ECRONICON OPEN ACCESS

EC NEUROLOGY
Review Article

Causes, Consequences, and Differential Diagnoses of Spinal Muscular Atrophy (SMA)

A Concise and Constructive Model for the Investigation, Evaluation, and Medical Management of Joint Hypermobility Syndrome (JHS)

Nicholas A Kerna[1,2]*, Hilary M Holets[3,4], Joseph Anderson II[5], Sudeep Chawla[6], ND Victor Carsrud[7], Kevin D Pruitt[8,9], Dabeluchi C Ngwu[10,11] and John V Flores[3,4]

[1]*Independent Global Medical Research Consortium, USA*

[2]*First InterHealth Group, Thailand*

[3]*Beverly Hills Wellness Surgical Institute, USA*

[4]*Orange Partners Surgicenter, USA*

[5]*International Institute of Original Medicine, USA*

[6]*Chawla Health & Research, USA*

[7]*Lakeline Wellness Center, USA*

[8]*Kemet Medical Consultants, USA*

[9]*PBJ Medical Associates, LLC, USA*

[10]*Cardiovascular and Thoracic Surgery Unit, Department of Surgery, Federal Medical Center, Umuahia, Nigeria*

[11]*Earthwide Surgical Missions, Nigeria*

***Corresponding Author:** Nicholas A Kerna, (mailing address) POB47 Phatphong, Suriwongse Road, Bangkok, Thailand 10500. Contact: medpublab+drkerna@gmail.com.

Received: October 30, 2022; **Published:** November 29, 2022

DOI: 10.31080/ecne.2022.14.01073

Abstract

Mutations in the surviving motor neuron 1 gene (SMN1) cause an autosomal recessive condition known as spinal muscular atrophy (SMA), characterized by the degeneration of motor neurons in the spinal cord. SMA is characterized by generalized muscle weakness and atrophy predominating in the proximal limb muscles. Depending on the age of onset and the level of motor function achieved, the phenotypic is divided into four severity classes (SMA I–SMA IV).

Differential diagnosis should be investigated for various neuromuscular diseases—disorders that do not present as infantile hypotonia or limb-girdle muscle weakness later in life and are not associated with elevated CK. The therapeutic options available to these patients have significantly changed in recent years. These options include gene therapy, muscle promotor therapies, up-regulation or down-regulation of modifier genes, and clinical trials of genetic-modifying treatments to improve the level of SMN protein indirectly and, thus, strength. Nusinersen, zolgensma, and risdiplam are three different disease-modifying medications made available in the past four years.

These medications have been proven to be both safe and effective. Numerous different drugs are being investigated; some are new, while others are well known, including valproic acid, salbutamol, or myostatin. However, paralysis can be stopped but not reversed. This overview covers the history, definition, pathophysiology, types, epidemiology, causes, consequences, diagnosis, differential diagnosis, therapy, and future.

Keywords: *Modifier Genes; Motor Neuron Mutation; Muscle Weakness and Atrophy; Differential Diagnosis of Neuromuscular Diseases*

Abbreviations

CNS: Central Nervous System; CPK: Serum Creatine Phosphokinase; EMG: Electromyography; HDACi: Histone Deacetylase Inhibitor; IPS: Induced Pluripotent Stem; MFM: Motor Function Measure; NIV: Noninvasive Nocturnal Ventilation; QoL: Quality of Life; SMA: Spinal Muscular Atrophy; SMN1: Surviving Motor Neuron 1 Gene; WHO: World Health Organization

Introduction

SMA is a rare and fatal genetic condition caused by the absence of a functional SMN1 gene, resulting in an abrupt and irreversible loss of motor neurons, affecting muscle function and essential mobility [1]. The first accounts of SMA came from the last decade of the nineteenth century. Guido Werdnig (1844 – 1919) described two brothers with paralyzes whose autopsies revealed loss of anterior horn cells in 1891. In the same decade, Johan Hoffmann (1857 – 1919) reported a more extensive series (7 more instances) [2].

In 1899 and 1903, Sylvestre and Beevor first reported severe infantile SMA. However, a milder variant of SMA with more prolonged survival was not publicly characterized until the 1950s by Wohlfart, Fez, and Eliasson and, in further detail, by Kugelberg and Welander. These descriptions identified and outlined the primary pathology of anterior horn cell degeneration and relevant clinical symptoms of symmetrical and proximal predominant extremities affecting the axial, intercostal, and bulbar muscles [3].

Another critical study in the realm of SMA was a monograph that Sven Brandt wrote in 1950 for his medical doctoral thesis and included 112 patients from 89 Danish families, 97 of which were infants. A sizable fraction was of the severe form; however, some also fit the mold of the intermediate. Several vintage images of the extreme form were also featured [4].

Victor Dubowitz (professor emeritus at Imperial College London at the time of this writing), another significant figure in SMA history, wrote a thorough and witty historical overview that included details of the earliest published clinical findings. Dubowitz (2009) reported 12 instances of "essentially non-progressive" neurogenic muscle atrophy beginning in infancy and more prolonged survival than Werdnig and Hoffmann's infantile form in 1964 [5].

These findings offer the first comprehensive description of the "intermediate" form, a novel phenotype with an early start and moderate development [2,4]. The next significant milestone in SMA was the discovery of the SMA gene (mild variant) in 1990, first by Gilliam's group in New York [5] and then by Melki's group in Paris [6]. Shortly after, Gilliam [7] and Melki [8] were both able to validate the exact gene location for the severe type.

The variability in severity was further recognized and characterized in the following years. In addition, there has been disagreement regarding whether infantile, juvenile, and adult variants of SMA comprise one or several diseases. Finally, the numerous characteristics were formalized into a classification system by the International Consortium, supported by the Muscular Dystrophy Association [3,9].

Based on the age of onset and the maximal level of motor function (standing or sitting), this classification identified three types of SMA. Later additions included a type 4 for adult-onset instances, a type 0 for babies with prenatal onset who died within weeks, and a division of the type 3 group by the age of onset. Although there are variations in severity within a single type and up to 25% of patients defy categorization, this system is still applicable in genetic age and offers valuable clinical and prognostic data [3].

Melki and her group found and ascertained the DNA makeup of SMN1 in 1995. They showed that this gene had been deleted or altered in people with SMA. In 1999, researchers Umrao Monani and Chris Lorson, working in Arthur Burghes' and Elliot Androphy's laboratories, respectively, described the SMN2 splicing defect [10,11]. Figure 1 depicts a timeline of events in SMA [3].

