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CLINICAL CASE

Pharmacological and respiratory treatment in three patients with Spinal Muscular Atrophy type 1

Tratamiento farmacológico y respiratorio en 3 pacientes con Atrofia Muscular Espinal tipo 1

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What do we know about the subject matter of this study?

Spinal muscular atrophy type 1 (SMA 1) is a disease that, if not treated, leads to early death of those who suffer from it. However, with the development of disease-modifying antirheumatic drugs and respiratory care, a significant decrease in morbidity and mortality has been evidenced.

What does this study contribute to what is already known?

This article presents the experience in the clinical management of 3 patients with SMA 1 who have achieved significant improvements in survival and evolution through management that allows modification of the course of the disease. In Latin American countries, there are few publications on this subject. Our casuistry helps to focus the management of other patients.

Abstract

Spinal muscular atrophy type 1 (SMA 1) is a progressive neuromuscular disease with high morbidity and mortality, especially due to respiratory and nutritional complications. **Objective:** To present 3 patients who managed to diverge from the natural history described for this disease due to the implementation of standards of care and disease-modifying therapies. **Clinical Case:** We report three female patients with SMA 1 from the *Fundación Hospital Pediátrico la Misericordia* (HOMI), Colombia, with diagnosis and treatment before 6 months of age. Two of them managed to overcome respiratory failure and all 3 have been maintained without invasive respiratory support and with oral feeding, without gastrostomy. **Conclusions:** Pediatric patients with SMA 1 have a serious disease that leads to respiratory failure and a high probability of early death. The implementation of multidisciplinary management strategies allows for preserving respiratory function, initiating specific disease-modifying therapies, improving their survival, and decreasing associated morbidity.

Keywords:
Werdnig-Hoffman Disease;
Noninvasive Ventilation;
Spinal Muscular Atrophy;
Nusinersen

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Introduction

Spinal muscular atrophy (SMA) 5q, OMIM #253300 is a genetic neuromuscular disease, of autosomal recessive inheritance. It is characterized by degeneration of alpha motor neurons in the spinal cord, causing progressive weakness along with motor, swallowing, and secondary respiratory involvement[1]. Worldwide, an estimated incidence of 1 in 10,000 live births has been reported[2]. We do not have data from Colombia given the scarcity of reports[3].

It is characterized by an alteration in the production (loss or dysfunction) of the survival motor neuron (SMN) protein, encoded by the *SMN1* gene. The *SMN2* gene is a paralog of the *SMN1* gene. The copy number of *SMN2* affects the phenotypic presentation because this gene produces low levels of functional protein, due to a defect in the splicing process of its messenger RNA. This defect is because, in *SMN2*, exon 7 is frequently skipped during splicing, resulting in a non-functional protein that fails to compensate for the lack of expression of the *SMN1* gene[4]. For this reason, *SMN2* is a target for the treatment of patients with SMA.

Historically, the disease has been classified into 5 subtypes from 0 to 4, according to the motor milestones reached at the time of the disease presentation[1]. Spinal muscular atrophy type 1 (SMA 1) is a severe form that manifests before six months of age and patients never manage to sit up, evolve with respiratory failure, and die before two years of age if they do not receive comprehensive treatment[5].

The natural course of the disease has been documented both worldwide[6] and in Latin America[7,8]. It should be noted that currently, survival in children with SMA 1 is associated with the early implementation of non-invasive respiratory interventions after diagnosis[9].

In 2016, the U.S. Food and Drug Administration (FDA) approved the first treatment for SMA called Nusinersen. Its efficacy was confirmed in the ENDEAR trial that included 122 symptomatic patients with SMA 1, showing improvement in motor scales and an acceptable safety profile[10]. Nusinersen is a synthetic antisense oligonucleotide, approved for the management of SMA in several countries. This drug modifies splicing within intron 7, resulting in the inclusion of exon 7 in the SMN pre-mRNA transcript. As a result, it increases the production of full-length functional SMN protein[11]. This drug is administered intrathecally and has shown clinically significant improvement in motor function and motor milestones of up to 93% and has a favorable risk-benefit profile, with few adverse effects[11]. Its effectiveness has also been evaluated in children with late-onset SMA, after 6 months of age, finding improvement in motor scales compared to the control group that did not receive the drug[12].

