Spinal Muscular Atrophy: What We Know

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ABSTRACT

Introduction: Spinal muscular atrophy (SMA) is a genetic neurodegenerative disease. Historically, treatment of SMA was supportive. However, there are now two medications which are FDA approved to treat SMA. The purpose of this review article is to provide a brief overview of SMA. **Methods:** A literature review was completed using the database PubMed. Search terms included spinal muscular atrophy, SMA, and survival of motor neuron. Articles used were published in English, in the United States, and after the year 2000. **Results:** This article provides an overview of the pathophysiology of SMA, its clinical presentation, diagnostic methods, and treatments. **Conclusion:** Though it is the most common cause of genetic infantile death, SMA is still relatively rare. Due to new, disease modifying treatments, early identification and intervention for these patients is essential. However, with these advances also comes great cost, as these medications are some of the most expensive medications ever developed.

INTRODUCTION

Spinal muscular atrophy (SMA) is an inherited neurodegenerative disorder which leads to motor neuron death and, in its more severe forms, respiratory collapse.[1] With an incidence of 1 in every 6,000-10,000 births, it's the most common genetic cause of infantile death.[2] Until recently, treatment of SMA was supportive.[2] However, there are now two FDA approved treatments for SMA. Due to the prevalence of this disease and the recent emergence of therapies aimed to halt disease progression, it is important for clinicians to be able to understand the pathophysiology and be able to recognize the signs and symptoms of SMA, as well as be able to make a definitive diagnosis, in order to provide the earliest intervention possible with these new therapies.

METHODS

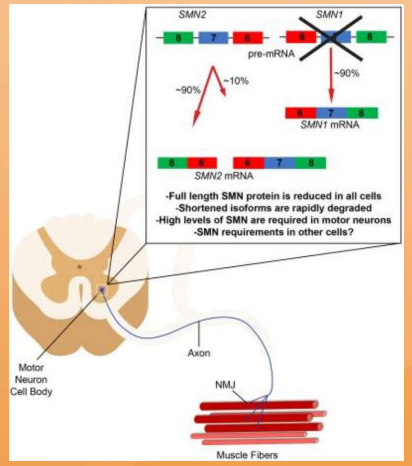
A literature review was performed using PubMed. Inclusion criteria were articles covering all subtypes of SMA and articles published in the United States. Articles were not included if they were not published in English and if they predated the year 2000. Search terms included spinal muscular atrophy, SMA, and survival of motor neuron. 8 articles were selected and used for this literature review.

RESULTS

Pathophysiology

Spinal muscular atrophy is an autosomal recessive condition involving a protein called survival of motor neuron protein (SMN protein), which is expressed ubiquitously in all cells and plays a role in numerous vital cellular processes.[2] SMN protein is found in higher concentrations in motor neuron cells.[2]

SMN protein is encoded by two genes: survival of motor neuron gene 1, or SMN1, and survival of motor neuron gene 2, or SMN2.[2] In 95% of patients with SMA, there is a homozygous deletion of SMN1.[2] The majority of the remaining patients will have a heterozygous deletion of one copy of the SMN1 gene and a concomitant mutation of the other copy.[2] SMN2 differs from SMN1 by a single nucleotide. This difference leads to an error in alternative splicing which leads to a truncated, dysfunctional protein 90% of the time SMN2 is transcribed and translated, while the other 10% of the time the protein produced is full length and fully functional.[2] In most healthy individuals, there is a normal variation in the number of copies of the SMN2 gene ranging from 0-3 copies.[2] Therefore, in patients with SMA, those who have more copies of SMN2 may have a less severe form of the disease, though the number of copies of SMN2 is not the only predictor of disease severity.[3]



Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve. 2014;51(2):157-67. doi: 10.1002/mus.24497.

A deficiency in SMN protein leads to motor neuron death and subsequent muscular weakness and atrophy.[2] This atrophy more commonly affects the lower limbs and is progressive in nature.[2] In severe cases, respiratory failure can occur due to muscular weakness and is a common cause of death in SMA patients.[2]

Clinical Presentation and Diagnosis

SMA is divided into 5 subtypes, types 0-4, based on the severity of disease, with type 0 being the most severe.[2] Signs of SMA include hypotonia, poor head control, facial weakness, abnormal gaits, propensity to aspiration, and areflexia.[1,2,4] Patients with less severe forms of the disease may only exhibit hypotonia.[1,2]

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

Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin. 2015;33(4):831-46. doi: 10.1016/j.ncl.2015.07.004.

Patients with SMA are at risk for developing sequalae. Some of the most common sequalae include scoliosis, joint contractures, joint overuse, foot abnormalities, and ankylosis of the mandible.[1,2,4]

Historically, SMA was diagnosed via muscle biopsy which would show evidence of muscle atrophy.[2] In addition, EMG and nerve conduction studies can be used to support the diagnosis.[2] The gold standard of diagnosis is molecular genetic testing, which, in the majority of cases, will show a homozygous deletion of SMN1.[2] In patients with a heterozygous deletion, dosage analysis and sequencing of the remaining SMN1 copy must be performed.[2] For patients which the diagnosis is suspected but genetic testing is inconclusive, EMG and nerve conduction studies may be used as an adjunct.[2] Carrier testing and testing in utero, in the form of chorionic villus sampling, is also available. The incidence of carriers in the normal population is 1 in 47-72.[2]

Treatment

Before the FDA approval of Spinraza and Zolgensma, treatment of SMA was symptomatic and supportive. As SMA patients are prone to respiratory complications, respiratory support is essential. This includes vaccinations, assistance with clearing secretions, non-invasive ventilatory support, such as Bi-PAP, and ventilator support.[1,2] Gastrointestinal and musculoskeletal complications are also very common.[1,2] Gastrointestinal interventions include liquid diets, gastrostomy tubes, and prophylactic Nissen Fundoplications.[1,2] Orthopedic interventions include bracing and stretching exercises, ankle and foot orthoses, and surgical intervention in patients who develop severe scoliosis.[1,2]

In 2016, the FDA approved Spinraza, the first disease modifying treatment for SMA. Spinraza is a antisense oligonucleotide which functions to correct the alternative splicing error of SMN2.[5] It has been shown to prolong life, reduce the need for mechanical ventilation, and improve motor milestones.[5] Moreover, no severe side effects were reported during clinical trials.[5] However, the cost of the drug may be a barrier to treatment: the first year of treatment is $750,000, followed by $375,000 per year thereafter for the remainder of the patient's life.[5] The second drug to be approved was Zolgensma, a viral vector that delivers a fully functional copy of the SMN gene.[6,7] Similarly to Spinraza, Zolgensma results in an improvement of motor milestones and a decrease in mortality.[7,8] It is administered as a one-time IV infusion and has the primary adverse effect of increased liver enzymes.[7] The cost is $2.125 million per dose.[8]

CONCLUSION

SMA is a common cause of infantile death. It is imperative that clinicians are familiar with the disease, how it is diagnosed, and the newly approved treatment options.

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