SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is an inherited disease. It robs people of physical strength by affecting the motor nerves in the spinal cord, causing muscle weakness and atrophy (wasting). These motor nerve cells control muscles used for breathing, crawling, walking, head and neck control, and swallowing.

FACTS:

- SMA is a rare disorder affecting approximately 1 in every 11,000 births.
- Approximately 1 in 50 people carry one non-working gene for SMA and do not have symptoms.
- SMA is an autosomal recessive disease.
- An affected person has 2 non-working genes for SMA, one from each parent.

SMA is caused by a mutation in the survival motor neuron gene 1 (SMN1). In a healthy person, this gene produces a protein that is critical to the function of the nerves that control the muscles. Without it, those nerve cells cannot properly function and eventually die, leading to debilitating and sometimes fatal muscle weakness. In SMA, a backup gene, survival motor neuron gene 2 (SMN2), also produces the SMN protein, but is less efficient than SMN1. The number of SMN2 copies has an impact on motor function, in that fewer SMN2 gene copies are associated with greater weakness, but there are exceptions.

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SMA affects muscles throughout the body. In the most common types of SMA, the legs are weaker than the arms. Also, the muscles for feeding, swallowing, and breathing are weak, which can cause difficulty eating and gaining weight. Due to weak breathing muscles, coughing and taking big breaths can also be difficult, especially during sleep. When experiencing colds or respiratory infections, individuals with SMA have a higher risk for pneumonia and may have difficulty breathing due to muscle weakness and increased fatigue. However, the brain's ability to think and the body's ability to feel touch and pain are not affected.

Individuals with SMA are often classified into four types based on the age when symptoms began and the highest level of motor milestone development. Typically, individuals with SMA have progressive loss of motor function starting when symptoms begin.

Type 1 SMA

Onset: Before 6 months
Milestones: No sitting

Type 2 SMA

Onset: 6 - 18 months
Milestones: Sitting, not walking

Type 3 SMA

Onset: Childhood after 12 months
Milestones: Walking

Type 4 SMA

Onset: After 30 years old
Milestones: Normal

SMA affects individuals differently. Symptoms that begin in childhood may have different levels of severity and rates of progression. There may be improvements in some abilities and losses in others. Some individuals with SMA may present as adults with mild symptoms, which may progress very slowly. Since the introduction of treatments for SMA in recent years, this classification of types is shifting and the course of the disease is changing. This means that the experience of SMA for an individual depends on their time of diagnosis, their genetics, if and when treatment is started, and the severity of SMA symptoms when treatment is given. Early diagnosis and treatment are associated with better outcomes. SMA care and symptom management is based on level of function as non-sitters, sitters, and walkers.

SMA TYPE CLASSIFICATION PRIOR TO SMA TREATMENTS (2016)

TYPE	AGE AT SYMPTOM ONSET	INCIDENCE	PREVALENCE	MAXIMUM MOTOR FUNCTION ACHIEVED	SMN2 COPY NUMBER	LIFE EXPECTANCY
0	IN UTERO	<1%	<1%	NONE; DECREASED FETAL MOVEMENT; CONTRACTURES AT BIRTH	**1**	Days-Weeks
1	<6 MONTHS	60%	15%	NEVER SITS INDEPENDENTLY	1,**2**,3	<2 Years
2	6-18 MONTHS	25%	70%	SITS INDEPENDENTLY	2,**3**,4	20-40 Years
3	1.5-10 YEARS	15%	15%	WALKS, THEN REGRESSION	**3**,**4**,5	Normal
4	>35 YEARS	<1%	<1%	SLOW DECLINE	**4,5**	Normal

Table 1 highlights clinical classification of SMA pre-gene modifying therapy, correlating SMA type with age at symptom onset, and maximum motor function achieved. Bold numbers indicate the most common number of SMN2 copies for each type.

Table modified from SMA Europe and TREAT-NMD (2016). Briefing Document to the Clinical Trial Readiness in Spinal Muscular Atrophy (SMA) SMA Europe, TREAT-NMD and European Medicines Agency meeting. London: European Medicines Agency. *

***https://www.ema.europa.eu/en/documents/other/briefing-document-clinical-trial-readiness-spinal-muscular-atrophy-sma-sma-europe-treat-nmd-european_en.pdf**

NON-SITTERS/TYPE 1

While learning about categories of function, keep in mind that people may change categories over time with SMA treatments. Individuals who cannot sit on their own are functionally classified as non-sitters. Non-sitters are the most severely affected by SMA. Individuals who are non-sitters have early onset of symptoms by 6 months of age or younger, and most likely have fewer copies of the SMN2 gene.

