ECUADORIAN JOURNAL OF PEDIATRICS
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CLINICAL CASES

Case series of patients diagnosed with Spinal Muscular Atrophy Type I (Werdnig-Hoffmann) in Ecuador.

Álvaro Nicolay Astudillo Marino*[1], Patricia Cecilia Erazo Noguera[1]
https://orcid.org/0000-0001-7908-1808

1. Center for Neurological and Nutritional Diseases of children and adolescents - CENNA, Quito-Ecuador.
2. Pediatric Department, Axxis Hospital, Complementary Health Network, Quito-Ecuador.

Abstrac

Introduction: Spinal muscular atrophy, the leading genetic cause of infant death, is a heterogeneous group of diseases characterized by the degeneration of motor neurons in the spinal cord and brainstem, resulting in hypotonia and muscle weakness. The objective is the description of 5 cases of patients with a genetic diagnosis of SMA type I, all patients with copy number for SMN2: 2 copies and SMN Gene 1 with homozygous deletion.

Methods: The clinical manifestations and genetic results of 5 patients diagnosed with SMA type I are described. The possibilities of treatment and multidisciplinary approach in the patients are also described.

Results: Five patients with a clinical and genetic diagnosis of Spinal Muscular Atrophy type I were included, two were male, three female, with an age range between 11 months and 22 months. The male: female ratio was 2: 3. The history of a first-line relative with spinal muscular atrophy was recorded in 1 of 5 patients. The absence of muscle stretch reflexes in the upper and lower extremities was a sign shared by 100% of the patients.

Conclusions: Increased attention to early diagnosis and management of spinal muscular atrophy has stimulated the development of guidelines and standards of care that have affected survival and the natural history of the disease. There is no effective medical treatment for spinal muscular atrophy. However, since discovering the disease-causing gene, significant progress has been made in understanding molecular pathogenesis, leading to the development of treatment options.

Keywords:

MESH: Muscular Atrophy, Spinal; Spinal Muscular Atrophies of Childhood; Muscle Hypotonia; Neurodevelopment Disorders.

Received: January 2, 2022
Accepted: March 2, 2022
Published: April 25, 2022
Editor: Dr. Paul Astudillo Silva.

Bibliographic letterhead:
Astudillo A, Erazo P. Case series of patients diagnosed with Spinal Muscular Atrophy Type I (Werdnig-Hoffmann) in Ecuador Rev. Ecuat. Pediatr. 2022;23(1):62-70.https://doi.org/10.52011/132

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* Corresponding author.

Email: nicoastudilloneuropedia@hotmail.com (Álvaro Nicolay Astudillo Mariño) /Telephone: +593 998699079/Address: Calle N43 Oe7-41 y Alonso de Torres, CENNA Building