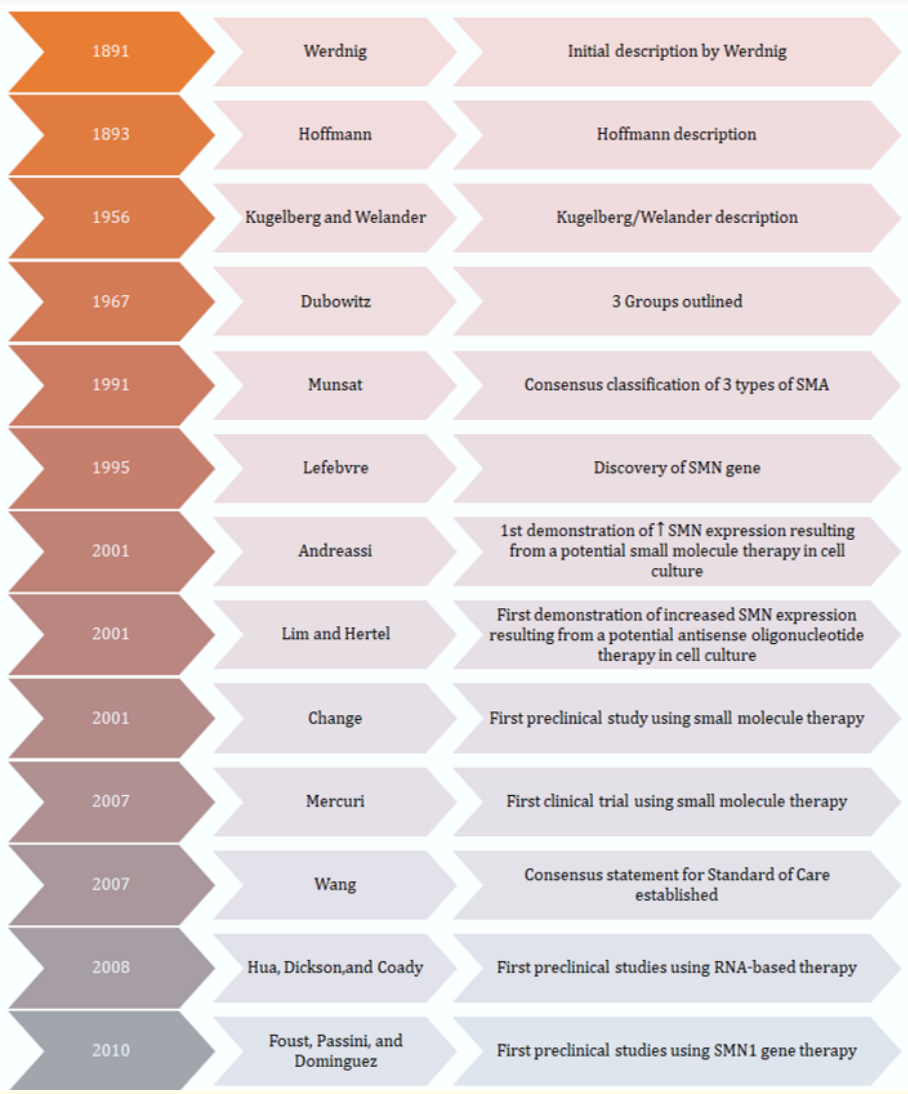

Figure 1: *Head screw size vs frequency of usage.*

Discussion

Spinal musculature

The spine consists of 33 separate bones layered on top of each other. The spinal column houses the spinal cord, a crucial part of the central nervous system (CNS). Reflex coordination, sending sensory information from the body to the brain, and sending motor instructions from the brain to the body are the three primary functions of the spinal cord. The spinal cord uses reflex arcs to synchronize reflexes autonomously.

The body can react to sensory information through reflex arcs without requiring cerebral input. The reflex arc begins with a sensory receptor that travels from the sensory nerve fiber to the spinal column. Then, it synapses with an interneuron and travels to the nerve cell, activating an effector muscle or organ [12].

The spinal column serves as the primary support of the body and allows upright standing, bending, and twisting, while protecting the spinal cord.

Strong muscles and bones, malleable ligaments and tendons, and sensitive nerves characterize a healthy spine. However, these strained, injured, or infected systems can cause discomfort. In addition, the muscles in the back and abdomen muscles support the spine's natural curvature [13,14]. Spine muscles are classified into three types: 1) superficial muscles, 2) intermediate muscles, and 3) intrinsic or deep muscles (Figure 2) [14,15].

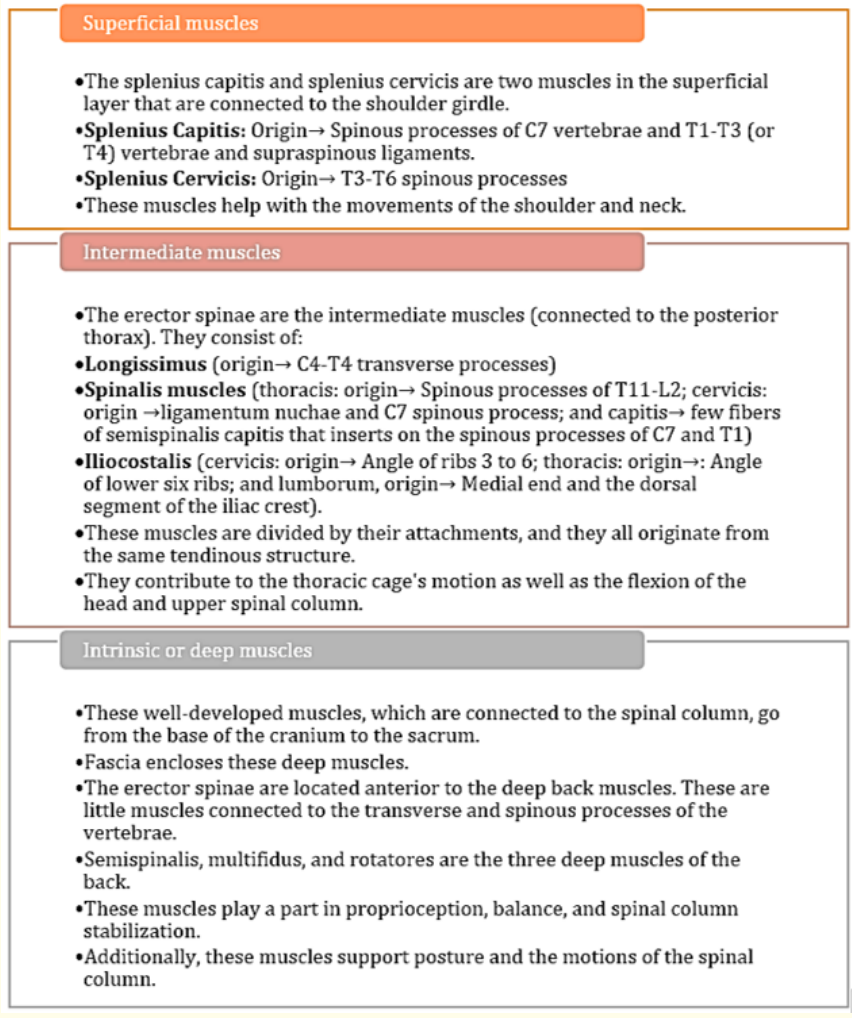

Figure 2: *Intrinsic/deep muscles, superficial muscles, and intermediate spine muscles.*

The somatic mesoderm, which develops through epitheliomesenchymal transformation, is the source of skeletal muscles. Epaxial myotomes develop the extensor muscles of the vertebral column. Since it is difficult to determine the orientation of the muscle bundles with existing preparation techniques, studying the embryological development of the back muscles has proven to be difficult [14].

