Spinal muscular atrophy (SMA)

What is spinal muscular atrophy?

SMA – more than a disease of the motor nerve cells?

Spinal muscular atrophy, or SMA for short, is a rare, progressive neuromuscular disease that affects around one in 10,000 newborns.[1] It is the most common hereditary disease causing infant mortality and is usually diagnosed during early childhood.[2]

With SMA, nerve cells that control muscle movements – known as motor neurones – are damaged and this leads to the progressive loss of these cells.[2] As a result, those affected suffer from increasing muscle weakness, which is the main symptom of SMA, as well as muscular atrophy and signs of paralysis.[4] In addition to affecting motor nerve cells, SMA also impairs the function of other organs such as the heart and digestive tract.

Pathological picture

Cause of SMA

Spinal muscular atrophy is caused by a loss or mutation, i.e. a change in the so-called SMN1 gene. This gene forms the blueprint for the protein called "Survival of Motor Neuron" – SMN for short. SMN is important in a wide variety of body cells and, among other things, plays a key role, enabling nerve cells to communicate with muscle cells and muscles to function correctly.[2] In addition to the SMN1 gene, there is a second gene in the human body that produces the SMN protein – the SMN2 gene. However, the body can only use this gene to produce around 10 % of functional SMN protein.[2]

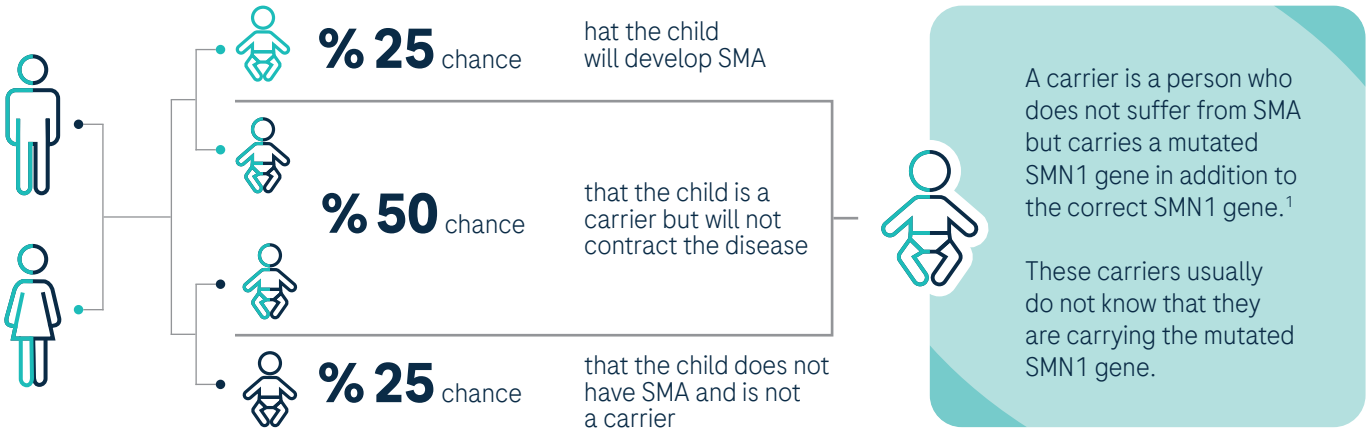
If the genetic defect causes a loss of the SMN1 gene, as is the case in people with SMA, they are only able to rely on the SMN2 gene to produce the vital SMN protein. The amount of SMN protein that can be produced depends largely on how many copies of the SMN2 gene a person with SMA has. SMA patients with a higher number of SMN2 gene copies are less severely affected by the disease in general. This is what also gives rise to the different types of the disease.[2]

Inheriting SMA

SMA is what is known as an autosomal recessive hereditary disease. This means that only those people who inherit a defective SMN1 gene from both their father and their mother are affected. If the parents each have one correct and one faulty SMN1 gene copy, making them carriers of the SMA gene, there is a 25 % probability that any children they have together will develop SMA. Studies have shown that around 1 in 50 people are carriers.[1]

Knowledge both of the effects of the SMN1 gene defect on the human body and of possible approaches to treating people with SMA has increased significantly in recent years. Roche is seizing this opportunity with its research programme, and aims to develop new treatment methods for people with SMA.