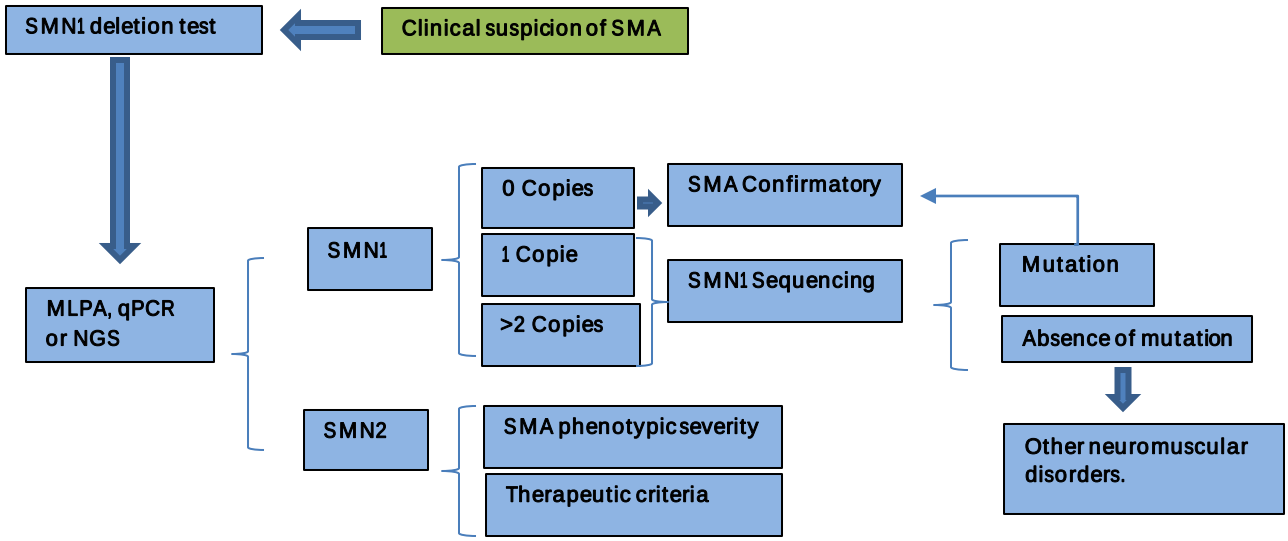

Figure 1. Diagram of the diagnostic scheme for SMA type I. Adapted from Mercuri et al. (2018) [4]

Introduction

Spinal muscular atrophy, the leading genetic cause of childhood death, is a heterogeneous set of diseases characterized by degeneration of motor neurons in the spinal cord and brainstem, resulting in hypotonia and muscle weakness [1]. In most patients, the diagnostic test demonstrates the homozygous deletion of the SMN1 gene, which generally shows the absence of exon 7 of SMN1. The test achieves up to 95% sensitivity and almost 100% specificity [2].

Differential diagnosis should be considered with other neuromuscular disorders that are not associated with increased creatine kinase (CK) manifesting as infantile hypotonia or limb-girdle weakness beginning later in life [2].

Spinal muscular atrophy is divided into three clinical types based on the age of onset and motor function achieved: type I, severe; intermediate type II; and mild type III. Adult-onset type IV has been added to include very mild disease [3].

Increased attention to early diagnosis and management of spinal muscular atrophy has stimulated the development of guidelines and standards of care that have affected survival and the natural history of the disease [4].

There is no effective medical treatment for spinal muscular atrophy. However, since the discovery of the disease-causing gene, significant progress has been made in understanding the molecular pathogenesis, leading to the development of treatment options [5].

Population and methods

Study design

The design is a retrospective descriptive study of 5 pediatric patients with a clinical and genetic diagnosis of spinal muscular atrophy type I.

Stage

The study was carried out in the Pediatric Neurology service of the Center for Neurological and Nutritional Diseases in Children and Adolescents (CENNA) in the City of Quito, Ecuador. The study period was established between October 2020 and October 2021.

Participants

A comprehensive assessment was carried out of the neurological and genetic characteristics of the five patients who started with symptoms of hypotonia and neurodevelopmental delay. The five patients showed no muscle stretch reflexes (MSRs) in the upper and lower extremities.

All five patients were evaluated for a complete neurological history and neurological examination, and multiplex ligation-dependent probe amplification (MLPA) was performed for the genetic diagnosis of SMA.

Data source

Information was taken from the clinical history of each of the evaluated patients, and the information came from the Clinical Records Registration System of the Center Institution. The genetic results of each of the patients were reviewed with the specific assessment of the number of copies of SMN2.

Results

Participants

The present case series includes five patients with a shared history of hypotonia and neurodevelopmental delay. Their ages of presentation were between 11 months and 22 months, and the male:female ratio was 2:3. The clinical and genetic findings were evaluated, and the comorbidities occurred over time, including pneumatological, nutritional, and swallowing symptoms.

Characteristics of the study population

There were 5 cases of these, 3 cases (60%) corresponded to female patients, and 2 cases (40%) were male. Four of the five patients required hospitalization for respiratory complications, and three of the five patients required an intensive care unit. Two of the five patients died during follow-up.

