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Spinal Muscular Atrophy

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ABSTRACT

Spinal muscular atrophy (SMA) could be a neurodegenerative disease characterized by loss of motor neurons within the anterior horn of the spinal cord and resultant weakness. The foremost common form of SMA, accounting for 95% of cases, is autosomal recessive proximal SMA related to mutations within the survival of motor neurons (SMN1) gene. Electromyography and muscle biopsy features of denervation were once the basis for diagnosis, however molecular testing for homozygous deletion or mutation of the SMN1 gene allows efficient and specific diagnosis. Until the top of 2016, no cure was available for SMA, and management consisted of supportive measures. Either using antisense oligonucleotides (ASOs) or virus-mediated gene therapy has recently been approved as two breakthrough SMN-targeted treatments.

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INTRODUCTION

The term spinal muscular atrophy (SMA) refers to a group of genetic disorders which is characterized by degeneration of anterior horn cells and resultant muscle atrophy and weakness. The most common SMA is an autosomal recessive disorder accounting for over 95% of cases those results from a homozygous deletion or mutation in the 5q13 survival of motor neuron (SMN1) gene. A large, multi-ethnic study was conducted to test the feasibility of high-throughput genetic testing for SMA carriers, the overall carrier frequency was one in 54 with an incidence of 1 in 11,000 [1,2].

In SMA, a point mutation or homozygous deletion in the survival motor neuron 1 (SMN1) gene leads to loss of SMN production from this particular gene [4]. But, a paralogous copy of SMN1, named SMN2, is present on the same chromosome [5]. Thus the severity of SMA is highly variable and the clinical features can be classified into four main phenotypes based on the age of onset and maximum motor function achieved [2]. There is no cure for SMA; however, an understanding of the molecular genetics of SMA has led to the development of pre-clinical models and various potential therapeutic approaches [3–5].

CLINICAL FEATURES

Muscle weakness and atrophy are the predominant clinical features of SMA. Reports that detailing the clinical manifestations and wide range of clinical severity have all been recognized over the last 125 years. They emphasized the seminal pathology as anterior horn cell degeneration, as well as the pertinent clinical features of symmetrical, proximal predominant extremity weakness that additionally affects axial, intercostal, and bulbar musculature [10]. The multiple delineated phenotypes were eventually formalized into a classification scheme at an International Consortium on Spinal Muscular Atrophy which is sponsored by the Muscular Dystrophy Association (MDA) in 1991 [11].

Table No. 1: SMA Classification

Type	Age of Onset	Highest Function	Natural Age of Death	SMN2 #
0	Prenatal	Resp support	<1 mo.	1
1	0 – 6 mos.	Never sit	<2 yrs.	2
2	< 18 mos.	Never stand	>2 yrs.	3,4
3	> 18 mos.	Stand alone	Adult	
3a	18 mos. - 3 years	Stand alone	Adult	3,4
3b	> 3 years	Stand alone	Adult	4
4	>21 years	Stand alone	Adult	4–8

SMA type 0

Spinal muscular atrophy type 0 is used to describe neonates who present with severe weakness and hypotonia with a history of decreased foetalmovements[12].

SMA type 1

Infants with type 1 SMA, also known as Werdnig-Hoffman disease, present with hypotonia, poor head control, and reduced or absent tendon reflexes before 6 months of age. By definition, they never achieve the ability to sit unassisted [13].

SMA type 2

Children with type 2 SMA can sit unassisted at some point during their development; however, they are never able to walk independently (Table 1). This intermediate form of SMA tends to manifest as progressive proximal leg weakness that is greater than weakness in the arms [14].

SMA type 3

Children and adults with type 3 SMA, also referred to as Kugelberg-Welander disease can walk unassisted at some point during their lifetime (Table 1). They present with progressive proximal weakness of the legs more than the arms. The leg weakness may necessitate the need for a wheelchair at some point[15, 16].

SMA type 4

At the mild end of the continuum are individuals classified as having SMA type 4. They represent < 5% of SMA cases and have the mildest form of the disease. These individuals are ambulatory and they are similar to type 3, however, onset is in adulthood, often considered to present at age 30 or later but can be of juvenile-onset[17, 18].

