Chapter 15

SPINAL MUSCULAR ATROPY (SMA) IN CHILDREN AND CURRENT THERAPIES

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INTRODUCTION

SMA, a hereditary motor neuron disease, occurs due to motor nerve degeneration with the burden of survival motor neuron (SMN) protein pores, resulting in weakness and muscle atrophy (1). This progressive muscle atrophy causes respiratory failure and infant death in its most severe form (2).

SMA is regarded as the second most prevalent fatal childhood autosomal recessive disease and has an impact on children's functional status throughout their lives. The most prevalent and severe form of SMA, Type I, commonly known as Werdnig-Hoffmann disease, typically causes mortality by the age of two. According to reports, this kind of SMA has a prevalence of 1/80,000 and an incidence of 1/50.000 (2,3).

Werdnig and Hoffmann provided the initial definitions of SMA in the 1890s. (2011) D'Amico et al. One in 6000 to 10000 births worldwide are affected by SMA, and Caucasians have a carrier frequency of 2.7% (1/37), according to research. As of 2020, there were approximately 1300 SMA patients in Turkey, according to data from the Social Security Institution (SGK); it is estimated that there are between 30 and 50 thousand SMA patients worldwide (4). Because of the anomalies seen in the anterior horn cells in spinal muscular atrophy, a problem in muscle conduction occurs when the voluntary muscles in our bodies get a signal from the anterior horn cells in the spinal cord. (5).

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These genetically flawed anterior horn cells, which are found at 5q13, are inherited as autosomal recessive diseases in SMA. The majority of patients have this gene deletion, and there is a correlation between the quantity of survival motor neuron protein in anterior horn cells inversely with the disease severity (6). The copy number of the "spare gene" survival motor neuron 2 (SMN2), which varies across the population, is the best predictor of severity. Children who have more copies of SMN2 reach more motor milestones. SMA is classified based on the maximum motor functions attained.

Children with SMA type 1, the most prevalent kind, have 2-3 copies of SMN2 and have generally been unable to sit or stand. Patients with kinds 2-4 of milder SMA typically exhibit clinical symptoms after six months of age and typically have three or more copies of SMN2 on their bodies (7). It can range from basically total paralysis and the need for breathing support from birth to muscle weakness that first manifests in adults (6).

Given the scarcity of data on SMA treatments, establishing outcome measures to monitor and measure treatment response has grown in importance. The SMA Functional Rating Scale (SMAFRS), developed for this purpose, demonstrated that it discriminates between adults with SMA who had 3 versus 4 copies of SMN2 more effectively than evaluating muscle strength (8). Amyotrophic Lateral Sclerosis Functional Rating Scale was modified to create the SMA Functional Rating Scale (SMAFRS) (ALSFRS). The first SMAFRS was regarded as reliable and capable of differentiating SMA subtypes. Later, SMAFRS was created by removing extraneous components in accordance with patient feedback. The modified version evaluates ten facets of daily living, including breathing, eating, clothing, bathing, using the restroom, grooming, turning the bed or changing the bedding, transfers, walking, and ascending stairs (9).

GENETICS

The human genome is known to encode rich information about human evolution as well as containing genetic instructions for human physiology (10). Chromosome 5, being one of the largest human chromosomes, contains multiple intrachromosomal copies but has one of the lowest gene densities. Deletions in regions of chromosome 5 probably have a mechanical role in a human spine variation, as they are the cause of debilitating disorders (11).

In the early 1990s, the q13 region of human chromosome 5's long arm was discovered to be the SMA locus. Two SMN genes, telomeric SMN1-SMNt and centromeric SMN2-SMNc, are identical to one another and only deviate by five nucleotides. Although the SMN1 gene has homozygous deletions in the majority of SMA patients, it is thought that the SMN2 gene copy number has a substantial impact on how the disease develops (12).

Alpha motor neurons (MNs) in the brainstem and ventral horns of the spinal cord are impacted by the loss of these SMN genes, which causes progressive skeletal muscle weakening, atrophy, and, in severe cases, early patient death (13).

It was first proposed in 1995 by Lefebvre and colleagues that the SMN1 (survival motor neuron 1) gene, which is located on chromosome 5q13, is a candidate gene for SMA. The SMN1 gene is a 20 kb long gene with nine exons that is located close to chromosome 5's telomere (14). SMN2 is found in the telomeric and centromeric halves of a large reverse repeat in chromosome region 5q13, like SMN1 (15). The human SMN1 and SMN2 genes both encode SMN mRNA and make SMN protein, but the SMN1 gene produces higher levels of SMN protein than SMN2. Therefore, in the absence of SMN1, SMN levels drop and SMA occurs (16). Because of the severity of this disorder, the American College of Medical Genetics (ACMG) has advised that SMA carrier screening be performed on all reproductive couples since the year 2008 (17).