Spinal deformities can result from various conditions, including broken bone, vertebral malformation, congenital anomalies (manifest since conception), dwarfism, spondylolisthesis, Scheuermann's disease, spina bifida, degenerative wear and tear, or abnormalities, such as a hematoma, tumor, or herniated disk. However, the three most common conditions causing spinal abnormalities are lordosis, kyphosis, and scoliosis [16-18]. All are related to SMA.

SMA definition and distinctions

SMA, a degenerative neuromuscular disease [19], occurs in both humans and various animal species (including canids, felids, and bovids) [20]. Fasciculations, abnormal responses, joint damage, respiration problems, and inadequate nutrition are clinical hallmarks of SMA19. According to Burr and Reddivari (2022): "The prevalence of carriers of SMN1 mutation in the general population ranges from 2 to 3% (1 in 40), with an estimated incidence of SMA of 1 in 6000 to 11000. However, the incidence varies by ancestry, with the incidence recorded as 8/100,000 for people of white ethnicity, 0.89/100,000 for those of black ethnicity, and 0.96/100,000 for people of mixed heritage" [21].

SMA is a common genetic disorder that primarily affects children and newborns; however, it can also affect adults [22,23]. It is debatable if gender impacts the clinical phenotype of SMA [24]. But demographic research related to sex has shown that men are more frequently affected by SMA than women. In a 2:1 ratio, men outnumber women [25].

Defects in both copies of SMN1 located on chromosome 5q are the most frequent precipitating causes or events leading to SMA. SMA patients have low amounts of SMN protein, which causes the spinal cord to lose motor neurons, resulting in weakness and atrophy of the skeletal muscle. The trunk, upper leg, and arm muscles are often more severely affected by this weakness than the feet and hands. Other precipitating factors include mutations in other genes, including the X chromosomes UBA1 gene, the DYNC1H1 gene, the BICD2 gene, the DYNC1H1 gene, and the VAPB gene [26].

SMA patients can experience the following issues that impair their quality of life (QoL) and are potentially life-threatening:

- Gastrointestinal (bulbar dysfunction, delayed stomach emptying, and constipation),
- Cardiac (arrhythmia, hypertension, atrial or ventral septal defects, hypoplastic left heart syndrome, and abnormal cardiac outflow tract anomalies),
- Pulmonary (aspiration pneumonia,
- Chronic and acute respiratory failure),
- Muscular and skeletal (scoliosis, kyphosis, lordosis, pelvic obliquity, or joint contracture) [21,27-29].

Also, patients with SMA are more likely to develop metabolic acidosis during illness or fasting. Although the root cause of this pattern is unknown, it has been hypothesized that abnormal pancreatic function and impaired glucose metabolism are responsible [30].

SMA signs and symptoms

SMA signs and symptoms vary depending on the type and severity of the disease and the age at which it manifests (Figure 3) [23,31–34].

Figure 3: *Characteristic signs and symptoms of SMA.*

Genetic influences on SMA

SMA is located in a complex region with several duplicated and inverted sequences [33]. There are two SMN genes in each person, SMN1 (telomeric form) and SMN2 (centromeric version) [35]. SMN1 transcription generates a fully functioning mRNA, which may be encoded to generate the SMN protein. However, fewer SMN proteins are encoded by SMN2 transcription than SMN1 because only 10 to 15% of functionally complete mRNA is produced.[21] Due to mutation, deletion, or rearrangement, 90% of patients with SMA have a homozygous abnormality of the SMN1 gene, which produces 90% of the SMN protein on chromosome 5q [35].

The only difference between SMN2 and SMN1 was the single C-T change in exon 7. This change encourages splicing 80 to 85% of the time during transcription, resulting in exon 7 being removed.

This mRNA's truncation produces similar truncated nonfunctional proteins. Due to the absence of SMN1 in patients with SMA, the function of alpha motor neurons and consequent survival depend on the residual synthesis of the functional SMN protein SMN2. As a result, there is a positive association between the severity of the phenotypic and the number of copies of SMN2, with SMA type 1 often having one to two copies and SMA type 4 usually having three to five copies [21].

SMA typology

SMA has several forms. These forms differ in when symptoms first arise and how they impact the QoL and life expectancy (Figure 4) [1,21,32,35–40].

Figure 4: *Different types of SMA.*

SMA diagnosis

Physicians should evaluate for SMA newborns with unexplainable weakness or hypotonia. Additional diagnosis indicators in newborns, children, or adults include a history of motor problems, loss of motor abilities, proximal muscle weakness, hyporeflexia or areflexia, tongue fasciculations, and physical symptoms of lower motor neuron disease [40]. Figure 5 summarizes the diagnostic algorithm that should be used as a reference for evaluating SMA [2,41].

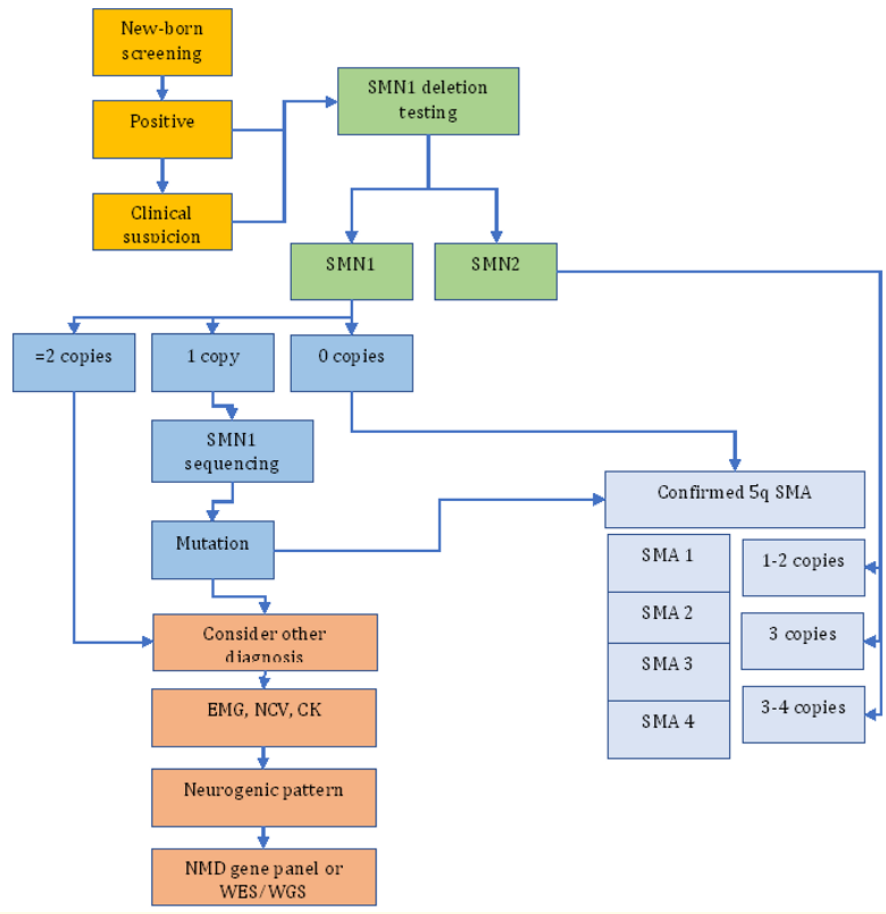

Figure 5: *SMA diagnosis algorithm.*

The first inspection line in a typical case where the illness is suspected is the genetic test for SMN1/SMN2, which is quite reliable [2]. Homozygous deletions in exon 7 of SMN1 can be identified using targeted mutation analysis and molecular genetic testing. Although point mutations can occur, exon 7 deletion is the most frequent SMA mutation. Therefore, if clinical symptoms are characteristic of SMA and only a single deletion is found, sequencing of SMN1 should be sought to test for a point mutation [40].

