ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 9| Issue: 4| April 2023|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2023: 8.224 || ISI Value: 1.188

SPINAL MUSCULAR ATROPHY CLINICAL FEATURES, CLASSIFICATION, NATURAL HISTORY, GENETICS, DIAGNOSIS, COMPLICATIONS AND TREATMENT OF THE DISEASE

Bryam Esteban Coello García[1], Cynthia Carolina Cañar Santos[2], Christian Paul Flores Tapia[3], Vilma Alexandra Mingo Morocho[4], Luis Antonio Moreira Moreira[5], Angel Patricio Fajardo Zhao[6], Johnny Javier Noblecilla Arce[7]

[1]Postgraduate Doctor in Orthopedics and Traumatology at Faculdade de Ciências Médicas Minas Gerais. Belo Horizonte - Brasil. ORCID https://orcid.org/0000-0003-2497-0274
[2]General Practitioner at "Hospital básico de Paute" Azuay-Ecuador. ORCID https://orcid.org/0009-0000-5025-5376
[3]General Practitioner in Independent Practice, faculty of Medical Sciences, Universidad Católica de Cuenca. Azuay- Ecuador ORCID https://orcid.org/0000-0002-7580-2919
[4]General Practitioner in Independent Practice, Faculty of Medical Sciences, Universidad Católica de Cuenca. Azuay- Ecuador ORCID https://orcid.org/0009-0000-0665-6148
[5]General Practitioner in "Hospital General Rafael Rodríguez Zambrano". Manta-Ecuador. ORCID https://orcid.org/0000-0003-3353-1126
[6]General Practitioner graduated in Universidad Católica de Cuenca. Cuenca. Azuay - Ecuador. ORCID https://orcid.org/0000-0003-2280-5777
[7]General Practitioner in "Clínica Santa Ana". Cuenca-Ecuador. ORCID https://orcid.org/0009-0005-6961-0426
Corresponding Author. *Bryam Esteban Coello García.* ***Address:*** *Rua Tiradentes 266.Campo Belo. Minas Gerais. Brasil* ***Postal Code:*** *37270-000*

Article DOI: https://doi.org/10.36713/epra12994
DOI No: 10.36713/epra12994

ABSTRACT

Introduction: *Spinal muscular atrophy (SMA) is a complex neuromuscular disorder, it is the most usual autosomal recessively inherited lethal neuromuscular disease in pediatrics, it presents a defective alteration in the survival motor neuron 1 (SMN1) gene. Spinal muscular atrophy clinically shows progressive weakness of skeletal and respiratory muscles. In recent years, drugs with encouraging results from phase II and III clinical trials have been presented.*

Objective: to detail current information related to spinal muscular atrophy, clinical features, classification, natural history, genetics, diagnosis, complications and treatment of the disease.

Methodology: *a total of 40 articles were analyzed in this review, including review and original articles, as well as clinical cases, of which 31 bibliographies were used because the other articles were not relevant to this study. The sources of information were PubMed, Google Scholar and Cochrane; the terms used to search for information in Spanish, Portuguese and English were: spinal muscular atrophy, Spinal Muscular Atrophy, spinal muscular atrophy and spinal muscular atrophy.*

Results: *About 95 % of the occurrences of spinal muscular atrophy are generated by homozygous deletions. Individuals with 5q mutation make up 95% of cases of spinal muscular atrophy and the remaining 5% are generated by mutations in 5q1-5. Targeted treatments may prevent or delay the progression of some symptoms of spinal muscular atrophy.*

Conclusions: *Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by muscle atrophy and weakness resulting from irreversible loss and progressive degeneration of the brainstem nuclei and anterior horn cells in the spinal cord (lower motor neurons). Clinically it presents with symmetrical proximal limb weakness that also impacts the axial muscles, intercostal and bulbar musculature and is progressive, and the classification protocol is important in genetics, as well as providing prognostic and clinical information. The natural history of the disease is variable and complicated. It is made by demonstrating a history of proximal muscle weakness, motor difficulties or regression, diminished or absent deep tendon reflexes. Among the most frequent complications in unsupported individuals are those previously mentioned such as poor weight gain with growth retardation, scoliosis, restrictive lung disease, joint contractures and sleep difficulties. In terms of treatment, several different compounds have been investigated in recent years, focused on increasing muscle strength and function. Proactive supportive treatment involving a multidisciplinary team is paramount to decrease the severity of symptoms.*