Main results

Five patients with clinical and genetic diagnoses of spinal muscular atrophy type I were included; two were male, and three were female, in an age range between 11 months and 22 months. The male:female ratio was 2:3. The genetic result in all patients was two pathogenic variants identified in SMN1. SMN2 copy number = 2. A first-line family history of spinal muscular atrophy was recorded in 1 of 5 patients. The absence of muscle stretch reflexes (MSRs) in the upper and lower limbs was a sign shared by 100% of the patients. All patients presented hypotonia and neurodevelopmental delay. Only one of the patients achieved head support. All patients were originally from Ecuador, belonging to Quito, Cuenca, Ambato, and Portoviejo. At the onset of clinical manifestations, the age was three months, with a minimum of 1 month and a maximum of 6 months. All patients started with hypotonia and neurodevelopmental delay. The diagnosis was established at seven months (median seven months, minimum two months, and maximum ten months).

All patients underwent nutritional and pneumatological assessments. One of our patients had a degree of malnutrition; the remaining four were eutrophic. Comorbidities associated with patients with spinal muscular atrophy were studied. Three of the patients were found to have chronic lung disease, and three were associated with impaired swallowing mechanics. All patients with SMA I had comorbidity with respiratory infections or malnutrition. Three of our patients required tracheostomy, and two required a gastric button. Four of our patients had a history of hospitalization secondary to respiratory complications. The mean length of stay was 150 days, and 1 of the five hospitalized patients completed a stay of more than 180 days in pediatric intensive care.

Table 1. Hypotonia of central origin vs. peripheral hypotonia.

Hypotonia of Central Origin	Hypotonia of Peripheral Origin
Prenatal history: IUGR, pathological pregnancy.	Difficulty moving secretions (coughing).
Dysmorphia, genetic stigmata, Macro-microcephaly.	Weakness of the facial and bulbar muscles.
sensory deficits	Axial muscle weakness.
Lack of response to stimuli.	Diaphragmatic breathing.
Epileptic seizures, involuntary movements, and dystonias.	Appendicular muscle weakness.
hyperreflexia	Decreased plantar and palmar pressure.
Compromise of other systems.	Weak cry.
sensory deficits	Swallowing disorder.

Adapted from Avaria, M., Kleinsteuber, K. & Pinto, A. (2014).

Discussion

Spinal muscular atrophy is one of the most devastating disorders in childhood, with an incidence of approximately one in 10,000 live births and a carrier frequency of one in 50 [3, 6]. Related to SMA type I, the incidence has been estimated at 1 in 6700 [7].

After cystic fibrosis, spinal muscular atrophy is the second most common fatal autosomal recessive disorder [8]. Moreover, the second most common neuromuscular disorder in childhood is Duchenne disease [4].

In more than 95% of cases, the most common SMA results from a deletion or homozygous mutation in the survival motor neuron gene 5q13 (SMN1) [9].

Through an epidemiological study of different ethnic groups in North America, the frequency of carriers was determined (Markowitz et al., 2012). The carrier frequency was highest in Caucasians at 1 in 37 (2.7%) and lowest in Hispanics at 1 in 125 (0.8%). Jewish 1 in 46 (2.2%) and African Americans 1 in 56 (1.8%) had an intermediate frequency. Despite the high frequency of carriers, the incidence of spinal muscular atrophy was lower than expected. This finding may reflect that some fetuses have a 0/0 SMN1/SMN2 genotype (i.e., no SMN protein is present), which is known to be lethal to the embryo [10].

There are no epidemiological data on patients with spinal muscular atrophy in Ecuador. It is cataloged within rare or low prevalence diseases (1 per 10,000 people).

Diagnosis

The diagnostic process of spinal muscular atrophy is guided by the clinical signs found (Figure 1).

These patients are characterized as hypotonic, with symmetric and proximal progressive weakness that affects their legs more than their arms, sparing the facial muscles. In addition, weakness in the intercostal muscles with preservation of the diaphragm results in a typical bell-shaped chest and a paradoxical breathing pattern [11].

SMA is caused by the homozygous absence of exons 7 and 8 of the SMN1 gene or, in some cases, only exon 7 [12].

The diagnosis of SMA is based on molecular genetic testing of SMN1/SMN2, which represents the first line of clinical suspicion [12]. These genetic tests include multiple ligation-dependent probe amplification (MLPA), quantitative polymerase chain reaction (qPCR) or next-generation sequencing (NGS) [13].

