

## Reporte de Caso - Case Report

# Fatal Disseminated Histoplasmosis with Cervical Lymph Nodes and Tongue Involvement in an Infant with Spinal Muscular Atrophy Type I (Werdnig-Hoffman disease)

Libia Jiménez,<sup>1</sup> Enrique Sanabria,<sup>1</sup> Sonia M. Dickson-Gonzalez,<sup>1,2</sup> and Alfonso J. Rodriguez-Morales.<sup>2,3</sup>

<sup>1</sup>Anatomopathological Institute JAOD, Central University of Venezuela, Caracas, Venezuela

<sup>2</sup>Collaborative Group of Clinical Infectious Diseases Research, Caracas, Venezuela.

<sup>3</sup>Experimental Institute JWT, Universidad de Los Andes, Trujillo, Venezuela.

[Histoplasmosis Diseminada Fatal con Compromiso en Ganglios Cervicales y Lengua en un Infante con Atrofia Muscular Espinal Tipo I (Enfermedad de Werdnig-Hoffman)]

### Abstract

Disseminated histoplasmosis has been predominantly reported and recognized as a serious opportunistic infection in adults with AIDS, but not in children with other types of immune compromise. Due to the observed serious respiratory infectious complications in patients with spinal muscular atrophy, immune system compromise has been previously suggested in this congenital pathology. We describe a patient with SMA-I and a fatal disseminated histoplasmosis involving cervical lymph nodes and the tongue.

**Key Words:** spinal muscular atrophy, type I, histoplasmosis, fatal, tongue, lymph nodes. *Rev Soc Med Quir Hosp Emerg Perez de Leon* 2008; 39(1):15-18. Received 30 November 2007, Accepted 20 January 2008.

### Introduction

Spinal muscular atrophy (SMA) is a clinically heterogeneous disease inherited in a predominantly autosomal recessive pattern. It is the most prevalent autosomal recessive neuromuscular disorder and, after cystic fibrosis, the most common recessive condition leading to death in children<sup>1-3</sup>. This disorder is characterized by degeneration of motor neurons within anterior horn of spinal cord and brainstem leading to a progressive symmetrical paralysis of the limbs and trunk associated with muscular atrophy<sup>1-3</sup>. Three subtypes can be differentiated according to age of onset and outcome. Spinal muscular atrophy type I (SMA-I), or Werdnig-Hoffmann disease, is the most severe form with early onset, before 6 months of age. These patients are never able to sit without support, with life not exceeding infancy in most cases due to different complications<sup>2,3</sup>. Due to the observed serious respiratory infectious complications in these patients, immune system compromise has been previously suggested in this congenital pathology<sup>4,5</sup>.

Although this, infectious diseases in SMA have been rarely reported<sup>6,7</sup>.

### Case Report

An 11-month-old female infant with severe hypotonia was referred to our institution for further evaluation. She was born, as a floppy infant with symmetrical muscle weakness that was more extensive in the proximal part of the limbs, from an 18-year-old healthy mother at 34 weeks of gestation. Vaginal delivery was complicated due to a podalic presentation. There was no history of radiation exposure, infectious disease, drug ingestion, gestational diabetes, hypertension, or smoking during the pregnancy. Fetal movements were few felt by the mother after 20 weeks of gestation. The pregnancy was complicated at 27 weeks of gestation due to oligoamnios detected by echography, and due to severe pre-eclampsia at 29 weeks of gestation. Family history was otherwise unremarkable.

The patient's birth weight was 1050 grams. She required ventilatory support after birth because of respiratory failure. The

physical examination revealed severe hypotonia with frog-leg posture, high-arched palate, low-set ears, triangular facies, depressed nasal bridge, contractures (arthrogryposis), and clinodactyly in both hands (Figure 1). No abnormalities were seen on both feet. She was not able to swallow or cry. Neurologic examination of the patient also revealed absence of deep tendon, Moro, grasping, rooting, sucking, and tonic neck reflexes.