KEY WORDS: *muscle atrophy, spine, spinal, spinal cord, motor neuron.*

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 9| Issue: 4| April 2023|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2023: 8.224 || ISI Value: 1.188

INTRODUCTION

Spinal muscular atrophy (SMA) is a complex neuromuscular disorder, it is the most common autosomal recessive lethal neuromuscular disease in pediatrics, it presents a defective alteration in the survival gene of motor neuron 1 (SMN1), located in chromosome 5 (5q13.2) that generates continuous impairment of motor neurons of the brain stem and medullary anterior horn which results in weakness and progressive symmetrical muscle atrophy. The severity of this condition will depend on the age of onset. Some authors show a variable incidence of this disease between 1 in 6000 live births and 1 in 11000 live births(1,2).

On chromosome 5 there are 2 SMN genes. The first, SMN1 gene generates SMN protein in large quantities and is necessary to maintain the normal function of medullary motor neurons. The second, SMN2 gene generates approximately 10% of all SMN proteins, since it presents a skipping of exon 7 (skipping), which is essential for the development of this protein. The most severe subtype is SMN1 or Werdnig-Hoffmann, which accounts for more than 60% of the universal types of spinal atrophy, Dubowitz disease or SMN2 accounts for about 20%, Kugelberg-Wellander disease or SMN3 for about 10% and SMN4 or the adult form of the disease has the lowest incidence in relation to the previous cases. Individuals with 5q mutation make up 95% of cases of spinal muscular atrophy and the remaining 5% are generated by mutations in 5q1-5(2).

Spinal muscular atrophy clinically shows progressive weakness of skeletal and respiratory muscles. There is no cure for SMA, however, understanding the molecular genetics of the disease has led to the development of preclinical models and several potential therapeutic approaches. In recent years, drugs with encouraging results from phase II and III clinical trials have been presented(3,4).

METHODOLOGY

A total of 40 articles were analyzed in this review, including review and original articles, as well as cases and clinical trials, of which 31 bibliographies were used because the information collected was not of sufficient importance to be included in this study. The sources of information were Cochrane, PubMed and Google Scholar; the terms used to search for information in Spanish, Portuguese and English were: spinal muscular atrophy, Spinal Muscular Atrophy, spinal muscular atrophy and spinal muscular atrophy.

The choice of bibliography exposes elements related to spinal muscular atrophy, clinical characteristics, classification, natural history, genetics, diagnosis, complications and treatment of the disease.

DEVELOPMENT

Clinical Features

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by muscle atrophy and weakness resulting from irreversible loss and progressive degeneration of brainstem nuclei and anterior horn cells in the spinal cord (lower motor neurons). The onset of weakness can be at different times of life, both before birth and in adulthood. Clinically, it presents with symmetrical weakness of the proximal extremities that also impacts the axial muscles, intercostal and bulbar musculature, as well as being progressive. Prior to the knowledge of the genetic basis of spinal muscular atrophy, it was classified into clinical subtypes, depending on the maximum motor function achieved. Some common complications triggered by the clinical presentation of patients with SMA are restrictive lung disease, scoliosis, poor weight gain with growth retardation and joint contractures; however, current therapeutic options may modify the natural history of the disease(4-6).

Classification

The classification system of the different phenotypes found was made in an International Spinal Muscular Atrophy Consortium in 1991, in which three types of SMA are highlighted according to the highest level of motor function and the years of onset of the disease. Subsequently, the third type was modified by years of onset and type 4 was increased to include adult-onset cases, in addition to type 0, which includes patients with prenatal onset and death within weeks. This classification protocol continues to be important because of the genetic epoch, in addition to providing convenient prognostic and clinical information; however, approximately 25% of affected individuals do not benefit from a precise classification(4,7,8).