Electromyography is not among the first lines of diagnostic tests for spinal muscular atrophy, and it can be helpful when the phenotype is less striking. Serum CK levels are not helpful in diagnosis, as they are usually normal or slightly elevated [13]. Central versus peripheral hypotonia may guide (Table 1).

Classification and clinical diagnosis

SMA type 0

Age of onset: Prenatal or at birth. They never achieve sitting without support; they never achieve head control. Life expectancy is less than one month. Clinically, they present joint contractions, heart defects, facial diplegia, and immediate respiratory failure after birth. Estimated SMN2 copies: 1 SMN2 copy in ~100% of patients.

SMA type I (Werdnig-Hoffman disease)

It is severe or acute SMA. The age of onset was between 0-3 months of life. Clinically, they are characterized by hypotonia and generalized muscle weakness, with greater crural and proximal muscle involvement. MSRs abolished. The "open book" or "frog legs" posture can be identified in the newborn. Sucking and swallowing are weak. They present with diaphragmatic breathing with the typical bell-shaped chest. In its evolution, the marked weakness of the axial muscles stands out, not achieving head support or sitting without support. It is rapidly progressive; children die before two from respiratory failure, usually aggravated by recurrent respiratory infections. [14]. Estimated SMN2 copies: 1 or 2 SMN2 copies in ~80% of patients.

A subclassification of SMA Type I has been described [15]:

1A: Starts less than one month, generally at two weeks, and lack head support. Life expectancy <6 months. Clinical features are similar to SMA type 0.

1B: Start 1-3 months; poor or absent head support. Life expectancy <2 years. Clinical features: fasciculation of the tongue, difficulty swallowing, and early respiratory failure.

1C: Start 3-6 months; head support was achieved. Life expectancy <2 years. Clinical features: fasciculation of the tongue, difficulty swallowing, and early respiratory failure.

SMA type II (Dubowitz disease).

It is the intermediate AME. Start between 3 and 12 months. After normal neurodevelopment for up to 6 months, they achieved a sitting position without support. They never achieve independent ambulation. They are characterized by symmetrical and proximal weakness, with greater involvement of the lower extremities and abolished MSRs. Presence of fasciculations, lingual atrophy, and delicate hand tremor. Moderate involvement of intercostal muscles. Life expectancy is between 10 and 40 years. Presence of frequent contractures and deformities, the most critical being scoliosis [14]. Estimated SMN2 copies: 3 SMN2 copies in >70% of patients.

A subclassification for SMA type II has also been described [15]:

2A: Independent sitting may lose the ability to sit later in life.

2B: Sits independently and maintains the ability to sit according to a functional level.

Natural history: Types 2A and 2B have a life expectancy greater than two years, with ~70% alive to 25 years.

SMA type III (Kugelberg-Welander disease)

It is a juvenile SMA with insidious onset after two years. They achieve independent ambulation. They are characterized by progressive pelvic girdle weakness, hyporeflexia, frequent falls, and difficulty getting up and climbing stairs. The commitment of the shoulder girdle is present in the last stages of the disease. Hand tremor is frequent, but tongue twitches are not. These children reach adulthood and remain ambulant for years, with an indeterminate life expectancy [14]. Estimated SMN2 copies: 3 or 4 SMN2 copies in ~95% of patients.

SMA type III subclassification [15]:

3A Onset between 18 and 36 months. Usually, characterized by early loss of ambulation.

3B: Start > 3 years. Natural history: survival to adulthood.

SMA type IV

Age of onset: 10-30 years, usually >21 years. They manage to stand and walk. Natural history: survival to adulthood. It is characterized in that the ability to walk is preserved. Estimated copies of SMN2: 4 or more copies of SMN2 by ~90% [15].

Genetic Basis

Messenger RNA is responsible for transmitting information from DNA for protein synthesis. This process has two stages: transcription and translation. The first stage consists of mRNA synthesis from DNA, and the second is the synthesis of proteins by ribosomes from mRNA.

The copy of one of the two DNA chains results in the pre-mRNA, which has regions that must be eliminated, known as introns, and elements to be incorporated for its stabilization [16].

