Spinal Muscular Atrophy

What is spinal muscular atrophy?

Spinal muscular atrophy (SMA) is one of several hereditary diseases that progressively destroy lower motor neurons—nerve cells in the brain stem and spinal cord that control essential voluntary muscle activity such as speaking, walking, breathing, and swallowing. Lower motor neurons control movement in the arms, legs, chest, face, throat, and tongue.

When there are disruptions in the signals between lower motor neurons and muscles, the muscles gradually weaken and may begin wasting away and develop uncontrol-lable twitching (called fasciculations). When there are disruptions in the signals between the upper motor neurons (located in the brain) and the lower motor neurons, the limb muscles develop stiffness (called spasticity), movements become slow and effortful, and tendon reflexes such as knee and ankle jerks become overactive. Over time, the ability to control voluntary movement can be lost.

What causes SMA?

SMA is caused by defects in the gene SMN1, which makes a protein that is important for the survival of motor neurons (SMN protein). In SMA, insufficient levels of the SMN protein
lead to degeneration of the lower motor neurons, 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.

**How is it inherited?**

SMA disorders in children are inherited in an autosomal recessive manner. Autosomal recessive means the child must inherit a copy of the defective gene from both parents. These parents are likely to be asymptomatic (without symptoms of the disease). Autosomal recessive diseases often affect more than one person in the same generation (siblings or cousins).

Kennedy’s disease, an adult form of SMA, is X-linked inherited, which means the mother carries the defective gene on one of her X chromosomes and passes the disorder along to her sons. Males inherit an X chromosome from their mother and a Y chromosome from their father, while females inherit an X chromosome from each parent. Daughters have a 50 percent chance of inheriting their mother’s faulty X chromosome and a safe X chromosome from their father, which would make them asymptomatic carriers of the mutation.

**What are the types of SMA?**

SMA in children is classified into three types, based on ages of onset, severity, and progression of symptoms. All three types are caused by defects in the SMN1 gene.

- **SMA type I**, also called *Werdnig-Hoffmann disease or infantile-onset SMA*, is evident by the time a child is 6 months old. Symptoms
may include hypotonia (severely reduced muscle tone), diminished limb movements, lack of tendon reflexes, fasciculations, tremor, swallowing and feeding difficulties, and impaired breathing. Some children also develop scoliosis (curvature of the spine) or other skeletal abnormalities. Affected children never sit or stand and the vast majority usually die of respiratory failure before the age of 2. However, the survival rate in individuals with SMA type I has increased in recent years, in relation to the growing trend toward more proactive clinical care.

- Symptoms of **SMA type II, the intermediate** form, usually begin between 6 and 18 months of age. Children may be able to sit without support but are unable to stand or walk unaided, and may have respiratory difficulties, including an increased risk of respiratory infections. The progression of disease is variable. Life expectancy is reduced but some individuals live into adolescence or young adulthood.

- Symptoms of **SMA type III (Kugelberg-Welander disease)** appear between 2 and 17 years of age and include abnormal gait; difficulty running, climbing steps, or rising from a chair; and a fine tremor of the fingers. The lower extremities are most often affected. Complications include scoliosis and joint contractures—chronic shortening of muscles or tendons around joints, 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 may have a normal lifespan.
Other forms of SMA include:

- **Congenital SMA with arthrogryposis** (persistent contracture of joints with fixed abnormal posture of the limb) is a rare disorder. Manifestations include severe contractures, scoliosis, chest deformity, respiratory problems, unusually small jaws, and drooping of the upper eyelids.