Spinal Muscular Atrophy Type 0.

It encompasses newborns with respiratory distress at birth, severe weakness and hypotonia with a history of reduced intrauterine fetal movements. Weakness begins before birth. Infants may manifest atrial septal defect, areflexia, joint contractures and facial diplegia. Respiratory failure is an early warning sign. Most of those affected do not manage to live more than 6 months. At the moment there is no clear evidence on patients with spinal muscular atrophy type 0 treated with gene therapy or the antisense oligonucleotide called nusinersen which increases the amount of complete SMN protein produced by the SMN2 gene, optimizing the survival of neurons(4,6,9,10).

Spinal Muscular Atrophy Type 1.

Also called Werdnig-Hoffman disease, it encompasses patients with marked weakness and regression of motor development prior to six months of age, although usually showing at 2.5 months of age. Infants attain head control and the ability to roll, but these abilities disappear early. As for the ability to sit up, those children affected with spinal atrophy type 1 usually fail to do so, especially those with only supportive care.

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 9| Issue: 4| April 2023|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2023: 8.224 || ISI Value: 1.188

Profound hypotonia may be seen as a "frog-legged" pose when lying down, coupled with poor or absent head control. Notable clinical features include:

- Proximal symmetrical muscle weakness.
- Lack of motor development with regression of motor function.
- Decreased or absent deep tendon reflexes.
- Poor muscle tone.

Mild contractures may also be found in the knees and sporadically in the elbows.

The fragility of the intercostal muscles, with apparent preservation of the diaphragm, generates a bell-shaped thorax accompanied by a paradoxical respiratory pattern or abdominal breathing. The diaphragm is not altered until late in the course of the disease.

Infants with type 1 muscular atrophy have weakness of the tongue and swallowing; tongue twitching is present in most, but not all, infants.

Facial weakness develops although the affected muscles are relatively intact in the initial manifestation. Bulbar weakness is present in the neonatal period or during the first months. As the tongue and pharyngeal muscles become weaker, affected infants remain at risk for aspiration as they often have difficulty swallowing or sucking, leading to growth retardation.

Infants with spinal muscular atrophy type 1 mostly present with respiratory failure before the age of 2 years. Cognition in these infants is normal so they are usually alert and attentive at diagnosis. Infants may develop severe symptomatic bradycardia. Some studies have shown an average survival of 24 months; in contrast, more current trials have shown an average survival to death of 8 to 13.5 months. With proactive attention to nutritional and respiratory support, survival is increasing.New therapies are modifying the natural history of spinal muscular atrophy type 1, especially if therapy is started prior to the onset of clinical manifestations(4,6,11-13).

Spinal Muscular Atrophy Type 2

Most cases present between six and 12 months of age; however, the average age of symptom presentation is 8.3 months. Inadequate muscle tone may be noticeable in the first few months of life or at birth, however, individuals with SMA 2 may reach motor milestones slowly up to five years of age. Children with SMA type 2 usually sit up unaided at some point in their development, but are unable to walk independently. Those affected later show a slow reduction in motor function, with the competence to sit up fading away by mid-adolescence on average. This type of SMA has the propensity to show as progressive weakness of the proximal part of the legs being greater in comparison with the weakness of the arms. On physical examination there is evidence of areflexia and hypotonia. Hand tremor is frequent. Deep tendon reflexes are reduced or absent.

Most of the comorbidities presented in this group of patients correlate with complications in bone and joint development such as muscle weakness, scoliosis, jaw ankylosis and joint contractures. The conjugation of intercostal muscle weakness and scoliosis can generate a remarkable restrictive lung disease, which is related to morbidity and mortality in these patients. In affected children, cognition is normal and the development of cardiac abnormalities is infrequent. Standing sufficiency is largely interrelated with improved pulmonary performance and long-term survival. With the advent of new therapies it is possible that the natural history of the disease may improve(4,6,14).

