CURE SMA

CARE SERIES BOOKLET

GUIDE FOR HEALTHCARE PROVIDERS

WHAT YOU NEED TO KNOW AND DO ABOUT AN SMA DIAGNOSIS

cure SMA

Make today a breakthrough.

Dear Healthcare Provider,

You are likely receiving this guide because one of your patients is suspected to have spinal muscular atrophy (SMA) following newborn screening. SMA is a rare genetic condition that many health professionals never see.

This guide is intended to provide you with a foundation for understanding SMA. Here are the most important things to know:

- Treatment is available
- You may need to act quickly

Do not wait for signs of SMA to consider treatment options with your patient's parents or caregivers. If you wait until you notice the muscle weakness that is the hallmark sign of SMA, your patient will have already lost some function that may never be regained.

We have resources beyond this guide available and ways to connect you to other experts. Contact us for information, guidance, and support.

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Make today a breakthrough.

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WHAT'S INSIDE

"We want to make sure we understand the impact of the disease and what patients prioritize in the treatment of their disease."

– Dr. Billy Dunn MD, Director, Division of Neurology Products, CDER, FDA

SPINAL MUSCULAR ATROPHY
OVERVIEW

Spinal muscular atrophy (SMA) is a genetic neuromuscular disease characterized by weakness of the skeletal and respiratory muscles. SMA is a rare disorder occurring in about 1 in 11,000 births and is inherited in an autosomal recessive manner. About 1 in 50 Americans are genetic carriers. Historically, SMA has been the most frequent genetic cause of death in infants.

SMA is caused by a missing or faulty gene, the survival motor neuron 1 (SMN1) gene; this is the gene that encodes SMN protein. SMN protein is critical to the health and survival of motor neurons.

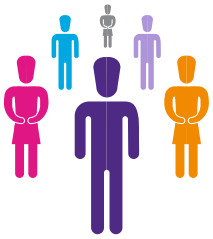
FREQUENCY

After cystic fibrosis, SMA is the most common fatal autosomal recessive disease in the United States.

SMA is the most common genetic cause of infant death.

INCIDENCE

1 in 11,000 live births.



PREVALENCE

About 10,000 to 12,000 individuals in the United States.

CARRIER FREQUENCY

1 in 50 individuals.

THE CAUSE OF SPINAL MUSCULAR ATROPHY

SMA is caused by homozygous deletions or mutations in the survival motor neuron 1, or SMN1, gene. The SMN1 gene is typically responsible for the body's production of SMN protein, which is needed throughout the body but is particularly important to the function of motor neurons. Without SMN protein, motor neurons progressively degenerate and eventually die, leading to muscle atrophy.

SMA TYPES

Before newborn screening was available for SMA, doctors diagnosed patients after they presented with symptoms and then categorized the disease into four main types depending on the age when symptoms first appeared and the highest motor milestone the patient had achieved. Now that newborns can be diagnosed before they have symptoms, types may not always be used in diagnosing SMA. It may still be useful, nonetheless, to be familiar with the different types of SMA, especially in cases where a patient has a mutation in the SMN1 gene not identified through newborn screening.

TYPE I

Also known as Werdnig-Hoffmann disease or infantile SMA. SMA type I is the most severe and most common form of SMA, with symptoms of hypotonia appearing within six months after birth. Babies with SMA type I cannot perform tasks like rolling over or sitting on their own and, if untreated, often die before age two years.

TYPE II

Also known as intermediate SMA. Onset of symptoms (such as delayed motor milestones and muscle weakness) occurs between age six and 18 months. Children with SMA type II can typically sit up without help, but they're never able to stand, and they require wheelchairs.

