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A Review on Spinal Muscular Atrophy: Clinical Classification, Etiology, Diagnosis and Treatment

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ABSTRACT

Spinal muscular atrophy (SMA) is an inherited, progressive neuromuscular disease that can cause weakness, degeneration of anterior horn cells, and muscle atrophy. It was first discovered in infants by physicians Guido Werdnig and Johan Hoffmann. SMA is mainly caused due to the mutation of the survival motor neuron 1 (SMN1). Based on phenotype it is classified into four grades of severity as SMA I, SMA II, SMA III and, SMA IV. SMA is diagnosed by Molecular genetic testing such as Multiplex Ligation-Dependent Probe Amplification (MLPA) and real-time polymerase chain reaction(PCR);laboratory examination includes creatine kinase dosage and electrophysiological tests such as electromyography (EMG), and nerve conduction studies. Various drugs used for the treatment of SMA are Nusinersen, Risdiplam, Zolgensma, Reldesemtiv, and Combination therapy. Spinal muscular atrophy (SMA) Foundation and Pharmacy and therapeutic Committee (PTC), have been conducting many clinical trials for a potential SMA treatment.

KEY WORDS: *Spinal muscular atrophy; Clinical classification; Etiology; Diagnosis; Treatment*

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INTRODUCTION:

The term spinal muscular atrophy (SMA) is a group of genetic disorders which is characterized by weakness, degeneration of anterior horn cells, and resultant muscle atrophy.[1] SMA, a genetic cause of infantile mortality is an autosomal recessive neurodegenerative disorder.[5] It accounts for over 95% of cases, that result from a homozygous deletion or mutation in the 5q13 survival of motor neuron (SMN1) gene.[1]SMA was first described in the 1890s by Guido Werdnig and Johan Hoffmann. The genetic defect was localized to 5q11.2-q13.3 and years later survival motor neuron gene (SMN) gene was identified as the disease-causing gene in 1995.[2] The estimated incidence of SMA is 1 in 6000 to 1 in 10,000 live births and 1 of 40 to 1 of 60 carrier frequency. It is characterized by atrophy and generalized muscle weakness mainly in proximal limb muscles. Based on phenotype it is classified into four grades of severity as SMA I, SMA II, SMA III and, SMA IV.[3]Electromyography and muscle biopsy features of denervation and molecular testing for homozygous mutation or deletion of the SMN1 gene provide efficient and specific diagnosis and molecular testing achieves up to nearly 100% specificity and 95% sensitivity.[4] In most patients, the diagnostic test shows the absence of SMN1 exon 7.[3] Although there is no cure for SMA, and a better understanding of the molecular genetics of SMA has however led to the development of pre-clinical models and numerous potential therapeutic approaches.[1]Various drug used for the treatment of SMA is Nusinersen, Risdiplam, Zolgensma, Reldesemtiv, and Combination therapy. Many clinical trials for a potential SMA treatment have been conducted by SMA Foundation and PTC Therapeutics.[11]

CLINICAL CLASSIFICATION

SMA is categorized based on the age of onset and maximum function attained into types 0, 1, 2, 3, and 4 which are inherited as autosomal recessive genetic disorders. It is associated with mutations in the Spinal motor neuron 1 and Spinal motor neuron2 genes which are located on chromosome 5.[6]

➢ SMA TYPE 0

SMA type 0 is defined by decreased fetal movement, difficulty swallowing,joint abnormalities, and respiratory failure. Lifeexpectancy is reduced and most are unable to survive beyond 6 months of age and it is the most severe form of the disease.[1,6]

➢ SMA TYPE 1

SMA type 1 also known as Werdnig-Hoffmann disease is a serious condition and it usually appears before the age of 6 months. It is the common type and most severe, which accounts for about 50% of patients diagnosed with SMA. Inability to move limbs, muscle twitching and weakness, difficulty feeding, and spine curvature are the symptoms in SMA type 1. It can be fatal within a year without treatment as the child born will be presented with breathing problems. Paradoxical breathing is a result of the spared diaphragm along with weakened intercostal muscles. Due to the involvement of bulbar motor neurons, it shows poor suck and swallows with an increase in swallowing and feeding time and tongue fasciculation. Here, the important reason for morbidity and mortality is Aspiration pneumonia. It has 3 subgroups divided according to the severity of the clinical signs:

A. since birth/neonatal period, severe weakness and no head control;
B. after the neonatal period, the onset of weakness is generally within 2 months and no head control;
C. after the neonatal period, the onset of weakness but head control is achieved and some can sit with support.[7]

➢ SMA TYPE 2

SMA type 2 appears with symptoms at the age of 6-18 months. Most SMA type 2 patients survive into young adulthood or adolescence. The infants learn to sit but will not be able to walk and stand. In the first years of life, joint contractures, kyphoscoliosis, tremors in the upper extremities, and masticatory muscle weakness are common. The spectrum ranges from weak children who can sit unsupported and are more prone to early scoliosis and respiratory weakness is relatively strong in children with strong limb, trunk, and respiratory muscles. The patient develops a respiratory failure at the weak end of the spectrum and may require mechanical ventilation.[7]

➢ SMA TYPE 3

SMA type 3 or Kugelberg-Welander disease usually appears after the age of 18 months. This type is presented with shortening of tendons or muscles and scoliosis, which prevents the joints from moving freely. Most of them will be able to walk but experience difficulty in running, climbing stairs, or rising from a chair and have an unusual gait with a slight tremor of fingers. Respiratory infections can occur and it is at high risk. With proper treatment, life expectancy can be improved.[7]

➢ SMA TYPE 4

SMA type 4 is also known as Adult SMA. It is a rare type and usually begins after the age of 21 years. It affects the muscles closer to the center of the body andis presented with mild to moderate proximal weakness. In this group, the patient can walk in adulthood and without nutritional and respiratory problems. This type will not affect life expectancy.[2,7]

ETIOLOGY

SMA gene exists in two forms in humans on each allele: a telomeric form as SMN1 and another a centromeric form as SMN2. SMN1 gene when transcripted produces full-length mRNA transcripts which encode for the SMN protein. SMN2 gene is identical to SMN1 gene except for a C to T substitution during the splicing of exons that results in the exclusion of exon 7 on transcription. Thus, the truncated protein produced is not functional and is rapidly degraded. Critically, the exclusion of exon 7 from SMN2 mRNA is incomplete, so a small fraction of mRNA transcripts that do contain exon 7 from the SMN2 gene, encodes the normal SMN protein. RNA splicing defects can result in disease-pertinent transcripts which are isoform-specific to motor neuron function. This theory explains why only the motor neurons seem to be affected in SMA in spite of the spinal motor neuron's ubiquitous nature that is it is expressed in the body by all tissues. Altered transcripts in the position of Spinal motor neuron deficiency are identified and a definite line to the pathogenesis is not confirmed. In the SMA disease pathogenesis, SMN deficient disruption of other cellular processes and axonal mRNA impairment may also be important. Animal models demonstrate the selective and early vulnerability of the neuromuscular junction. These findings suggest high levels of spinal motor neurons for synaptic maturation and maintenance as the primary requirement. Also, represent the loss of motor neuron function associated with secondary failure of the terminal motor axons.[1,4]

DIAGNOSIS

The SMA is diagnosed when symptoms are present and is confirmed with molecular genetic testing. Molecular genetic testing helps in determining if a mutation is present in the SMN1 gene. SMA types 0,1,2,3,4 are caused due to partial or complete loss of the spinal motor neuron 1 gene. About 95% of those affected show deletion of both copies of exon 7 or exon 8 specific portions of the gene. And about 5% of those affected show exon 7 deletions in one copy of the SMN1 gene and mutations in the other copy. The

number of copies of the SMN2 genes present is determined using molecular genetic testing.[6]If the first level assay tests negative, further laboratory examination includes creatine kinase dosage and electrophysiological tests such as electromyography (EMG), and nerve conduction studies are performed. If electromyography shows a motor neuron disease, then further testing for spinal motor neuron mutations should be pursued. Genetic tests offer reliable and quick spinal motor neuron 1 gene copy number testing with the use of multiplex ligation-dependent probe amplification (MLPA) and real-time polymerase chain reaction (PCR). Semi quantitative assays improve diagnostic sensitivity up to 98%.[8,9]