MOLECULAR GENETICS AND ETIOLOGY

Two almost identical *SMN* genes are present on chromosome 5q13: the telomeric or *SMN1*gene, which is the spinal muscular atrophy-determining gene, and the centromeric or *SMN2* gene. The coding sequence of *SMN2* differs from that of *SMN1* by a single nucleotide (840C > T), which does not alter the amino acid sequence but results in alternative splicing of exon 7 [19]. About 95% of patients have a homozygous disruption of *SMN1* due to deletion or gene conversion of *SMN1* to *SMN2* [20].

About 3% of affected individuals are compound heterozygotes for deletion of one *SMN1* allele and subtle intragenic mutations. All patients, however, retain at least one copy of *SMN2*, generally 2-4. [21].*SMN* genes encode for SMN protein which is ubiquitously expressed and localized in the cytoplasm and the nucleus and is particularly abundant in motor neurons of the spinal cord [22].

DIAGNOSIS

The standard tool for diagnosis of SMA is Molecular genetic testing. Due to the efficiency of molecular testing and the high frequency of SMA in the hypotonic or “floppy” infant, it should be an early consideration in any infant with weakness or hypotonia[23].

Molecular Diagnosis

Importantly, patients with SMA have a homozygous loss of function of both SMN1 copies; genetic testing for homozygous deletion will confirm the disease in 95% of patients irrespective of disease severity [24].

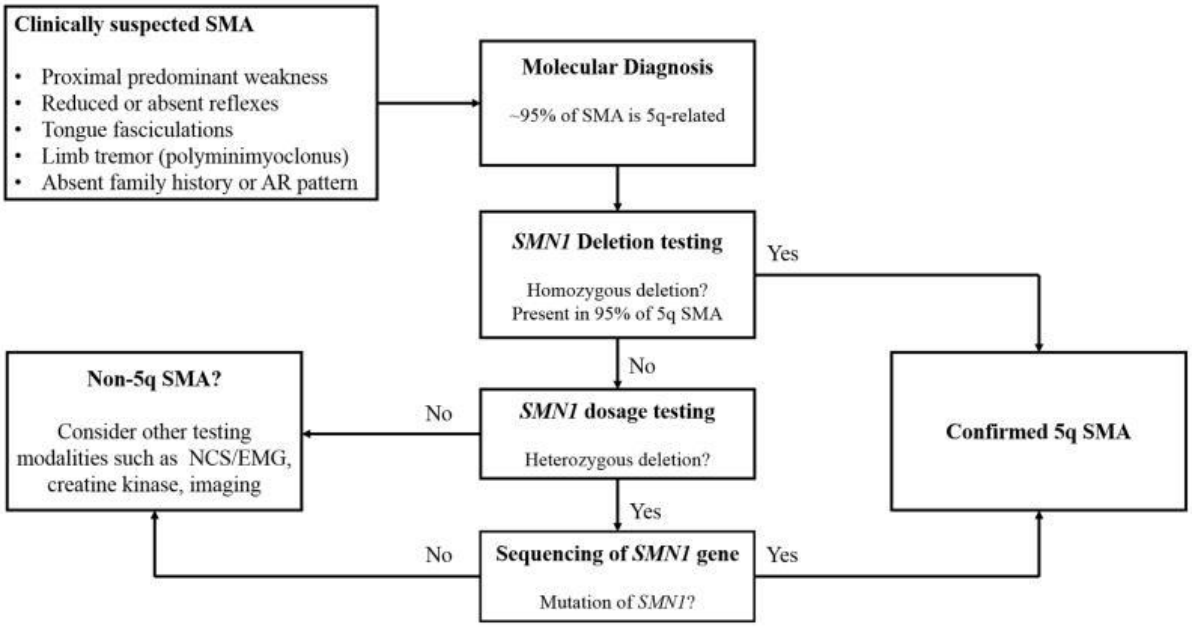

Figure No. 1: Approach to molecular diagnosis of SMA.

Other Testing Modalities

Before the availability of molecular testing, other diagnostic studies to demonstrate the presence of denervation, such as electrodiagnostic studies and muscle biopsy, were important tools for evaluating suspected SMA.

Electrodiagnostic studies show variable features of motor neuron/axon loss consistent with loss of motor neuron function[25-27.] Sensory involvement is usually lacking, but exceptional cases have been reported with association sensory neuropathy or sensory ganglionopathy [28]. In atypical cases and non-5q related SMA Electro diagnosis remains an important diagnostic tool to demonstrate the neurogenic nature of the illness.

