



Muscular Dystrophy New Zealand

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a genetic disorder that affects the control of muscle movement. It is caused by a loss of anterior horn cells (spinal motor neurons). Messages from the nerve cells in the brain (called upper motor neurons) are transmitted to nerve cells in the brain stem and spinal cord (called lower motor neurons) and from them to specific muscles. Upper motor neurons instruct the lower motor neurons to produce movements in the arms, legs, chest, face, throat and tongue. This loss of spinal motor neurons means that there is a lack of nerve signal from the spinal motor neurons to bunches of muscle fibres. Having no nerve signal causes these groups of muscle fibres to waste away (atrophy) which leads to weakness of muscles used for activities such as crawling, walking, sitting up, and controlling head movement. In severe cases of SMA, the muscles used for breathing and swallowing are affected. There are many types of spinal muscular atrophy distinguished by the pattern of features, severity of muscle weakness, and age when the muscle problems begin. SMA Types I – IV are different levels of severity of the same genetic defect. Xlinked spinal muscular atrophy (X-linked SMA), spinal muscular atrophy, lower extremity, dominant (SMA-LED) and adult onset spinal muscular atrophy are all caused by defects in different genes. Approximately 1 in 6,000 to 1 in 10,000 babies are born with SMA.

Features of SMA

Type I spinal muscular atrophy (also called Werdnig-Hoffman disease) is a severe form of the disorder that is evident at birth or within the first few months of life. Affected infants are developmentally delayed; most are unable to support their head or sit unassisted. Children with this type have breathing and swallowing problems that may lead to choking or gagging. It is unusual for these children to live past 2 years old.

Type II spinal muscular atrophy is characterized by muscle weakness that develops in children between ages 6 and 12 months. Children with type II can sit without support, although they may need help getting to a seated position. Individuals with this type of spinal muscular atrophy cannot stand or walk unaided.

Type III spinal muscular atrophy (also called Kugelberg-Welander disease or juvenile type) has milder features that typically develop between early childhood and adolescence. Individuals with type III spinal muscular atrophy can stand and walk

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unaided, but walking and climbing stairs may become increasingly difficult. Many affected individuals will require wheelchair assistance later in life.

The signs and symptoms of type IV spinal muscular atrophy often occur after age 30. Affected individuals usually experience mild to moderate muscle weakness, tremor, twitching, or mild breathing problems. Typically, only muscles close to the center of the body (proximal muscles), such as the upper arms and legs, are affected in type IV spinal muscular atrophy.

The features of X-linked spinal muscular atrophy appear in infancy and include severe muscle weakness and difficulty breathing. Children with this type often have joint deformities (contractures) that impair movement. In severe cases, affected infants are born with broken bones. Poor muscle tone before birth may contribute to the contractures and broken bones seen in these children.

Spinal muscular atrophy, lower extremity, dominant (SMA-LED) is characterized by leg muscle weakness that is most severe in the thigh muscles (quadriceps). This weakness begins in infancy or early childhood and progresses slowly. Affected individuals often have a waddling or unsteady walk and have difficulty rising from a seated position and climbing stairs.

Contractures are muscles or tendons that have remained too tight for too long, thus becoming shorter. Once they occur they cannot be stretched or exercised away.

An adult-onset form of spinal muscular atrophy that begins in early to mid-adulthood affects the proximal muscles and is characterized by muscle cramping of the limbs and abdomen, weakness in the leg muscles, involuntary muscle contractions, tremors, and a protrusion of the abdomen thought to be related to muscle weakness. Some affected individuals experience difficulty swallowing and problems with bladder and bowel function.