Spinal Muscular Atrophy Type 3

Called Kugelberg-Welander disease, children and adults with this type of spinal muscular atrophy are able to walk unaided at some point in their lives. It usually presents after 18 months of age, the average age of onset is 39 months ± 32.6 months. The lower limbs are severely affected compared to the upper limbs. The fragility of the proximal musculature of the lower extremities can cause habitual falls, difficulty to go up or down stairs, this fragility causes the need to use wheelchairs by the patients. Fatigue causes a marked impairment of function and quality of life.

Generally, patients with Kugelberg-Welander disease who have been managed with supportive care alone will show improvement in motor function around the age of six years, and then experience a progressive reduction in functional abilities until around puberty. Puberty may generally be associated with an earlier decline in function. People with SMA 3 have the ability to walk, however, most of those affected will lose this ability over time. If clinical onset is before the age of three years, incompetence of ambulation sometimes occurs in the second decade. However, when clinical onset is between 3 and 12 years of age, gait incompetence usually occurs in the fourth decade of life. Compared to type 2, these patients commonly do not have the comorbidities of scoliosis and usually show little or no respiratory muscle weakness. Cognitive and cardiac functions are normal, and life expectancy is not altered in this group. With the advent of new treatments it is possible that the natural history of the disease may improve(4,6,8,15).

Spinal Muscular Atrophy Type 4

This type is the least frequent form of SMA and is usually seen in less than 5% of individuals with SMA. Typically, individuals in this category show muscle weakness in the second or third decade of life, although there are cases of juvenile onset. It has a specific sequence of muscle involvement, with weakness that greatly impairs the deltoids, triceps and quadriceps. They may also present loss of patellar reflexes, maintaining deep tendon reflexes in the upper extremities and Achilles tendon. Hand

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 9| Issue: 4| April 2023|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2023: 8.224 || ISI Value: 1.188

tremor is occasionally observed. Cognitive and cardiac skills are normal. With supportive care alone, the results are similar to those of SMA 3, but less severe, and gait impairment usually occurs after the fifth decade of life. Life expectancy is normal(4,6,11,16).

Natural History

The natural history of the disease is variable and complicated. Infants with spinal muscular atrophy type 1 never manage to sit up independently. Children with spinal muscular atrophy type 2 are able to sit up at some time during infancy, however they usually do not walk independently. Adults and children with spinal muscular atrophy type 3 usually reach autonomous walking at some interval in their childhood(4).

Genetics

About 95% of the occurrences of spinal muscular atrophy are generated by homozygous deletions. A smaller number occur due to point mutations in the SMN1 gene on the long arm of chromosome 5 "5q-SMA"; however, SMA mutations in other genes can also be the origin of "non-5q-SMA". Disease-causing alterations in SMN1 prevent the manufacture of functional SMN protein from this gene. The extremely variable phenotypic range of SMA is especially attributable to variable copy numbers of the neighboring SMN2 gene. This gene is virtually analogous to SMN1 except for a few nucleotides and is of no significance in healthy individuals. A single nucleotide move of SMN2 results in the predominant skipping of exon 7 and produces an unstable protein. In individuals with spinal muscular atrophy, SMN2 can generate minute amounts of full-length, fully functional SMN protein, so high SMN2 copy number is associated with milder phenotypes(17-23).

Diagnosis

It is made by demonstrating a history of proximal muscle weakness, motor difficulties or regression, diminished or missing deep tendon reflexes, certainty of motor unit disease, as well as through the recognition of pathogenic bi-allelic variants in SMN1 in molecular genetics, or by demonstrating the increase in SMN2 copy number(6).

Complications

Among the most frequent complications in individuals who do not receive support are those previously mentioned, such as poor weight gain with growth retardation, scoliosis, restrictive lung disease, joint contractures and difficulties in falling asleep.

