Original article

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The difficult path to diagnosis of the patient with spinal muscular atrophy

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ABSTRACT

Introduction. News treatments, make early diagnosis of spinal muscular atrophy (SMA) critical. The objective of this study is to analyze the different factors that influence delay in diagnosis.

Population and methods. Patients with a molecular diagnosis of types I, II, and III SMA were included. Several parameters were studied, such as age at onset of first sign, what sign it was, and the time from recognition of first sign to confirmed diagnosis. Neurologists specialized in SMA conducted interviews, supported by the review of medical records when deemed necessary.

Results. A total of 112 patients were interviewed. SMA I n = 40, SMA II n = 48, SMA III n = 24. The median age in months at the time of reporting the first sign was SMA I: 1.5 (R: 0–7), SMA II: 9 (R: 2–20), SMA III: 18 (R: 8–180). In all subtypes, first signs were identified by parents from 75% to 85% of the times. The median time from first sign to first medical consultation was less than a month in all 3 types. The median time in months, from first sign to confirmed molecular diagnosis in SMA I was: 2 (R: 0–11), in SMA II: 10 (R: 3–46), in SMA III: 31.5 (R: 4–288).

Conclusions. There is a significant delay in SMA diagnosis mainly related to the absence of clinical suspicion. The delay is shorter in SMA I and longer in SMA III. Other factors include deficiencies in the health care system.

Key words: *spinal muscular atrophy; muscular hypotonia; neuromuscular diseases; late diagnosis; congenital genetic diseases.*

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INTRODUCTION

Spinal muscular atrophy (SMA) is a neuromuscular disease with an estimated incidence of 1 in 6000 to 1 in 11 000 live births[1–4] and a carrier frequency of up to 1 in 60. It is considered the second leading cause of death from an autosomal recessive disease, behind cystic fibrosis.[3,4] It is caused by mutations in the motor neuron survival gene 1 (*SMN1*) located on the long arm of chromosome 5 (locus 5q13.2), leading to the degeneration of motor neurons in the spinal cord resulting in atrophy and progressive muscle weakness. Another gene, *SMN2*, encodes a protein similar to that produced by *SMN1*, but in smaller quantities; compensating in some way for the loss of *SMN1* and rendering the disease less severe.[3,5–8]

A higher number of *SMN2* copies is usually correlated with a less severe phenotype.

SMA is classified into types 0 to IV according to the age at onset and severity of symptoms.. We will discuss types I, II, and III. Approximately 50% of patients with SMA have type I, the most severe and with the earliest onset. They will not survive beyond 2 years of age, will not be able to sit independently, and will have difficulty swallowing, feeding, and breathing.[8-10]

In type II SMA, symptoms appear later. Children can sit up unaided and some manage to stand (with assistance), but will never be able to walk independently. They may experience weakness when swallowing or chewing, and respiratory distress. Survival rate is higher than that of type I.[4,8]

Patients with SMA III are able to walk, but as the disease progresses they often lose the ability to do so.[4,8]

Clinical signs in SMA can vary widely; some, such as muscle hypotonia and motor delay, are common to other neuromuscular conditions.[11] Although awareness of SMA is increasing, delay in diagnosis is common and the first alert depends on the observation and recognition of early signs.

In recent years, novel therapies have been developed changing the concept that defined SMA as an untreatable disease.[12] The first transformational therapy for SMA,[13] using *SMN2* RNA transcript modification, was approved for all ages by the Food and Drug Administration (FDA) in December 2016 and the second,[14] *SMN1* gene replacement, was approved for children under the age of 2 in May 2019. Both therapies are changing the natural history of the disease. A third treatment with a small molecule which is able to modify the *SMN2* splicing site has recently been approved by the FDA.[15]

This study attempts to reconstruct the path to diagnosis endured by patients with SMA by identifying milestones such as age at onset of first signs, time of clinical suspicion, and age at diagnostic confirmation, as well as time elapsed between each of these. This study made it possible to explore some of the causes leading to delays in diagnosis.

POPULATION AND METHODS

A cross-sectional observational study was conducted in 112 patients who could be contacted (convenience sampling) and who had been diagnosed with types I, II and III SMA between November 2020 and September 2021 in Argentina. Forty patients with SMA I, 48 patients with SMA II, and 24 patients with SMA III were included.

