WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 7, 187-195. Review Article ISSN 2277– 7105

SPINAL MUSCULAR ATROPHY: A CLINICAL WALKTHROUGH

Kuldeep Saini*

Student-Pharm D., Near Sant Sai School, Adinath Nagar Bhosari, Pune, Maharashtra, India.

Article Received on
25 April 2021,

Revised on 14 May 2021,
Accepted on 04 June 2021

DOI: 10.20959/wjpr20217-20713

***Corresponding Author**
Kuldeep Saini
Student-Pharm D., Near Sant Sai School, Adinath Nagar Bhosari, Pune, Maharashtra, India.

ABSTRACT

Spinal muscular Atrophy (SMA) refers to a group of inherited genetic disorders due to loss of motor neurons or anterior horn cells. As a result, wasting (atrophy) & weakness is there in the skeletal muscles, which are the muscles used for movements. Weakness is more severe in the proximal muscles than distal ones. The symptoms worsen with progression of age. SMA may alter motor movements in the child like his/her crawling, walking ability and controlling head movements. In severe conditions the muscles that control breathing and swallowing may also get affected. Most common type of SMA is an Autosomal recessive disorder (95% of cases). Autosomal Recessive disorder is when the affected subject will have two mutated genes, often inheriting one from each parent. An individual with only one mutated gene will act as the carrier of the disease without any symptoms. On the basis of highest motor milestone achieved, SMA is divided into 4 main types. A Diagnosis is made on the basis of a blood test, Molecular Genetic Testing, an electromyography (EMG) test, a Creatinine Kinase (CK) test- to differentiate one type of neuromuscular disease from other. There is no complete cure for the condition; however the symptoms and complications can be prevented. Treatment options include Gene Replacement therapy called Zolgensma & drug called Nusinersen (Spinraza). To improve the posture, prevent joint immobility and to slow down atrophy and weakness of muscles Physical therapy, occupational therapy and rehabilitation may help.

INTRODUCTION

Spinal muscular Atrophy (SMA) refers to a group of inherited genetic disorders due to loss of motor neurons or anterior horn cells.[1] As a result, wasting (atrophy) & weakness is there in the skeletal muscles, which are the muscles used for movements. Weakness is more severe in the proximal muscles than distal ones. The symptoms worsen with progression of age.[2]

SMA may alter motor movements in the child like his/her crawling, walking ability and controlling head movements. In severe conditions the muscles that control breathing and swallowing may also get affected.[3]

Epidemiology

- Frequency -This condition is known to be the second most fatal Autosomal recessive disorder preceded by Cystic fibrosis. The estimated incidence is 1 in 6,000 to 1 in 10,000 live births, the carrier frequency 1/40-1/60.[4, 5] Ethnicity is known to cause a variation in the incidence of the disease, people with White ethnicity have a reported incidence of 8/100,000 whereas Black have an incidence of 0.89 in 10,000 and people with Mixed ethnicity have an incidence of 0.96/100,000.[6]
- Mortality- Mortality/Morbidity rates of SMA have an inverse relation with age of onset. Higher death rates are seen with early onset of disease. With Type 1 SMA, median survival is 7 months, mortality rate being 95% by age 18 months. Most deaths are attributed due to Respiratory infections. In Type 2 SMA, there's a variation in age of death, but death is mostly due to Respiratory complications.[7]
- Gender Predisposition – With early- onset forms of SMA (Type 1 & Type 2), Men are affected more than women.[8]
- Age- Based on the age of onset, ISMAC classification divides SMA into following types-
- SMA type I (acute infantile or Werdnig Hoffman): Onset is from birth to 6 months.
- SMA type II (chronic infantile): Onset is between 6 and 18 months.
- SMA type III (chronic juvenile): Onset is after 18 months.
- SMA type IV (adult onset): Onset is in adulthood (mean onset, mid 30s).[9]

Types- In 1991, the Muscular Dystrophy Association formulated a classification scheme which highlighted three SMA types depending on age of onset & highest level of motor function (i.e. standing or sitting).Further amendments divided the Type 3 category into two subdivisions, added a Type 4 category based on age of onset, for prenatal onset and death within few weeks a Type 0 was included.[10,11] The examination findings and natural history in SMA are dependent on variation in Phenotypes and are clinically classified into SMA types.[12] In all types of SMA, the patients have average to above average intelligence and cognition is not affected.[13]

- Type 0 is seen before birth and is the most severe form of the types. The affected neonates show less movements in the womb and thus, are born with joint deformities