In Colombia, until 2023, Nusinersen was the only SMA-modifying drug approved for use. However, there are two other drugs worldwide that have demonstrated effectiveness such as Risdiplam and Onasemnogene abeparvovec. Risdiplam is the first oral drug developed for the treatment of SMA. It is administered daily and acts as a pre-mRNA splicing modifier of SMN2, increasing the production of full-length SMN protein[13]. Onasemnogene abeparvovec is a single-application gene therapy, which promotes *SMN1* gene replacement by a modified adenovirus[14].

The objective of this report is to describe three cases of patients with SMA type 1 who received comprehensive management, including modifying treatment and proactive respiratory care from diagnosis, and who were maintained without invasive ventilatory support or gastrostomy. These patients were treated at the *Fundación Hospital Pediátrico la Misericordia* (HOMI), Bogotá, Colombia. This institution receives patients from all over the country since it has all the pediatric subspecialties.

Clinical Cases

Case 1

Female patient, born from the fourth pregnancy of non-consanguineous parents. She had a family history of a deceased brother with SMA 1 and Down syndrome. At 45 days of age, she presented loss of voluntary lower limb movements against gravity and loss of head control. At 3 months, she was evaluated by a pediatric neurologist who identified hypotonia and areflexia. Multiplex ligation-dependent probe amplification (MLPA) confirmed homozygous deletion of exons 7 and 8 of the *SMN1* gene and the presence of two copies of the *SMN2* gene.

At 4 months of age, she presented signs of respiratory distress, fever, rhinorrhea, and paradoxical breathing, therefore, she was referred to our institution for multidisciplinary treatment.

The patient was admitted presenting with thoracoabdominal dissociation, bell-shaped chest, abundant secretions, almost no cough, weak cry, severe hypotonia, areflexia, and tongue fasciculations. In the Intermediate Care Unit, oxygen therapy and non-invasive ventilation (NIV) with bilevel-positive airway pressure (BiPAP) were initiated, and a mechanical cough assist device was implemented. No virus was isolated in respiratory secretions. On the third day of hospitalization, the patient was stable, receiving low-flow oxygen therapy while awake and positive airway pressure during nocturnal sleep. The following scales were

administered: The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) with a score of 33/64, and the Hammersmith Infant Neurological Examination Part 2 (HINE-2) with a score of 2/26 (5%).

On the fourth day of hospital stay, rhinovirus/enterovirus and parainfluenza were identified. Chest X-ray showed right apical opacity and required increased NIV time. After showing improvement, the duration of noninvasive ventilation support was reduced again, and it was maintained during nocturnal sleep. However, on the 15th day of admission, she again presented respiratory failure, fever, and diarrhea secondary to adenovirus infection. Support with BiPAP was intensified and a nasogastric tube was placed, achieving stability and progressive reduction of ventilatory support, which was maintained during nocturnal sleep, as well as reinitiation of oral feeding.

At 5 months of age, disease-modifying treatment started with intrathecal Nusinersen on the 23rd day of her hospitalization. Currently, at 24 months of age and with 7 doses of Nusinersen, she has normal swallowing and has had no new episodes of respiratory failure. She uses BiPAP during sleep and a mechanical cough assist device. At the motor level, she has head control, grasps objects with her hands, crosses the midline, moves all four limbs against gravity, and can sit with support. Regarding orthopedic aspects, she presented with bilateral hip dysplasia, for which she is undergoing treatment with a hip flexion and abduction brace, and scoliosis under follow-up.

Case 2

Female patient, daughter of non-consanguineous parents, born from the fourth pregnancy. Her brother died at age 5 months with suspected, but unconfirmed, SMA. At 40 days of life, the mother noticed decreased movements in the lower limbs and decreased intensity of crying. At 4 months of age, a diagnosis of SMA 1 was confirmed, due to homozygous deletion of exons 7 and 8 of the *SMN1* gene with two copies of the *SMN2* gene. Simultaneously, she scored 13/64 on the CHOP INTEND scale; she had no cough reflex and a bell-shaped thorax. Based on these findings, during an outpatient visit, support with BiPAP and a mechanical cough assist device was recommended but not implemented. At 4 and a half months, she received her first dose of Nusinersen. After the second dose, she presented with rhinoenterovirus infection, and respiratory failure, and required admission to the intensive care unit, with continuous support with BiPAP ST mode. Upon recovery, the time of BiPAP use was progressively reduced until support was provided only during nocturnal sleep.

Initially, she was unable to adapt to the mechanical cough assist device, so its use was discontinued. Due to swallowing disorder, nasogastric tube feeding started, and the patient was discharged from the hospital 3 months later with ventilatory support during sleep and exclusive tube feeding.

