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CASE REPORT OF DOUBLE HETEROZYGOUS PATIENT WITH SPINAL MUSCULAR ATROPHY

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Abstract

Spinal muscular atrophy is an autosomal-recessive disorder characterized by degeneration of motor neurons in the spinal cord and caused by mutations in the survival motor neuron 1 gene, SMN1. In most patients with SMA, the disease is caused by a homozygous deletion or mutation.

However, approximately 5% of patients present as compound heterozygotes in which they have only one deletion of SMN1 and a subtle mutation of the other chromosome. The phenotype in these rare cases is much milder than the "classic" forms of SMA, which brings bigger challenge regarding the diagnosis.

To describe a case of SMA compound heterozygote and discuss the challenges regarding the diagnosis.

Patient's blood was taken for genetic analysis for SMN1 gene. Automatic DNA extraction, using MLPA method.

We present a female patient on the age of 15 months, with clinical features and genetically confirmed spinal muscular atrophy type 2. The genetic analysis showed double heterozygosity for deletion of SMN1, inherited from her mother, as well as genetic conversion of the SMN1 to SMN2 pseudo gene, inherited from the father.

The analysis also showed absence of the SMN1 gene and presence of 3 copies of the SMN2 pseudo gene. Fortunately, at our department we are able to treat SMA patients with oral (Risdiplam) and intrathecal therapy (Nusinersen), which both have shown particular improvement in these patients.

Accurate diagnosis of SMA is challenging for compound heterozygotes, but is crucial now, as treatments and gene therapy have become available.

Keywords: SMN1 gene, heterozygous, mutation, deletion

Introduction

Spinal muscular atrophy is an autosomal-recessive disorder characterized by degeneration of motor neurons in the spinal cord and caused by mutations in the survival motor neuron 1 gene, SMN1 on chromosome 5. A It affects 1 per 8 000 to 10 000 people worldwide [1].

In most of the patients with SMA, the disease is caused by a homozygous deletion or mutation in a segment known as exon 7. This area is located in the long arm of the chromosome 5, in the 5q13.2 region.

However, approximately 5% of the patients present as compound heterozygotes in which they have only one deletion of SMN1 and a subtle mutation of the other chromosome [2].

Recessive genetic disorders occur when a person inherits a pathogenic gene variant for the disease from each parent.

The risk for two carrier parents to both pass the variant gene and, therefore have an affected child is 25 % with each pregnancy. The risk to have a child who is a carrier, like the parents, is 50% with each pregnancy. The chance for a child to receive normal genes from both parents is 25%. There is no risk difference regarding the gender.

Parents who are close blood relative (consanguineous) are more likely to have the same harmful gene variant and to have an affected child.

The phenotype in these rare cases, called compound heterozygotes, is much milder than the "classic" forms of SMA. Mutation in the SMN1 gene leads to deficiency of a motor neuron protein

called SMN, which stands for "survival of motor neuron" [3]. As its name implies, this protein is responsible for gene expression necessary for normal motor neuron function.

The paralog of SMN1 is SMN2, which also encodes the protein SMN and partially compensate for the loss of the SMN1 gene. Most SMN protein that is produced by the SMN2 is not functional, which means that the SMN2 gene can only partially compensate for the loss of the SMN1 gene.

A patient with SMA who has more copies of the SMN2 gene will produce more functional SMN protein and may be better able to compensate for the loss of the SMN1 gene, resulting with less severe form of the disease. More copies of SMN2 are associated with milder form of the disease, although there are exceptions [4].

