Spinal Muscular Atrophy (SMA)

Understanding the recessive genetic disorder

Spinal muscular atrophy (SMA) is a recessive genetic disorder. It is caused by a loss of anterior horn cells (spinal motor neurons). Messages from the nerve cells in the brain (called upper motor neurons) are transmitted to nerve cells in the brain stem and spinal cord (called lower motor neurons) and from them to specific muscles. Upper motor neurons instruct the lower motor neurons to produce movements in the arms, legs, chest, face, throat and tongue. This loss of spinal motor neurons means that there is a lack of nerve signal from the spinal motor neurons to the muscle, which causes the muscle to waste away (atrophy) leading to weakness. The muscles affected are used for activities such as crawling, walking, sitting up, and controlling head movement. In some cases of SMA, the muscles used for breathing and swallowing are affected.

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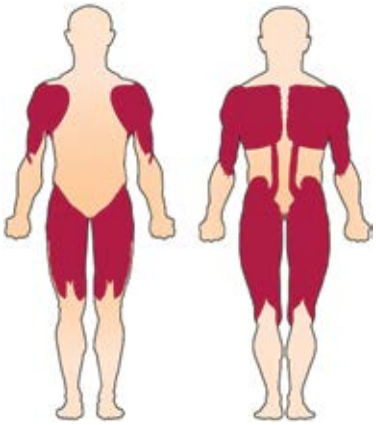
Causes of SMA

SMA Types I-IV is a result of a lack of a protein called survival motor neuron protein (SMN). The reduced amounts of this protein result in the spinal motor neurons not being maintained properly and they die. This in turn leads to atrophy of the muscle because the muscle is no longer being innervated. SMA is an autosomal recessive condition meaning that an affected person has inherited a faulty SMN gene from each of his or her parents.



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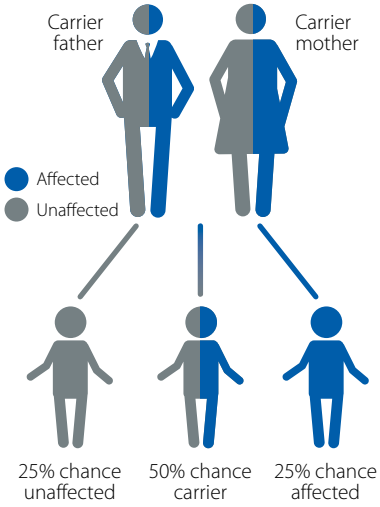
Levels of SMN protein is primarily controlled by the *SMN1* gene and influenced by the *SMN2* gene. Alterations in *SMN1* causes SMA and the number of copies of *SMN2* influence the severity of the condition with type 1 being the most severe through to type IV being the least severe. The *SMN2* gene makes some SMN protein but most of what it makes is non-functional and is discarded by the cell. The small amount of functional SMN that *SMN2* produces influences the severity of SMA, with the greater the number of *SMN2* copies a person has the less severely affected they will be. The extra amounts of survival motor neuron protein produced by the 3 or more extra copies of the less efficient *SMN2* gene has a protective effect and the severity of the condition is reduced.

Other forms of SMA include; X-linked spinal bulbar muscular atrophy (Kennedy's disease), dominant spinal muscular atrophy with affected lower extremity (SMA-LED) are all caused by defects in different genes.

Inheritance Pattern

Spinal muscular atrophy is inherited in an autosomal recessive pattern, which means both copies of the *SMN1* gene have mutations that affect the production of SMN protein from the gene. The parents of an individual with an autosomal recessive condition usually each carry one copy of the mutated gene, hence they are called carriers. Carriers typically do not show signs and symptoms of the condition as they each still have one functional gene, which is sufficient to avoid symptoms. Two carrier parents



When two carrier parents have a child, there are three possible outcomes. With each pregnancy, there is a 25% chance that the child will be affected.

have a 1 in 4 chance (25%) in each pregnancy of having a child affected with the condition. In rare cases (approximately 2%) people with the condition have a new defect in one of their genes. In this situation only one parent is a carrier and the other defect occurred randomly within the individual. This is called a *de novo* mutation (new and not inherited).

Diagnosis of SMA

The diagnosis of spinal muscular atrophy (SMA) is established in individuals who have;

- A history of motor difficulties
- Evidence of motor unit disease on physical examination
- Mutation detected in the *SMN1* gene (this can be carried out via a blood test or saliva sample) which indicates whether there is a deletion or other mutation of the *SMN1* gene. This test identifies at least 95 percent of SMA Types I, II, and III.
- Electromyography (EMG) records the electrical activity from the brain and/or spinal cord to a peripheral nerve in the arms or legs that controls muscles during contraction and at rest and nerve conduction velocity studies (NCS), which measure electrical energy by assessing the nerve's ability to send a signal.