The introns are eliminated by splicing, leaving only the exons, which are spliced together to form the messenger RNA involved in protein synthesis.

Two SMN (survival motor neuron) genes are present on chromosome 5q13: telomeric or SMN1, which determines spinal muscular atrophy, and the centromeric gene or SMN2.

The coding sequence of SMN2 differs from that of SMN1 by a single nucleotide, resulting in alternative splicing of exon 7. Due to this process, SMN2 genes produce a reduced number of full-length transcripts and proteins and a reduced number of protein and full-length transcripts. Variable mRNA that lacks exon 7 gives rise to a truncated and unstable protein. Unlike SMN1 ç, which is complete, the vast majority of the protein that SMN2 produces is incomplete without the part of exon seven that makes it partially functional and rapidly degradable [7].

The loss of SMN1 is essential for the pathogenesis of SMA, while the severity of the disease is mainly related to the number of copies of SMN2. Most patients with SMA type I have two copies of SMN2; three copies of SMN2 are usually present in SMA type II, while those with types III and IV usually have three or four [16].

The SMN genes encode the SMN protein expressed in spinal cord motor neurons. Within the nucleus, the SMN protein is concentrated in "gems." Although the function of the SMN protein is unknown, cells from patients with spinal muscular atrophy contain fewer gems than controls and carriers.

Two hypotheses have been postulated that could explain the pathogenesis of spinal muscular atrophy:

1. SMN is involved in small nuclear ribonucleoprotein (snRNP) biogenesis and mRNA splicing.

The SMN protein is required to assemble the core Smith-class proteins into uridine-rich snRNPs. U snRNPs are the main components of spliceosomes, the cellular particles that carry out presplicing to mRNA. It has been suggested that the SMN protein might play a key role in cellular functions unique to motor neurons [2].

2. SMN has a motor neuron-specific function, independent of snRNP assembly, such as the transport of mRNA along the axon.

The SMN protein may support motor neuron survival by allowing regular axonal transport and maintaining the integrity of neuromuscular junctions. Low concentrations of SMN protein could be specifically detrimental to motor neurons due to the length of the axons and their unique interactions with skeletal muscles. The SMN protein could be involved in the transport of ribonucleoprotein complexes containing β-actin or specific mRNAs [2].

Mode of Inheritance and Recurrence

Spinal muscular atrophy is a disease with an autosomal recessive pattern of inheritance. This inheritance pattern occurs when both parents of individuals affected by the disease are heterozygous carriers. A quarter of the children of two heterozygotes will be unaffected homozygotes, half will be heterozygous carriers without phenotypic involvement, and a quarter will be homozygotes affected by the disease. Autosomal recessive inheritance is seen as a horizontal appearance of the trait, with multiple affected siblings but without transmission from parents to children. On occasion, heterozygotes can manifest a mild phenotype, which has been called semidominant inheritance. If the heterozygous phenotype is very mild or only detectable with sophisticated and sensitive phenotyping techniques [17]. The risk of recurrence in couples who have previously had a child affected by SMA is 25%. The disease is usually seen in one or more children but not in previous generations. Men and women are affected in the same proportion. A quarter of the children of two heterozygous carriers will be affected by the disorder. Consanguinity is more frequently present in pedigrees with autosomal recessive diseases than in those involving other types of inheritance [18].

Recurrence Risk

The most common pairing in recessive disease is heterozygous carrier parents [18]. A quarter of the children will be homozygous for the disease gene and affected. The risk of recurrence of autosomal recessive diseases is 25%. Quasi-dominant inheritance, with a 50% recurrence risk, occurs when an affected homozygote mates with a heterozygous [18].

