

Spinal Muscular Atrophy

An Overview

What Is Spinal Muscular Atrophy?

Spinal muscular atrophy (SMA) is a genetic condition which affects the nerves that control muscle movement– the motor neurons.

It is named 'spinal' because most the motor neurons are located in the spinal cord. 'Muscular' is in the name because it primary affects the muscles which don't receive signals from the motor neurons. 'Atrophy' is the medical term for wasting away or getting smaller, which is what generally happens to muscles when they're not active.

There is wide variability in age of onset, symptoms and rate of progression of SMA and it is often classified into types 1 to 4 based on the physical milestones achieved. The age at which symptoms start generally predicts how severe the condition is. For example, babies who have symptoms at birth have the most severe symptoms and most do not live beyond the age of two (type 1 SMA). Whereas people whose symptoms appear as adults may not develop severe disability and have a normal life expectancy (type 4 SMA). It is important to note that the course of the disease may be different for each child and adult.

SMA affects muscles throughout the body, although the muscles closest to the trunk of the body – the shoulders, hips, and back – are often most severely affected. Sometimes feeding and swallowing can be affected. Involvement of respiratory muscles (muscles involved in breathing and coughing) can lead to an increased tendency for pneumonia and other lung problems. Sensation and the ability to feel are not affected. Intellect is normal and it is often observed that people with SMA are bright and sociable.

SMA is a relatively common 'rare disorder' approximately 1 in 6000 babies born are affected, and about 1 in 40 people are genetic carriers.

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What are the different types of Spinal Muscular Atrophy?

SMA Type 1 (also called infantile onset or Werdnig-Hoffmann disease)

Age of onset: birth to 6 months. Symptoms include generalised muscle weakness, weak cry, trouble breathing swallowing and sucking. Babies do not reach the developmental milestone of being able to sit up unassisted. Life span rarely exceeds age 2. More information about SMA type 1 can be found on the MDA website (<http://www.mda.org.au/Disorders/Atrophies/SMAI.asp>).

SMA Type 2 (also called intermediate SMA)

Age of onset: 7 to 18 months. Symptoms include weakness in arms, legs, lower torso and respiratory muscles. Spinal curvature (scoliosis) is often a problem requiring bracing and surgery. Children learn to sit unassisted but generally do not stand or walk independently. Although respiratory complications are a constant threat, children with type 2 SMA usually live to young adulthood and many live longer. More information about SMA type 2 can be found on the MDA website (<http://www.mda.org.au/Disorders/Atrophies/SMAII.asp>).

SMA Type 3 (also called Kugelberg-Welander disease)

Age of onset: 18 months to 15 years. This is the mildest form of childhood onset SMA. Symptoms include weakness in leg, hip, shoulder, arm and respiratory muscles. Children learn to stand and walk but some lose the ability to walk in adolescence, others walk well into their adult years. Life span is unaffected. More information about SMA type 3 can be found on the MDA website (<http://www.mda.org.au/Disorders/Atrophies/SMAIII.asp>).

SMA Type 4 (adult-onset SMA)

Age of onset: 18 to 50 years. . Symptoms usually include mild muscle weakness, tremor and twitching. Life expectancy is normal and the muscles for swallowing and breathing are rarely affected. Only a small number of patients eventually require wheelchair assistance. More information about SMA type 4 can be found on the MDA website (<http://www.mda.org.au/Disorders/Atrophies/SMAIV.asp>).

Other rare types of SMA

The types of SMA described above are the most common types of SMA which are caused by changes to a gene on chromosome 5 called SMN1. There are also some other very rare types of SMA caused by other genetic changes. For example, an X chromosome gene called UBE1 has been identified that, when mutated, causes X-linked SMA. Flaws in the cytoplasmic dynein 1 heavy chain 1 (DYNC1H1) gene on chromosome 14 also have been found to lead to a rare form of SMA, called SMA-LED, which predominantly affects the leg muscles.

There is also an extremely rare form of SMA which particularly affects the breathing muscles. It is called Spinal Muscular Atrophy with Respiratory Distress (SMARD). SMARD1 is caused by mutations in the IGHMBP2 gene (immunoglobulin mu-binding protein 2) on chromosome 11. It is sometimes called autosomal recessive Distal Spinal Muscular Atrophy 1 (DSMA1) or Distal Hereditary Motor Neuropathy Type VI3.

What Causes Spinal Muscular Atrophy?

