

CLINICAL CASE

Type I spinal muscular atrophy: Werdnig-Hoffmann disease

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ABSTRACT

Background. Childhood spinal muscular atrophy is an autosomal recessive neuromuscular disease characterized by degeneration of the anterior horn cells of the spinal cord. SMA type I, the most severe form (Werdnig-Hoffmann disease) can be detected in utero or during the first months of life. Death typically occurs within the first 2 years of life.

Case report. A 6-month-old female was admitted to the emergency room for severe respiratory distress. She had muscular hypotonia, intercostal muscle weakness and tongue fasciculations. Electromyography was compatible with motor polyneuropathy with axonal and myelin damage. Molecular analysis of *SMN-1* gene reported homozygous for deletion of exons 7 and 8 of *SMN-1* gene.

Conclusions. It is imperative to recognize and diagnose this entity in order to provide genetic counseling to the family as well as to offer support and advice in the care of the patient.

Key words: type I spinal muscular atrophy, Werdnig-Hoffmann disease.

INTRODUCTION

Under the classification of childhood spinal muscular atrophy (SMA), a number of processes are grouped that share certain characteristics such as being genetically determined as an autosomal recessive condition and present with muscle atrophy due to neuronal degeneration in the anterior horn of the spinal cord and, in the most severe forms, of the nuclei of the last few cranial nerves.^{1,2} SMA continues as the second cause attributed to lethal autosomal recessive diseases after cystic fibrosis³ with a worldwide incidence described between 1/6,000 and 1/10,000 births and with a carrier rate between 1/35 and 1/50.^{3,4} In Mexico, the incidence is 0.5 to 1/25,000 of births and there are only isolated case reports.⁵⁻⁹

The common gene of the childhood form of SMA is located on chromosome 5.¹⁰ Its product has been cloned and identified.¹¹ Although the affected gene is the same, from the clinical point of view we have considered several forms of the disease according to age at onset and evolution. These are listed below:^{12,13}

- Type I or Werdnig-Hoffmann disease (WHD) —the most severe form. It begins in utero or during the first months of life. Death usually occurs before the age of 2 years.
- Type II or intermediate —occurs before 18 months of age. Survival of these individuals depends on the degree of respiratory complications. In this clinical form, with the current approach (rehabilitation, scoliosis surgery and especially noninvasive ventilation) surviving patients reach adulthood.
- Type III or Kugelberg-Welander disease —presents after 18 months of age. Its gravity is highly variable because it depends on when the disease begins: before or after 3 years of age.

In 1978, citing the difficulty of specifying the age of onset and that severity does not always relate to this data, except for WHD, Dubowitz proposed an eminently pragmatic classification, although the three forms based on the

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child's ability to remain sitting, standing or to walk without assistance are also considered. The first is so severe that head control is not possible and the child is unable to sit unaided. In the intermediate form, the child is able to sit but is not able to stand or walk. In the mild form, the child can remain standing or is able to walk.¹⁴

From a molecular standpoint, the cause is a homozygous mutation in the survival gene of the motor neuron (SMN), which is located on the long branch of chromosome 5 (5q11.1-13.3). This gene is present in multiple copies in the human genome: a telomeric (SMN1) and several copies of centromeric (SMN2), which differ by only five nucleotides. The SMN2 gene has a tendency to an alternative gene assembly (*alternative splicing*) during the transcription of mRNA, which results in a truncated protein that conserves only 10% of the full SMN protein. This normal protein fails to compensate for the loss of the protein by mutation of the SMN1 gene.^{15,16} Deletions of exon 7 and 8 or only deletion of 7 of the SMN1 gene are responsible for >95% of cases of SMA.¹⁷ Thus, detecting a homozygous deletion of at least exon 7 of the SMN1 gene constitutes a tool for the diagnosis of SMA, which reaches a sensitivity close to 95% and a specificity of 99%.¹⁷

CLINICAL CASE

We present the case of a 6-month-old female patient, the product of GIII, full-term pregnancy and born via cesarean section. The patient presented no history of perinatal asphyxia, with birth weight of 3200 g and length of 49 cm. She was exclusively breast-fed. She presented with the complete schedule of immunizations for her age. Her father is 32 years old and her mother is 30 years old with a history of a spontaneous abortion during GII. Both parents appear healthy. They are from a small community and share the same last name, but deny consanguinity. The patient has one healthy 5-year old brother. She was admitted to the emergency department with an acute respiratory infection of 5 days duration, manifested by rhinorrhea, cough and unquantified fever. On admission she showed severe respiratory distress with severe bronchospasms. This warranted controlled mechanical ventilation, and the patient was managed with bronchodilators, steroids and muscle relaxants. Our attention was drawn to the difficulty of ventilator weaning because, after stopping the muscle relaxant, the patient did not show an adequate respiratory effort. On

physical examination, the patient presented hypotonicity of all four limbs with characteristic position of the upper extremities, consisting of extended arms along the trunk, pronation of forearms as well as legs apart and resting on the supporting surface (Figure 1), with marked muscular hypotonia (Figures 2 and 3). The intercostal muscle weakness determined diaphragmatic breathing that gave the abdomen the appearance of a balloon. The facie was hypomimia and the patient gave the appearance of being alert. She presented twitching of the tongue with discrete folds, producing a cerebroid appearance. As an important



Figure 1. Hypotonicity of the four extremities with characteristic position: arms extended along the trunk, forearm pronation as well as legs apart and resting on the supporting surface.