At 9 months, she presented a new respiratory failure secondary to rhinovirus/enterovirus infection and massive left lung atelectasis, requiring hospitalization for a month. BiPAP was adjusted, with good response, resuming outpatient management. The patient had new hospitalizations at 11, 13, and 14 months of age, all due to respiratory causes.

Currently, at 20 months of age, she has received 7 doses of Nusinersen. She demonstrates partial head control and incomplete rolling from prone to supine and vice versa. She has started oral feeding, combined with nasogastric tube feeding. She presents bilateral congenital hip dysplasia, currently being treated with hip flexion and abduction brace. A scoliosis study is pending. She has not had any new admissions due to respiratory intercurrences and uses BiPAP during nocturnal sleep and a mechanical cough assist device.

Case 3

Female patient born from a multiple pregnancy, dichorionic, and diamniotic. She was delivered by cesarean section at 37 weeks of gestation, with normal weight and length. This is the second pregnancy of non-consanguineous parents. The first child died at 8 months of age due to respiratory failure and suspected SMA 1, but genetically unconfirmed.

From birth, she has presented limited limb movement and neurodevelopmental delay compared to her healthy twin brother. In the evaluation by pediatric neurology, axial hypotonia, general hyporeflexia, and weakness were observed. MLPA was performed and confirmed SMA 1 with homozygous deletion of exon 7 of the *SMN1* gene and the presence of two copies of the *SMN2* gene at 3 and a half months of age.

At 4 months of age, she was hospitalized due to mild bronchiolitis. She had a bell-shaped chest and tongue fasciculations. She received treatment for respiratory symptoms without the need for oxygen therapy. BiPAP was started during sleep as early management of respiratory involvement secondary to SMA 1. Swallowing evaluation was normal and oral feeding was continued. The day after admission, the CHOP INTEND scale was administered with a score of 21/64 (39%). On the 27th day of admission (5 months old), she started treatment with Nusinersen. It was not possible to start it previously due to difficulties in the authorization by her social security.

She is currently 16 months old, has received 6 total doses of Nusinersen, and has had no new admissions because of respiratory infections. She continues with

BiPAP mode ST support, daily mechanical cough assist device, and oral feeding. Regarding the motor aspects, she can roll from prone to supine and vice versa and can sit with support.

These three patients received treatment with Nusinersen since, at the date of their respective assessments, it was the only specific treatment authorized in Colombia. Management has been carried out jointly with multidisciplinary follow-up, according to international guidelines for the treatment of patients with SMA[17,18] and including the different specialties (Figure 1). The criteria for the initiation of NIV are according to the criteria of Great Ormond Street Hospital (GOSH)[19]. Table 1 shows nutritional follow-up data and motor scales.

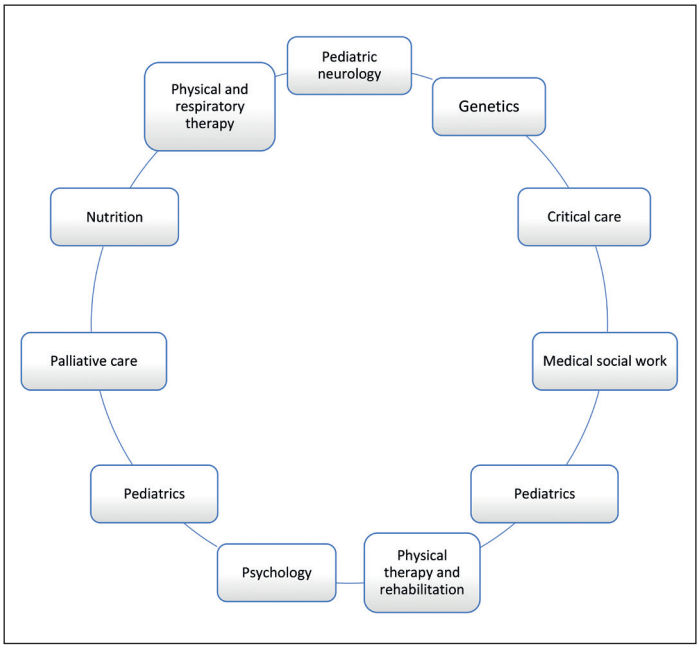

Figure 1. Specialties involved in the multidisciplinary management of patients with SMA type 1.