Inclusion criteria for participation in the study were, on the one hand, that the patient had a confirmed genetic diagnosis with mutations in the *SMN1* gene (including deletions, duplications, and point mutations) and that the patient, a family member and/or a caregiver were able to participate in the interview. Time elapsed since diagnosis was not a conditioning factor for inclusion. An exclusion criteria was that patients did not have to have a family member diagnosed before as that would have made their diagnosis easier.

Neurologists specialized in neuromuscular diseases conducted telephone or face-to-face interviews with patients and/or their relatives. These were supported by a review of medical records whenever there were any doubts or inconsistencies in the data collected. Parents and/or relatives or the patients themselves, as applicable, were informed of the objectives of the study. There was either a single interview or this was split up to a maximum of 4 as per the interviewer´s decision. No predetermined guidelines were used.

In each case, the interview was adapted to obtain the following data: first symptom/s (or sign/s) related to the disease, time of onset, and who recognized it/them, first health care provider consulted (specialist or other), diagnoses provided, referral to other specialists and time of referral, age when SMA diagnosis was clinically suspected, time of diagnostic confirmation by molecular analysis, specialist who made the diagnosis, other studies requested.

The study was approved by the Ethics Committee. The information obtained was handled confidentially. All necessary measures were taken to protect participants´ privacy and keep information confidential.

Data were analyzed using descriptive statistics. Continuous variables were reported as median (Me), interquartile range (IQR), and range (R), while categorical variables were reported as percentage (%).

RESULTS

Demographic data

The sample consisted of 112 patients (45% female), of whom 40 had type I SMA, 48 type II SMA, and 24 type III SMA.

The age range of patients at the time of the survey was 10 months to 38 years.

First signs and recognition

Table 1 shows, for each type of SMA, data referring to the age at which first sign was noted, time of first consultation, time of clinical suspicion, and diagnosis confirmation by molecular testing. Time from recognition of first sign to first consultation, from first consultation to clinical suspicion of SMA, from clinical suspicion to diagnosis confirmation are detailed. Finally, time from recognition of first sign to confirmed diagnosis is shown.

Considering the increased availability of diagnostic molecular tests in the country in recent years, and taking 2018 as a reference, in SMA I, time from first signs to confirmed diagnosis was shorter for those patients born between 2018 and 2020 than for those born between 2005 and 2018. For the former group, the median (Me) time was 1 month (m) (IQR: 1–3; R: 0–11 m), while for the group of older children, the Me time was 2.5 months (IQR: 1–4.3; R: 0–10 m).

The first clinical signs noted by physicians and relatives are summarized in *Table 2*.

First signs in SMA I were noted by parents in 72.5% of the cases (n = 29), a neonatologist in 5% (n = 2), a pediatrician in 12.5% (n = 5), grandparents in 7.5% (n = 3), and a multidisciplinary team (MT) which consisted of a group of physicians working together during a hospitalization or an emergency department visit without identifying which specialist had indicated the diagnostic test in 2.5% (n = 1).

In SMA II, signs were noted by parents in 85% of cases (n = 41), grandparents in 10.4% (n = 5), and aunts or uncles in 4.2% (n = 2).

In SMA III, signs were noted by parents in 75% of the times (n = 18), a pediatrician in 4.2% (n = 1), a teacher in 8.3% (n = 2), and grandparents, aunts or uncles or patients themselves in 4.2% (n = 1) in each case.

Table 1. Chronological events in months

	SMA I	SMA II	SMA III
Age at the time of first sign	1.5 (0–4) Range: 0–7	9 (6.75–12) Range: 2–20	18 (15–24) Range: 8–180
Delay in first sign - first consultation	0 (0–0) Range: 0–3	0 (0–1) Range: 0–6	0 (0–9) Range: 0–41
Age at the time of first consultation	2.5 (0–4) Range: 0–7	9.5 (7–12) Range: 2–24	24 (15–28.5) Range: 8–180
Delay in first consultation - clinical suspicion	1 (0–2.25) Range: 0–8	5 (3–9) Range: 0–39	22 (8.5–57) Range: 0–180
Age at the time of clinical suspicion	4 (2–6) Range: 0–15	17 (12.75–21) Range: 8–44	44 (33.5–97.5) Range: 22–240
Delay in clinical suspicion - confirmed diagnosis	0 (0–1) Range: 0–6	20 (1–6) Range: 0–37	2.5 (1–8.75)a Range: 0–177
Age at confirmed diagnosis	4 (2.5–7.0) Range: 0–17	20 (16.75–27.25) Range: 9–301	52.5 (42–148.25) Range: 23–307
Delay in first sign - confirmed diagnosis	2 (1–4) Range: 0–11	10 (6–16.25) Range: 3–46	31.5 (14.25–98.25) Range: 4–288

Data are expressed as median, interquartile range (25%-75%), and range (minimum and maximum values).
SMA: spinal muscular atrophy.