SMA is a genetic condition caused by a change in a gene called 'survival motor neuron 1' (SMN1). Everybody has two copies of the SMN1 gene – one inherited from each parent. People with SMA have both copies of the SMN1 gene containing a change (which is often referred to as a 'mutation'). This is what is called an 'autosomal recessive' inheritance.

The parents of an individual with SMA each carry one copy of the mutated SMN1 gene, and are known as ‘carriers’, but they typically do not show signs and symptoms of the condition. In order for carrier parents to have a child affected by SMA, both parents must pass the mutated SMN1 gene on to their child. If both parents are carriers the likelihood of a child inheriting the disorder is 25 percent, or 1 in 4. About 1 in every 40 people is a carrier of the gene mutation that causes SMA.

The SMN1 gene mutation usually involves the entire gene being missing or occasionally some of the code of the gene is changed rendering it inactive. The role of the SMN1 gene in the body is the production of a protein called Survival of Motor Neuron (SMN). If this protein isn’t produced in sufficient amounts motor neurons start to die. Motor neurons are nerve cells in the spinal cord which send out nerve fibres to muscles throughout the body and control their movement.

But why are some people affected much more severely by the SMN1 gene mutation than others? This is primarily due to the presence of another gene called SMN2. This gene produces several different versions of the SMN protein; however, it only produces a small amount of the full size and functional version. Some people have three or four copies of the SMN2 gene which can result in larger amounts of full-length SMN protein being produced and reduced severity of the disease. As a general rule SMA type 1 patients have one or two SMN2 copies while most SMA type 2 patients carry three SMN2 copies and SMA type 3 and 4 patients have four or more SMN2 copies. There are exceptions to this rule though and it has even been observed that siblings with the same number of SMN2 genes can have very different severities.

SMA severity also may depend on levels of other proteins that people naturally produce in their body. These are called ‘disease modifiers’. Two such proteins that have been identified so far are ‘plastin 3’ and ‘ZPR1’. Patients who naturally produce higher amounts of these proteins tend to have less severe symptoms, but more research is required to fully understand this.

How is Spinal Muscular Atrophy diagnosed?

If symptoms and a physical examination suggest that a baby, child or adult might have SMA the first diagnostic test to be done is a blood test which looks for the presence or absence of the SMN1 gene. In approximately 95% of patients with SMA there is complete absence of the SMN1 gene.

If the genetic test shows that the SMN1 gene is present, further physical examination is done to look for symptoms indicative of rare types of SMA caused by mutations in other genes. Other laboratory tests may also be done to rule out other neuromuscular conditions, which may include:

- Electromyography (EMG) which measures the electrical activity of muscle. Small recording electrodes (needles) are inserted into the patient's muscles, usually the arms and thighs, while an electrical pattern is observed and recorded.
- Nerve conduction velocity test (NCV) is performed to help assess how well the nerves are functioning in response to an electrical stimulus. Small shocks are repeatedly administered to help assess nerve integrity and function.
- A blood test for the muscle enzyme ‘creatinase’ – a positive result is indicative of a muscular dystrophy.
- Occasionally, doctors may request a muscle biopsy

If these tests suggest a motor neuron disease, then further genetic testing for SMN mutations should be pursued. In two to five percent of patients with SMA the SMN1 gene is not missing but some of the code of the gene is changed rendering it inactive. Testing for this type of mutation is more complicated so it may take some time to obtain a result.

What can we expect for the future?

In general the later the symptoms begin, the milder the course of the disease is likely to be. In the past, babies with SMA type 1 typically did not survive more than two years; today most doctors now consider SMA to be a continuum and prefer not to make rigid predictions about life expectancy or weakness based strictly on age of onset.

There is a wide range of variability in the symptoms and severity of SMA. This is crucial to remember when considering different aspects of an individual's care. No two children will be exactly the same and thus treatment and care plans for each family should be tailored to meet their individual needs.

Ideally children and adults with SMA should enlist a team of clinicians that specialise in SMA and its specific complications to look after their medical needs and allow them to live life to the full. Interdisciplinary teams caring for people with SMA are often comprised of neurologists, nurses/nurse practitioners, pulmonologists, orthopaedics, genetic counsellors, physiotherapists, occupational therapists, nutritionists, and social workers. Individuals with SMA and their family members work together with these interdisciplinary teams to create goals and personalised plans of care that best meet their needs as they change throughout the journey with SMA.

The brains of children and adults with SMA are not affected at all and should be encouraged to participate in as many age- and developmentally-appropriate activities as possible, with adaptations made whenever necessary.

What research is being done?

It is an exciting time for SMA research with several clinical trials underway to test promising new potential treatments.