TYPE III

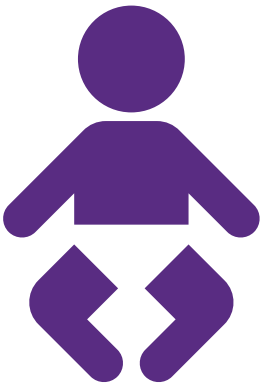
Also called Kugelberg-Welander disease or juvenile SMA. SMA type III is usually diagnosed when a child is between 18 months and three years old but may be diagnosed as late as the teen years. Patients with SMA type III are able to walk on their own but may lose that ability over time.

TYPE IV

SMA type IV is very rare. Onset occurs during adulthood and leads to mild muscle weakness. While symptoms can begin as early as age 18, they usually begin after age 35, and life expectancy is equal to that of an unaffected individual.

DIAGNOSING
SPINAL MUSCULAR ATROPHY

Some states began screening newborns for SMA in 2018. Parents of babies who screen positive receive a notice that their baby likely has SMA. Newborn screening can detect when both SMN1 genes are deleted, which accounts for more than 95% of cases of SMA. In the remaining 5% of cases, SMA is caused by a mutation rather than an SMN1 deletion. In these rare cases, SMA cannot be identified via newborn screening and must be diagnosed clinically.



SMA AFFECTS APPROXIMATELY 1 *IN* 11,000 & AFFECTS ANY GENDER OR RACE

The addition of SMA to newborn screening panels has greatly improved the chance that a baby with the condition will be diagnosed and treated early, before symptoms appear. This is the best way to prevent serious, life-threatening manifestations of the disease.

Without a newborn screening test, doctors and other healthcare providers diagnose SMA after noticing symptoms, such as a delay in reaching motor milestones. Because more common causes for delays in physical development are usually considered first, SMA is not always quickly diagnosed.

Genetic tests must be done to confirm diagnosis after a positive newborn screen or clinical suspicion. Many pediatricians or primary care doctors often refer children with suspected or confirmed cases of SMA to pediatric neurologists.

In addition to newborn screening tests and confirmation tests to determine that a patient has SMA, additional tests may be conducted to estimate how serious the form of SMA is and to determine the best course of treatment. Some of these tests look at how many copies a patient has of the SMN2 gene—the backup survival motor neuron gene. Generally, the more copies of SMN2 that a patient has, the more SMN protein they produce and the milder the illness.

PRESENTATION
AND SYMPTOMS

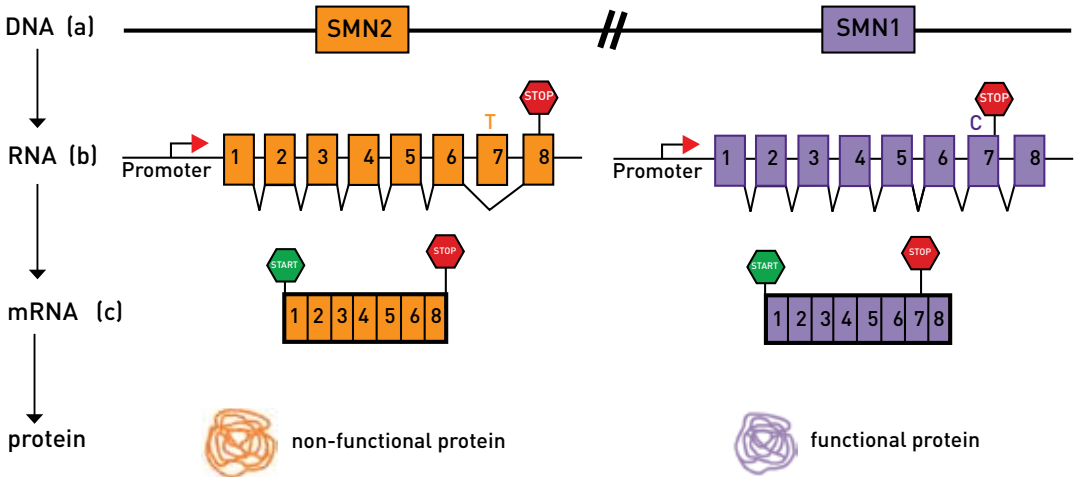
Most cases of SMA—about 95%—will involve SMN1 deletions that should be detected through newborn screening. The other 5% of cases, however, are the result of loss of function mutations and continue to be diagnosed only through clinical observation. We list here some ways that babies present with SMA type I, the most common and severe form of SMA, and also the type that is most crucial to diagnose and treat early.