Table 2. First detected sign

SMA I n = 40			SMA II n = 48			SMA III n = 24		
	n	%		n	%		n	%
Hypotonia	15	38.5	Unable to stand	11	23	Frequent falls	12	50
Developmental delay	13	33.3	Unable to walk unaided	11	23	Unsteady gait	5	20.8
Feeding difficulties	7	17.9	Proximal weakness	11	23	Developmental delay	4	16.7
Decrease in proximal movements	6	15.4	Unable to crawl	8	17	Difficulty in climbing up stairs	3	12.5
Respiratory distress	5	12.8	Developmental delay	7	15	Loss of previously attained motor functions	1	4.2
Weak cry	4	10.3	Hypotonia	6	13	Difficulty in getting up from the floor	1	4.2
Prenatal (↓ of fetal movements)	3	7.7	Developmental regression	4	8	Dyspnea	1	4.2
Developmental regression	1	2.6	Did not sit by themselves	3	6			
			Tremor	2	4			

The n represents the number of patients who had the described sign.
Each patient could have had more than one sign.
SMA: spinal muscular atrophy.

Of a total of 72 patients (48 type II SMA + 24 type III SMA) in whom routine medical check-ups are less frequent than in the first months of life, only 1 physician was able to note first signs of the disease.

The specialist most frequently visited at the first consultation was the pediatrician (82.5%, n = 33 in SMA I; 95.8%, n = 46 in SMA II, and 66.6%, n = 16 in SMA III). The other specialists visited are shown in *Figure 1*.

Table 3 summarizes the diagnoses provided to the family prior to clinical suspicion of SMA.

The median number of consultations until clinical suspicion was the following, SMA I: 3 (IQR 2–3, R: 1–6), SMA II: 4 (IQR 3–4, R: 2–15) and SMA III: 4 (IQR 3–5, R: 2–11).

The number of patients who consulted different specialists until diagnostic suspicion were the following: in SMA I (n = 40): pediatrician 39, neurologist 33, MT 7, clinical geneticist 4, pneumonologist 3, and obstetrician 1. In SMA II (n = 48): pediatrician 44, neurologist 43, traumatologist 11, clinical geneticist 7, endocrinologist 2, ENT specialist 1, physiatrist 1,

Table 3. Diagnoses provided to the family prior to clinical suspicion of SMA

SMA I	SMA II	SMA III
Hypotonia	Hypotonia	Muscular dystrophy
Idleness	Developmental delay	*Pes planus*
Botulism	Neuromuscular disease	Foot conditions
Brachial palsy	Neurological disease	Neuromuscular disease
Hip displasia	Idleness	Hyperlaxity
Guillain-Barré Syndrome	Hip dislocation	*Pes cavus*
Lejeune Syndrome	Overweight	Patellar condition
Neuropathy	Hyperlaxity	Tendinopathy
Muscular dystrophy (type not specified).	Duchenne muscular dystrophy	Duchenne muscular dystrophy
Immaturity	Metabolic disease	Pyramidal syndrome
Pompe disease	Guillain-Barré Syndrome	Gait disorder
Spinal disease	Hydrocephalus	Idleness
		Motor neuron disease
		Achilles shortening
		Genu valgum

SMA: spinal muscular atrophy.

ophthalmologist 1, and kinesiologist 1. In SMA III (n = 24): neurologist 22, pediatrician 17, traumatologist 17, physiatrist 2, kinesiologist 2, rheumatologist 1, neurosurgeon 1.

In SMA I, the diagnostic molecular study was requested by the neurologist in 82.5% of cases (n = 33), by the MT in 15% (n = 6), and by the geneticist in 2.5% (n = 1). In SMA II, by the neurologist in 95.8% (n = 46) and by the geneticist in 4.2% (n = 2). In SMA III, by the neurologist in 91.7% of cases (n = 22), and by a neuroorthopedic specialist and the geneticist in 4.2% (n = 1) in both cases.