**Figure 1.** Clinical appearance of the patient at the moment of death.



Brain MRI shown a cortical dyskinetic pattern with frontal and central cerebral atrophy, interhemispheric asymmetry, 3rd and 4th ventricles were dilated, and the corpus callosum and cavum septum pellucidum were thinned. Auditive- and visual-evoked potentials were normal. Electromyography revealed motor neuron disease pattern. The results of blood analysis shown an haemoglobin of 6.9 g/dL, haematocrite of 26.5%, WBC of 7,000 cells/mm<sup>3</sup>; the electrolytes, blood glucose, calcium, phosphorus, alkaline phosphatase, lactic dehydrogenase activity, magnesium, thyroid-renal and hepatic function tests, screening of amino acids, tandem mass neonatal screening and blood gases were within the normal limits. The creatine phosphokinase was 217 UI/L and the CKMB was 52 UI/L.

During the second week of hospitalization presented hyaline anterior rhinorea, with fever and diarrhea, during 3 days. At the third, she presented again fever, hyporexia and a urinary tract infection. One week later presented a severe respiratory failure, at the chest x-ray a bilateral infiltrate and left and basal right paracardiac condensation blocks were observed, also seen in the right apex. She died after 18 days of hospitalization.

The postmortem examination revealed degeneration of the spinal and brainstem motor neurons, compatible with the diagnosis of SMA type I, cerebral atrophy and edema. Variation in fiber size was detected in the examined muscles. There were degeneration and a marked decrease in the number of anterior motor neuron cells of the spinal cord. At lungs tissues, the necropsy revealed a necrotizing bronchopneumonia due to *Histoplasma capsulatum*.

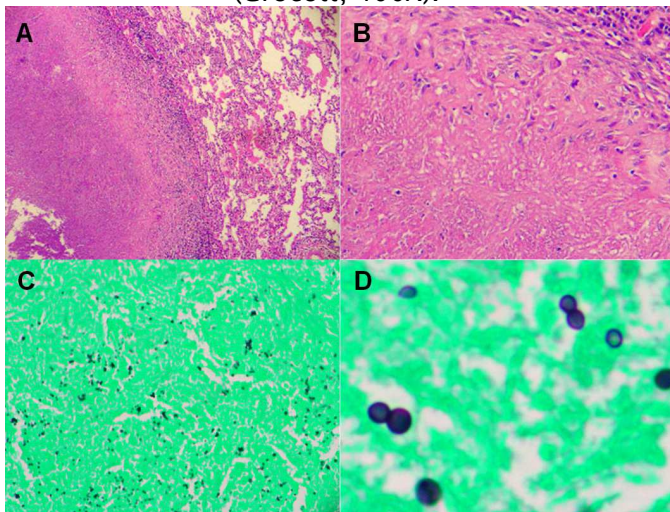
Multiple samples, lesser than 0.5 cm, of all the tissues were collected, and formalin-fixed, paraffin-embedded blocks were done. Three micrometer sections were obtained for each block, and then stained with hematoxylin-eosin (HE). Silver and acid-fast staining procedures were performed. Pulmonary tissue showed fibrosis and necrotizing epithelioid granulomatous response (Figure 2A and 2B), which resembles caseous tuberculosis, due to the extensive central necrosis with numerous round to oval yeast, 2-4  $\mu$ m in diameter, in some areas with distending macrophages.

In cervical lymph node sections the *Histoplasma capsulatum* infection was also evidenced; extensive necrotic areas and numerous yeast cells were also demonstrated, some of them with budding yeast (Figure 2C). Tongue tissue showed the same granulomatous process due to *Histoplasma capsulatum* (Figure 2D). Silver stains were also positive for *Histoplasma capsulatum* and all the acid-fast stainings were negative. The muscle sections revealed atrophic rounded muscle fibers and microscopic fields with other fibers higher in size (hypotrophic); the connective tissue size within the muscle fibers was not increased, but the neural fibers were

increased in size. These histopathological findings were related to the disseminated histoplasmosis infection.