SYMPTOMS

- Severe, progressive muscle weakness and hypotonia (a "floppy" baby) are common signs.
- Bulbar dysfunction, including poor sucking ability, reduced swallowing, weak cry, and respiratory difficulty with tachypnea and belly breathing that can progress to respiratory failure especially during a cold, are frequently observed.
- Babies have no involvement of the extraocular muscles, and facial weakness is often minimal or absent.
- There is no evidence of cerebral involvement, and infants are bright-eyed, alert, and socially engaged.

PREDICTING
THE SEVERITY OF SMA

The severity of SMA is influenced by the presence of a second survival motor neuron gene, the SMN2 gene. It's similar to SMN1 and serves as a partial backup to SMN1. However, SMN2 only produces about 10% of functional SMN protein. So even with one or many SMN2 genes, the disease will progress.



The number of copies of the SMN2 backup gene varies from person to person and is a predictor of disease severity in patients with SMA. Generally, the more copies of SMN2, the milder the disease. A treatment currently available for SMA focuses on increasing the amount of functional SMN protein produced by the patient's SMN2 genes.

The number of SMN2 copies that a patient has will help determine whether you should recommend immediate treatment or monitoring.

A treatment algorithm was recently developed and published by a panel of experts to guide treatment decisions based on SMN2 copy number. In rare cases where your patient has four or more copies of SMN2, the recommendation is to monitor the patient carefully before considering treatment. In the majority of cases, however, treatment should begin as soon after birth as possible.

Schematic of a portion of chromosome 5 that contains the two SMN genes. The major difference between the two SMN gene copies is the C (SMN1) to T (SMN2) nucleotide change in exon 7 in their DNA. SMN2 mostly makes mRNA message that excludes exon 7 and produces a smaller, unstable SMN protein. SMN1 makes mRNA message that includes exon 7 and makes functioning full-length SMN protein. (a) The SMN1 and SMN2 gene organization on chromosome 5. (b) The SMN genes are turned on by their respective promoters (transcription). Transcription results in a preliminary RNA that contains an intermediate blueprint for protein production. (c) The preliminary RNA message is processed in RNA splicing to become a blueprint for protein production. Notice exon 7 is missing from the SMN2 mRNA. (d) The final mRNA message that results from the splicing process is used as the template for protein production.

TREATMENTS

The first FDA-approved treatment for SMA, SPINRAZA, was approved in 2016. Other treatments are currently being studied in clinical trials. SPINRAZA, made by Biogen, increases the body's ability to produce functional SMN protein via the backup SMN2 genes. The body is then able to produce more functional SMN protein, helping motor neuron cells to stay healthy. SPINRAZA is injected intrathecally and only at designated treatment centers. The treatment begins with four loading doses, followed by maintenance doses every four months.

SPINRAZA cannot repair the damage done by SMA before treatment started but may be able to halt the progression of SMA disease so that muscles stay as strong as they were when the patient started receiving the medication.

The Cure SMA website has information on clinical trials for other SMA treatments. As of this printing, SMA treatments being investigated include gene replacement therapy (aimed at introducing a working SMN1 gene into the body) and an oral medication (aimed at increasing the amount of functional SMN protein the SMN2 gene makes). Another drug in development is intended to preserve or improve muscle function.

Early Is Better

Early treatment offers the best chance that your patient will remain as healthy as possible.

Without enough protein from the missing or faulty SMN1 gene or the backup SMN2 gene, survival motor neurons die quickly. Without any treatment, babies with SMA type I lose 90% of their motor neurons by age six months.