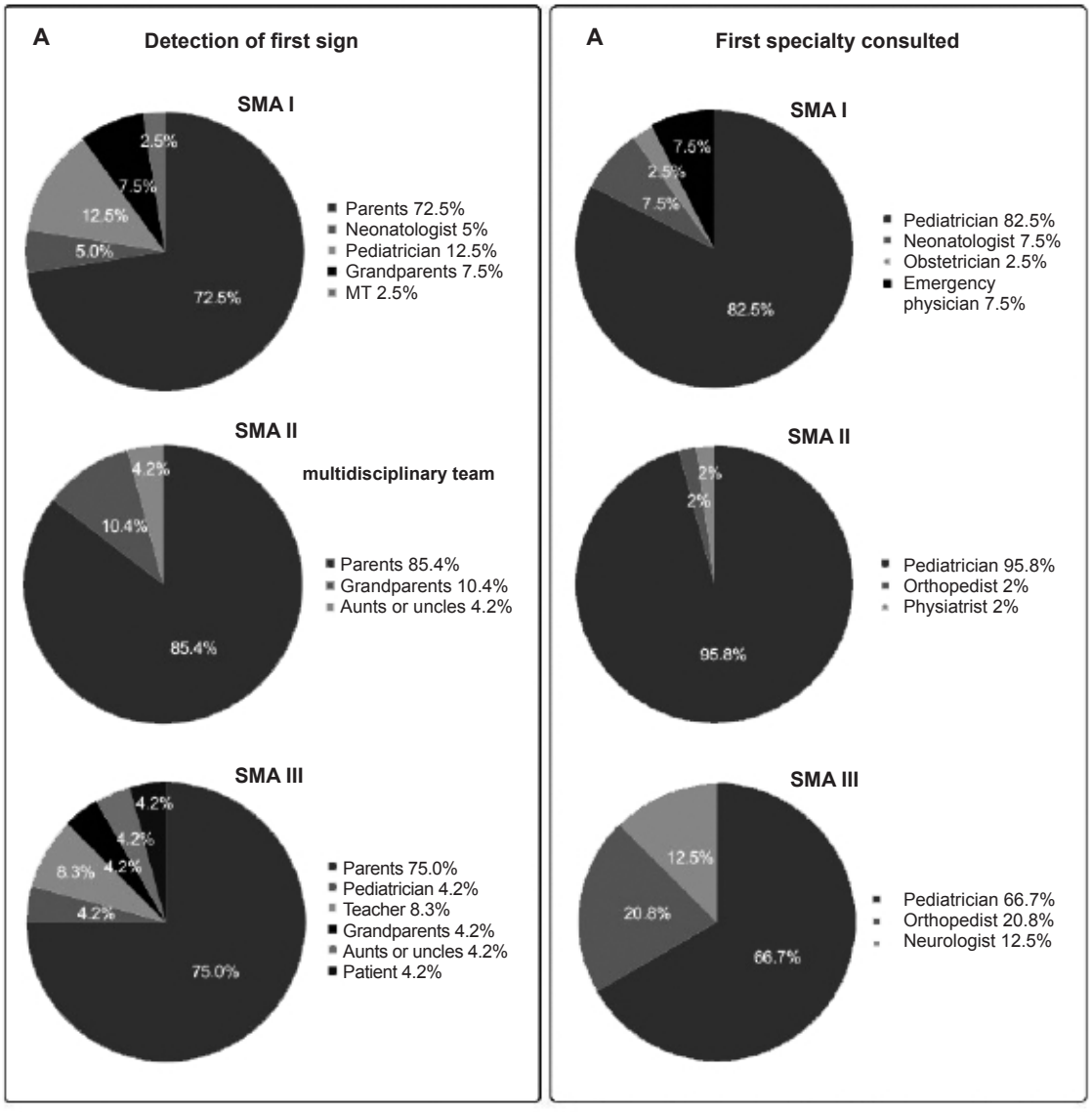
The complementary studies requested included electromyography, brain ultrasound scan, brain magnetic resonance imaging (MRI), chest/hip X-ray, brain CAT scan, creatinine kinase (CPK) test, muscle/nerve biopsy, botulinum toxin, alpha-glucosidase test, video swallowing exam, spinal MRI, karyotyping, electroencephalogram, and lumbar puncture.