Individuals with SMA who cannot sit may experience the following:

- Fatigue.
- Decreased to no head control.
- Decreased movement of arms and legs.
- Quiet cry.
- Difficulty speaking.
- Twitchy tongue (fasciculations).
- Sweaty during sleep.
- Difficulty feeding and swallowing. May choke on or inhale food or drink. After eating or drinking breathing may sound wet or rattley in the throat and chest. In this case, a feeding tube is used to provide nutrition safely.
- Constipation.
- Small chest.
- Fast belly breathing.
- Weak cough.
- Breathing muscle weakness. Equipment is available to assist with breathing and coughing, and to monitor breathing.
- Spine curvature (scoliosis).
- Hip dislocation.
- Weak bones that could possibly break easily. Vitamin D and Calcium intake should be optimized.

SITTERS/TYPE 2

Individuals who have the ability to sit upright and unsupported are functionally classified as sitters. Some may require assistance getting into a seated position.

Individuals with SMA who can sit without assistance, but do not walk, may also experience:

- Fatigue.
- Decreased movement of arms and legs.
- Twitchy tongue (fasciculations).
- Sweaty during sleep.
- Difficulty eating enough food by mouth to maintain weight and growth. In this case, a feeding tube (temporary or permanent) may become necessary.
- Constipation.
- Smaller chest.
- Difficulty coughing especially during a cold due to increased fatigue and weakness.
- Breathing muscle weakness. Equipment is available to assist with breathing and coughing, and to monitor breathing.
- Spine curvature (scoliosis).
- Hip dislocation.
- Weak bones that could possibly break easily. Vitamin D and calcium intake should be optimized.
- Use of a wheelchair, either motorized or manual.

WALKERS/TYPE 3

Individuals with SMA who have the ability to stand and walk, either independently or with assistance, are referred to as walkers.

These individuals who can walk may experience:

- Fatigue.
- Difficulty walking, running, and climbing stairs. Some will lose the ability to walk independently, while others may remain able to walk with or without SMA drug treatments.
- Spine curvature (scoliosis).
- Weakness of the breathing muscles during illness or associated with anesthesia. Breathing may become weaker in adulthood.
- Shaking and twitching (tremors) of the fingers and hands and other muscles.
- Symptoms of joint and muscle aches and overuse.
- Weak bones that could possibly break easily. Optimizing Vitamin D and calcium can help strengthen bones.

ADULT ONSET/TYPE 4

These are individuals with SMA who develop symptoms after 18 years of age. Most commonly symptoms begin after 35 years of age. The impact on breathing, musculoskeletal systems, and individual nutrition tends to be mild. Motor weakness typically progresses more slowly.

Individuals with adult onset SMA may experience:

- Fatigue.
- Shaking or twitching (tremors) of the fingers and hands or other muscles.
- Muscle discomfort and achiness.
- Weakening bones that could possibly break easily. Optimizing Vitamin D and calcium can also help strengthen bones.

DIAGNOSIS

Individuals with SMA can be diagnosed in the following ways:

- Pre-natal genetic testing.
- Newborn screening.
- Clinical presentation/symptoms confirmed by genetic testing.

Earlier diagnosis allows early opportunity for treatment. With increased access to pre-natal genetic testing, more individuals may be diagnosed before birth.

As of 2018, the United States federal government added SMA to the Recommended Uniform Screening Panel (RUSP), a list of 35 core conditions that all newborns in the U.S. are recommended to be screened for. Each state determines which conditions will be added to newborn screening. A positive newborn screen for SMA triggers follow-up genetic testing. Newborn screening allows for early treatment of SMA, before symptoms are present. It is important to note that up to 5% of all individuals with SMA will not be identified by newborn screening for SMA. If SMA is suspected and SMN1 testing shows one copy of SMN1, SMA gene sequencing can be ordered by your physician to further test for SMA.

In the absence of newborn screening, or lack of a positive newborn screen result, SMA is diagnosed based on signs and symptoms of muscle weakness. SMA may be suspected when individuals are noted to be weak, or to have a delay or loss of their developmental milestones. In children, these developmental milestones include: holding their head up, rolling over, sitting independently, standing, or walking later than would be expected. In adolescents and adults, SMA may be suspected when individuals experience a loss of motor function. After a thorough medical history is reviewed and a physical exam is performed, the healthcare provider should order SMA genetic testing through a blood sample, and an individual may be referred to a neuromuscular specialist.

In some cases, it is difficult to diagnose SMA, particularly in the milder forms. Similar symptoms may mimic other neurologic disorders.