Nutrition-gastrointestinal: bulbar dysfunction is universal in people with SMA 1, this becomes a difficult inconvenience for people with SMA 2 and a very late complication in the course of the disease for people with SMA 3. Some of the alterations of the gastrointestinal system that occur are delayed gastric emptying, constipation and gastroesophageal reflux with high probability of death by aspiration. For growth retardation, a gastrostomy tube may be placed, depending on the patient's needs. Individuals with SMA 2 and 3 who do not walk are at increased risk of obesity.

Respiratory: Individuals with SMA 1 and 2 and sporadically type 3 who have supportive therapy alone have a progressive decrease in lung function due to a mixture of reduced chest wall compliance, weak respiratory muscles, decreased lung compliance and decreased alveolar multiplication. Respiratory failure is the most frequent cause of death in SMA 1 and 2. Reduced respiratory capacity leads to impaired cough with inadequate excretion of mucus from the lower airways, accompanied by hypoventilation during sleep and recurrent pneumonia. Airway clearance techniques and BiPAP or other noninvasive ventilation techniques are frequently used in respiratory failure in people with SMA to try to improve their capacity.

Orthopedic: Scoliosis, hip dislocation and joint contractures are frequently seen in individuals with spinal muscular atrophy. Scoliosis is a major issue in a large proportion of those affected with SMA 2 and in about 50% of individuals with SMA 3. With support alone, nearly 50% of children with the disease, primarily those who are unable to ambulate, create spinal curvatures greater than 50 degrees by age 10, usually requiring a surgical approach. If the development of the disease continues, those affected may develop thoracic kyphosis. This progressive scoliosis alters pulmonary competence and in complex cases can lead to reduced cardiac output. The use of a titanium vertical expandable prosthetic rib is a potential treatment for complicated scoliosis.

Metabolic: Prolonged fasting should be avoided, because a possible unanswered complication of SMA is severe metabolic acidosis plus dicarboxylic aciduria and low serum carnitine pools in the intervening stages or prolonged fasting. Whether the metabolic abnormalities are primary or consequent to the underlying disturbance in SMA is not known for certain at this time. Although the cause of these metabolic disturbances remains obscure at this time, one reference reports that aberrant glucose metabolism may play an important role(6).

Treatment

Within the treatment of the clinical manifestations presented by patients with spinal muscular atrophy there are therapies that are exclusively directed to the underlying action of the ailment among these 2 drugs stand out:

- Nusinersen, an antisense oligonucleotide, can be used for the therapy of all types of SMA.
- Onasemnogene abeparvovec-xioi, a gene replacement therapy for the management of SMA type 1.

These targeted treatments may prevent the formation of symptoms or delay them. If started prior to the onset of symptoms, the efficacy of the therapy is increased, however, it is not yet clear what long-term effect they may have, or whether different phenotypes will appear in treated patients.

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 9| Issue: 4| April 2023|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2023: 8.224 || ISI Value: 1.188

When nutritional disorders or dysphagia occur, early gastrostomy tube placement may be considered, in addition to treatment for gastroesophageal reflux disease and chronic constipation. Formal review and follow-up by a pulmonary specialist familiar with the disease is mandatory. With worsening respiratory symptoms, tracheostomy or noninvasive respiratory support may be considered. Surgical repair of scoliosis should be chosen depending on the progression of the curvature, pulmonary function and bone maturity(6).

Within the perspective of symptom-free treatment, it can be said that being a monogenetic neuromuscular disease, the final phenotypic range is labyrinthine and SMA is most of the time perceived as a systemic disease. Therefore, the care of patients with SMA needs a correct interdisciplinary management of nutritional-gastroenterological, respiratory-ventilatory, orthopedic-postural and psychosocial problems. This proactive multidisciplinary supportive therapy is extremely important to reduce the severity of symptoms, especially in the most severe cases. The activation of standards of care is highly mutable and is usually affected by socioeconomic factors, availability of regional assets and cultural views. In recent times, there are new updates of useful recommendations for the diagnosis of spinal muscular atrophy, as well as for the best patient care(1,17,24-26).