Discussion

SMA 1 is a severe neuromuscular disease, that leads to early death in infants who suffer from it. This outcome is related to the rapid onset of respiratory failure that is characteristic of the disease[20]. We present the clinical cases of 3 patients aged 24, 20, and 16 months, respectively, who achieved extended survival and remained off invasive ventilation, following the standards of care for patients with SMA. We highlight the benefits of early diagnosis, and multidisciplinary treatment, especially respiratory, added to the initiation of disease-modifying therapy, in a Latin American country.

In patients with SMA 1, muscle weakness predominates in the proximal and axial regions, with involvement of the intercostal muscles while diaphragmatic function is partially preserved. This imbalance between diaphragm contractility and rib cage distensibility explains the thoracoabdominal dissociation and the bell-shaped chest observed in all 3 patients.

As the disease progresses, the involvement leads to the absence of cough reflex and increased dead space with decreased tidal volume[20]. Because of these characteristics, they require early respiratory support and the treatment of acute respiratory failure should be different from that offered to patients whose involvement is secondary to acute infection and/or bronchial obstruction in which hypoxemia predominates and not hypercapnia as in SMA patients. In children with SMA 1, treatment of hypoventilation should be prioritized and the need for oxygen therapy should be individualized, considering that increasing oxygen saturation may worsen hypercapnia[21]. All 3 patients had a respiratory infection and because of the alteration in normal respiratory physiology, a mechanical cough assist device was used, and hypoxemia and hypoventilation were treated together. A better understanding of the disease has led us to preventive and anticipatory respiratory management of SMA (Figure 2)[20].

Survival in patients with SMA 1 has changed with the development of disease-modifying therapies. It had previously been documented that children with SMA

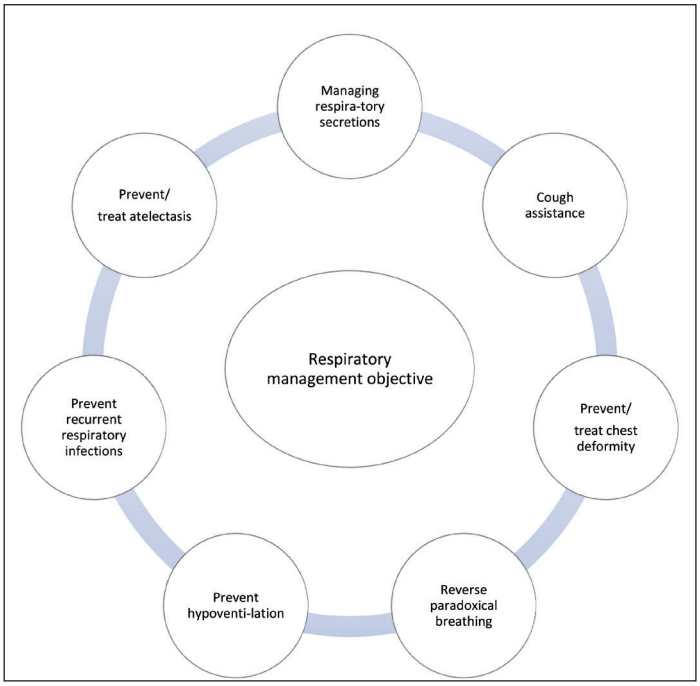

Figure 2. Objectives of respiratory care in patients with SMA type 1.

Table 1. Clinical characteristics of children reported with SMA type 1

Variable	Caso 1	Caso 2	Caso 3
Gender	Female	Female	Female
Age at admission to the institution (months)	4	4	4
Number of SMN2 copies	2	2	2
Age at first administration of Nusinersen (months)	5	4	5
Weight at the time of administration (kg) Height at the time of administration (cm)	6.8 65	Not available	7.06 60.5
GOSH criteria at admission			
Major criteria 1. Acute exacerbation 2. Recurrent chest infection 3. Increased work of breathing/dyspnea 4. Chronic or acute respiratory failure documented	Present Absent Present Present	Present Absent Present Present	Present Absent Present Absent
Support criteria 1. Poor weight gain despite optimized feeding 2. Chest deformity	Absent Present	Absent Present	Absent Present
Tracheostomy	No	No	No
Gastrostomy	No	No	No
Use of NIV at last follow-up	Yes, during sleep	Yes, during sleep	Yes, during sleep
Videofluoroscopic swallow study	Normal	Swallowing disorder	Normal
Feeding route	Oral	Oral and nasogastric tube	Oral
PSG AHI IACAI OAI Hypopneas	 1,4 0 0.6 0.9	 	 14,20 1,07 0,47 12,31
Motor scales at treatment initiation CHOP Intend HINE 2	 33/64 2/26	 13/64 Not available	 21/64 3/26
Follow-up scales CHOP Intend after HINE 2	7 doses 49/64 10/26	7 doses 60/64 10/26	4 doses 52/64 10/26
Age at the time of report (months)	24	20	16
Weight at last follow-up (kg) Height at last follow-up (cm)	7,9 79	8,3 86	8,8 78