Diagnostic Approach

The most frequent sign of neurological dysfunction in newborns is hypotonia. The orderly investigation of this sign

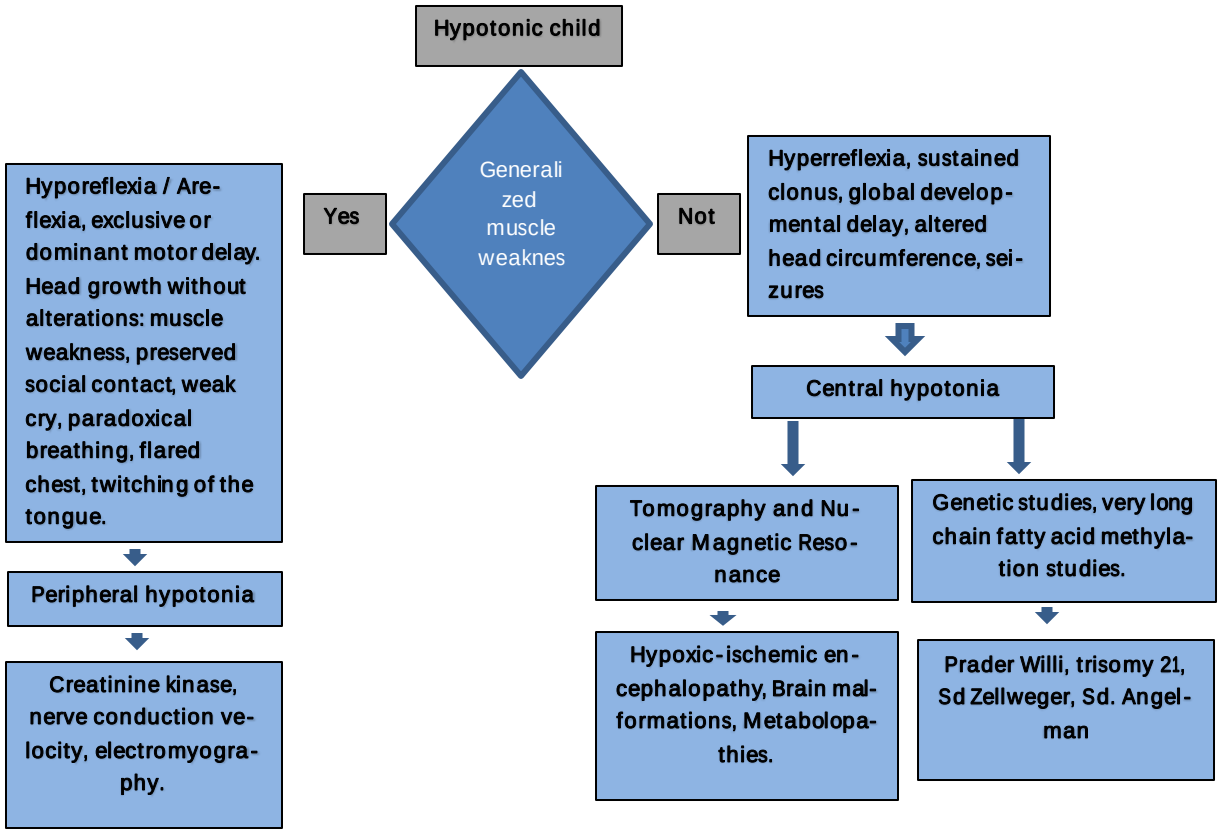

Figure 2. Approach to the hypotonic child Adapted from Avaria, M., Kleinsteuber, K. & Pinto, A. (2014). Clinical approach to the infant and newborn hypotonic. Electronic Pediatric Journal (11) 3, 280 –286. ISSN 0718-0918.

and its companions allows us to determine the etiology and guide the initial approach for an opportune diagnosis.

1. Anamnesis: Define signs and symptoms that accompany the disease. Family history, such as consanguinity and relatives affected by neuromuscular or genetic pathologies, should be highlighted. SMA is a disorder with an autosomal recessive inheritance pattern in which consanguinity is more frequently present. It is common to find a history of affected siblings but no parent-to-child transmission [19].

2. Physical examination: Establishment of the anatomical-functional location. Hypotonia is manifested by unusual postures (frog or open book), decreased resistance to passive mobilization, increased joint range, and usually decreased spontaneous movement. Greater crural and proximal muscle involvement can be assessed and MSRs can be abolished. It is necessary to differentiate between hypotonia of central origin and those of peripheral origin. The following table shows the characteristics to be taken into account in each case.

3. Plan initial studies When the etiology is not evident, studies should be carried out to rule out the most frequent causes.