Muscle biopsy is no longer performed to diagnose SMA. Muscle biopsy cannot distinguish clearly between SMA subtypes; however certain histological features are related to disease severity. Muscle biopsy in infants with types 1 and 2 shows large groups of atrophic fibers interspersed with fascicles of hypertrophied and normal fibers [29-30].

THERAPEUTIC STRATAGIES

At present, there are no effective disease-modifying treatments for SMA. Regardless, precisely designed supportive, rehabilitative, and palliative care can partly reduce the disease burden and alter the natural history [31].

Pharmacological therapies

Several mechanisms are targeted in SMA drug trials like neuroprotective medication to rescue motor neurons (as riluzole), creatine to enhance energy metabolism, and albuterol for its anabolic properties and the molecular effect on SMN2 gene expression [32].

An alternative strategy has been proposed by Mattis et al. (2006) [33]: aminoglycosides induce the read-through of the stop codon located in exon 8 of the SMN-del7 protein, thus elongating the C-terminus and stabilizing the protein in vitro. Successful read-through has also been achieved using different scaffolds with acceptable safety profiles as shown by PTC Therapeutics in a clinical trial with cystic fibrosis patients [34].

Gene therapy

In addition to possible drug therapy, gene therapy approaches have been evaluated for SMA, using viral vectors to replace SMN1. Perhaps the most direct approach to SMA therapy is to correct the fundamental cause of the disorder by replacing the missing SMN1 gene [35]. In a series of experiments, self-complementary AAV8-hSMN was injected at birth intrathecally into the CNS of SMA-like mice, increasing the median life span of affected animals up to 50 days, compared with 15 days for untreated controls[36]. Adeno-associated virus (AAV) vectors have also been used to deliver ASOs to the central nervous system by intrathecal infusion[37].

RNA-based Therapy

Alteration of *SMN2* splicing to favor inclusion of exon 7 into the final mRNA transcript and increased expression of the full-length SMN protein is a second promising strategy to treat SMA. These approaches target interactions between cis-acting sequence motifs found in the introns and exons of *SMN2* pre-mRNA and the various trans-acting splicing factors involved in the regulation of exon 7 splicing. Antisense oligonucleotides (ASOs) are therapeutic RNA molecules designed to bind to their complementary sequences within a targeted intron or exon that can either enhance or disrupt the targeted splicing event. Initial efforts to increase the inclusion of exon 7 from *SMN2* pre-mRNA utilized an ASO designed to inhibit a 3' spice site of exon 8 [38].

Since then, additional splice site regulators have been identified and refinements have been made to the chemical stability of ASOs[39].There are now several variations on the theme of RNA-based therapies for SMA that are in various stages of preclinical development [40].

CLINICAL MANAGEMENT

Musculoskeletal

Weakness and impaired mobility, the central features of SMA, predispose to numerous musculoskeletal issues. Early recognition and appropriate management help maintain function, prevent deterioration in vital capacity, and improving quality of life. Similar to other aspects of the disease, a multidisciplinary approach is best suited to implement efficient and effective treatment [41.] Manual and motorized wheelchairs may be initiated as early as 18–24 months of age. Children who can bear some weight and have some trunk control may utilize a standing frame or mobile-stander with ankle-foot orthoses. Physical therapy can help to maximize endurance, fitness, and safety by incorporating activities such as swimming, aquatic therapy, and adaptive sports. Neuromuscular fatigue appears to contribute to functional limitations in individuals with SMA [42].

Scoliosis is a major musculoskeletal issue that mostly impacts patients with intermediate forms of the disease, and it is almost universally present in non-ambulatory patients with types 2 and 3 SMA[43.] Surgery is the treatment of choice for scoliosis. Spinal bracing does not prevent scoliosis, but it may slow down the rate of progression in some patients for a limited time[44].

Pulmonary Care

The ultimate cause of death in infants and children with type 1 and 2 SMA is usually respiratory failure [45.] Infants at risk for mucus plugging should be monitored with overnight oximetry during acute illnesses and assisted airway clearance methods, such as manual suctioning, are recommended. Generally, the use of antibiotics should be applied to these infants during any acute illness because of the risk of pneumonia and associated pulmonary complication [46-47].

