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Spinal Muscular Atrophy

Information for Physicians and Other Health Care Professionals

Definition

Spinal muscular atrophy (SMA) is a genetic disease that affects muscle strength and movement. There is a loss of motor neurons in the spinal cord and the brainstem which leads to atrophy of the muscles used in breathing, swallowing, crawling, walking, sitting up, and head control. This is a progressive, degenerative condition that can lead to various symptoms depending on the type of SMA, age of onset, and the severity of the muscle wasting. There are clear genotype-phenotype associations.

Clinical Symptoms

There is a broad spectrum of severity of weakness in SMA. The unifying feature is that, with only symptomatic treatment, all forms of SMA demonstrate progressive loss of muscle strength and function. Before the gene was identified and clarified that the disorders were all different phenotypes of dysfunction of the same gene, clinicians separated SMA into different clinical types:

Type 0 (most severe spinal muscular atrophy): The characteristic features include decreased fetal movements in utero, joint abnormalities, difficulty swallowing, severe weakness, hypotonia and respiratory failure at birth. Babies typically die by six months of age.

Type 1 (severe spinal muscular atrophy, Werdnig-Hoffmann disease): The characteristic clinical features include symmetric muscle weakness, lack of motor development, and poor muscle tone are the major clinical manifestations. These symptoms present before six months of age. Babies do not achieve the ability to sit and if untreated, death occurs around two years of age secondary to respiratory failure.

Type 2 (intermediate spinal muscular atrophy, Dubowitz disease): This type manifests around six months to a year of age. Babies can present with low muscle tone but are able to gradually reach milestones such as sitting. Around their teen years, tremors and progressive muscle weakness start to develop. Individuals can live into their 3rd or 4th decades. Often the major cause of morbidity is respiratory failure and musculoskeletal abnormalities such as scoliosis.

Type 3 (juvenile spinal muscular atrophy, Kugelberg-Welander disease): Individuals with this type have symptom manifestation around 18 months of age. The prominent characteristic is the ability to walk independently. Individuals may need wheelchair assistance later in life due to progressive muscle weakness and loss of ambulation. The lifespan of individuals is similar to the general population.

Type 4: The onset of muscle weakness is typically in the 2nd or 3rd decade of life. Affected individuals have mild symptoms including muscle twitching, tremor, and mild breathing problems. The life expectancy of these individuals is normal.

Neuromuscular specialists now recognize that SMA has a continuum of severity which is inversely related to the number of copies of *SMN2* producing small amounts of SMN protein. However, the relationship between *SMN2* copy number and clinical severity is not exactly linear. Therefore, *SMN2* copy count is only an approximate guide to future disease severity.

Newborn Screening and Definitive Diagnosis

In Illinois, newborn screening for SMA is performed by testing for the presence of the Survival Motor Neuron 1 (*SMN1*) gene. If newborn screening results indicate the *SMN1* gene is absent or significantly reduced in signal as compared to normal (positive result), immediate referral should be made to a pediatric multidisciplinary neuromuscular center for diagnostic testing and evaluation.

Treatment

Treatment for SMA was limited to supportive treatments relating to improving ventilation, nutrition and posture. However, the natural history of SMA with only supportive treatments is progressive loss of strength. After infantile onset, infants did not survive past two years of age without technological support of breathing or nutrition. However, in the past decade, translational science and clinical trials have led to two FDA approved drugs for treatment of SMA

Spinraza™ (nusinersen) was the first drug to be approved by the Food and Drug Administration (FDA) for the treatment of SMA for both pediatric and adult individuals. This is an antisense oligonucleotide (ASO) that facilitates pre mRNA splicing of the *SMN2* gene to increase the amount of SMN protein produced. This prevents loss of muscle strength and function in individuals with SMA. Spinraza™ is administered into the cerebrospinal fluid via an intrathecal injection first through a series of loading doses then every four months as maintenance dosing.

Zolgensma (onasemnogen abeparvovec) is an FDA-approved gene therapy treatment used to treat children less than two years of age with SMA. Zolgensma is administered as a one-time intravenous treatment. This gene replacement therapy uses adeno-associated viral capsids to enclose new, working copies of human SMN gene.

There are a number of other treatments currently under investigation for SMA.

Incidence

The incidence of SMA is 1 in 6,000 to 1 in 10,000 individuals worldwide (males and females both). This condition occurs in similar frequencies in all populations.

Inheritance Patterns

SMA is inherited in an autosomal recessive pattern. As an autosomal recessive disorder, the parents of a child with SMA are unaffected, healthy carriers of the condition and have one normal gene and one abnormal gene. With each pregnancy, carrier parents have a 25 percent chance of having a child with two

copies of the abnormal gene resulting in SMA. Carrier parents have a 50 percent chance of having a child who is an unaffected carrier and a 25 percent chance of having an unaffected, non-carrier child. These risks hold true for each pregnancy. All siblings of newborns diagnosed with SMA should receive medical evaluation and/or testing for SMA, and genetic counseling services should be offered to the family.

Pathophysiology

In SMA, the *SMN1* gene is deleted or mutated, causing there to be a deficiency of SMN protein, which is essential for motor neuron function and muscle strength. When there is absent *SMN1* function, the body relies on copies of *SMN2* to produce small amounts of SMN protein. The more copies of *SMN2* an individual has, the more likely they are to have milder symptoms.

95-98% of individuals with SMA have absent *SMN1* genes. However, a smaller percentage of individuals have a mutation in the *SMN1* gene that makes it non-functional but requires additional testing to make the diagnosis of SMA.

Key Points for Parents

Reassure parents that not all newborns identified with an abnormal newborn screening result will have disease. Additional testing and diagnostic evaluation are needed when there is an abnormal newborn screening result. Primary care providers should make certain the parents understand the importance of following the recommendations for additional testing and referrals. If a newborn is diagnosed SMA, treatment is now available and clinical trials have demonstrated that the earlier the treatment is initiated, the better the ultimate motor function is for that individual. Therefore, prompt evaluation following the abnormal newborn screen is essential.

Following Confirmation of Diagnosis

1. Follow up with the newborn's pediatric multidisciplinary neuromuscular team.
2. Recommend genetic counseling services to help the parents understand the complexity surrounding the carrier state and inheritance of this disease.
3. Provide families with resources concerning SMA including the Illinois Department of Public Health Newborn Screening Program and the local health department.

Additional information about newborn screening can be found at:

- Baby's First Test: <http://www.babysfirsttest.org/> Health Resource and Service Administration (HRSA), Grant no. U36MC16509, Quality Assessment of the Newborn Screening System.
- National Center for Biotechnology Information: <http://www.ncbi.nlm.nih.gov/gtr/> National Center for Biotechnology Information, U.S. National Library of Medicine, 8600 Rockville Pike, Bethesda, MD 20894 USA.
- NewSTEPS: <https://www.newsteps.org/> 8515 Georgia Avenue, Suite 700, Silver Spring, MD 20910 USA.
- Cure SMA: <https://www.curesma.org/> 925 Busse Road, Elk Grove Village, IL 60007 USA.
- Muscular Dystrophy Association National Office: <https://www.mda.org/> 1611 N. Clark, Suite 3550, Chicago, IL 60601 USA.