Additional laboratory tests include the measurement of creatine kinases and electrophysiological assessments, including electromyography (EMG) and nerve conduction studies [34]. Serum creatine phosphokinase (CPK) levels help distinguish neurogenic disorders, such as SMA, from myopathic conditions, such as dystrophies, in which muscle injury increases CPK levels. As molecular genetic testing has become more accessible, electromyography and muscle biopsy, once a staple of the diagnostic assessment for SMA, are now seldom required. SMA electromyography reveals aberrant spontaneous activity, including fibrillations and positive sharp waves.

A muscle biopsy exhibits thick clusters of circular type 1 and 2 atrophic muscle fibers scattered within fascicles of type 1 hypertrophy. Expanded fibers, three to four times larger than average, have been reinnervated by branching the surviving nerves [40-43]. Studies on nerve conduction frequently reveal signs of persistent motor axonal degeneration while preserving sensory nerve action potentials [41].

Differential diagnosis

Several rare disorders of various etiologies (often due to a genetic abnormality) can appear similar to SMA but frequently have distinct symptoms not seen in SMA (known as non-5q13-associated SMAs). Thus, a detailed history and physical examination, along with CK, EMG, nerve conduction investigations, muscle biopsy, or magnetic resonance imaging, are used to diagnose individuals for whom SMA is clinically suspected. However, genetic tests cannot confirm the diagnosis. Figure 6 depicts the disorders to consider in the differential diagnosis of SMA [21,33,44,45].

Disorder	Signs common with SMA	Signs distinctive from SMA
X-linked infantile SMA	Hypotonia, weakness, areflexia	Multiple congenital contractures and intrauterine fractures
Prader-Willi syndrome	Hypotonia, swallowing difficulties	Poor respiratory effort is rare
Myotonic dystrophy type 1	Hypotonia, muscle weakness	Marked facial weakness
Congenital muscular dystrophy	Hypotonia, muscle weakness	CNS, eye involvement and possible increased tone
Zellweger spectrum disorder	Hypotonia	Hepatosplenomegaly and CNS
Congenital myasthenic syndromes	Hypotonia	Ophthalmoplegia, ptosis and episodic respiratory failure
Pompe disease	Hypotonia	Cardiomegaly
Guillain-Barré syndrome	Muscle weakness	Subacute onset and sensory involvement
Duchenne muscular dystrophy	Muscle weakness, motor regression	Serum creatine kinase concentration >10–20x normal
Hexosaminidase A deficiency	Lower motor neuron disease	Slow progression, progressive dystonia, spinocerebellar degeneration
Fazio-Londe syndrome	Bulbar weakness	Limited to lower cranial nerves, death in 1–5 years
Monomelic amyotrophy	Muscle weakness	Predominantly cervical and tongue may be affected
Hypermobility syndrome	Muscle weakness, hereditary	Ligamentous extensibility
Age > 6 Months	Age > 6 Months	

Figure 6: *Disorders to consider in the differential diagnosis of SMA.*

SMA causes, characteristics, and comorbidities

SMA can be caused by several factors, such as injury, respiratory muscle weakness, medical treatment, idiopathic inflammation, or hereditary causes (Figure 7).

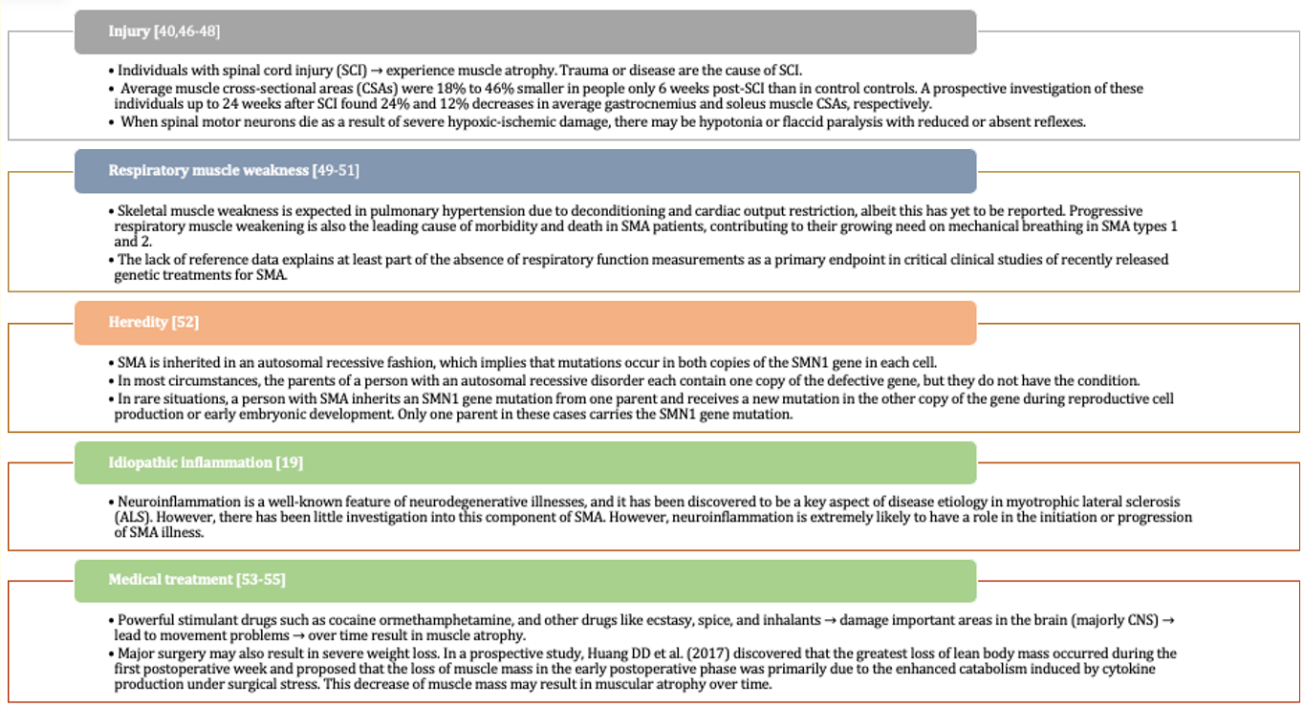

Figure 7: *Causes of SMA.*

SMA consequences and sequelae

Figure 8 depicts the consequences and sequelae of SMA [39,56–62].

SMA medical management

A multidisciplinary approach is essential in the care of patients with SMA. Owing to the many forms of SMA and clinical symptoms, therapy is tailored to the specific needs of each patient (Figure 9) [2,34].

