Spinal Muscular Atrophy

U.S. DEPARTMENT OF HEALTHAND
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What is spinal muscular atrophy?

Spinal muscular atrophy (SMA) is a group of hereditary diseases that progressively destroys motor neurons—nerve cells in the brain stem and spinal cord that control essential skeletal muscle activity such as speaking, walking, breathing, and swallowing, leading to muscle weakness and atrophy. Motor neurons control movement in the arms, legs, chest, face, throat, and tongue. When there are disruptions in the signals between motor neurons and muscles, the muscles gradually weaken, begin wasting away and develop twitching (called *fasciculations*).

What causes SMA?

The most common form of SMA is caused by defects in both copies of the survival motor neuron 1 gene (SMN1) on chromosome 5q. This gene produces the survival motor neuron (SMN) protein which maintains the health and normal function of motor neurons. Individuals with SMA have insufficient levels of the SMN protein, which leads to loss of motor neurons in the spinal cord, producing weakness and wasting of the skeletal muscles. This weakness is often more severe in the trunk and upper leg and arm muscles than in muscles of the hands and feet.

There are many types of spinal muscular atrophy that are caused by changes in the same genes. Less common forms of SMA are caused by mutations in other genes including the VAPB gene located on chromosome 20, the DYNC1H1 gene on chromosome 14, the BICD2 gene on chromosome 9, and the UBA1 gene on the X chromosome. The types differ in age of onset and severity of muscle weakness; however, there is overlap between the types.

How is it inherited?

Except in the rare cases caused by mutations in the UBA1 gene, SMA is inherited in an *autosomal recessive* manner, meaning that the affected individual has two mutated genes, often inheriting one from each parent. Those who carry only one mutated gene are carriers of the disease without having any symptoms. Autosomal recessive diseases may affect more than one person in the same generation (siblings or cousins).

What are the types of SMA?

There is a wide range of impairment seen in SMA caused by defects in the SMN1 gene, from onset before birth with breathing difficulties at birth to mild weakness in adults. Accordingly, this most common form of SMA can be classified into four types, based on highest motor milestone achieved.

- **SMA type I, also called Werdnig-Hoffmann disease or infantile-onset SMA**, is evident usually before 6 months of age. The most severely affected infants have reduced

movements even in utero and are born with contractures (chronic shortening of muscles or tendons around joints) and breathing difficulties, with death occurring in the first year of life without treatment. Symptoms of SMA type I include hypotonia (reduced muscle tone), diminished limb movements, lack of tendon reflexes, fasciculations, swallowing and feeding difficulties, and impaired breathing. These children also develop scoliosis (curvature of the spine) or other skeletal abnormalities as they get older. Without any treatment, affected children never sit or stand and the vast majority usually die of respiratory failure before the age of 2 years. Children with SMA type I now live longer and can reach higher motor milestones like sitting and even walking with more proactive clinical care and newly available disease modifying treatment.

- Children with **SMA type II, the intermediate form**, usually show their first symptoms between 6 and 18 months of age although some can present earlier. They are able to sit without support but are unable to stand or walk unaided, and some may lose the ability to stay seated independently over time without treatment. They may have respiratory difficulties including hypoventilation (breathing at an abnormally slow rate) in sleep. The progression of disease is variable without treatment. Life expectancy is reduced but most individuals live into adolescence or young adulthood. With disease modifying treatment and proactive clinical care, children with SMA type II have improved motor outcomes.

- Children with **SMA type III (Kugelberg-Welander disease)** develop symptoms after 18 months of age and can walk independently. They first show difficulty walking and running, climbing steps, or rising from a chair. The proximal leg muscles (muscles closest to the body) are most often affected first, with a tremor seen in the hands. Complications include scoliosis and joint contractures caused by abnormal muscle tone and weakness, which prevents the joints from moving freely. Individuals with SMA type III may be prone to respiratory infections, but with care most have a normal lifespan. Disease modifying treatment can improve outcomes.
- **Individuals with SMA type IV** develop symptoms after 21 years of age, with mild to moderate proximal muscle weakness and other symptoms.

How is SMA diagnosed?

A blood test is available to look for deletions or mutations of the SMN1 gene. This test identifies at least 95 percent of SMA Types I, II, and III and may also reveal if a person is a carrier of a defective gene that could be passed on to children. If the SMN1 gene is not found to be abnormal or the individual's history and examination are not typical of SMA, other diagnostic tests may include electromyography (which records the electrical activity of the muscles during contraction and at rest), nerve conduction velocity studies (which measure the nerve's ability to send an electrical signal), muscle biopsy (used to diagnose many neuromuscular disorders), and other blood tests.