(contractures). The muscle tone is very weak at birth (hypotonia). Some also have heart defects present from birth (congenital).[14] On examination, the infants may have facial diplegia, joint contractures and atrial septal defects. Respiratory failure is of major concern.[15,16]

- SMA Type 1(Werdnig-Hoffman disease) presents with poor head control, hypotonia and absent tendon reflexes prior to 6 months of age. They never achieve the ability to sit unassisted. Hypotonia can manifest as "Frogleg" posture. Infants usually suffer from respiratory failure prior to 2 years of life.[17]
- SMA Type 2- Children suffering from this condition sit unassisted at some instances however they can never walk independently. On examination areflexia and hypotonia is seen. Greater proximal weakness in legs than in hands is observed. Significant restrictive lung disease can be seen due to the combination of Intercostal muscle weakness and scoliosis.[18]
- SMA type 3(Kugelberg-Welander disease)- They may walk unassisted sometimes in their life. Like Type 2, greater proximal weakness of legs than arms is seen. They are however spared of the co-morbidities like scoliosis and have rare respiratory muscle weakness.[19]
- SMA Type 4 – This is the mildest form of the disease and contributes for <5% of SMA cases. The patients are ambulatory and similar to Type 3, provided the onset is in adulthood (may be of juvenile onset too).[20] Usually manifestations are seen after 21 years of age.[21] Muscle weakness occurs after 10 years age, and they remain ambulatory till 60.[22]

Diagnosis- Neuromuscular diseases are diagnosed by in-office physical examination and reviewing family history.[23] Molecular Genetic testing is the gold standard for diagnosis of SMA. Being an efficient method and due to high frequency of SMA in floppy(hypotonic) infant, it's an early consideration in babies with hypotonia or weakness.[24] Individuals suffering from SMA show homozygous deletion of both SMN1 copies. Thus, homozygous deletion confirms disease in 95% of patients.[25] Carrier testing is also available, in which carrier frequencies depending on the population studied have a range from 1 in 47 to 1 in 72.[26] A PCR(Polymerase Chain Reaction) or MLPA (Multiplex ligation probe amplification) is used to detect the homozygous exon 7 deletion in SMN1 gene.[27]

Other testing methods

- An Electrodiagnostic study reveals motor axon/neuron loss with loss of function. It's an important tool in diagnosing non-5q related SMA and atypical cases. An EMG tells about motor neuronal loss in form of action potential enlargement and active denervation.[28]
- Nerve conduction studies- Motor nerves show a diminished action potential as compared to sensory nerves that will demonstrate a normal action potential.[29]
- A blood test for determination of CK(Creatinine Kinase), it is though a nonspecific test. CK levels may be normal in Type 1 disease but there can be a mild elevation in Type 2&3.
- A muscle biopsy may be done though rarely.[30] Although obsolete due to the advancements in genetic testing but if performed it shows a neurogenic pattern.[31]
- A pre-pregnancy testing must be done if there's a family history of SMA, or the if the Mother has a child with SMA before.

Tests during Pregnancy- if already pregnant, following 2 main tests are done to check the condition.

1. Amniocentesis- During 15-20 weeks of pregnancy, sample of amniotic fluid is tested.
2. CVS (Chorionic villus sampling) - During 11-14 weeks, sample containing cells of placenta is tested.[32]

Management

- Therapeutic – SMA due to an underlying genetic cause has led to the discovery of two treatment options: A drug Nusinersen(Brand name Spinraza) and a gene replacement therapy with Zolgensma(AVXS-101 previously). Gene therapy involves replacement of missing or defective SMN1 gene with a working copy by a onetime infusion. The new gene will increase the SMN (Survival motor neuron) protein level in order to improve the functioning of the motor neuron. Nusinersen on the other hand is an FDA approved drug for all types of SMA with SMN1 mutation (Type1-Type 4). The drug uses a synthetic genetic material (antisense oligonucleotide) which improves the splicing of SMN2 gene. This will help in enhancing the proteins required for healthy motor neurons.[33] Three medications are FDA approved for the management of SMA, these are Onasemnogene abeparvovec-xioi(Zolgensma), Nusinersen(Spinraza) and Risdiplam(Evrysdi). The latter one stops the SMN2 gene from disrupting production of protein, so the proteins can reach the nerve cells. Trails have shown the improvement in muscle function in 41% of Subjects after a period of 12 months.[34] Nusinersen

is approved for use in Europe, Japan, Australia and USA. One vial costs $118,000 and the first year of treatment may $708,000. [35, 36] On the other hand, Onasemnogene abeparvovec is known to be the most expensive drug in the world and costs around $2.125 million for a single injection.[37] It's licensed for use in USA currently.[38,39]

