CURE SMA

CARE SERIES BOOKLET

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, which 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.

cure SMA® 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

SMA

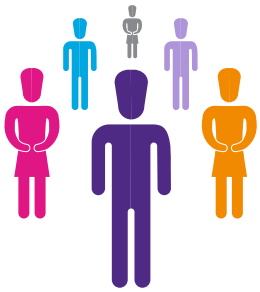
OVERVIEW

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 our muscles. Individuals with SMA produce low levels of survival motor neuron (SMN) protein. Without this protein, those nerve cells cannot properly function and eventually die, leading to debilitating and sometimes fatal muscle weakness..

SMA affects approximately one in 15,000 births in the U.S., and about one in every 50 Americans is a genetic carrier. SMA can affect any race or gender.

INCIDENCE

1 in 15,000 live births.



PREVALENCE

An estimated 9,000-9,500 individuals are living with SMA in the U.S.

CARRIER FREQUENCY

1 in 50 individuals.

THE CAUSE OF SMA

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

The SMA community of healthcare providers, people with SMA, and their families are having many conversations about how to best describe SMA disease in the era of disease modifying SMA treatment. Characteristics that have risen to the top and that are generally used together include:

- *SMN2* copy number
- Maximum motor function achieved, for example non-sitter, sitter, and walker
- Age of symptom onset
- Impact of symptoms or the severity of symptoms
- Age at first treatment

TYPE 0

SMA Type 0 is very rare and very severe. Symptoms begin prior to birth and are seen as decreased fetal movement in the weeks prior to delivery. At birth, the infant has severe weakness and often difficulty breathing and feeding and may have joint contractures and heart problems. These infants typically require breathing and feeding support prior to confirming the diagnosis. These infants historically survived a few months.

TYPE 1

Also known as Werdnig-Hoffmann disease, SMA Type 1 is the most common (60%) and a severe form, usually diagnosed during an infant's first six months. Babies with SMA Type 1 face many physical challenges, including muscle weakness and trouble breathing, coughing, and swallowing. Historically they often needed breathing assistance and a feeding tube. If not treated, Type 1 can be fatal early on in life.

TYPE 2

Type 2 is usually diagnosed after six months of age, but before two years of age. The first sign is often a delay in meeting motor milestones or failing to meet milestones entirely. Individuals with SMA Type 2 can typically sit up without help, though they may need assistance getting into a seated position. Historically, they are unable to walk and will require a wheelchair.

TYPE 3

Also called Kugelberg-Welander disease or juvenile SMA, Type 3 is usually diagnosed after 18 months of age and before three years of age. However, SMA Type 3 can be diagnosed as late as the teenage years. Individuals with SMA Type 3 are initially able to walk and historically have increasingly limited mobility as they grow, and eventually, many need to use a wheelchair.

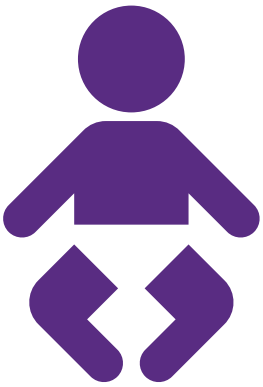
TYPE 4

SMA Type 4 is very rare–less than 1% of all diagnosed cases. It usually surfaces in adulthood, and it leads to mild motor impairment. While symptoms can begin as early as age 18 years, they often begin after age 35 years.

DIAGNOSING

SMA

Some states began screening newborns for SMA in 2018. Parents of babies who screen positive are notified 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. As of 2024, all 50 states screen for SMA.



SMA AFFECTS APPROXIMATELY

1 *IN* 15,000

& 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 or other neuromuscular disease specialists knowledgeable about SMA.

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

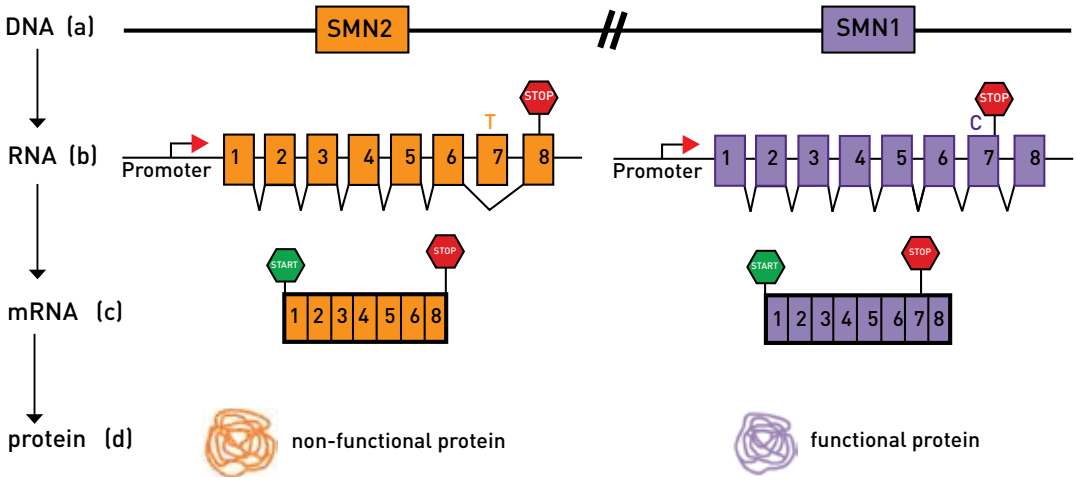
Most cases of SMA—about 95%—will involve SMN1 deletions that are detected through newborn screening. The other 5% of cases, however, are the result of loss of function mutations and continue to be diagnosed only through clinical observation. We list here some ways that babies present with SMA Type 1, 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.
- 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. 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. Some treatments currently available for SMA focus 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 more than 4 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.

Description of Figure Above:
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.

TREATING
SMA

There are two ways of treating SMA that researchers are studying. One way of treating SMA is to address the underlying disease cause by targeting the gene and increasing the amount of SMN protein in the body. These approaches are called "SMN-based" or "SMN-enhancing" approaches.

Currently, three SMN-enhancing treatments for SMA are approved by the U.S. Food and Drug Administration (FDA). Evrysdi (risdiplam) is a small molecule taken daily by mouth or through a g-tube that causes the SMN2 gene to make more complete SMN protein. Spinraza (nusinersen) is an injection that targets the SMN2 gene, causing it to make more complete protein. Zolgensma (Onasemnogene abeparvovec-xioi) is a gene therapy injection that replaces the function of the missing or mutated SMN1 gene. Other types of therapies are in clinical trials or at even earlier stages of research, and these may become available in the future.

Other types of therapies are in clinical trials and in earlier states of research, and these may become available in the future. Some of these approaches are targeting "non-SMN" approaches, focusing on other systems, pathways, and processes in the body that are affected by SMN protein. Examples of such approaches are drugs that increase muscle strength or motor neuron 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, motor neurons die quickly. Without any treatment, babies with SMA Type 1 lose 90% of their motor neurons by age 6 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 out the Cure SMA website at https://www.curesma.org/clinical-trials/ 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 cause fatigue and 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

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.

The Cure SMA Newborn Screening Registry (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 having your patient's family go to the NBSR website at www.curesma.org/nbsr and following the instructions to provide Cure SMA with information and consent so that you can provide information in the registry about your patient.

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 moving research and clinical care forward.

Visit the NBSR portal at www.curesma.org/nbsr to receive additional information or register your patient.

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