Once lost, motor neurons cannot be restored. The body does not generate new motor neurons, and none of the treatments available or being researched will do so either.

The goal of early treatment is to save the greatest possible number of motor neurons to maintain the health and strength of the patient.

Check the Cure SMA website at www.curesma.org/research/our-strategy/clinical-trials/trials-currently-recruiting/ for clinical trials in SMA that are currently recruiting patients.

LIVING WITH SMA

With newborn screening, early diagnosis, and early treatment, many patients with SMA may be able to live healthier lives. Nonetheless, patients may occasionally require help with physical needs and daily activities.

Food and Nutrition

Getting proper nutrition can be a challenge for some patients with SMA because weak muscles make it difficult to chew and swallow food. Close monitoring of growth is important.

Consider referring your patient to a nutritionist, who can recommend changes to their diet depending on individual needs. These can include soft foods that are easy to swallow or foods that do not aggravate acid reflux caused by weak muscles around the stomach and esophagus.

Adaptive Equipment

A variety of supportive and assistive devices exist to help with daily challenges caused by muscle weakness. The Cure SMA website lists many options.

BREATHING AND COUGHING

People with SMA can have difficulty breathing or coughing strongly enough to clear their airways. This is because the intercostal muscles between the ribs are very weak. This can be a problem especially when a patient has a virus that affects the lungs or upper airways, including the nose and throat. Viruses exacerbate motor weakness transiently.

The diaphragm becomes the primary muscle used for breathing. The result is manifested as prominent belly breathing and tachypnea with minimal movement of the chest wall. Due to the intercostal muscle weakness and stronger diaphragm, the chest wall may appear bell shaped, and there is increased risk for hypoventilation. Oxygen therapy alone does not address hypoventilation.

Common recommendations include:

- Referral to a pulmonologist, who can monitor your patient's breathing capacity
- Techniques to mobilize secretions and a cough assist device to help your patient clear mucus, phlegm, and other secretions from their airways
- Breathing support may be needed especially during sleep, when the muscles for breathing are relaxed or when a patient is sick. Bi-level positive airway pressure, or BiPAP ™, is a way to provide noninvasive breathing support through a mask

LIVING WITH SMA

Orthopedics

Some common musculoskeletal issues among patients with SMA include contractures, bone fractures, hip dislocation, and spinal deformities like scoliosis and kyphosis. Treatment can include modification of the wheelchair seating system, use of braces, and consideration of surgical interventions that help straighten the spine. The course of treatment differs depending on whether the patient is a nonsitter, sitter, stander, or walker.

COMMON RECOMMENDATIONS

Common recommendations include:

- Referral to a physical therapist, who will provide therapy and monitor your patient's progress
- Referral to a rehabilitation medicine physician, who will oversee therapy and equipment needs
- Referral to an orthopedic surgeon, who will monitor your patient's spine and joints

References: 1. Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment algorithm for infants diagnosed with spinal muscular atrophy through newborn screening. J Neuromuscul Dis. 2018;1-14. 2. Govoni A, Gagliardi D, Comi GP, Corti S. Time is motor neuron: therapeutic window and its correlation with pathogenetic mechanisms in spinal muscular atrophy. Mol Neurobiol. 2018.

NEWBORN SCREENING REGISTRY

The Cure SMA Newborn Screening Registry NBSR (NBSR)

is an online Registry established to help our SMA community (including affected individuals, families, clinicians and researchers) learn more about SMA, better manage symptoms over time, and develop new treatments.

We invite you to participate by going to the NBSR website and following the instructions to provide Cure SMA with information about your child.

The NBSR is a program of Cure SMA. Cure SMA is the sole guardian of NBSR and its material. NBSR information can be used to improve clinical care and to support new therapy development. Registries in other diseases also have a long history of success in movig research and clinical care forward.

To access the NBSR portal click here_____(will insert URL to portal) to receive additional information or to register your child or patient.

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