Within the therapeutic perspective and drug treatment, there are several studies of different compounds in recent years among which are some with approaches to increase muscle strength and function through:

- ➢ Hyperacetylating agents such as phenylbutyrate or valproic acid.
- ➢ Anabolic agents such as thyrotropin-releasing hormone, albuterol and growth hormone.
- ➢ Neuroprotective agents such as olesoxime, gabapentin and riluzole.

The actual therapeutic developments can be subclassified into treatments whose mission is to modify the SMN2 connection, to substitute the SMN1 gene or to regulate the increase of muscle growth(1,17,27-31).

CONCLUSIONS

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease characterized by atrophy and muscle weakness resulting from irreversible loss and progressive degeneration of the brainstem nuclei and anterior horn cells in the spinal cord (lower motor neurons). Clinically it presents with symmetrical proximal limb weakness that also impacts the axial muscles, intercostal and bulbar musculature and is progressive, and the classification protocol is important in genetics, as well as providing prognostic and clinical information. The natural history of the disease is variable and complicated. About 95% of the occurrences of spinal muscular atrophy are generated by homozygous deletions. This is done by demonstrating a history of proximal muscle weakness, motor difficulties or regression, diminished or missing deep tendon reflexes. Among the most frequent complications in individuals who do not receive support are those previously mentioned such as poor weight gain with growth retardation, scoliosis, restrictive lung disease, joint contractures and difficulties in falling asleep. In terms of treatment, several different compounds have been investigated in recent years, focused on increasing muscle strength and function. Proactive supportive treatment involving a multidisciplinary team is paramount to decrease the severity of symptoms.

BIBLIOGRAPHY

1. *Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103–15.*
2. *Erazo Torricelli R. [Update on spinal muscular atrophy treatment]. Medicina (Mex). 2022 Aug 30;82 Suppl 3:76–81.*
3. *Messina S, Sframeli M. New Treatments in Spinal Muscular Atrophy: Positive Results and New Challenges. J Clin Med. 2020 Jul 13;9(7):2222.*
4. *Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin. 2015 Nov;33(4):831–46.*
5. *Dubowitz V. Ramblings in the history of spinal muscular atrophy. Neuromuscul Disord NMD. 2009 Jan;19(1):69–73.*
6. *Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJ, Gripp KW, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993 [cited 2023 Apr 3]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK1352/*
7. *Russman BS. Spinal Muscular Atrophy: Clinical Classification and Disease Heterogeneity. J Child Neurol. 2007 Aug;22(8):946–51.*
8. *Zerres K, Davies KE. 59th ENMC International Workshop: Spinal Muscular Atrophies: recent progress and revised diagnostic criteria 17-19 April 1998, Soestduinen, The Netherlands. Neuromuscul Disord NMD. 1999 Jun;9(4):272–8.*
9. *Dubowitz V. Very severe spinal muscular atrophy (SMA type 0): an expanding clinical phenotype. Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc. 1999;3(2):49–51.*
10. *MacLeod MJ, Taylor JE, Lunt PW, Mathew CG, Robb SA. Prenatal onset spinal muscular atrophy. Eur J Paediatr Neurol EJPN Off J Eur Paediatr Neurol Soc. 1999;3(2):65–72.*
11. *Zerres K, Rudnik-Schöneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. Arch Neurol. 1995 May;52(5):518–23.*
12. *Finkel RS, McDermott MP, Kaufmann P, Darras BT, Chung WK, Sproule DM, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014 Aug 26;83(9):810–7.*
13. *Thomas NH, Dubowitz V. The natural history of type I (severe) spinal muscular atrophy. Neuromuscul Disord NMD. 1994;4(5–6):497–502.*
14. *von Gontard A, Zerres K, Backes M, Laufersweiler-Plass C, Wendland C, Melchers P, et al. Intelligence and cognitive function in children and adolescents with spinal muscular*

ISSN (Online): 2455-3662
EPRA International Journal of Multidisciplinary Research (IJMR) - Peer Reviewed Journal
Volume: 9| Issue: 4| April 2023|| Journal DOI: 10.36713/epra2013 || SJIF Impact Factor 2023: 8.224 || ISI Value: 1.188

atrophy. Neuromuscul Disord NMD. 2002 Feb;12(2):130–6.