Are there treatments for SMA?

There is no complete cure for SMA. Treatment consists of managing the symptoms and preventing complications.

In December 2016 the U.S. Food and Drug Administration (FDA) approved nusinersen (Spinraza™) as the first drug approved to treat children and adults with SMA. The drug is administered by injection into the fluid surrounding the spinal cord. It is designed to increase production of the full-length SMN protein, which is critical for the maintenance of motor neurons. The benefit is best documented in infants and children, particularly when started early.

In May 2019 the FDA approved onasemnogene abeparovec-xioi (Zolgensma™) gene therapy for children less than 2 years old who have infantile-onset SMA. A safe virus delivers a fully functional human SMN gene to the targeted motor neurons, which in turn improves muscle movement and function, and also improves survival.

Several other therapies are in late stages of development and may become available to affected individuals in the near future.

Physical therapy, occupational therapy, and rehabilitation may help to improve posture, prevent joint immobility, and slow muscle weakness and atrophy. Stretching and strengthening exercises may help reduce contractures, increase range of motion, and keeps circulation flowing. Some individuals require additional therapy for speech and swallowing difficulties. Assistive devices such as supports or braces, orthotics, speech synthesizers, and wheelchairs may be helpful to improve functional independence.

Proper nutrition and calories are essential to maintaining weight and strength, while avoiding prolonged fasting. People who cannot chew or swallow may require insertion of a feeding tube. Non-invasive ventilation at night can improve breathing during sleep, and some individuals also may require assisted ventilation during the day due to muscle weakness in the neck, throat, and chest.

What is the prognosis?

Prognosis varies depending on the type of SMA. Some forms of SMA are fatal without treatment.

People with SMA may appear to be stable for long periods, but improvement should not be expected without treatment.

What research is being done?

The National Institute of Neurological Disorders and Stroke (NINDS), a component of the National Institutes of Health (NIH), conducts basic, translational, and clinical research on SMA in laboratories at the NIH and also supports research through grants to major medical institutions across the country.

Cellular and molecular studies seek to understand the mechanisms that trigger motor neurons to degenerate.

Scientists have analyzed human tissue and developed a broad range of model systems in animals and cells to investigate disease processes and expedite the testing of potential therapies. Among these efforts:

- Gene therapy and specific drugs have been shown to halt motor neuron destruction

and slow disease progression in mouse models and individuals with SMA. NINDS has supported research to establish these methods and to provide a path toward clinical tests in patients. Clinical trials for gene therapy in SMA are ongoing.

- Animal models of SMA represent critical tools in discovering and developing new therapies for SMA. Scientists have developed zebrafish, mouse, and pig models, including models of less severe SMA types II and III, which may greatly aid the identification of new therapeutic targets and candidate therapies.

NIH-supported scientists have collected longitudinal data on pre-symptomatic or recently diagnosed children with SMA types I, II, or III and their healthy siblings. The goal of this study is to provide counselling and education to the parents about possible clinical trial opportunities.

NINDS established the NeuroNext (NINDS Network for Excellence in Neuroscience Clinical Trials) clinical trials network to promote the rapid development and implementation of trials for neurological disorders that affect adults and/or children. Among its goals, the network is designed to develop early-phase trials aimed at identifying biomarkers—usually a physical trait or substance in the blood or other bodily fluids that can be measured to determine the presence and severity of a disease—and testing promising, emerging therapies. One project was to identify biomarkers for SMA and to understand the cause and mechanisms underlying the disease. The natural history

data obtained through this study led to the approval decision for nusinersen. Knowledge gained from this study has enhanced the design of additional clinical trials in SMA.

Where can I get more information?

For more information on neurological disorders or research programs funded by the National Institute of Neurological Disorders and Stroke, contact the Institute's Brain Resources and Information Network (BRAIN) at:

BRAIN
P.O. Box 5801
Bethesda, MD 20824
800-352-9424
www.ninds.nih.gov

Information also is available from the following organizations:

CureSMA
925 Busse Road
Elk Grove Village, IL 60007
847-367-7620
800-886-1762
www.curesma.org

Spinal Muscular Atrophy Foundation
126 East 56th Street, 30th Floor
New York, NY 10022
646-253-7100
877-386-3762
www.smafoundation.org

Muscular Dystrophy Association
161 N. Clarke, Suite 3550
Chicago, IL 60601
800-572-1717
www.mda.org

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