Supportive therapy for SMA

Supportive treatment aims to treat or prevent weakness problems by providing feeding and breathing aids as needed. When nighttime hypoventilation is identified, noninvasive nocturnal ventilation (NIV) with bilevel positive pressure support must be initiated. NIV can be used as standard therapy (as well as throughout the day when needed) or as a palliative strategy. An important objective is to avoid pediatric ICU hospitalizations and, if possible, tracheotomy [34].

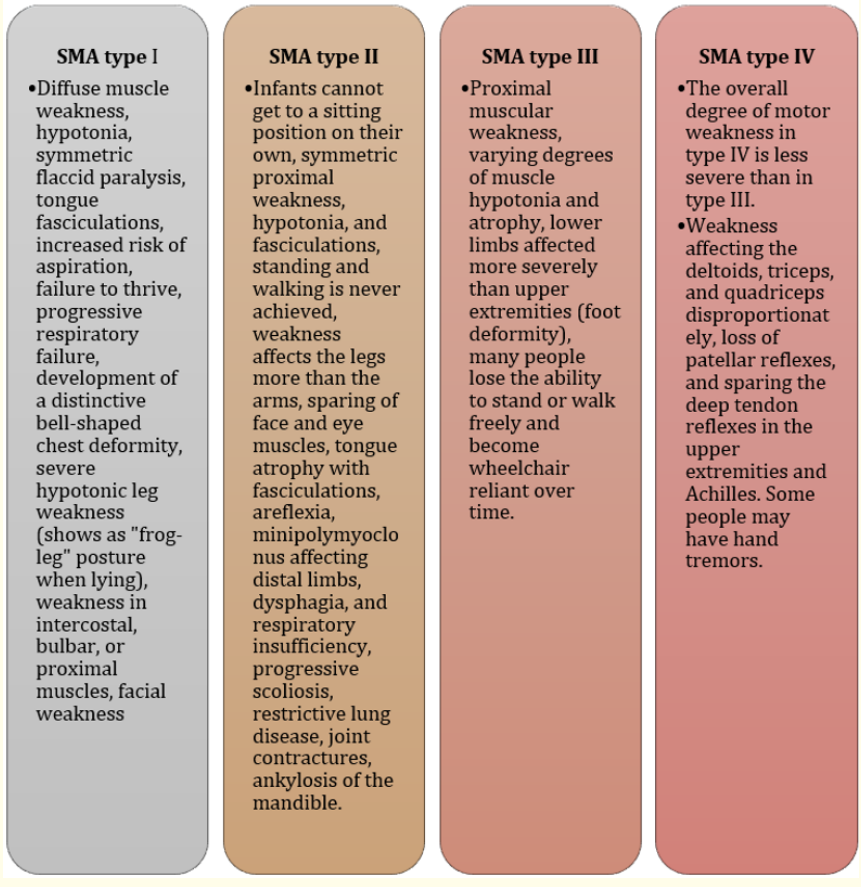

Figure 8: *Consequences and sequelae of SMA.*

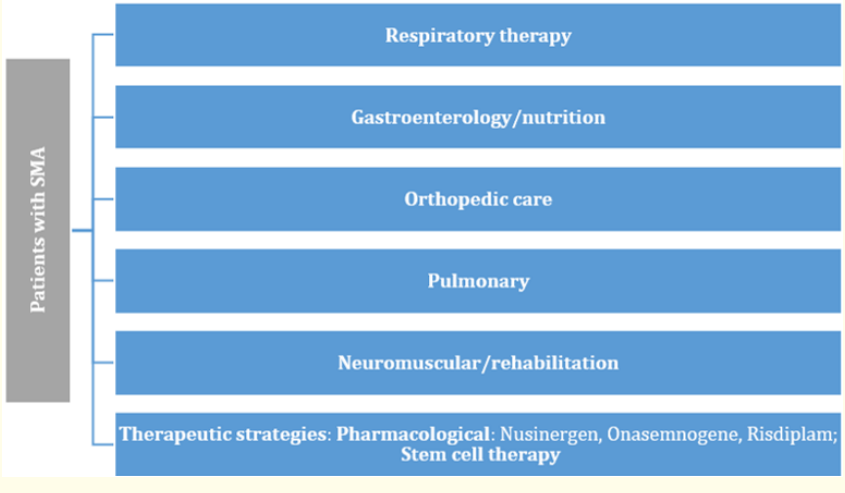

Figure 9: *Consequences and sequelae of SMA.*

Orthopedic and musculoskeletal: Spinal bracing can help postpone the progression of progressive scoliosis caused by muscle weakening. However, spinal bracing performed on individuals with SMA types 1 or 2 while sitting reduces expiratory tidal flow and should be performed cautiously.

Nutrition and gastrointestinal: Ensuring optimum caloric intake allows patients to use weak muscles to their full potential without developing obesity as a concomitant disease [39].

In newborns with type 1 SMA, early gastrostomy can help maintain optimal feeding and minimize the risk of aspiration.

Therapeutic approaches

Nusinersen: The Nusinersen clinical program began in 2011 and was the first in people. Nusinersen is an antisense oligonucleotide that can change the SMN2 splicing to include exon 7, resulting in higher levels of full-length SMN protein63 in phase 3 studies using intrathecal injection and a sham technique as a placebo in 6 months of type I SMA babies (ENDEAR, n = 121) and late-onset non-ambulant SMA patients (between 2 and 12 years) (CHERISH, n = 126), efficacy was observed.

These findings led to FDA and EMA approvals of the first customized therapy for SMA in 2016 and 2017 [2]. In addition, open-label trials and real-world data verified safety and effectiveness in a larger group of SMA patients (> 8000 globally) [64].

Another open-label study (NURTURE) discovered that early nusinersen therapy improves motor function. According to the World Health Organization (WHO) motor milestone criterion, all (n = 25) patients achieved independent sitting, 22 of 25 walked with help, and 17 of 25 walked independently [65].

Risdiplam: Risdiplam is a phase 2 clinical study of a small-molecule SMN2 splicing modifier. It has been shown to boost blood levels of SMN protein (more than two times in SUNFISH) and is well tolerated in SMA type I, II, and III patients. SUNFISH was a randomized, double-blind, placebo-controlled phase II/III study in SMA type 2 and 3 individuals aged 2 to 25.

After one year, 63% of the participants improved by 3 points or more on the Motor Function Measure (MFM). These were seen in both groups, with 76% in children under 12 and 46% in children over 12 [66,67].

Histone deacetylase inhibitor (HDACi): HDACi was thoroughly researched in the early 2000s. Although phenylbutyrate was shown to increase SMN protein levels and gems numbers in fibroblast cultures, no substantial improvement in motor performance was found in a randomized, placebo-controlled experiment. Another HDACi, valproic acid, mainly used to treat epilepsy, has increased SMN protein levels and the number of Gems in fibroblasts.

Phase 2 open-label studies evaluated SMA types 1, 2, and 3 and found no hepatotoxicity; however, some patients had low levels of free or total plasma carnitine [65].

Salbutamol: β-adrenergic agonists have been shown to increase FL SMN mRNA, SMN protein, and Gem numbers *in vitro* by promoting the inclusion of exon 7 in SMN2. Although therapeutic efforts to address this have not been randomized control trials, the outcomes of open-label trials have been positive, with improvements in strength, stability, and forced vital capacity found in patients with type 2 and type 3 SMA [68].