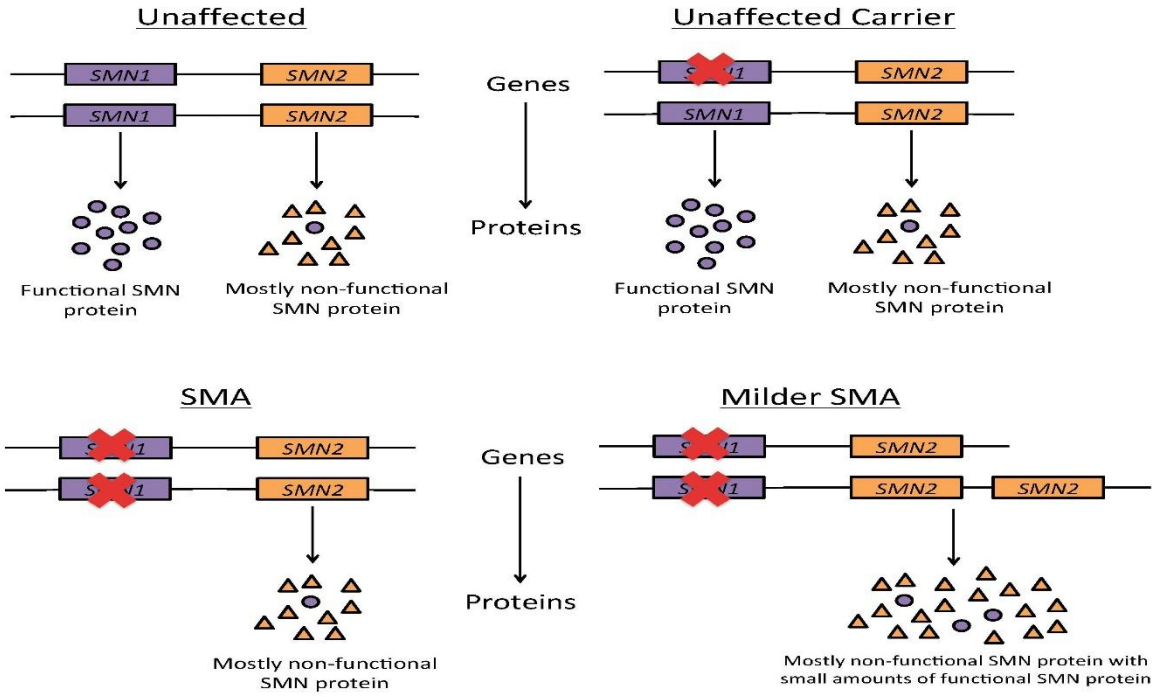

Figure 1.Genes involves in SMA

Case report

We present a female patient at the age of 15 months, who firstly visited the neurology department because of delay in the motor development.

The child presented with generalized muscle weakness, especially on the upper limbs, she could not raise her hands, but could turn to her side/ She alsocould not sit by herself , did not walk alone. Also an attenuated bilateral deep tendon reflexes were noted.

The gross motor skills were developed well, but fine motor skills were poorly developed.

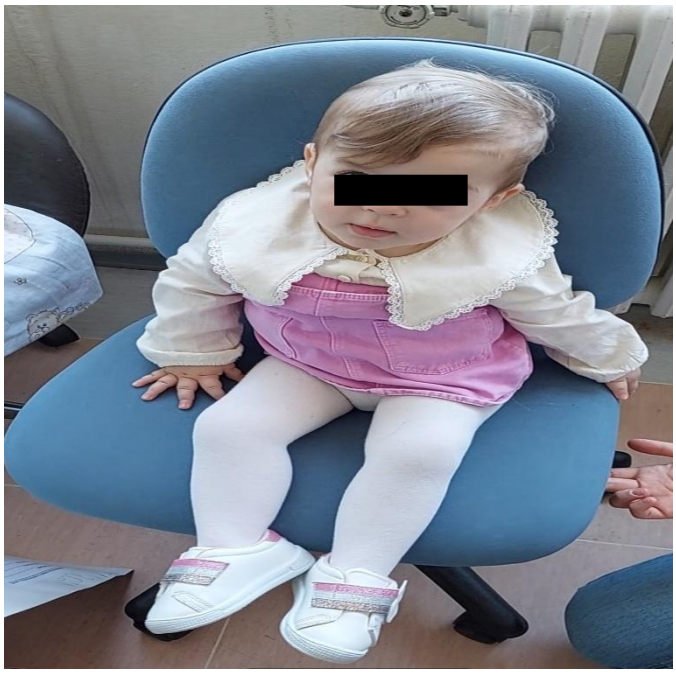

Figure 2. and figure 3-Patient with SMA

We made a laboratory investigation and metabolic screening, both with normal findings. Molecular genetic analysis for SMA were taken, which came positive for spinal muscular atrophy type 2. We used MLPA method for automatic DNA extraction.