TREATMENT

Nusinersen

Nusinersen is manufactured by Biogen, Inc with the brand name Spinraza was the first drug approved for SMA. It was approved in June 2017 by European Medical Agency (EMA)and December 2016 by Food and Drug Administration (FDA) for pediatric and adult patients with spinal muscular atrophy. It is an ASO –antisense oligonucleotide that promotes the inclusion of exon 7 in mRNA transcripts of SMN2. It binds to an intronic splice-silencing site in intron 7 of SMN2 and inhibits the action of other splice-factors by promoting exon 7 incorporation into the mRNA. The approval and commercialization of the Nusinersen have been supported by several trials that show efficacy without any major drug-related adverse event. Antisense oligonucleotides do not cross the blood-brain barrier and hence in all clinical trials, nusinersen was administered intrathecally with a frequency of four times over two months in the initial loading period and every four months in the maintenance period.[6,10]

Risdiplam

Risdiplam is manufactured by Genetech with the brand name Evrysdi. It was approved by the Food and Drug Administration (FDA)in August 2020 for the treatment of spinal muscular atrophy in patients 2 months of age and older. It was previously known as RO703406 and RG7916. It is a small molecule that modulates SMN2 gene splicing and it binds to two sites in SMN2 pre-mRNA: 5' splice site(5'ss) of intron 7 and exonic splicing enhancer 2(ESE2) in exon 7. Theunique and specific binding of two sites increases the levels of full-length Spinal motor neuron mRNA and protein while reducing the impact on splicing of other pre-mRNA and avoiding the possibility of off-target effects. The oral route of administration is one of the advantages of this drug whereas the intrathecal administration route of Nusinersen limits its effect on motor neurons of the central nervous system.[6,10]

Zolgensma

Onasemnogeneabeparvovec with the brand name Zolgensma was manufactured by AveXis, Inc. It was FDA-approved in May 2019 for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the SMN1 gene includes those who are pre-symptomatic at diagnosis. It was previously known as AVXS-101 and is an SMN1 gene replacement therapy. It has a non-replicating adeno-associated virus capsid(scAAV9) and delivers the wild-type spinal motor neuron 1 gene to motor neuron cells. In May 2020 the European Commission (EC) granted approval to Zolgensma for SMA type I patients who are with a bi-allelic mutation in the spinal motor neuron 1 gene or for SMA patients with a bi-allelic mutation in the spinal motor neuron 1 gene and three copies of the spinal motor neuron 2 gene. In each of the cases, Zolgensma is provided for SMA patients weighing up to 21 kg based on the dosing guidance.[6,10]

Reldesemtiv

Reldesemtiv is also known as CK-2127107 is a fast skeletal muscle troponin activator. It improves physical performance and muscle function in SMA. It was demonstrated to increase skeletal muscle force in response to stimulation of nerve and is associated with a calcium-sensitizing effect. It provides promising results demonstrating modest improvement in pulmonary function and prolonged stamina. To examine the efficacy of oral administration twice a day in non-type 1 SMA patients, a double-blind phase 2 trial is ongoing.[11]

Combination therapy

A combination of different therapeutic strategies which could maximize the benefits of SMA treatment is fascinating. Combination treatment with Nusinersen and Zolgensma has been given recently in a small group of patients and although the long-term benefit is still unclear. Both Nusinersen and Zolgensma have different mechanisms of action, so the drug-to-drug interaction is less likely. Nusinersen works by targeting the sequence of the intron and enhance exon 7 inclusion. Its translation will not interfere with Nusinersen because the transferred gene of Zolgensma lacks in introns. The adverse event ofNusinersen is found to be Thrombocytopenia, so caution is required when Zolgensma treatment is considered. To assess the efficacy and risks of combination therapy, long-term follow-up data, especially in the treatment of pre-symptomatic patients, should be accumulated.[11,12]

CONCLUSION

Spinal muscular atrophy is the most widely occurring genetic disease and is the leading cause of death in infants. It is a motor neuron disease affecting infants, childhood, and adulthood. It is associated with the mutations in the SMN1 and SMN2 genes on the chromosomes. Spinal muscular atrophy is further subdivided into five subtypes based on the age of onset and its severity. The etiology and pathophysiology have been under study for about the last 20 years. Various treatment goals and therapeutic approaches are focused on the development of the drug for treating SMA. Many drugs are identified for their treatment, some are FDA-approved for use. However, most of the drugs are still in the phases of their clinical trials. Therapy is started based on the patient's clinical features and compliance and feasibility of drug administration. A combination of drugs that can enhance SMN levels is still in the clinical trials. FDA-approved drugs such as Nusinersen, Risdiplam, and Zolgensma are currently used to treat SMA along with other interventions and supportive care.

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