Olesoxime: Olesoxime is a unique mitochondrial-targeted neuroprotective drug evaluated in patients with type 2 and 3 SMA, as reported in the Lancet Neurology journal in 2017**.** Although the primary target was not reached, secondary endpoints and sensitivity analyzes show that olesoxime may maintain motor function in individuals with type 2 or 3 SMA over 24 months [69].

Fast skeletal troponin activator (CK-2127107): Troponin regulates muscular contraction and has an aberrant distribution in patients with SMA. It improves muscular contraction by sensitizing the muscles to calcium. The FDA has awarded CK-2127107 Orphan Drug status for treating SMA sufferers [65].

Myostatin inhibition: Follistatin inhibits myostatin, which downregulates muscle development. This myostatin-follistatin route has been used in multiple research projects, notably those on muscular dystrophies, and trials are now being conducted on Duchenne muscular dystrophy. In SMA, reduced myostatin expression and elevated levels of follistatin have been found in both biopsies and serum levels, indicating that this may have a role in SMA treatment, particularly in reducing muscle wasting and weakness [70].

Zolgensma (Onasemnogene abeparvovec-xioi): It was the first gene therapy licensed to treat children over the age of 2 who have biallelic alterations in the SMN1 gene [36,63]. With a single, one-time IV infusion, this medicine directly addresses the genomic root cause of the disease by restoring the functionality of the missing or nonfunctioning SMN1 gene to arrest disease development through sustained SMN protein production. It is approved in more than 40 countries and has been used to treat more than 2,000 people worldwide [56,57,60]. The effectiveness of zolgensma was studied in the SPR1NT, START, STR1VE-EU, and STR1VE-US trials.

The SPR1NT trial, a phase 3 open-label, single-arm, multicenter study, found that children with three copies of the SMN2 backup gene, which have been treated symptomatically, achieved age-appropriate motor milestones. For example, 93% (14/15) of the SPR1NT three-copy cohort children continued to walk independently, with the majority (11/15 (73%)) falling within the WHO window of expected growth and development.

Also, 100% of the children achieved the primary objective of standing alone for 3 seconds, and 93% (14/15) were within the WHO range of normal development. Furthermore, after 14 months, all children lived without a permanent ventilator; 67% (10) maintained body weight (third WHO percentile) without feeding support, and none needed nutrition or respiratory care. There were also no major treatment-related side events recorded [61].

Furthermore, descriptive post hoc analyses of START (n = 11), STR1VE-EU (32), and STR1VE-US (n = 22) data revealed that children with type 1 SMA achieved or retained essential measures of bulbar function after the Zolgensma intervention, along with the ability to speak—95% [19/20); swallow—92% [60/65); and meet nutritional needs, and maintain airway protection—92% (60/65).

In total, 80% (16/20) met the end objective of obtaining all three outcomes [62]. The abovementioned trials concluded that Zolgensma® would be a good alternative for treating SMA. Furthermore, intrathecal injection in older people is being studied in a clinical study (STRONG, NCT03381729) [60].

Stem cell therapy: Stem cell therapies are now attracting much attention as a potential cellular replacement technique for treating SMA. The effective creation of induced pluripotent stem (iPS) cells from patient fibroblasts is a significant step toward synthesizing genetically suitable neurons for stem cell treatment [71].

Surgical intervention: Surgical revision may provide stable spinal correction, and early orthopedic surgery may be recommended for people who are expected to live a long time. Given the high risk of recurrent dislocation, nonsurgical therapy is often preferred until the pain is severe. According to reports, noninvasive breathing and percutaneous gastrostomy increase QoL while having little influence on survival. These treatments can be particularly beneficial in extending the lives of individuals with slowly progressing diseases [39].

Future perspectives regarding SMA

The study of SMA has undergone unprecedented changes in recent years. Families with children diagnosed with SMA now have robust therapy options, albeit very expensive, thanks to the discovery of innovative SMN replacement techniques [72]. In addition, newborn screening programs allow earlier identification, treatment, and improved results.

It is anticipated that the next phase of SMA treatment will predominantly involve combinatorial SMN plus approaches. Although this concept is intriguing from a scientific and clinical perspective, it will be challenging to develop and thoroughly assess the effectiveness of such treatment approaches when most patients eligible to participate in trials already receive SMN-targeted therapy, which varies in effectiveness depending on the circumstances [73].

Conclusion

SMA is a motor neuron disease that affects infants, children, and adults, and its genetics and pathophysiology have been extensively studied over the last two decades. The knowledge of the many SMA subtypes and the development and dissemination of standard-of-care guidelines have benefitted from this enhanced attention.

The past several years have seen sustained advances in understanding SMA's molecular genetics and etiology, creating a rare opportunity for logical and successful treatment trials. Increasing the expression levels of the SMN protein in the appropriate cells at the correct times is the objective of SMA treatment. Now that this goal is within reach, researchers are better equipped to screen prospective therapies *in vitro*, test them in precise, trustworthy animal models, advance promising treatments to clinical trials, and correctly identify patients at an early or presymptomatic disease stage.

Conflict of Interest Statement

The authors declare that this paper was written without any commercial or financial relationship that could be construed as a potential conflict of interest.

References

1. Spinal muscular atrophy (SMA). Novartis (2022). https://www.novartis.com/diseases/spinal-muscular-atrophy-sma

2. Mercuri E. "Spinal muscular atrophy: from rags to riches". *Neuromuscular Disorders* 31.10 (2021): 998-1003. https://pubmed.ncbi.nlm.nih.gov/34736637/

3. Kolb SJ and Kissel JT. "Spinal muscular atrophy: a timely review: A timely review". *Archives of Neurology* 68.8 (2011): 979-984. https://jamanetwork.com/journals/jamaneurology/fullarticle/1107831

4. Dubowitz V. "Ramblings in the history of spinal muscular atrophy". *Neuromuscular Disorders* 19.1 (2009): 69-73. https://pubmed.ncbi.nlm.nih.gov/18951794/

5. Brzustowicz LM., *et al*. "Genetic mapping of chronic childhood-onset spinal muscular atrophy to chromosome 5q11.2-13.3". *Nature* 344.6266 (1990): 540-541. https://read.qxmd.com/read/2320125/genetic-mapping-of-chronic-childhood-onset-spinal-muscular-atrophy-to-chromosome-5q11-2-13-3

6. Melki J., *et al*. "Gene for chronic proximal spinal muscular atrophies maps to chromosome 5q". *Nature* 344.6268 (1990): 767-768. https://pubmed.ncbi.nlm.nih.gov/1970420/

7. Gilliam TC., *et al*. "Genetic homogeneity between acute and chronic forms of spinal muscular atrophy". *Nature* 345.6278 (1990): 823-825. https://pubmed.ncbi.nlm.nih.gov/1972783/

8. Melki J., *et al*. "Mapping of acute (type I) spinal muscular atrophy to chromosome 5q12-q14". *Lancet* 336.8710 (1990): 271-273. https://pubmed.ncbi.nlm.nih.gov/1973971/