If two people who carry the modified gene have children together, there is a



SMA – more than a disease of the motor nerve cells?

Depending on the severity, the lack of the SMN protein affects the whole body and is associated with a variety of complications. These include respiratory, cardiovascular and digestive problems, swallowing disorders and reduced bone density with an increased risk of fractures.[6,7,9,10] These symptoms tell us that the SMN protein is involved in important basic functions of every body cell.[8]

Regardless of the severity, all SMA patients can suffer a loss of function[10]

The implications of SMA are far-reaching

- Progressive decline in mobility[4]
- Muscular atrophy and weakness[4]
- Difficulty swallowing and eating[4]
- Bone complications[9]
- Respiratory complications[6]
- Potential cardiovascular complications[10]

Types

Every person with SMA presents differently – the three most common types of SMA

The three most common types of SMA and what characterizes them at a glance:

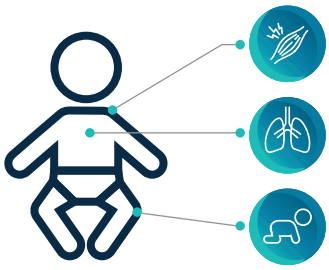
SMA type 1: As a rule, SMA is already apparent at the age of 0 to 6 months; babies can only lie down and never manage to sit up.[5]

SMA type 2: Most of the time, it is infants between the ages of 6 and 18 months that are affected. They can sit up but never get to standing.[5]

SMA type 3: SMA in infants usually presents from 18 months, but it can also appear for the first time in people in early adulthood. Those affected do learn to walk, but can lose this ability again due to the progression of the disease.[5]

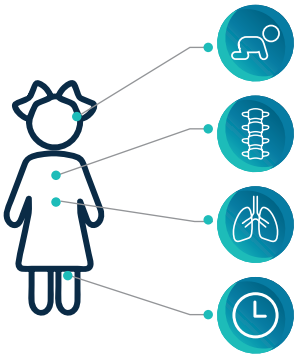
It should be noted that the transitions between the types are fluid. Every patient presents differently.

New presentations and characteristics are also emerging as a result of the therapies now available, which means that categorisation based on type is no longer applicable.[3]



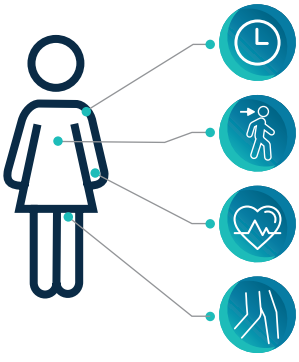
Type 1 spinal muscular atrophy

The first signs of type 1 SMA appear in babies before the age of 6 months. In this severe form, the disease is characterized by a pronounced inability to move. Babies also often find it very difficult to breathe and swallow. If left untreated, babies with type 1 SMA never reach the important motor milestones of childhood development, such as the ability to sit unaided, and often die of respiratory failure before reaching the age of two.[5]



Type 2 spinal muscular atrophy

The first symptoms of type 2 SMA appear around 6 to 18 months of age. In the case of type 2 SMA, motor development is also severely delayed. Although these children can sit without help, they often need to be supported to get into the correct position for this. They will never be able to stand or walk without therapy. This form of SMA can also significantly shorten life expectancy compared to healthy people.[5]



Type 3 spinal muscular atrophy

People with type 3 SMA are able to walk for at least some of their lives. However, as SMA progresses, they may lose this ability again. With type 3 SMA, muscle weakness is often more pronounced in the legs than in the arms. Type 3 SMA usually appears after 18 months of age. In contrast to SMA types 1 and 2, people with type 3 SMA largely have a normal life expectancy, even if the condition goes untreated.[5]

Diagnosing SMA

In the severe type 1 SMA, the suspicion of the condition initially arises through observation of the characteristic physical abnormalities. This primarily includes muscle weakness in the legs and arms.
A bell-shaped chest is an important indication of spinal muscular atrophy, especially in infants.[4]
Since many SMA patients are often small children, parents play an important role in being able to answer questions relevant to the diagnosis.