- Pulmonary care- SMA can result in issues with Respiration which may manifest as hypoventilation and weak cough.[40] The weakened muscles may prevent the air from moving easily in and out of lungs. In such cases, the child may require a mouthpiece or a special mask. In case of severe condition, a machine to facilitate breathing may be used.[41]

- Nutrition & Swallowing- Due to weak muscles of throat and mouth, swallowing may be difficult and hence proper nutrition isn't received by the babies. Either consider a Nutritionist or sometimes a feeding tube may be needed. Due to decreased bone mineral density and advancing age of the patient, proper intake of Calcium and Vitamin D is must.[42] Swallowing difficulties can lead to negative compounding effect on muscle weakness and failure to thrive. GI symptoms can also include delayed emptying and reflux and constipation.[43]

- Musculoskeletal- Scoliosis is a major problem which is almost universally seen in non-ambulatory patients of Type 2 & 3 SMA.[44] The treatment of choice for Scoliosis is Surgery. For patients who are not able to undergo Surgery, Spinal bracing may help. However it might not be tolerated and can lead to restriction of vital capacity.[45] Other orthopedic complications may include susceptibility to fractures and hip subluxation.[46] To optimize and preserve function and mobility of joints and in order to avoid joint contractures Physiotherapy may help.[47]

- Novel therapies – There's no disease altering agent, the management includes optimizing the clinical manifestations.[48]

- Complications – As discussed patients may suffer from Gastrointestinal, Respiratory and orthopedic complications that may affect their quality of life and can sometimes be even life threatening.[49] They may suffer from metabolic acidosis during fasting periods or periods of illness.[50]

CONCLUSION

The onset of Spinal Muscular Atrophy (SMA) is discouraging and damaging event for a patient & his/her family. The patient is unable to control the movement of their muscles.

There is however no complete cure for this rare genetic condition, research is still going on to find new treatments. Current treatment and support focuses on managing the symptoms, however the underlying treatment is known to be amongst the most expensive medicines available.

REFERENCES

1. Russman BS. Spinal Muscular Atrophy. In: The NORD Guide to Rare Disorders, Philadelphia, PA: Lippincott, Williams and Wilkins.
2. U.S. National Library of Medicine (2020) Spinal Muscular Atrophy, Available at: https://medlineplus.gov/genetics/condition/spinal-muscular-atrophy/ (Accessed: 5/01/2021).
3. Mena T. Scavina (2018) 'Spinal Muscular Atrophy', KidsHealth from Nemours.
4. Ogino S, Leonard DG, Rennert H, Ewens WJ, Wilson RB: Genetic risk assessment in carrier testing for spinal muscular atrophy.
5. Prior TW et al. Newborn and carrier screening for spinal muscular atrophy.
6. Zaldívar et al. Evidence of reduced frequency of spinal muscular atrophy type I in the Cuban population. Neurology, 2005.
7. Jeffrey Rosenfeld (2020) Spinal Muscular Atrophy, Available at: https://emedicine.medscape.com/article/1181436-overview#a6 (Accessed: 5th May 2021).
8. Hausmanowa-Petrusewicz I et al. Chronic proximal spinal muscular atrophy of childhood and adolescence: sex influence. J Med Genet, 1984
9. Munsat TL, Davies KE. International SMA consortium meeting. (26-28 June 1992, Bonn, Germany). Neuromuscul Disord, 1992.
10. Russman BS. Spinal muscular atrophy: clinical classification and disease heterogeneity. J Child Neurol, 2007
11. Zerres K, Davies KE. 59th ENMC International Workshop: Spinal Muscular Atrophies: recent progress and revised diagnostic criteria, 1998.
12. 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 Neuro, 1995.
13. Von Gontard A et al. Intelligence and cognitive function in children and adolescents with spinal muscular atrophy. Neuromuscul Disord, 2002.
14. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin, 2015 Nov.