Gene therapy

The aim of gene therapy for SMA is to introduce a healthy synthetic copy of the SMN1 gene into the motor neurons so that SMN protein can be made. Effective delivery of the gene to the difficult-to-access motor neurons has been considered an almost impossible challenge until very recently. Several research groups published results of experiments in 2010 and 2011 showing that a virus called 'adeno-associated virus type 9' (AAV9) is effective at delivering the SMN1 gene to the motor neurons of mice when injected into the blood stream. The gene therapy dramatically improved the life span and motor function of mice that had severe SMA.

In June 2014 a phase 1 clinical trial of this type of gene therapy for SMA was started by US company Avexis Inc. The trial will involve about nine SMA type 1 patients younger than nine months of age. More information about the trial is available on the clinicaltrials.gov website.

Utilising the SMN2 gene

Several research strategies involve manipulating the genetic instructions provided by the SMN2 gene so that more full-length SMN protein can be made. Some researchers are discovering potential drugs in what could be considered a 'trial and error' approach – testing thousands of molecules to find any that increase production of SMN protein. Others are using a more targeted approach – specifically designing drugs to alter the way the SMN2 gene works.

One example of the former approach is a potential drug called RG 3039. Screening of over 500,000 potential drugs by researchers in the USA discovered a type of compound that was capable of

increasing the production of full-length SMN protein from the SMN2 gene. The composition of this compound was then optimised to produce the drug RG3039 which was tested in mice. It was shown to improve the lifespan and various disease symptoms including motor neuron survival in the mice. RG3039 is now being tested by Repligen Corporation in Phase 1 clinical trial in healthy volunteers to determine the safety and pharmacokinetics (see glossary below) of the drug. It is hoped that the information gained from these Phase 1 trials will aid in the future design of clinical trials of RG3039 in SMA patients. Pharmaceutical company Pfizer has now bought the licence to RG3039 and will continue the development and testing. RG3039 is also known by the names PF-06687859 and Quinazoline.

Using the more targeted approach is Isis Pharmaceuticals who are currently testing a potential drug called ISIS-SMNRx in clinical trial. ISIS-SMNRx is an antisense oligonucleotide (AONs) – small pieces of genetic material that can specifically manipulate the way that the genetic code is read. The aim of using AONs for SMA is to encourage the cells to produce more of the full length SMN protein from the SMN2 gene. Administration of ISIS-SMNRx to mice with SMA has previously been shown to target many neuromuscular symptoms leading to a large increase in survival.

Isis Pharmaceuticals has reported positive results part-way through two clinical trials of ISIS-SMNRx. The first of the ongoing trials aims to test two different doses of ISIS-SMNRx in infants with SMA type 1 and the second aims to test four different doses in children with the less severe types 2 and 3 SMA. In both studies the results are encouraging with the children faring better than the typical course of the disease. Importantly, ISIS-SMNRx has been well tolerated.

The ISIS-SMNRx trials involve only a small number of participants and assessments have only been made over a short time period, so further clinical trials will be needed to further assess the safety and effectiveness. However, the results so far are encouraging enough for plans to already be in place to start larger Phase 3 studies. More information about the ISIS clinical trials is available on the clinicaltrials.gov website (<http://tinyurl.com/keboq23>).

Protecting motor neurons

Olesoxime (TRO19622) is a cholesterol-like compound being developed by Trophos, a French pharmaceutical company. Olesoxime has been shown to protect nerve cells from damage and improve neuronal growth and function, effects that could prove beneficial to SMA patients.

Following a successful phase 1 trial, Trophos conducted a larger phase 2 trial involving 165 people with SMA types 2 and 3, aged between three and 25 years. Results were announced in March 2014. The trial showed that loss of motor function was prevented in those taking olesoxime for two years while those taking the placebo had the typical progressive loss of motor function. Participants taking the olesoxime also had fewer of the medical complications that are normally associated with SMA such as lower respiratory tract infections. The safety of olesoxime was also confirmed and Trophos plans to file for regulatory approval in both the US and Europe as soon as possible. More information about the Olesoxime trial is available on the clinicaltrials.gov website (<http://tinyurl.com/lj5b6as>).

Ongoing searches for new drugs

There are many ongoing efforts to identify other new drugs for SMA, both in research institutions and by pharmaceutical companies. Companies involved include Novartis, Merck, Roche and PTC Therapeutics. In August 2013 PTC Therapeutics announced that it had selected and will continue to develop a candidate drug that has the potential to treat SMA.