15. *Zerres K, Rudnik-Schöneborn S, Forrest E, Lusakowska A, Borkowska J, Hausmanowa-Petrusewicz I. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci. 1997 Feb 27;146(1):67–72.*
16. *Piepers S, van den Berg LH, Brugman F, Scheffer H, Ruiterkamp-Versteeg M, van Engelen BG, et al. A natural history study of late onset spinal muscular atrophy types 3b and 4. J Neurol. 2008 Sep;255(9):1400–4.*
17. *Schorling DC, Pechmann A, Kirschner J. Advances in Treatment of Spinal Muscular Atrophy - New Phenotypes, New Challenges, New Implications for Care. J Neuromuscul Dis. 2020;7(1):1–13.*
18. *Lorson CL, Hahnen E, Androphy EJ, Wirth B. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. Proc Natl Acad Sci U S A. 1999 May 25;96(11):6307–11.*
19. *Calucho M, Bernal S, Alías L, March F, Venceslá A, Rodríguez-Álvarez FJ, et al. Correlation between SMA type and SMN2 copy number revisited: An analysis of 625 unrelated Spanish patients and a compilation of 2834 reported cases. Neuromuscul Disord NMD. 2018 Mar;28(3):208–15.*
20. *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 Jan 13;80(1):155–65.*
21. *Feldkötter M, Schwarzer V, Wirth R, Wienker TF, Wirth B. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet. 2002 Feb;70(2):358–68.*
22. *Butchbach MER. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci. 2016;3:7.*
23. *Prior TW, Swoboda KJ, Scott HD, Hejmanowski AQ. Homozygous SMN1 deletions in unaffected family members and modification of the phenotype by SMN2. Am J Med Genet A. 2004 Oct 15;130A(3):307–10.*
24. *Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol. 2007 Aug;22(8):1027–49.*
25. *Lipnick SL, Agniel DM, Aggarwal R, Makhortova NR, Finlayson SG, Brocato A, et al. Systemic nature of spinal muscular atrophy revealed by studying insurance claims. PloS One. 2019;14(3):e0213680.*
26. *Bladen CL, Thompson R, Jackson JM, Garland C, Wegel C, Ambrosini A, et al. Mapping the differences in care for 5,000 spinal muscular atrophy patients, a survey of 24 national registries in North America, Australasia and Europe. J Neurol. 2014 Jan;261(1):152–63.*
27. *Tzeng AC, Cheng J, Fryczynski H, Niranjan V, Stitik T, Sial A, et al. A study of thyrotropin-releasing hormone for the treatment of spinal muscular atrophy: a preliminary report. Am J Phys Med Rehabil. 2000;79(5):435–40.*
28. *Kinali M, Mercuri E, Main M, De Biasia F, Karatza A, Higgins R, et al. Pilot trial of albuterol in spinal muscular atrophy. Neurology. 2002 Aug 27;59(4):609–10.*
29. *Merlini L, Solari A, Vita G, Bertini E, Minetti C, Mongini T, et al. Role of gabapentin in spinal muscular atrophy: results of a multicenter, randomized Italian study. J Child Neurol. 2003 Aug;18(8):537–41.*
30. *Russman BS, Iannaccone ST, Samaha FJ. A phase 1 trial of riluzole in spinal muscular atrophy. Arch Neurol. 2003 Nov;60(11):1601–3.*
31. *Bertini E, Dessaud E, Mercuri E, Muntoni F, Kirschner J, Reid C, et al. Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2017 Jul;16(7):513–22.*

Conflict of Interest Statement

The authors report no conflicts of interest.

Funding

The authors report no funding by any organization or company.