Figure 2. Supine muscular hypotonia.



Figure 3. Muscular hypotonia in the prone position.

precedent, the father noted lack of head support as well as some degree of hypotonicity. The mother reported that fetal movements were appropriate during pregnancy. PKC and aldolase tests were requested and reported as normal.

Electromyographic study was performed, which reported images of instability of the membrane in 100% of the muscles studied, with abundant fibrillations and positive waves. There were no fasciculations reported. Poor motor unit potentials reflecting loss of anterior horn cells of the spinal cord were obtained. The interference pattern was found to be greatly decreased and incomplete, with a limited potential number and greater involvement of lower limb muscles. Motor potentials were found to be missing when we examined nerve conduction velocity in the median and right peroneal nerve. It was concluded that the study was abnormal and compatible with motor polyneuropathy with severe myelinic axonal damage, secondary to progressive acute SMA.

Molecular analysis of the *SMN-1* gene was performed from genomic DNA obtained from complete peripheral blood leukocytes. We reported the absence of exons 7 and 8 corresponding to the *SMN-1* gene and the integrity of exons 7 and 8 of the *SMN-2* pseudogene (Figure 4). This indicates a homozygote state for a deletion that involves both *SMN-1* alleles.

DISCUSSION

WHD is the most severe form of childhood SMA and manifests itself during the first months of life, as in the

case presented here. Diagnostic suspicion is mainly clinical; therefore, childhood muscle atrophy should be suspected when examining an infant with marked hypotonia.

It is important to consider that the hypotonia may go unnoticed by the family. The cause for hospitalization may be respiratory failure as was the case in this patient, which can be mistaken for pneumonia if proper questioning and an adequate physical exploration are not performed. It should be kept in mind that during the study of a hypotonic patient, differential diagnoses may be metabolic diseases, e.g., glycogen storage disease, hypothyroidism, poisoning (botulism) and congenital neuromuscular diseases. For diagnostic confirmation it is necessary to carry out neurophysiological studies, muscle biopsy (in cases of doubt) and, currently, molecular study, which is the gold standard for definitive diagnosis. In this patient, a muscle biopsy was not performed; however, electromyography was consistent with SMA and molecular analysis confirmed the clinical diagnosis of SMA due to a homozygous state for deletion of exons 7 and 8 of the *SMN-1* gene. The result of the molecular study allows appropriate genetic counseling for the family because it indicates a probability >99% that the biological parents of the patient are heterozygous or healthy carriers of the deletion of exons 7 and 8 corresponding to the *SMN-1* gene. Because SMA has an autosomal recessive inheritance, the risk of disease recurrence in the offspring of parents, regardless of gender, is 25% with each pregnancy. Recent progress in identifying molecular alterations in these conditions, as well as advances in medical technology, led to the creation of a multidisciplinary committee of experts for management of SMA. After analyzing the existing studies, a consensus was carried out that is used to guide the care of patients with SMA, including diagnosis and new interventions in the management of respiratory, gastrointestinal, nutritional, orthopedic, and rehabilitation complications, as well as in regard to palliative care.¹⁸ However, there is no cure for WHD, only for prevention and management of complications. Ventilatory support is important, as well as infection management.^{18,19} Noninvasive ventilatory management can be offered,^{18,20} although for this clinical form of SMA there is no consensus and, in most centers, there is no procedure for the application of noninvasive ventilatory management. Unfortunately, short-term prognosis is poor. Our patient showed respiratory improvement and no longer required ventilatory management and she was discharged for maximum quality of