9. Munsat TL. "International SMA collaboration". *Neuromuscular Disorders* 1.2 (1991): 81. https://www.semanticscholar.org/paper/International-SMA-Collaboration-Munsat/596f9853181e3dc37f614bae86fed160caeb33f4

10. Winfrey S and Berman EO. The history of spinal muscular atrophy (2022). https://www.mysmateam.com/resources/the-history-of-spinal-muscular-atrophy

11. The discovery of SMA. Cure SMA (2022). https://www.curesma.org/the-discovery-of-sma/

12. Harrow-Mortelliti M., *et al*. "Spinal Cord".

13. Spine anatomy, anatomy of the human spine (2022). https://mayfieldclinic.com/pe-anatspine.htm

14. Henson B., *et al*. "Anatomy, Back, Muscles". In: Stat Pearls. Stat Pearls Publishing (2021).

15. Maish W. "Deep back muscles". Geeky Medics (2022). https://geekymedics.com/deep-back-muscles/

16. Spine AZ. "Types of spine curvature disorders". Spine Institute of Arizona (2022). https://www.webmd.com/back-pain/guide/types-of-spine-curvature-disorders

17. Marks H. Types of Spine Curvature Disorders (2022). https://www.webmd.com/back-pain/guide/types-of-spine-curvature-disorders

18. Dulka B and Berman EO. "Scoliosis in spinal muscular atrophy (SMA) (2022). https://www.mysmateam.com/resources/scoliosis-in-spinal-muscular-atrophy

19. Deguise MO., *et al*. "Metabolic dysfunction in spinal muscular atrophy". *International Journal of Molecular Sciences* 22.11 (2021): 5913. https://pubmed.ncbi.nlm.nih.gov/34072857/

20. Cagnotti G., *et al*. "Spinal muscular atrophy in Blonde D'Aquitaine calves is not associated with FVT1 gene mutation". *Frontiers in Veterinary Science* 7 (2020): 348. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7344245/

21. Burr P and Reddivari AKR. "Spinal Muscle Atrophy". In: Stat Pearls (2022). https://www.ncbi.nlm.nih.gov/books/NBK560687/

22. Howell MD., *et al*. "Gender-specific amelioration of SMA phenotype upon disruption of a deep intronic structure by an oligonucleotide". *Molecular Therapy* 25.6 (2017): 1328-1341. https://pubmed.ncbi.nlm.nih.gov/28412171/

23. Kraft S. "Spinal muscular atrophy (SMA): Types, symptoms, and treatment". *Medicalnewstoday* (2022). https://my.clevelandclinic.org/health/diseases/14505-spinal-muscular-atrophy-sma

24. Ar Rochmah M., *et al*. "Gender effects on the clinical phenotype in Japanese patients with spinal muscular atrophy". *Kobe Journal of Medical Sciences* 63.2 (2017): E41-E44. https://pubmed.ncbi.nlm.nih.gov/29434173/

25. Spinal muscle atrophy. Medscape (2022). https://emedicine.medscape.com/article/1181436-overview

26. Spinal muscular atrophy fact sheet. Nih (2022). https://www.ninds.nih.gov/spinal-muscular-atrophy-fact-sheet

27. Thomson SR., *et al*. "Morphological characteristics of motor neurons do not determine their relative susceptibility to degeneration in a mouse model of severe spinal muscular atrophy". *PLoS One* 7.12 (2012): e52605. https://pubmed.ncbi.nlm.nih.gov/23285108/

28. Özkaya Ö. "Spinal muscular atrophy comorbidities". Rare Disease Advisor (2022). https://www.rarediseaseadvisor.com/disease-info-pages/spinal-muscular-atrophy-comorbidities/

29. Kolb SJ and Kissel JT. "Spinal muscular atrophy". *Neurologic Clinics* 33.4 (2015): 831-846. https://pubmed.ncbi.nlm.nih.gov/26515624/

30. Bowerman M., *et al*. "Glucose metabolism and pancreatic defects in spinal muscular atrophy". *Annals of Neurology* 72.2 (2012): 256-268. https://pubmed.ncbi.nlm.nih.gov/22926856/

31. Spinal Muscular Atrophy (SMA). Cleveland Clinic (2022). https://my.clevelandclinic.org/health/diseases/14505-spinal-muscular-atrophy-sma

32. Spinal muscular atrophy (2022). https://www.uptodate.com/contents/spinal-muscular-atrophy

33. Prior TW. "Spinal muscular atrophy: newborn and carrier screening". *Obstetrics and Gynecology Clinics of North America* 37.1 (2010): 23-36. https://pubmed.ncbi.nlm.nih.gov/20494255/

34. D'Amico A., *et al*. "Spinal muscular atrophy". *Orphanet Journal of Rare Diseases* 6 (2011): 71. https://pubmed.ncbi.nlm.nih.gov/22047105/

35. Lashine ESM., *et al*. "Spinal muscle atrophy (types I and II and III and IV): Literature review". Pulsus (2022). https://www.pulsus.com/scholarly-articles/spinal-muscle-atrophy-types-l--ll--lll-lv-literature-review.pdf

36. Ross LF and Kwon JM. "Spinal muscular atrophy: Past, present, and future". *Neoreviews* 20.8 (2019): e437-e451. https://pubmed.ncbi.nlm.nih.gov/31371553/

37. Kolb SJ and Kissel JT. "Spinal muscular atrophy". *Neurologic Clinics* 33.4 (2015): 831-846. https://www.mda.org/disease/spinal-muscular-atrophy

38. Channon A and Berman EO. "Types of spinal muscular atrophy (SMA)". Mysmateam (2022). https://www.mda.org/disease/spinal-muscular-atrophy/types

39. Spinal muscular atrophy clinical presentation". Medscape (2022). https://emedicine.medscape.com/article/1181436-clinical

40. Bodamer OA., *et al*. Spinal muscular atrophy (2022). https://www.ncbi.nlm.nih.gov/books/NBK1352/

41. Arnold WD., *et al*. "Spinal muscular atrophy: diagnosis and management in a new therapeutic era: Spinal Muscular Atrophy". *Muscle and Nerve* 51.2 (2015): 157-167. https://pubmed.ncbi.nlm.nih.gov/25346245/

42. Baioni MTC and Ambiel CR. "Spinal muscular atrophy: diagnosis, treatment and future prospects". *The Journal of Pediatrics* 86.4 (2010): 261-270. https://pubmed.ncbi.nlm.nih.gov/20711542/

43. Spinal muscular atrophy workup. Medscape (2022). https://emedicine.medscape.com/article/1264401-workup

44. What you would expect to find in SMA. Signsofsma (2022). https://www.signsofsma.com/files/pdf/eu/SMA%20DIFFERENTIAL%20DIAGNOSIS.pdf

45. Jindal P., *et al*. "Muscle strength differences in healthy young adults with and without generalized joint hypermobility: a cross-sectional study". *BMC Sports Science, Medicine and Rehabilitation* 8.1 (2016): 12. https://bmcsportsscimedrehabil.biomedcentral.com/articles/10.1186/s13102-016-0037-x

46. Giangregorio L and McCartney N. "Bone loss and muscle atrophy in spinal cord injury: epidemiology, fracture prediction, and rehabilitation strategies". *The Journal of Spinal Cord Medicine* 29.5 (2006): 489-500. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1949032/