Stem cells

Another treatment strategy that is being actively investigated in SMA is to use stem cells to replace

the motor neurons that have died. SMA mice treated with stem cells displayed increased survival and improved mobility, as well as increased motor neuron number. Research is ongoing to understand the best type of stem cell to use, how to produce these cells in large numbers and how to control their development into motor neurons. California Stem Cell Inc. is particularly active in this area (<http://www.californiastemcell.com/clinical-pipeline/motorgraft/>)

Research challenges

One of the big challenges of developing a therapy for SMA is proving that a therapy works. The severity of symptoms from one patient to the next is very variable which makes it difficult to measure whether a new drug works. In addition, SMA type 2 and type 3 patients often have stable muscle strength for months and years making the detection of meaningful changes difficult, whereas infants with SMA type 1 are often too sick to take part in muscle strength tests. Preclinical research has shown that the timing of treatment may also be critical – early treatment, before too many motor neurons are lost, is likely to be most successful. The window of opportunity for treatment of people with SMA is not known which makes it difficult to plan clinical trials that will give positive results. If a successful treatment is found it may be beneficial for a newborn screening program for SMA to be introduced so that treatment can be started before symptoms appear and the motor neurons are lost.

NOTE: Research is moving forward at a fast pace, so this research summary may not be up-to-date at the time of reading. Feel free to contact MDA's Scientific Communications Officer for an update on the latest developments - kristina.elvidge@mda.org.au

I am a carrier of the SMA gene - what can I do?

If you find you are a carrier of the SMA gene, it is recommended that you seek the advice of a genetic counsellor. The genetic counsellor can help you to better understand the risks and chances of having an affected child. If you already have a child with SMA, the counsellor can discuss with you options that you may want to consider regarding future pregnancies.

Preimplantation genetic diagnosis (PGD) is an option that might be considered by some couples who are carriers of SMA. This involves using IVF to fertilise eggs outside the body and then testing the resulting embryos for the genetic mutation. Unaffected embryos are then chosen to be placed back in the woman's womb. Another option is prenatal diagnosis – testing the foetus once the woman is pregnant. The couple then has the option whether or not to continue the pregnancy if the foetus is affected. Alternatively some couples may choose to use egg or sperm donors, or adopt a child.

Further information

- Please see the individual factsheets for each type of SMA for more detailed information about the symptoms and how to manage the condition (<http://mda.org.au/>)
- Clinical trials – your questions answered (<http://www.mda.org.au/trials/index2.asp>)
- A Family Guide to the Standards of Care for Spinal Muscular Atrophy is available in two different formats and 16 different languages (<http://www.treat-nmd.eu/sma/care/family-guide-translations/>)
- More research news on the MDA website (www.mda.org.au/research/News.asp)
- For definitions of any terms that you are not familiar with please take a look at our glossary (www.mda.org.au/research/ResGlossary.asp)

- Learn about patient registries (<http://www.mda.org.au/registries/index.asp>) and join the Australian Spinal Muscular Atrophy Registry (<https://nmdregistry.com.au/sma/>)
- More research information is available on the Families of SMA website in the USA (<http://www.fsma.org/Research/>)
- You can get regular updates by becoming a friend of the MDA Facebook page (www.facebook.com/MDA.MuscularDystrophyAustralia) or follow our Scientific Communications Officer on Twitter (@kelvidge).

If you have any questions, please contact us at MDA:

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Glossary

Gene: Genes are made of DNA and each carries instructions for the production of a specific protein. Genes usually come in pairs, one inherited from each parent. They are passed on from one generation to the next, and are the basic units of inheritance. Any alterations in genes (mutations) can cause inherited disorders.

Mutation: A permanent change in the DNA code that makes up a gene. Depending on where the mutation occurs, and the type of mutation, they can either have no effect or result in genetic diseases such as muscular dystrophy. Mutations can be passed on from generation to generation.

Pharmacokinetics: the study of what happens to a drug from the moment that it is administered up to the point at which it is completely eliminated from the body. Pharmacokinetics describes how the body affects a specific drug after administration through the mechanisms of absorption and distribution, as well as the chemical changes of the substance in the body.

Protein: Proteins are large molecules composed of one or more chains of amino acids in a specific order. The order is determined by the gene that contains the instructions for the construction of the protein. Proteins are required for the structure, function, and regulation of the body's cells, tissues, and organs. They are the building blocks of our bodies. We have millions of different proteins in our body and each has unique functions. Two examples are the enzymes in our stomach that digest our food and the collagen which holds our skin together.

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