were not observed and patient´s symptoms were reverted without vitamin supplementation.

Developmental delay was also observed. It is reasonable to assume that malnutrition contributed to this symptom, but we believe it cannot explain the whole picture. We also believe the delay of developmental milestones was partly due to lack of appropriate stimulation in child's environment and psychosocial deprivation.

No other known causes of neuropathy were observed. The exact etiology of neurological manifestation in visceral leishmaniasis remains far unknown and requires further study.

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