The genetic analysis showed double heterozygosity for deletion of SMN1, inherited from her mother, as well as genetic conversion of the SMN1 to SMN2 pseudo gene, inherited from the father. The analysis also showed absence of the SMN1 gene and presence of three copies of the SMN2 pseudo gene.

Fortunately, at our department we are able to treat SMA patients with oral (Risdiplam) and intrathecal therapy (Nusinersen), which both have shown particular improvement in these patients. In this patient we started oral therapy with Risdiplam suspension.

In 2020, the FDA approved Risdiplam (Evrysdi) to treat patients starting from two months of age and older with SMA. Risdiplam is the first orally administered drug approved for the treatment of

SMA. It has a mechanism of action to modify splicing of the *SMN2* mRNA resulting in increased SMN protein, which leads to improvement of the patient's condition.

Discussion

Spinal muscular atrophy (SMA) is a genetic disease affecting the central nervous system, peripheral nervous system, and voluntary muscle movement (skeletal muscle). Most of the nerve cells that control muscles are located in the spinal cord, which accounts for the word spinal in the name of the disease.

SMA is muscular disease because its primary effect is on the muscles, which don't receive signals from these nerve cells.

Atrophy is the medical term for getting smaller, which is what generally happens to muscles when they're not stimulated by nerve cells. SMA involves the loss of nerve cells called motor neurons in the spinal cord and is classified as a motor neuron disease. SMA is divided into subtypes (SMA types 0 to 4) based on the age of symptoms onset and maximum motor function achieved, with a lower number representing a younger age of onset and more severe disease [5].

Genetic testing is available to diagnose SMA and determine if parents or other members of the family are carriers for SMA.

It is always best to start the genetic testing on the individual with SMA. Once the two mutations are identified in the person with SMA, the parents and/or siblings should be tested for the mutation identified in the SMA patient as well as the most common mutation (exon 7 deletion). Genetic testing will require one tube of blood and generally takes approximately 4 weeks until results are available.

If the genetic testing demonstrates that the relative of the patient with SMA is a carrier, the spouse or partner of that family member should then be genetically tested for the common exon 7 deletion. Because SMA is an autosomal recessive condition, both parents must be carriers to have a child with SMA. The genetic test results should be interpreted by a clinical geneticist to accurately determine the risk of having a child with SMA.

There are unusual circumstances in which the common exon 7 deletion will not be detected in the general population. Therefore, genetic counseling and interpretation should accompany any genetic testing for SMA.

If both parents are carriers, there is a 25% chance they will have a child with SMA. Regardless of how many previous children they have had with SMA, each pregnancy is independently at 25% risk of SMA. Prenatal testing with either amniocentesis or chorionic villus sampling is available to genetically test a fetus for SMA.

Amniocentesis and chorionic villus sampling are generally safe but carry 0.5% - 1%, risks of complication or pregnancy loss. Genetic results are usually available within a month of the procedure. In addition, in vitro fertilization with preimplantation genetic diagnosis is available to genetically test embryos prior to implantation. In vitro fertilization with preimplantation genetic diagnosis allows for reproductive choice prior to pregnancy.

Couples who are both carriers for SMA should consult a genetics consultant to review these reproductive options prior to conception to review the medical risks and benefits of each procedure [6].

Spinal muscular atrophy type 0 is prenatally evident and is the most severe form of the condition. Luckily, it is the rarest form. Affected infants move less in the womb, and as a result they are often born with joint contractures.

They have extremely weak muscle tone (hypotonia) at birth. Their respiratory muscles are very weak and they often do not survive late infancy due to respiratory failure. Some infants with spinal muscular atrophy type 0 also have heart conditions that are congenital.

Spinal muscular atrophy type I (Werdnig-Hoffmann disease) is the most common form of SMA. It is a severe form including muscle weakness evident at birth or within the first few months of life. Most affected children cannot control their head movements or sit unassisted. Children with this type may have swallowing problems that can lead to difficulty feeding and poor growth. They can also have breathing problems due to weakness of respiratory muscles and an abnormally bell-shaped chest that prevents the lungs from fully expanding. Most children with spinal muscular atrophy type I do not survive past early childhood due to respiratory failure.

Spinal muscular atrophy type II (Dubowitz disease) is characterized by muscle weakness that develops in children between 6 and 12 months. Children with this type can sit without support, although they may need help getting to a seated position.