The goal of pulmonary intervention in type 1 infants is to improve quality of life and not necessarily to prolong life [48.] The management of respiratory function in type 2 or non-ambulant SMA children (i.e. type 3 children who with the progression of illness eventually lose ambulation) is similar to that of type 1 infants; however, the complications are less severe [49].

Gastrointestinal and nutritional

Gastrointestinal complications are very common in SMA patients but they have received surprisingly little formal research attention [51.] These complications can cause primary and secondary morbidity and can increase the risk of aspiration and pneumonia. The management of aspiration associated with feeding and dysphagia includes changing food consistency to include semi-solid and thickened liquids. However, in infants with type 1 SMA, early gastrostomy and laparoscopic Nissen fundoplication (if gastrointestinal reflux is present) are recommended because of the importance of maintaining proper nutrition and reducing the risk of infection secondary to aspiration [52-54].

Malnutrition, secondary to decreased oral intake can also be an insidious problem for some type 2 SMA children and adolescents [55]. To manage these complications, each child should be evaluated individually during routine visits by a dietitian to maintain the growth curve and to avoid inadequate or excessive intake. Because of the tendency for decreased bone mineral density with increasing age, adequate intake of vitamin D and calcium should be provided [56].

CONCLUSION

SMA is the most common genetic disease of the spinal motor neuron. It can manifest any time from before birth to adulthood with varying severity and disease impact, and it is the most common genetic cause of death in infants. There is no treatment modality available even though the causative gene is discovered. The disease burden is reduced by the effectively designed supportive care and continued refinement of supportive care is needed. The current and planned clinical trials are designed to increase SNM expression in motor neurons hold great promise.

REFERENCES

1. Sugarman EA, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet.* 2012;20(1):27–32.
2. Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell.* 1995 Jan 13;80(1):155–165.
3. Lefebvre S., Bürglen L., Reboullet S., Clermont O., Burlet P., Viollet L., Benichou B., Cruaud C., Millasseau P., Zeviani M. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell.* 1995;80:155–165. doi: 10.1016/0092-8674(95)90460-3
4. Lorson C.L., Hahnen E., Androphy E.J., Wirth B. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. *Proc. Natl. Acad. Sci. USA.* 1999;96:6307–6311. doi: 10.1073/pnas.96.11.6307.
5. Munsat TL, Davies KE. International SMA consortium meeting. (26–28 June 1992, Bonn, Germany) *Neuromuscul Disord.* 1992;2(5–6):423–428

6. Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. *Arch Neurol.* 2011;68(8):979–984
7. Arnold WD, Burghes AH. Spinal muscular atrophy: development and implementation of potential treatments. *Ann Neurol.* 2013;74(3):348–362.
8. Lorson CL, Rindt H, Shababi M. Spinal muscular atrophy: mechanisms and therapeutic strategies. *Hum Mol Genet.* 2010;19(R1):R111–R118
9. Dubowitz V. Ramblings in the history of spinal muscular atrophy. *Neuromuscul Disord.* 2009;19(1):69–73.
10. Dubowitz V. Ramblings in the history of spinal muscular atrophy. *Neuromuscul Disord.* 2009;19(1):69–73.
11. Munsat TL. Workshop Report: International SMA collaboration. *Neuromuscul Disord.* 1991;1
12. Dubowitz V. Very severe spinal muscular atrophy (SMA type 0): an expanding clinical phenotype. *Eur J Paediatr Neurol.* 1999;3(2):49–51.
13. Finkel RS, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* 2014;83(9):810–817.
14. von Gontard A, et al. Intelligence and cognitive function in children and adolescents with spinal muscular atrophy. *Neuromuscul Disord.* 2002;12(2):130–136.
15. 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.* 1999;9(4):272–278.
16. Zerres K, et al. 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;146(1):67–72.
17. Zerres K, Rudnik-Schoneborn S. Natural history in proximal spinal muscular atrophy. Clinical analysis of 445 patients and suggestions for a modification of existing classifications. *Arch Neurol.* 1995;52(5):518–523.
18. Piepers S, et al. A natural history study of late onset spinal muscular atrophy types 3b and 4. *J Neurol.* 2008;255(9):1400–1404.
19. Vitte J, Fassier C, Tiziano FD, Dalard C, Soave S, Roblot N, Brahe C, Saugier-Veber P, Bonnefont JP, Melki J: Refined characterization of the expression and stability of the SMN gene products. Am J Pathol. 2007, 171: 1269-80. 10.2353/ajpath.2007.070399.
20. Wirth B: An update of the mutation spectrum of the survival motor neuron gene (SMN1) in autosomal recessive spinal muscular atrophy (SMA). Hum Mut. 2000, 15: 228-237. 10.1002/(SICI)1098-1004(200003)15:3<228::AID-HUMU3>3.0.CO;2-9.
21. Gavrilov DK, Shi X, Das K, Gilliam TC, Wang CH: Differential *SMN2* expression associated with SMA severity. Nat Genet. 1998, 20: 230-31. 10.1038/3030.
22. Coovert DD, Le TT, McAndrew PE, Strasswimmer J, Crawford TO, Mendell JR, Coulson SE, Androphy EJ, Prior TW, Burghes AH: The survival motor neuron protein in spinal muscular atrophy. Hum Mol Genet. 1997, 6: 1205-1214. 10.1093/hmg/6.8.1205.
23. Arnold WD, Flanigan KM. A practical approach to molecular diagnostic testing in neuromuscular diseases. *Physical medicine and rehabilitation clinics of North America.* 2012 Aug;23(3):589–608.
24. Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell.* 1995 Jan 13;80(1):155–165.
25. Buchthal F, Olsen PZ. Electromyography and Muscle Biopsy in Infantile Spinal Muscular Atrophy. *Brain: a journal of neurology.* 1970 Jan 1;93(1):15–30
26. Hausmanowa-Petrusewicz I, Karwanska A. Electromyographic findings in different forms of infantile and juvenile proximal spinal muscular atrophy. *Muscle Nerve.* 1986 Jan;9(1):37–46.
27. Swoboda KJ, Prior TW, Scott CB, et al. Natural history of denervation in SMA: Relation to age, SMN2 copy number, and function. *Annals of Neurology.* 2005;57(5):704–712.
28. Duman O, Uysal H, Skjei KL, Kizilay F, Karauzum S, Haspolat S. Sensorimotor polyneuropathy in patients with SMA type-1: electroneuromyographic findings. *Muscle Nerve.* 2013 Jul;48(1):117–121.
29. Fenichel GM, Engel WK. HISTOCHEMISTRY OF MUSCLE IN INFANTILE SPINAL MUSCULAR ATROPHY. *Neurology.* 1963 Dec;13:1059–1066.
30. Dubowitz V. Enzyme histochemistry of skeletal muscle. 3. Neurogenic muscular atrophies. *Journal of neurology, neurosurgery, and psychiatry.* 1966 Feb;29(1):23–28.
31. Oskoui M, Levy G, Garland CJ, et al. The changing natural history of spinal muscular atrophy type 1. *Neurology.* 2007 Nov 13;69(20):1931–1936.