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Features of SMA

Type I spinal muscular atrophy (also called Werdnig-Hoffman disease) is a severe form of SMA that is evident at birth or soon after birth and results in a rapid decline and death within two years. Affected infants may initially meet developmental milestones but then quickly decline and fail to meet motor milestones although they remain bright and have expressive faces. They have poor muscle tone (hypotonia) and most are unable to support their head or sit unassisted due to the severe muscle weakness. Babies with SMA type 1 have respiratory difficulties and usually require ventilation. They often have swallowing problems that may lead to feeding difficulties, choking or gagging. Other features can include small local involuntary contractions of the tongue, mild contractures often at the knees and an absence of tendon reflexes.

Type II spinal muscular atrophy is characterised by muscle weakness that develops in children between ages 6 and 12 months. Children with type II can sit without support, although they may need help getting to a seated position but they never achieve unaided walk. Fasiculations or trembling of the tongue and finger trembling is almost invariably present and approximately 70% of individuals have an absence of tendon reflexes. Individuals with SMA type II often have average intellectual skills during the formative years and above average by adolescence.

Type III spinal muscular atrophy (also called Kugelberg-Welander disease or juvenile type) has milder features that typically develop between early childhood, after ten months of age, and adolescence. Individuals with type III spinal muscular atrophy achieve walking but may lose this ability over time. Type III is characterised by proximal limb weakness with the legs more severely affected than the arms.

Type IV spinal muscular atrophy or adult onset spinal muscular atrophy is a relatively mild condition with affected individuals usually experience mild to moderate muscle weakness, tremor, twitching, or mild breathing problems with the onset

of these signs and symptoms not occurring until adulthood. Typically, only muscles close to the center of the body (proximal muscles), such as the upper arms and legs, are affected in type IV spinal muscular atrophy

Management of SMA

Treatment for SMA involves multi-disciplinary management of the symptoms and prevention of complications.

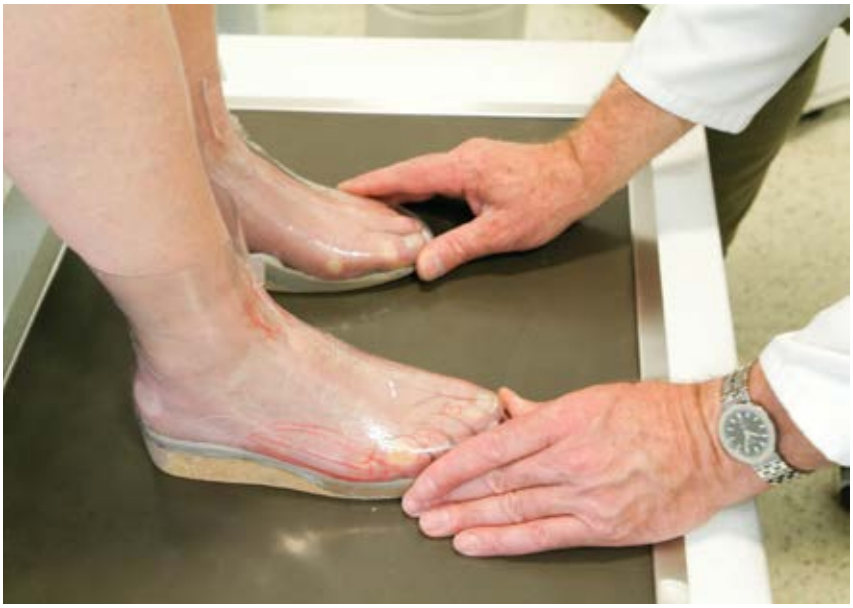
Poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures are common complications and management revolves around preventing or treatment of these.

Physiotherapy, occupational therapy, and rehabilitation may help to improve posture, prevent joint immobility, and slow muscle weakness and atrophy. Stretching and strengthening exercises may help reduce spasticity, increase range of motion, and keeps circulation flowing. Applying heat may relieve muscle pain.

Assistive devices such as supports or braces, orthotics and wheelchairs may helpful in maintaining mobility.

Good nutrition and a balanced diet are essential to maintaining weight. Chewing and/or swallowing difficulties can be addressed with input from speech language therapy and dietetics. When nutrition is a concern in SMA, placement of an naso-gastric feeding tube or gastrostomy (PEG) may be appropriate.

It is vital that respiratory problems are well-managed. As respiratory function deteriorates, ventilation, via tracheotomy or non-invasive intermittent positive-pressure breathing device, is effective.



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Weakened muscles may lead to curvature (scoliosis) of the spine. Surgery for scoliosis in individuals with SMA II and SMA III can be carried out safely if the forced vital capacity is greater than 30%-40% and can help maintain adequate respiratory function.

Muscle relaxants such as baclofen, tizanidine, and the benzodiazepines may reduce spasticity. Botulinum toxin (Botox therapy) may be used to treat jaw spasms or drooling. Excessive saliva can be treated with amitriptyline, glycopyolate, and atropine or by botulinum injections into the salivary glands.

Regular evaluation by a multi-disciplinary team every six months, or more frequently for children who are weak, to assess nutritional state, respiratory function, and orthopaedic status (spine, hips, and joint range of motion) is recommended.

Genetic counselling is available to families who have a diagnosis of SMA. This service provides information, helps families understand inheritance patterns and what this means in their family, as well as enabling people to make informed family-planning decisions. ®