15. Dubowitz V. Very severe spinal muscular atrophy (SMA type 0): an expanding clinical phenotype. Eur J Paediatr Neurol, 1999.
16. MacLeod MJ, et al. Prenatal onset spinal muscular atrophy. Eur J Paediatr Neurol. 1999
17. Thomas NH, Dubowitz V. The natural history of type I (severe) spinal muscular atrophy. Neuromuscul Disord, 1994.
18. von Gontard A, et al. Intelligence and cognitive function in children and adolescents with spinal muscular atrophy. Neuromuscul Disord, 2002.
19. Zerres K, Davies KE. 59th ENMC International Workshop: Spinal Muscular Atrophies: recent progress and revised diagnostic criteria, 1998.
20. Piepers S, et al. A natural history study of late onset spinal muscular atrophy types 3b and 4. J Neurol. 2008.
21. National Institute of Neurological disorders and Stroke (2020) Spinal Muscular Atrophy Fact Sheet, Available at: https://www.ninds.nih.gov/Disorders/Patient-Caregiver-Education/Fact-Sheets/Spinal-Muscular-Atrophy-Fact-Sheet (Accessed: 4th May, 2021).
22. Barry Russman (2012) Spinal Muscular Atrophy, Danbury: National Organization for rare disorders.
23. Zhang, Y et al. Value of muscle enzyme measurement in evaluating different neuromuscular diseases. Clin. Chim. Acta (2012)
24. Arnold WD, Flanigan KM. A practical approach to molecular diagnostic testing in neuromuscular diseases. Physical medicine and rehabilitation clinics of North America, 2012.
25. Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell, 1995.
26. Hendrickson BC, Donohoe C, Akmaev VR, et al. Differences in SMN1 allele frequencies among ethnic groups within North America. J Med Genet, 2009.
27. Taylor JL et al. Newborn blood spot screening test using multiplexed real-time PCR to simultaneously screen for spinal muscular atrophy and severe combined immunodeficiency. Clin Chem, 2015.
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.
29. Han JJ, McDonald CM. Diagnosis and clinical management of spinal muscular atrophy. Phys Med Rehabil Clin N Am, 2008.

30. Fraidakis, M. J. et al. Genotype-phenotype relationship in 2 SMA III patients with novel mutations in the Tudor domain. Neurology, 2012.
31. Han JJ, McDonald CM. Diagnosis and clinical management of spinal muscular atrophy. Phys Med Rehabil Clin N Am, 2008.
32. National Health Service (2020) Spinal muscular atrophy, Available at: https://www.nhs.uk/conditions/spinal-muscular-atrophy-sma/diagnosis/ (Accessed: 6th May 2021).
33. Boston Children's Hospital (2020) Spinal Muscular Atrophy (SMA) | Diagnosis & Treatment.
34. Amita Shroff (202) Spinal Muscular Atrophy, Available at: https://www.webmd.com/a-to-z-guides/spinal-muscular-atrophy#4 (Accessed: 15th May 2021).
35. Malone DC, Dean R, Arjunji R, Jensen I, Cyr P, Miller B, Maru B, Sproule DM, Feltner DE, Dabbous O. Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients. J Mark Access Health Policy, 2019.
36. Ludolph AC, Wurster CD. Therapeutic advances in SMA. Curr Opin Neurol. 2019 Oct.
37. Mahajan R. Onasemnogene Abeparvovec for Spinal Muscular Atrophy: The Costlier Drug Ever. Int J Appl Basic Med Res, 2019.
38. Malone DC, Dean R, Arjunji R, Jensen I, Cyr P, Miller B, Maru B, Sproule DM, Feltner DE, Dabbous O. Cost-effectiveness analysis of using onasemnogene abeparvocec (AVXS-101) in spinal muscular atrophy type 1 patients. J Mark Access Health Policy, 2019.
39. Hoy SM. Onasemnogene Abeparvovec: First Global Approval. Drugs, 2019.
40. Araki S, Hayashi M, Tamagawa K, et al. Neuropathological analysis in spinal muscular atrophy type II. Acta neuropathologica, 2003.
41. Amita Shroff (202) Spinal Muscular Atrophy, Available at: https://www.webmd.com/a-to-z-guides/spinal-muscular-atrophy#4 (Accessed: 15th May 2021).
42. Bone mineral density in a paediatric spinal muscular atrophy population, Kinali M, Banks LM, Mercuri E, Manzur AY, Muntoni F Neuropediatrics, 2004.
43. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin, 2015.
44. Proximal spinal muscular atrophy: current orthopedic perspective, Haaker G, Fujak A Appl Clin Genet, 2013.
45. Haaker G, Fujak A. Proximal spinal muscular atrophy: current orthopedic perspective. Appl Clin Genet, 2013.

46. Scoliosis in spinal muscular atrophy: review of 63 cases. Rodillo E, Marini ML, Heckmatt JZ, Dubowitz V J Child Neurol, 1989.
47. Haaker G, Fujak A. Proximal spinal muscular atrophy: current orthopedic perspective. Appl Clin Genet, 2013.
48. Ludolph AC, Wurster CD. Therapeutic advances in SMA. Curr Opin Neurol, 2019
49. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin, 2015 Nov.
50. Bowerman M et al. Glucose metabolism and pancreatic defects in spinal muscular atrophy. Ann Neurol, 2012.