However, as the muscle weakness worsens later in childhood, affected individuals may need support to sit. Individuals with this type cannot stand or walk alone. They often have involuntary trembling (tremors) in their fingers, scoliosis and respiratory muscle weakness that can be life-threatening.

The life span of individuals with spinal muscular atrophy type II varies, but many people with this condition live into their twenties or thirties.

Spinal muscular atrophy type III (Kugelberg-Welander disease) typically causes muscle weakness in late childhood. Individuals with this condition can stand and walk unaided, but after some time, walking and climbing stairs may become increasingly difficult. Many affected individuals require wheelchair assistance later in life. People with this type typically have a normal life expectancy.

Spinal muscular atrophy type IV is rare and often begins in early adulthood. Affected individuals usually experience mild to moderate muscle weakness, tremors, and mild breathing problems. People with type IV have a normal life expectancy [7].

The treatment of SMA requires a multidisciplinary team approach and should notably include neurologists, medical geneticists, physical therapists, speech pathologists, pulmonologists, respiratory therapists, medical social workers, nutritionists, psychologists and specialized nurses.

There are two main components to SMA management: treatment that slows the progression of the disease (disease-modifying therapy) and therapy that helps manage symptoms and improves quality of life (supportive therapy). Genetic counseling is recommended for affected individuals and their families.

Symptomatic therapy

The symptomatic management of SMA includes physical therapy, occupational therapy, monitoring respiratory function and intervening as clinically indicated, nutritional status monitoring and intervention, spine curvature monitoring and intervention and use of orthotics and adaptive equipment when needed.

Respiratory support for SMA type 1 (infants symptomatic prior to 6 months of age) includes providing breathing support called BiPAP (bi-level positive airway pressure) to manage hypoventilation and a mechanical insufflation-exsufflation device to support weak cough. Supportive management has been shown to increase comfort and life expectancy. Earlier in the disease, some affected infants might only require ventilation support at night.

Children with progressive respiratory insufficiency might require more invasive interventions to breathe, such as surgical placement of a breathing tube through the neck (tracheostomy). For infants and children with dysphagia, nutrition support may require gastrostomy tube placement to provide efficient nutrition safely.

Children with SMA may also require surgical intervention for musculoskeletal problems such as scoliosis and/or hip dislocation.

Disease-modifying therapy

Research efforts have led to therapies that can improve the course of SMA. The first disease-modifying therapy was approved by the U.S. Food and Drug Administration (FDA) in 2016. These therapies have shown promising results, notably developmental motor milestone achievement and improved survival in treated individuals.

In 2016, nusinersen (Spinraza) was approved by the FDA as the first drug to treat children and adults with SMA. Nusinersen is an injection administered into the fluid surrounding the spinal cord (intrathecal administration). Nusinersen acts by modifying the splicing of the *SMN2* gene product, mRNA, so that more full length and functional SMN protein is produced.

In 2019, the FDA approved onasemnogene abeparvovec-xioi (Zolgensma) for the treatment of children less than two years of age. It is a gene therapy that delivers a fully functional copy of human *SMN1* gene into the target motor neuron cells via a viral vector, AAV9. One-time intravenous

administration of the medication results in increased SMN protein in all cells including motor neurons.

In 2020, the FDA approved risdiplam (Evrysdi) to treat patients two months of age and older with SMA. Risdiplam is the first orally administered drug approved for the treatment of SMA. It has a mechanism of action to modify splicing of the *SMN2* mRNA resulting in increased SMN protein [8,9].

Conclusion

Spinal muscular atrophy is a complex disease requiring lifetime management involving a multidisciplinary team of health care providers.

It also requires effective communication between the health care team, the patient, and their family as much of the care for patients with SMA types 1 and 2 is provided at home. Although SMA types 3 and 4 may are less severe, patients and their health care providers need to be aware of how to manage this chronic disorder and optimize quality of life.

Knowing the essential assessments for monitoring disease progression, treatment outcomes, and potential complications is key to proactively caring for patients with SMA.

The availability of new targeted treatment options will likely change the natural history of this condition.

Furthermore, clinical symptom and early genetic molecular diagnosis, coupled with targeted therapies, will likely decrease the morbidity and mortality regardless of treatment strategy.

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