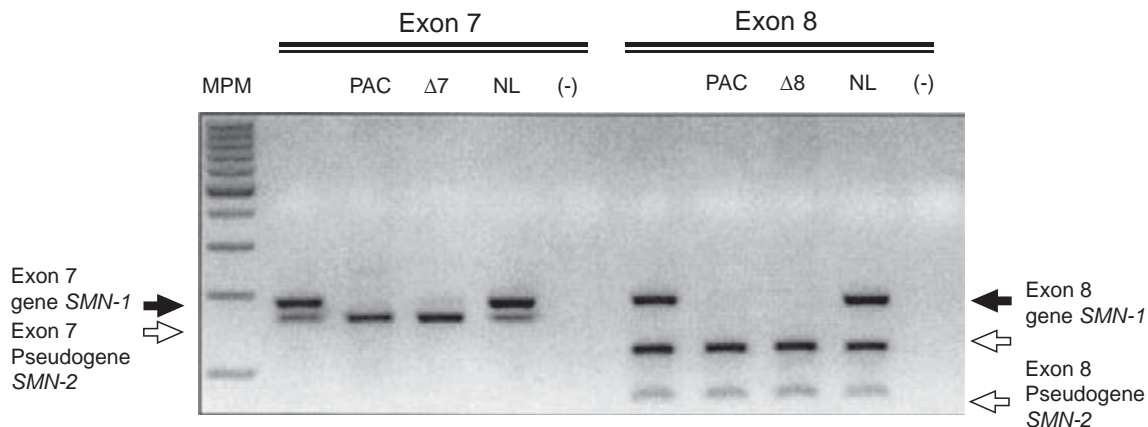


Figure 4. Molecular study of the *SMN-1* gene in patients with spinal muscular atrophy (SMA). Agarose gel electrophoresis (3%) of restricted PCR products of exons 7 and 8 of the *SMN-1* gene and pseudogene *SMN-2*. Note the presence of the amplified product corresponding to exons 7 and 8 of the *SMN-1* gene (black arrows) in the healthy control (Lanes NL) and its absence, both in the deletion control (Lanes 7 and 8) as well as in the patient (Lanes PAC). Both the patient and the healthy control and the controls with deletion presented integrity of exons 7 and 8 (restricted) of pseudogene *SMN-2* (white arrows). This indicates a homozygous state for deletion of exons 7 and 8 of the *SMN-1* gene. MWM, molecular weight marker, 100 bp.

life. The mother gave informed consent for the publication of the case, including photographs of the patient.

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REFERENCES

- Scheffer H. Spinal muscular atrophy. *Methods Mol Med* 2004;92:343-358.
- Iannaccone ST, Smith SA, Simard LR. Spinal muscular atrophy. *Curr Neurol Neurosci Rep* 2004;4:74-80.
- Monani UR. Spinal muscular atrophy: a deficiency in a ubiquitous protein; a motor neuron-specific disease. *Neuron* 2005;48:885-896.
- Lunn MR, Wang CH. Spinal muscular atrophy. *Lancet* 2008;371:2120-2133.
- Garza-Alatorre AG, Rodríguez-Bonito R, López-Espinoza JA, Nieto-Sanjuanero A. Atrofia muscular espinal tipo I. Reporte de un caso atípico. *Rev Mex Pediatr* 2001;68:69-71.
- Sánchez MJ, Moreno GAM, Romero BBL, Hernández AJ, García DC, Sánchez AA. Lactante con atrofia muscular espinal y encefalopatía hipóxico-isquémica. *Bol Med Hosp Infant Mex* 2010;67:63-73.
- Palmer-Morales Y, Pacheco-Flores G, Ames-Guevara Y, Gaxiola-Apodaca M, Gaspar-Franco D, Landavazo-Acuña G, et al. Enfermedad de Werdnig-Hofmann. Dos casos clínicos. *Rev Med Inst Mex Seguro Soc* 2010;48:317-319.
- Collado-Ortiz MA, Shkurovich-Bialik P, González de Leo S, Arch-Tirado E. Atrofia espinal tipo I (síndrome de Werdnig-Hoffmann). Reporte de un caso. *Cir Cir* 2007;75:119-122.
- Padrón-Arredondo G, López-Gómez L. Atrofia muscular espinal infantil tipo I. Presentación de un caso presuntivo y revisión de la literatura. *Salud Tab* 2007;13:700-703.
- Melki J, Abdelhak S, Sheth P, Bachelot MF, Burlet P, Marcdet A, et al. Gene for chronic proximal spinal muscular atrophies maps to chromosome 5q. *Nature* 1990;344:767-768.
- Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell* 1995;80:155-165.
- Brooke MH. A Clinician's View of Neuromuscular Diseases. London: Williams & Wilkins; 1985. pp. 36-80.
- Munsat TL, Davies K. Workshop report. Spinal muscular atrophy. 32nd ENMC International Workshop. Naarden, The Netherlands, 10-12 March 1995. *Neuromuscul Disord* 1996;6:125-127.
- Dubowitz V. *Muscle Disorders of Childhood*. Philadelphia: Saunders; 1978. pp. 146-190.
- Burlet P, Bürglen L, Clermont O, Lefebvre S, Viollet L, Munnich A, et al. Large scale deletions of the 5q13 region are specific to Werdnig-Hoffmann disease. *J Med Genet* 1996;33:281-283.
- Scheffer H, Cobben JM, Matthijs G, Wirth B. Best practice guidelines for molecular analysis in spinal muscular atrophy. *Eur J Hum Genet* 2001;9:484-491.
- Ogino S, Wilson R. Spinal muscular atrophy: molecular genetics and diagnostics. *Expert Rev Mol Diagn* 2004;4:15-29.
- Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Participants of the International Conference on SMA Standard of Care. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol* 2007;22:1027-1049.
- Castiglione C, Levicán J, Rodillo E, Garmendia MA, Díaz A, Pizarro L, et al. Atrofia muscular espinal: caracterización clínica, electrofisiológica y molecular de 26 pacientes. *Rev Med Chile* 2011;139:197-204.
- Petrone A, Pavone M, Testa MB, Petreschi F, Bertini E, Cutrera R. Noninvasive ventilation in children with spinal muscular atrophy types 1 and 2. *Am J Phys Med Rehabil* 2007;86:216-221.