The genetic study was requested initially in 9 SMA I patients (22.5%), in 8 SMA II (16.7%), and in none in the SMA III group.

DISCUSSION

SMA is a neuromuscular disease with high morbidity and mortality rates, particularly in types I and II. It entails serious complications and requires early care and support measures that

Figure 1. Detection of first signs (A) and first specialty consulted (B)



SMA: spinal muscular atrophy, MT: multidisciplinary team.

can be found in different treatment guidelines.[16–18]

The progressive decrease of motor neurons partially compensated by reinnervatory processes correlates with the onset of clinical signs.[19]

New therapies based on antisense oligonucleotides, gene transfer and splicing modifier molecules are improving the prognosis and course of the disease.[12–15] The earlier they are administered, the greater the treatment benefit. Early diagnosis is critical to improve the patients´ prognosis.[20]

A systematic review of the bibliography on diagnostic delay in SMA revealed information on age at onset in only 11 articles, while 5 reported age at onset and age at confirmed diagnosis, and concluded that diagnostic delay is common in SMA.[21]

A recent study conducted in 5 Italian centers that included a large number of patients also revealed a significant delay in SMA diagnosis.[22]

Our study is the first of its kind in Argentina and provides data about the age at onset of first signs and delays in diagnosis. It also provides additional data that allow analyzing its possible causes.

Results show that there is a significant delay from the onset of first signs to definitive diagnosis. It can be observed that there was no delay from the recognition of first sign to first consultation. However, the differences from recognition of first sign to diagnostic confirmation were progressive: smaller in SMA I, intermediate in SMA II, and maximum in SMA III, which correlates with the severity and the rapid progression of the disease.

The cause of delay in diagnosis is mainly the lack of clinical suspicion on the part of the intervening physician, who often disregards or misinterprets signs reported by parents, as reflected in the alternative diagnoses.

There are also significant delays from clinical suspicion to confirmed diagnosis, especially in types II and III. In SMA I, the onset is earlier and more striking: hence, the diagnostic process is faster. The organization of health care system and access to molecular studies, which are now more widely available, also play a role. In recent years, this fact, together with a greater awareness of SMA, has resulted in shortening of diagnostic times, as can be seen when dividing the SMA I population into those born before or after 2018.

In the absence of clinical suspicion, the most important factor in diagnostic delay, the corresponding referrals to neurologists were not made on a timely and early basis. It is worth noting that these specialists were the ones who requested the genetic study in 90% of cases.

Complementary studies requested show that a significant number are not oriented towards the diagnosis of SMA or other neuromuscular diseases, but towards conditions of central or orthopedic origin.

Only 6 primary care physicians in charge of the follow-up warned the family about the first sign in the 3 SMA types for the total number of patients (n = 112), accounting for 5.3% of the cases.

Cultural factors should also be considered, such as the misconceived perception that motor disorders are traumatic or orthopedic instead of neurological.

We can conclude that, similar to other regions in the world, there is still a diagnostic delay in SMA that is largely attributable to the absence of clinical suspicion of the disease. Shortening diagnostic times is critical for current therapies to be successful.

Neonatal SMA screening programs have great potential to identify affected children at an asymptomatic stage, which would allow initiation of therapy before the development of further motor neuron damage.[23]

In the meantime, it is particularly relevant to raise awareness among physicians who provide primary care to patients of these ages through medical education programs focusing on early recognition and diagnosis of SMA and other neuromuscular diseases. ■

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Other potential conflicts of interest in relation to the pharmaceutical industry are mentioned below:

Chloca, M.D., Morosini, M.D., Bolano, M.D., Jáuregui, M.D., Flores, M.D., no conflict of interest.

Mesa, M.D., has received fees for scientific advice from PTC, Sarepta, Biogen, Avexis, Novartis, and Roche laboratories. She has received fees for lectures from some of the above mentioned companies. Vazquez, M.D., has received fees for scientific advice from Biogen, Avexis, Novartis, and Roche laboratories. He has received a research grant from Novartis and academic activities fees from Biogen. He has received fees for lectures from some of the above mentioned industries, as well as from PTC and Sarepta.

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