4. Define the specific cause.

Significance of Findings

The present series of cases allows the assessment of multidisciplinary massage in patients with a definitive diagnosis of SMA type I. The importance of a comprehensive approach for each patient and the implementation of neurorehabilitation therapy, swallowing therapy, respiratory therapy, and subsequent evaluation of the specialties of neuropediatrics, pediatric pulmonology, and nutrition (Figure 2).

Studies with related findings
Case series of patients with type I spinal muscular atrophy are documented in the medical literature, which are of low prevalence and cause death and comorbidities, mainly respiratory. Our cohort of patients is smaller than that of other reported studies. The clinical manifestations vary from patient to patient, and their genetic studies report similar findings.

Clinical relevance of the findings
The diagnosis of spinal muscular atrophy should be considered a medical emergency that requires an immediate genetic approach to lay the foundations for treatment. The delay in the diagnosis of SMA type I decreases patients' life expectancy and quality of life. It is transcendental that patients can access the necessary therapies that allow delaying the progression of the disease.

Study Limitations
The sample size can be considered a nonsignificant cohort, but it must be considered that it is a disease of low prevalence.

Future investigations
Some treatments are currently available that could modify the disease. The early start of treatment would prevent the progression of the disease and improve the prognosis and quality of life of patients, being modifiers of motor function. Future research will focus on the development of gene therapy.

recommendations
Increased attention to early diagnosis and management of spinal muscular atrophy has stimulated the development of guidelines and standards of care that have affected survival and the natural history of the disease. There is no effective medical treatment for spinal muscular atrophy. However, since the discovery of the disease-causing gene, significant progress has been made in understanding molecular pathogenesis, leading to the development of treatment options.

Conclusions
Increased attention to early diagnosis and management of spinal muscular atrophy has stimulated the development of guidelines and standards of care that have affected survival and the natural history of the disease. There is no effective medical treatment for spinal muscular atrophy. However, since the discovery of the disease-causing gene, significant progress has been made in understanding molecular pathogenesis, leading to the development of treatment options.

Abbreviations
SMA: spinal muscular atrophy.
MERs: muscle stretch reflexes.

Supplementary information
Supplementary materials are not declared.

Acknowledgments
The work of the staff of the Center for Neurological and Nutritional Diseases in Children and Adolescents (CENNA) is recognized.

Author contributions
AA, PE: Research idea, article writing, critical analysis, editorial corrections.
AA, PE: Data compilation, Literature review.
AA: critical analysis, editorial corrections.
All authors read and approved the final version of the manuscript.

Financing
The authors provided resources.

Availability of data and materials
The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available through the corresponding author upon reasonable academic request.

Statements
Ethics committee approval and consent to participate
It was not needed.

Publication consent
Permission for publication from the patients' guardians was obtained in writing and is available upon request from the publisher.

Conflicts of interest
The authors report no conflict of interest.

Author Information
Álvaro Nicolay Astudillo: Pediatrician (UCE Ecuador), Pediatric Neurologist (UNAM Mexico), Master in Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder. (USIZ Spain), LINCA Certificate in medical treatment of Autism Spectrum Disorder. (Lima, Peru). Health Services Administration (Ecuador), Medical-Administrative Director of the Center for Neurological and Nutritional Diseases of Children and Adolescents (CENNA). Former Director of the District Health Directorate 18D02, zonal 3. Pediatric neurology physician associated with Hospital Clínica Axxis, Quito. Pediatric neurology treating physician associated with Hospital de Los Valles, Quito. Former Pediatric Neurology Treating Physician at the San Francisco de Quito Hospital of the Ecuadorian Institute of Social Security, IESS. Member of the European Society of Pediatric Neurology. University Professor at the UCE and PUCE.

https://orcid.org/0000-0001-9839-4965

Patricia Cecilia Erazo: Surgeon (PUCE Ecuador). Resident Physician in Pediatric Neurology at the Center for Neurological and Nutritional Diseases of Children and Adolescents - CENNA.

https://orcid.org/0000-0001-7908-1808).

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DOI: Digital Object Identifier PMID: PubMed Identifier SU: Short URL

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