**Figure 2.** Histopathological features seen at the autopsy. (A) Pulmonary necrotizing granuloma due to *Histoplasma capsulatum* infection (HE, 100X).

(B) Peripheral condensation of epithelioid histiocytes at the pulmonary granuloma (HE, 200X). (C) Cervical lymph node with central necrosis at the granuloma evidencing the presence of *Histoplasma capsulatum* (Grocott, 100X). (D) *Histoplasma capsulatum* at the tongue tissue (Grocott, 400X).



## Discussion

We describe a patient with SMA-I and a fatal disseminated histoplasmosis involving cervical lymph nodes and the tongue. The diagnosis of SMA-I, the most severe form of SMA, had been made in an 11-month infant in our case; the clinical onset in this pathology is usually before 6 months of age, and affected individuals rarely survive beyond 2 years of age without mechanical ventilation<sup>8</sup>. The prediction of progression and degree of disability is difficult and extremely variable<sup>6</sup>. The cause of death in these patients is often pulmonary diseases. Our patient suffered severe muscle weakness and the diagnosis and the cause of death were just established at the postmortem examination.

Neonatal hypotonia may have many different etiologies<sup>9,10</sup>. A variety of diagnostic tools are available for defining the source of hypotonia, but a thorough neurologic

examination is essential for the diagnosis before blood tests, muscle biopsies, electromyography, or nerve conduction studies are ordered. Appropriate and cost-effective use of laboratory investigations to establish a specific etiologic diagnosis is always desirable<sup>9,11</sup>. The first goal in diagnosing the source of neonatal hypotonia is to ascertain if it is central or peripheral<sup>10</sup>. In the present study, the patient's findings of profound generalized hypotonia and areflexia would have suggested a motor unit disorder, especially a muscle or anterior horn cell disorder. Electromyography was consistent with spinal muscular atrophy, but a muscle biopsy was not performed. The presence of myopathic facies and congenital contractures are part of the exclusion criteria of the International Spinal Muscular Atrophy Consortium (ISMAC)<sup>12</sup>. The findings of muscle biopsy and postmortem examination confirmed the diagnosis of spinal muscular atrophy in the case presented here, with an acute and severe form of spinal muscular atrophy that was complicated by a lethal disseminated histoplasmosis.

The low birth weight of our patient may well have played a role in the course of the disease. Defence mechanisms to infection have been shown to be strongly affected by nutritional status<sup>6,13</sup>. Both deficiency of protein energy and individual nutrients (trace minerals and vitamins, particularly zinc, iron, selenium, vitamins A, B6, C and E) are associated with impairment of cell-mediated immunology, complement activation and secretory immunoglobulin antibody response. This immune system compromise related to the nutritional status as well that previously suggested in the SMA<sup>4,5</sup> could be predisposing for the development of infectious complications such as disseminated histoplasmosis, as was seen in this case<sup>14,15</sup>.

Progressive disseminated histoplasmosis is often fatal without treatment and requires rapid and accurate laboratory diagnosis.<sup>16</sup> Unfortunately, the diagnosis was not suspected in the live patient, who did not presented suggestive signs of this pathology. In these patients, prolonged fever, weight

loss, hepatosplenomegaly and pancytopenia are observed<sup>17</sup>. Disseminated histoplasmosis has been predominantly reported and recognized as a serious opportunistic infection in adults with acquired immunodeficiency syndrome (AIDS), but not in children with other types of immune compromise<sup>18</sup>.

Disseminated histoplasmosis should be considered in infants from endemic areas who present with fever, hepatosplenomegaly and hematologic abnormalities. These patients develop transient hyperglobulinemia and T cell deficiency that resolve with treatment. Treatment with amphotericin B followed by an oral azole for 3 months is effective in most patients<sup>19,20</sup>.

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**Corresponding author:** Sonia Dickson, Universidad Central de Venezuela. Email: soniad15@hotmail.com.

**Conflict of Interests:** No declared.