SMN2: survival motor neuron 2, GOSH: Great Ormond Street Hospital, NIV: non invasive ventilation, PSG: polysomnogram, AHI: apnea hypopnea index, AHI: central apnea index, AHI: obstructive apnea index, CHOP Intend: The Children´s Hospital of Philadelphia Infant Test of Neuromuscular Disorders, HINE2: Hammersmith Infant Neurological Examination part 2.

1 could live up to 2 to 3 years with respiratory care alone or live beyond 2 years with tracheostomy and/or noninvasive ventilatory support, though with severely limited mobility[5].

Pneumonias and atelectasis caused by bacterial and/or viral infections, as well as by bronchoaspiration, are common complications in these children, leading to severe respiratory and hemodynamic deterioration[18]. Treatment should be intensive to control the infection and maintain airway patency, and NIV pressure support should be prioritized. High-flow nasal cannula (HFNC) and continuous positive airway pressure (CPAP) are not recommended because they do not improve respiratory mechanics or treat hypoventilation[18]. The three patients in this report had acute respiratory infections, which delayed the application of the disease-modifying treatment.

The use of NIV not only allows the treatment of respiratory intercurrences but also reduces the number of hospitalizations of patients. In addition, this ventilation modality does not generate limitations for patients to communicate, which is one of the reasons

for the protocols and standards of care in patients with SMA[5,18].

In this report, two of the three patients presented respiratory failure, which was successfully managed with NIV, without requiring the use of HFNC or invasive mechanical ventilation. The third patient, despite not having criteria for respiratory failure, was managed with NIV in an anticipatory manner, reducing the impact of infection and ventilatory failure. This treatment was offered because it has been shown that the use of BiPAP during sleep allows the management and/or prevention of pulmonary collapse in patients with SMA 1 and should be initiated early in the presence of paradoxical breathing, obstructive sleep apnea, mixed sleep-disordered breathing, recurrent acute respiratory infections, and abnormalities in chest morphology, such as bell-shaped chest[20].

In all three patients, respiratory support was initiated considering the findings on physical examination and it was not necessary to have a polysomnography, due to the clear benefits of the therapy on respiratory mechanics. The support was titrated following clinical and paraclinical progression[22]. The GOSH criteria allow standardizing the initiation of NIV and patients with more than 1 major criterion, with or without a support criterion, are candidates for initiation of therapy[19], as was the case of our patients, who met the criteria for initiation of NIV, treatment that has been maintained to date, achieving stability of respiratory mechanics and improvement in the morphology of the thorax. For secretion management, different methods have been described in the literature, but most of the devices are not available in our country[23]. Mechanical cough assistance was initiated during hospital stay in all 3 patients.

In addition to respiratory alterations, patients with SMA 1 present involvement of the bulbar muscles, with dysphagia, greater risk of bronchoaspiration and malnutrition, for which many require protection of the airway through a safe feeding route and continuous nutritional support to achieve adequate growth[17]. Only one of our patients showed an alteration in swallowing that has improved with the comprehensive treatment offered. It is noteworthy that, although the weight of our patients is lower for their age, it is similar to that described by other authors in children with SMA 1[24]. It is noteworthy that all 3 patients had a history of a first-degree relative with suspected or confirmed SMA 1, family information that should be prioritized when evaluating children with hypotonia in order to achieve timely diagnosis and treatment[8].

All 3 patients have had improvement in motor milestones and respiratory stability, which is in line with what has been published in the literature[25]. In their follow-up, we have faced challenges associated with increased life expectancy in children with SMA 1 and emerging phenotypes with the use of modifying therapies. These challenges include the occurrence of early scoliosis and its treatment and individualization of long-term respiratory support[26].

Conclusion

SMA 1 is a severe genetic disease that leads children to respiratory failure and a high probability of early death. Some interventions change the natural history, including treatment with disease-modifying drugs, and respiratory and nutritional support. Implementing these measures early and in a comprehensive care center can improve survival and decrease morbidity in this group of patients.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

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