It is simple to identify a homozygous SMN1 deletion, but it is more challenging to determine the number of copies of SMN1 and SMN2. Because of this, it is extremely important that SMN tests precisely detect the copy number of SMN1 for the purposes of SMA diagnosis and carrier testing, as well as the copy number of SMN2 for the purposes of clinical categorization and prognosis. In addition to this, the assessment of the SMN2 copy number is necessary for the classification of patients for a variety of clinical studies (18).

SMA TYPES

SMA is often divided into five subtypes: Type 0, Type I, Type II, Type III, and Type IV. These subtypes are defined by the age at which symptoms first appear and the highest motor milestone developed (19). The most severe type of SMA, Type I, is distinguished by a rapid decline in motor and respiratory function in the first year of life. According to studies, enteral feeding plus noninvasive breathing support can raise a Type I infant's chance of surviving for more than

a year by 70% or more. Research on the natural history of Type II and Type III, classified as milder variants of SMA, has revealed no deterioration in motor and respiratory function over the course of a year (20). SMA types III and IV are recognized as the disease's slowly progressing versions that last into adulthood. SMA type III symptoms typically appear after 18 months of age, and SMA type IV symptoms typically appear after the age of 18. A proximal to distal pattern of limb weakness and a moderate rate of advancement are characteristic features of both kinds (21).

SMA Type 0

Congenital or prenatal SMA are additional names for type 0 SMA. The newborns with SMA begin to exhibit symptoms as soon as they are born, and they pass away soon after (20). After six months, infants with type 0 SMA have severe respiratory failure and receive only supportive care; these infants rarely survive. Fetal movement is reduced in this type of SMA beginning in the 30th week of pregnancy. Furthermore, as a result of postnatal hypotonia and birth asphyxia, these babies exhibit respiratory failure symptoms (21).

SMA Type I

Werdnig first described Werdnig-Hoffmann illness, generally known as SMA type 1, in 1891 (22). He came up with this description after witnessing two brothers who, at the age of 10 months, started to lose strength in their proximal legs. He then went on to describe seven more individuals from three families between 1893 and 1900. The International SMA Consortium defined SMA type I as children with onset before 6 months who have never acquired the ability to sit unassisted (23). Werdnig-Hoffmann SMA is the most common type of SMA, accounting for approximately 80% of those affected and is also the most severe form of spinal muscular atrophy. Babies with Werdnig-Hoffmann syndrome develop severe muscle weakness before the age of six months, exhibiting symptoms such as severe motor weakness, low muscle tone, and a lack of motor development (24). Once they develop symptoms, babies with SMA Type I often do not achieve advances in motor milestones and motor function without treatment (25).

SMA Type II

SMA type II, also known as intermediate SMA, has an onset between 6 and

24 months and is characterized by some babies being able to stand and sit independently but not walk (26).

SMA Type III

Another name for SMA type III is the Kugelberg-Welander SMA. İt was named after the authors, due to its description in 1956. The "pseudo-myopathic" form of spinal muscular atrophy, according to the scientists, starts between the ages of 2 and 17. Although the advancement is gradual compared to other, more severe kinds, it is nevertheless apparent. SMA type III occurs less frequently (15%) than other types of SMA (27). Hip extensor muscle weakening is seen in people with this type, and they gradually lose their ability to walk. However, this variety has a typical life expectancy (20). Since type 3 SMA patients' lower extremities—their legs—are more afflicted than their upper extremities—their arms—they may eventually need to use wheelchair (21).

SMA Type IV

The least common form of SMA, type IV, is rarest and has the lowest morbidity (20,25); symptoms often appear after age 20 and cause very mild proximal muscular weakness. In line with what is anticipated for the general population, Type IV survival is comparable to SMA Type III survival .The signs of type 4 SMA appear after age 30. People with this diagnosis may have muscle fasciculation signs and lose their independence in ambulation within 20 years, however, data on these patients are extremely scarce (21).

DIAGNOSIS AND THERAPY

There is growing awareness of SMA, but delays in diagnosis are typical since SMA symptoms can differ greatly in their onset and severity and can resemble those of other disorders. The probable absence of experts in this field may also contribute to a delay in diagnosis. Although the type of functional loss that occurs during the delay is unknown, a delayed diagnosis could prevent SMA from receiving the best possible early care (22).

Molecular genetic testing is the common method for diagnosing SMA (23). In some cases, homozygous deletion of the telomeric SMN gene is sufficient to establish a diagnosis of the condition. A fetus with homozygous SMN gene deletion is considered to have the disease during prenatal testing. More than 95% of cases of genetic condition are deletion type disorders, while non-deletion type

disorders only account for about 5% of occurrences. In the non-deletion form, one parent unquestionably has the deletion whereas the other can only be identified after a careful analysis of the fragment left behind after the enzyme is cut (24).