- **Kennedy’s disease**, also known as progressive spinobulbar muscular atrophy, may first be recognized between 15 and 60 years of age. The onset of symptoms varies and includes weakness and atrophy of the facial, jaw, and tongue muscles, leading to problems with chewing, swallowing, and changes in speech. Early symptoms may include muscle pain and fatigue. Weakness in arm and leg muscles closest to the trunk of the body develops over time, with muscle atrophy and fasciculations. Individuals with Kennedy’s disease also develop sensory loss in the feet and hands. Nerve conduction studies confirm that nearly all individuals have a sensory neuropathy (pain from sensory nerve inflammation or degeneration). Affected individuals may have enlargement of the male breasts or develop noninsulin-dependent diabetes mellitus.

**How is SMA diagnosed?**

A blood test is available that can indicate whether there are deletions or mutations of the SMN1 gene. This test identifies at least 95 percent of SMA Types I, II, and III. Other diagnostic tests may include electromyography (which records the electrical activity from the brain and/or spinal cord to a peripheral
nerve root found in the arms and legs that controls muscles during contraction and at rest), nerve conduction velocity studies (which measure electrical energy by assessing the nerve’s ability to send a signal), muscle biopsy (used to diagnose neuromuscular disorders and may also reveal if a person is a carrier of a defective gene that could be passed on to children), and laboratory tests of blood, urine, and other substances.

Are there treatments for SMA?

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

Muscle relaxants such as baclofen, tizanidine, and the benzodiazepines may reduce spasticity. Botulinum toxin may be used to treat jaw spasms or drooling. Excessive saliva can be treated with amitriptyline, glycopyolate, and atropine or by botulinum injections into the salivary glands. Antidepressants may be helpful in treating depression.

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 spasticity, increase range of motion, and keeps circulation flowing. Some individuals require additional therapy for speech, chewing, and swallowing difficulties. Applying heat may relieve muscle pain. Assistive devices such as supports or braces, orthotics, speech synthesizers, and wheelchairs may help some people retain independence.
Proper nutrition and a balanced diet are essential to maintaining weight and strength. People who cannot chew or swallow may require insertion of a feeding tube. Non-invasive ventilation at night can prevent apnea in sleep, and some individuals may also require assisted ventilation due to muscle weakness in the neck, throat, and chest during daytime.

What is the prognosis?

Prognosis varies depending on the type of SMA. Some forms of SMA are fatal.

The course of Kennedy’s disease varies but is generally slowly progressive. Individuals tend to remain ambulatory until late in the disease. The life expectancy for individuals with Kennedy disease is usually normal.

People with SMA may appear to be stable for long periods, but improvement should not be expected.

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 are developing a broad range of model systems in animals and cells to investigate
disease processes and expedite the testing of potential therapies. Among these efforts:

- Scientists have used gene therapy to halt motor neuron destruction and slow disease progression in mouse models of SMA. The NINDS supports research to further explore this method and to provide a path toward clinical tests in patients.

- Scientists have found that a specific class of compounds referred to as anti-sense oligonucleotides can either block or correct the processing of RNA molecules, which are the intermediates between genes and proteins. These compounds have shown therapeutic promise in model systems of SMA.

- Animal models of SMA represent critical tools in discovering and developing new therapies for SMA. Scientists have developed new zebrafish, mouse, and pig models, including models of less severe SMA types 2 and 3, which may greatly facilitate the identification of new therapeutic targets and candidate therapies.

NINDS has established the NeuroNext 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 of the first projects in this new network will hope to identify biomarkers for SMA, which could speed the development of effective treatments for the disease.
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:

Fight SMA
1321 Duke Street, Suite 304
Alexandria, VA 22314
703-299-1144
www.fightsma.org

Families of Spinal Muscular Atrophy
925 Busse Road
Elk Grove Village, IL 60007
847-367-7620
800-886-1762
www.curesma.org

Muscular Dystrophy Association
3300 East Sunrise Drive
Tucson, AZ 85718-3208
520-529-2000
800-572-1717
www.mda.org

Spinal Muscular Atrophy Foundation
888 Seventh Avenue, Suite 400
New York, NY 10019
646-253-7100
877-FUND-SMA (386-3762)
www.smafoundation.org