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Diagnosis of SMA

The diagnosis of spinal muscular atrophy (SMA) is established in individuals with the following:

- A history of motor difficulties
- Evidence of motor unit disease on physical examination
- Mutation detected in the SMN1 gene

SMA I

- Onset age 0-6 months
- Poor muscle tone
- Muscle weakness
- Lack of motor development; ability to sit without support never achieved
- Facial weakness: minimal or absent
- Small local involuntary contractions of the tongue: seen in most but not all affected individuals
- Postural tremor of the fingers: seen occasionally
- Mild contractures: often at the knees, rarely at the elbows
- Absence of tendon reflexes
- No sensory loss
- Alert appearance
- Normal cerebral function including intellect

SMA II

- Onset of muscle weakness usually after age six months; ability to sit independently achieved when placed in a sitting position
- Finger trembling: almost invariably present
- Low muscle tone (flaccidity)
- Absence of tendon reflexes in approximately 70% of individuals
- Average intellectual skills during the formative years and above average by adolescence

SMA III

- Onset usually after age ten months, in some cases earlier; ability to walk at least 25 meters achieved
- Weakness manifests as frequent falls or trouble walking up and down stairs at age two to three years
- Proximal limb weakness; the legs more severely affected than the arms



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SMA IV

- "Adult" onset of muscle weakness

X-Linked SMA

The diagnosis of X-linked infantile spinal muscular atrophy (XL-SMA) should be considered in children who meet the following criteria:

- Stiff joints and muscles and below normal or absent reflexes from birth on physical examination
- Born with tight muscles that can't be lengthen and/or fractures
- Curled fingers that can't be straighten at birth. These usually remain throughout the child's life.
- Evidence of degeneration and loss of anterior horn cells (i.e., lower motor neurons) in the spinal cord and brain stem
- Normal SMN1 molecular genetic testing to rule out autosomal recessive spinal muscular atrophy
- One affected male only or X-linked pattern of inheritance in families with more than one affected individual

Causes of SMA

SMA Types I-IV lack a protein called survival motor neuron protein (SMN). The reduced amounts of this protein result in the spinal motor neurons not being maintained properly and they die. Because specific groups of muscle fibres are no longer being stimulated they also die resulting in muscles wasting (atrophy). SMN is controlled by two genes known as SMN1 and SMN2. The gene called SMN1 is the primary source of this protein and defects in this gene causes SMA types I – IV. The SMN2 gene makes variants of SMN but only one is full size and functional. People with SMA type II – IV have multiple copies of the SMN2 gene. The extra amounts of survival motor neuron protein produced by the 3 or more extra copies of the less efficient gene has a protective effect and the severity of the condition is reduced.

X-Linked SMA is caused by a defect in a gene called UBA1 which codes for the Ubiquitin-Like Modifier Activating Enzyme. This enzyme helps our cells break down proteins and repair our DNA. Not having this enzyme results in the same symptoms as SMA Type I and is considered a severe early onset type of SMA.



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SMA – LED is caused by a defect in a protein that forms part of a group of proteins called dynein. The gene that codes for this is called DYNC1H1. When there is a mutation in the DYNC1H1 gene the movement of proteins, cellular structures, and other materials within cells are impaired. A decrease in chemical messaging between neurons that control muscle movement is thought to contribute to the muscle weakness experienced by people with SMA-LED. It is unclear why this condition affects only the lower extremities.

The adult-onset form of spinal muscular atrophy is caused by a mutation in the VAPB gene. The VAPB gene provides instructions for making a protein that is found in cells throughout the body. Researchers suggest that this protein may play a role in preventing the build-up of unfolded or misfolded proteins within cells. It is unclear how a VAPB gene mutation leads to the loss of motor neurons. An impaired VAPB protein might cause misfolded and unfolded proteins to accumulate and impair the normal function of motor neurons. The slow build of these proteins accounts for the late age of onset.

Genetics of SMA

SMA Types I – IV are an inherited disease caused by a defect in the gene SMN1 which tells the body how to make survival motor neuron protein. We each have two copies of this gene in each cell. To be affected with the condition both copies need to be defective. This specific type of inheritance is called recessive. Each parent has one functional gene which is sufficient to avoid symptoms. Each parent is known as a carrier of the condition. Two carrier parents have a 1 in 4 chance (25%) in each pregnancy of having a child affected with the condition. In SMA approximately 2% of people with the condition have a new defect in one of their genes. In this situation only one parent is a carrier and the other defect occurred randomly within the individual. This is called a de novo mutation (new and not inherited).