SMA THERAPIES APPROVED BY FDA

Key measurements of SMA progress include many genetic treatment. Fixing the defective SMN1 gene by either replacing it or correcting it. Regulation of the SMN2 "back-up gene," which only partially functions. Protection of the muscles to forestall or reverse the function loss that is associated with SMA. Neuroprotection for the motor neurons that have been damaged as a result of the absence of SMN protein. Methods that are more recent and can discover new routes and systems that are impacted by SMA also we compared in Table 1 shows 3 drug and FDA approval comes.

Onasemnogene Abeparvovec (Zolgensma®)

Zolgensma® works to slow the progression of the illness by giving motor neurons with a functional copy of the human SMN gene. This increases the quantity of functional SMN protein found in motor neurons and prevents neuronal cell death. (25). It is an AAV vector-based, non-replication, self-complementing gene therapy (26). One intravenous dosage of Onasemnogene abeparvovec causes the motor neurons in the child to express the SMN protein, which aids in the survival and muscle movement of SMA patients. The ability of patients receiving Onasemnogene abeparvovec to achieve developmental motor milestones including head control and the capacity to sit unassisted improved significantly (27).

Govoni et. al. showed that spinal motor neurons from patients treated with this drug were similar in size and shape to those from a patient without SMA. Motor neurons in the untreated SMA patient were sparse and appeared atrophied (28). Vomiting and increased liver enzymes are Onasemnogene abeparvovec's most frequent side effects. As a result, patients should have their liver functions checked for at least 3 months after receiving Onasemnogene abeparvovec. Systemic injection of Onasemnogene abeparvovec as a single intravenous infusion improved motor milestones and survival in all newborns with SMA1 based on encouraging preclinical data. The majority of patients who took the prescribed dosage of this medication, according to research, were able to sit independently, stand independently, and walk after therapy (25,27).

Nusinersen

The US FDA approved the use of Nusinersen, also known as SPINRAZA® , a modified antisense oligonucleotide in December 2016 for both children and adult SMA patients (29). It is administered intrathecally through lumbar puncture and is the first disease-modifying medication licensed for the treatment of SMA (25). According to studies, Nusinersen improves motor function in patients suffering from all kinds of SMA, including SMA type 3. It is imperative that treatment for nusinersen start as soon as feasible. Treatment delays could have a negative impact on function recovery, especially in type 1 babies who experience rapid function loss. Prior to intrathecal injection of Nusinersen, testing for urine protein, platelet count, and coagulation are advised due to the possibility of thrombocytopenia, renal toxicity, and probable coagulation problems (30). In terms of expenditures, a 2016 study indicated that the annual cost of care for a patient with type 1 SMA who is not receiving Nusinersen is approximately €100,000 and type 2 SMA is approximately €90,000 (31) . Looking at the side effects of Nusinersen treatment, we see that some patients experience headaches and back discomfort as well as infections and respiratory problems, usually in youngsters, vomiting due to complications with lumbar puncture, drowsiness, and sedation(32).

Risdiplam

Risdiplam is an RNA splicing modifier for SMN2 that is taken orally (33). In a trial involving twenty-one babies with type 1 SMA, Baranello et al. split the babies into two groups and gave them either low-dose or high-dose risdiplam. Evrysdi ® called risdiplam baseline SMN protein concentrations were 3 times higher in the low Risdiplam group and 1.9 times higher in the high Risdiplam group after 1 year (34).Table shows 3 drug and fda approval comes.

Table 1. Compare of three Drugs SMA

	FDA approval	Type of Drug	Costs
Zolgensma	2019	AAV vector-based gene therapy (26)	2.1 million $ (single dose) (Yates & Hinkel, 2022) (35)

Spinraza	2016	splicing of SMN2 pre-mRNA	over $4 million (a 10-year period) (Yates & Hinkel, 2022) (35)
Risdiplam	2020	RNA splicing modifier for SMN2 (33)	$3.4 million (one decade of treatment) (Yates & Hinkel, 2022) (35)

CONLUSION

Progression in the therapy of SMA is largely determined by the number of genes targeted. Correcting or fixing the faulty SMN1 gene. Being the second most common fatal autosomal recessive illness in children, SMA affects children's functional status from early infancy through adulthood. A delayed diagnosis might prevent SMA from obtaining the best possible early therapy, although the nature of the functional loss that happens during the wait is uncertain. And countries have to screen before labor, so early screening is the best therapy. Drugs like Nusinersen, Risdiplam, and Onasemnogene abeparvovec are still accessible for the treatment of the condition. Establishing outcome measures to monitor and quantify therapy response has risen in relevance due to the lack of data on SMA therapies.

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