47. Boncompagni S. "Severe muscle atrophy due to spinal cord injury can be reversed in complete absence of peripheral nerves". *European Journal of Translational Myology* 22.4 (2012): 161-200. https://www.pagepressjournals.org/index.php/bam/article/view/bam.2012.4.161

48. Castro MJ., *et al*. "Influence of complete spinal cord injury on skeletal muscle cross-sectional area within the first 6 months of injury". *European Journal of Applied Physiology and Occupational Physiology* 80.4 (1999): 373-378. https://pubmed.ncbi.nlm.nih.gov/10483809/

49. Naeije R. "Breathing more with weaker respiratory muscles in pulmonary arterial hypertension". *European Respiratory Journal* 25.1 (2005): 6-8. https://erj.ersjournals.com/content/25/1/6

50. Riou M., *et al*. "Skeletal and respiratory muscle dysfunctions in pulmonary arterial hypertension". *Journal of Clinical Medicine* 9.2 (2020): 410. https://pubmed.ncbi.nlm.nih.gov/32028638/

51. Veldhoen ES., *et al*. "Natural history of respiratory muscle strength in spinal muscular atrophy: a prospective national cohort study". *Orphanet Journal of Rare Diseases* 17.1 (2022): 70. https://pubmed.ncbi.nlm.nih.gov/35189949/

52. Spinal muscular atrophy. Medlineplus (2022). https://medlineplus.gov/genetics/condition/spinal-muscular-atrophy/

53. Effects and dangers of substance abuse on the muscular system American Addiction Centers (2022). https://americanaddictioncenters.org/health-complications-addiction/muscular-system

54. Huang DD., *et al*. "Effect of surgery-induced acute muscle wasting on postoperative outcomes and quality of life". *Journal of Surgical Research* 218 (2017): 58-66. https://pubmed.ncbi.nlm.nih.gov/28985878/

55. Inflammatory muscle diseases. UCF Health (2022). https://ucfhealth.com/our-services/rheumatology/inflammatory-muscle-diseases/

56. Myshko D. "European study confirms safety and efficacy of zolgensma in SMA". *Managed Healthcare Executive* (2022). https://www.managedhealthcareexecutive.com/view/european-study-confirms-safety-and-efficacy-of-zolgensma-in-sma

57. Dangouloff T and Servais L. "Clinical evidence supporting early treatment of patients with spinal muscular atrophy: Current perspectives". *Therapeutics and Clinical Risk Management* 15 (2019): 1153-1161. https://pubmed.ncbi.nlm.nih.gov/31632042/

58. ZOLGENSMA® (onasemnogene abeparvovec-xioi) suspension, for intravenous infusion Initial U.S. Approval: 2019. Novartis (2022). https://www.fda.gov/media/126109/download

59. Novartis announces Nature Medicine publication of Zolgensma data demonstrating age-appropriate milestones when treating children with SMA presymptomatically". Novartis (2022). https://www.novartis.com/news/media-releases/novartis-announces-nature-medicine-publication-zolgensma-data-demonstrating-age-appropriate-milestones-when-treating-children-sma-presymptomatically

60. Poletti A and Fischbeck KH. "Combinatorial treatment for spinal muscular atrophy: An Editorial for "Combined treatment with the histone deacetylase inhibitor LBH589 and a splice-switch antisense oligonucleotide enhances SMN2 splicing and SMN expression in Spinal Muscular Atrophy cells" on page 264: An Editorial for 'Combined treatment with the histone deacetylase inhibitor LBH589 and a splice-switch antisense oligonucleotide enhances SMN2 splicing and SMN expression in Spinal Muscular Atrophy cells' on page 264". *Journal of Neurochemistry* 153.2 (2020): 146-149. https://pubmed.ncbi.nlm.nih.gov/32056234/

61. Strauss KA., *et al*. "Onasemnogene abeparvovec for presymptomatic infants with three copies of SMN2 at risk for spinal muscular atrophy: the Phase III SPR1NT trial". *Nature Medicine* 28.7 (2022): 1390-1397. https://pubmed.ncbi.nlm.nih.gov/35715567/

62. Meglio M. "Gene therapy zolgensma improves bulbar function in symptomatic SMA type 1". *Neurology Live* (2022). https://www.neurologylive.com/view/gene-therapy-zolgensma-improves-bulbar-function-symptomatic-sma-type-1

63. Talbot K and Tizzano EF. "The clinical landscape for SMA in a new therapeutic era". *Gene Therapy* 24.9 (2017): 529-533. https://pubmed.ncbi.nlm.nih.gov/28644430/

64. Gidaro T and Servais L. "Nusinersen treatment of spinal muscular atrophy: current knowledge and existing gaps". *Developmental Medicine and Child Neurology* 61.1 (2019): 19-24. https://pubmed.ncbi.nlm.nih.gov/30221755/

65. Willis TA. "Therapeutic advances in spinal muscular atrophy". *Paediatrics and Child Health* 29.11 (2019): 463-467. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7029319/

66. Mercuri E., *et al*. "CHERISH study group. Nusinersen versus sham control in later-onset spinal muscular atrophy". *The New England Journal of Medicine* 378 (2018): 625-635. https://pubmed.ncbi.nlm.nih.gov/29443664/

67. Mercuri E., *et al*. "SUNFISH Part 2: Efficacy and safety of risdiplam (RG7916) in patients with Type 2 or non-ambulant Type 3 spinal muscular atrophy (SMA)". *Ptcbio* (2022). https://n.neurology.org/content/94/15_Supplement/1260

68. Nicolau S., *et al*. "Spinal muscular atrophy". *Seminars in Pediatric Neurology* 37.100878 (2021): 100878. https://www.mda.org/disease/spinal-muscular-atrophy

69. Bertini E., *et al*. "Safety and efficacy of olesoxime in patients with type 2 or non-ambulatory type 3 spinal muscular atrophy: a randomized, double-blind, placebo-controlled phase 2 trial". *Lancet Neurology* 16.7 (2017): 513-522. https://pubmed.ncbi.nlm.nih.gov/28460889/

70. Abati E., *et al*. "Inhibition of myostatin and related signaling pathways for the treatment of muscle atrophy in motor neuron diseases". *Cellular and Molecular Life Sciences* 79.7 (2022): 374. https://pubmed.ncbi.nlm.nih.gov/35727341/

71. Dimos JT., *et al*. "Induced pluripotent stem cells generated from patients with ALS can be differentiated into motor neurons". *Science* 321.5893 (2008): 1218-1221. https://pubmed.ncbi.nlm.nih.gov/18669821/

72. Chaytow H., *et al*. "Spinal muscular atrophy: From approved therapies to future therapeutic targets for personalized medicine". *Cell Reports Medicine* 2.7 (2021): 100346. https://pubmed.ncbi.nlm.nih.gov/34337562/

73. Groen EJN., *et al*. "Advances in therapy for spinal muscular atrophy: promises and challenges". *Nature Reviews Neurology* 14.4 (2018): 214-224. https://pubmed.ncbi.nlm.nih.gov/29422644/

Volume 14 Issue 12 December 2022