The sex chromosomes X and Y determine if a baby will be a boy or a girl. X-Linked SMA is caused by a defect in the UBA1 gene on the X chromosome. One functioning copy is enough to prevent X-Linked SMA. Girls receive an X from mum and an X from dad and are described as XX. Boys receive a Y from dad and an X from mum and are described as XY. As boys have only one X chromosome if they inherit an X chromosome with the defective UBA1 gene then they will have X-Linked SMA. The mother is described as a carrier and with one functioning UBA1 gene is usually unaffected. A carrier mother has a 25% chance in each pregnancy of having an affected male child. SMA- LED defect in the DYNC1H1 gene is inherited in an autosomal dominant manner. This means that

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men and women are equally likely to be affected and that an affected person has a 50% chance in each pregnancy that their child will also be affected.

Family studies indicate that late onset SMA caused by a defect in the VAPB gene is inherited in autosomal dominant fashion in the same way as SMA-LED.

Genetic counseling is available to families who have had a diagnosis of SMA (as there are several different inheritance patterns it is important that the diagnosis is correct). This service provides information, helps families understand inheritance patterns and what this means in their family, as well as enabling people to make more informed family-planning decisions.

Management of SMA

Because poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures are common complications management revolves around treatment of the different presentations of these.

When nutrition is a concern in SMA, placement of a gastrostomy tube is appropriate. As respiratory function deteriorates, tracheotomy or noninvasive respiratory support is offered. Sleep-disordered breathing can be treated with nighttime use of continuous positive airway pressure. Surgery for scoliosis in individuals with SMA II and SMA III can be carried out safely if the forced vital capacity is greater than 30%-40%. A power chair and other equipment may improve quality of life.

Surveillance: Evaluation every six months or more frequently for children who are weak to assess nutritional state, respiratory function, and orthopedic status (spine, hips, and joint range of motion) is recommended.

For X-linked : Assure adequate caloric intake by caloric supplementation and/or gastrostomy feedings as necessary; manage constipation with diet; provide rigorous clearing of the airways, supplemental oxygen, and non-invasive ventilator support; Respiratory failure is common. Make use of orthopaedic consultation and physical and occupational therapy to manage muscle contractures.



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Research into treatments for SMA

Antisense oligonucleotide treatment. An antisense oligonucleotide (ASO) called ASO-10-27 has corrected the less effective SMN2 gene and restored SMN expression in mice motor neurons after intracerebroventricular injection. An open-label Phase I clinical trial completed in individuals with SMA type II-III showed that this drug could be delivered directly to the cerebral spinal fluid via lumbar puncture in this population with acceptable tolerability leading to two additional clinical studies: one with multiple doses in individuals with SMA type II-III and one in infants with SMA type I. Trials are currently underway and results are not yet available.

Quinazoline-related compounds. A cell-based high-throughput screening program has identified a class of pharmaceutical compounds referred to as quinazoline derivatives. These compounds increased SMN protein levels and nuclear gem numbers in cells derived from affected individuals. Oral administration of three quinazoline-related compounds to neonatal mice has shown a dose-dependent increase in SMN promoter activity. Further, delivery of these compounds to SMA mice significantly increased the mean life span by approximately 21%-30%. This finding led to a recently completed Phase Ia trial in healthy volunteers; results are not yet available.

Hydroxyurea is a medication that enhances expression of the human gene encoding fetal hemoglobin. Treatment of cells from individuals with SMA with hydroxyurea resulted in an increase in SMN protein levels and intranuclear protein levels. Clinical trials with hydroxyurea in SMA are underway.

Sources

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