How is spinal muscular atrophy diagnosed?

The only way to reliably diagnose SMA is through genetic testing. This involves taking blood from the affected person in order to examine the blood cells for a defect in the SMN1 gene.

Since June 2021, all newborns in Austria have been screened for spinal muscular atrophy. This means that almost all cases of SMA can be identified at an early stage, i.e. SMA can be treated early on, which improves the chances of infant development.[11]

Being diagnosed as quickly as possible and starting causal therapy at an early stage can impede the loss of motor neurons and significantly improve the treatment results for SMA patients.

Therapy

The first drug therapy for spinal muscular atrophy became available in Austria in 2017.[12] This works via the SMN2 gene by improving the translation of the SMN2 gene into functional SMN protein (known as “splicing modification”). Another so-called “gene therapy” was approved in Austria in 2020 in which a modified virus introduces a defect-free SMN1 gene into the body’s cells.[13] The first oral SMA therapy was approved in 2021.[14] This therapy also works using a “splicing modification” approach and increases the amount of functional SMN protein through modified splicing of the pre-mRNA of the SMN2 gene.

All available therapies aim to increase the amount of functional SMN protein. Other therapeutic approaches are currently being developed by various companies.

The central contact point for SMA patients should be neuropaediatric or neurological centres. However, due to the complexity of the disease, treatment requires comprehensive, multidisciplinary medical care. The main areas include nutrition, orthopaedics, pulmonary care, acute care, medication and care of other organs. Furthermore, rehabilitation measures such as regular physiotherapy can help people with SMA to positively influence the course of the disease.[4]

What treatment options exist?

- Disease-modifying therapies (splicing modifiers and gene therapy)
- Symptomatic therapy
- Respiratory therapy
- Physiotherapy
- Orthopaedic technology

Research into SMA continues

To date, there is increasing evidence that the lack of SMN protein not only affects the nerve cells that control muscles, but also the normal functions of other cells in the body.[7,15] With this in mind, here at Roche, we have set up a long-term research programme targeting spinal muscular atrophy. The aim is to develop modern treatment options based on the latest findings in order to sustainably improve the lives of people with SMA.

References

1. Verhaart IEC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis 2017; 12:124.
2. Bowerman M, et al. Therapeutic strategies for spinal muscular atrophy: SMN and beyond. Dis Model Mech 2017; 10:943-954.
3. Kölbel H, Müller-Felber W. Gesellschaft für Neuropädiatrie. Leitlinie Spinale Muskelatrophie (SMA), Diagnostik und Therapie. 2021
4. Mercuri E, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord 2018; 28:103-115.
5. Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin 2015; 33:831-846.
6. Lipnick SL, et al. Systemic nature of spinal muscular atrophy revealed by studying insurance claims. PLoS One 2019; 14:e0213680.
7. Simone C, et al. Is spinal muscular atrophy a disease of the motor neurons only: pathogenesis and therapeutic implications? Cell Mol Life Sci 2016; 73:1003-1020.
8. Farrar MA, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol 2017; 81:355-368.
9. Finkel RS, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord 2018; 28:197-207.
10. Nash LA, et al. Spinal Muscular Atrophy: More than a Disease of Motor Neurons? Curr Mol Med 2016; 16:779-792.
11. https://www.meduniwien.ac.at/hp/neugeborenen-screening/
12. https://www.ema.europa.eu/en/documents/product-information/spinraza-epar-product-information_de.pdf
13. https://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-product-information_de.pdf
14. https://www.ema.europa.eu/en/documents/product-information/evrysdi-epar-product-information_de.pdf
15. Yeo CJJ et al. Overturning the Paradigm of Spinal Muscular Atrophy as Just a Motor Neuron Disease. Pediatr Neurol. 2020 Aug;109:12-19.

Roche Austria GmbH, Engelhorngasse 3, 1211 Wien, www.roche.at

M-AT-00003202