32. Tiziano FD, Lomastro R, Pinto AM, Messina S, D'Amico A, Fiori S, Angelozzi C, Pane M, Mercuri E, Bertini E, Neri G, Brahe C: Salbutamol increases survival motor neuron (SMN) transcript levels in leucocytes of spinal muscular atrophy (SMA) patients: relevance for clinical trial design. J Med Genet. 2010, 47: 856-858. 10.1136/jmg.2010.080366.
33. Mattis VB, Rai R, Wang J, Chang CW, Coady T, Lorson CL: Novel aminoglycosides increase SMN levels in spinal muscular atrophy fibroblasts. Hum Genet. 2006, 120: 589-601. 10.1007/s00439-006-0245-7.
34. Kerem E, Hirawat S, Armoni S, Yaakov Y, Shoseyov D, Cohen M, Nissim-Rafinia M, Blau H, Rivlin J, Elfring GL, Northcutt VJ, Miller LL, Kerem B, Wilschanski M: Effectiveness of PTC124 treatment of cystic fibrosis caused by nonsense mutations: a prospective phase II trial. Lancet. 2008, 372: 719-727. 10.1016/S0140-6736(08)61168-X.
35. Foust KD, et al. Rescue of the spinal muscular atrophy phenotype in a mouse model by early postnatal delivery of SMN. *Nat Biotechnol.* 2010
36. Passini MA, Bu J, Roskelley EM, Richards AM, Sardi SP, O'Riordan CR, Klinger KW, Shihabuddin LS, Cheng SH: CNS-targeted gene therapy improves survival and motor function in a mouse model of spinal muscular atrophy. J Clin Invest. 2010, 120: 1253-1264. 10.1172/JCI41615.
37. Passini MA, Bu J, Richards AM, Kinnecom C, Sardi SP, Stanek LM, Hua Y, Rigo F, Matson J, Hung G, Kaye EM, Shihabuddin LS, Krainer AR, Bennett CF, Cheng SH: Antisense oligonucleotides delivered to the mouse CNS ameliorate symptoms of severe spinal muscular atrophy. Sci Transl Med. 2011, 3: 72ra18. 10.1126/scitranslmed.3001777.
38. Hua Y, et al. Antisense correction of SMN2 splicing in the CNS rescues necrosis in a type III SMA mouse model. *Genes Dev.* 2010;24(15):1634–1644.
39. Singh NK, et al. Splicing of a critical exon of human Survival Motor Neuron is regulated by a unique silencer element located in the last intron. *Mol Cell Biol.* 2006;26(4):1333–1346. [
40. Osman EY, et al. Morpholino antisense oligonucleotides targeting intronic repressor Element1 improve phenotype in SMA mouse models. *Hum Mol Genet.* 2014;23(18):4832–4845.
41. Wang HY, Ju YH, Chen SM, Lo SK, Jong YJ. Joint range of motion limitations in children and young adults with spinal muscular atrophy. *Archives of Physical Medicine and Rehabilitation.* 2004;85(10):1689–1693.
42. Montes J, et al. Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. *Neurology.* 2010;74(10):833–838.
43. Haaker G, Fujak A. Proximal spinal muscular atrophy: current orthopedic perspective. *The application of clinical genetics.* 2013;6(11):113–120.
44. Rodillo E, Marini ML, Heckmatt JZ, Dubowitz V. Scoliosis in spinal muscular atrophy: review of 63 cases. *J Child Neurol.* 1989 Apr;4(2):118–123.
45. Kuru S, et al. An autopsy case of spinal muscular atrophy type III (Kugelberg-Welander disease) *Neuropathology.* 2009;29(1):63–67.
46. Schroth MK. Special considerations in the respiratory management of spinal muscular atrophy. *Pediatrics.* 2009;123(Suppl 4):S245–S249.
47. Wang CH, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol.* 2007;22(8):1027–1049.
48. Roper H, Quinlivan R, Workshop P. Implementation of "the consensus statement for the standard of care in spinal muscular atrophy" when applied to infants with severe type 1 SMA in the UK. *Arch Dis Child.* 2010;95(10):845–849.
49. Markstrom A, Cohen G, Katz-Salamon M. The effect of long term ventilatory support on hemodynamics in children with spinal muscle atrophy (SMA) type II. *Sleep Med.* 2010;11(2):201–204.
50. Karasick D, Karasick S, Mapp E. Gastrointestinal radiologic manifestations of proximal spinal muscular atrophy (Kugelberg-Welander syndrome) *Journal of the National Medical Association.* 1982 May;74(5):475–478.
51. Birnkrant DJ, Pope JF, Martin JE, Repucci AH, Eiben RM. Treatment of type I spinal muscular atrophy with noninvasive ventilation and gastrostomy feeding. *Pediatric neurology.* 1998 May;18(5):407–410.
52. Durkin ET, et al. Early laparoscopic fundoplication and gastrostomy in infants with spinal muscular atrophy type I. *J Pediatr Surg.* 2008;43(11):2031–2037.

53. Yuan N, et al. Laparoscopic Nissen fundoplication during gastrostomy tube placement and noninvasive ventilation may improve survival in type I and severe type II spinal muscular atrophy. *J Child Neurol.* 2007;22(6):727–731.
54. Birnkrant DJ, et al. Treatment of type I spinal muscular atrophy with noninvasive ventilation and gastrostomy feeding. *Pediatr Neurol.* 1998;18(5):407–410.
55. Chen YS, et al. Prevalence and risk factors for feeding and swallowing difficulties in spinal muscular atrophy types II and III. *J Pediatr.* 2012;160(3):447–451. e1.
56. Kinali M, et al. Bone mineral density in a paediatric spinal muscular atrophy population. *Neuropediatrics.* 2004;35(6):325–328.