



Facts About Spinal Muscular Atrophy

MDA® Muscular
Dystrophy
Association
Fighting Muscle Disease

Dear Friends:

I've had symptoms of spinal muscular atrophy since I was a baby. When most children were beginning to walk, my parents noticed that my head would flop to the floor as I crawled. Doctors said I had amyotonia congenita and predicted I wouldn't live past my 8th birthday. When I turned 14, the diagnosis was changed to benign congenital hypotonia.

It wasn't until I was leaving for college at age 18 that the label was changed again, to spinal muscular atrophy. These changes didn't reflect anything new in my condition, but a change in the understanding of the disease called SMA.

This pamphlet is designed to help you better understand the causes, symptoms and progression of the different forms of SMA. It's hoped that this knowledge will help you plan for the future and take heart in the present, knowing that a diagnosis of SMA doesn't preclude leading a full and rewarding life.

Since "officially" learning that I have SMA, I've gone on to earn both bachelor's and master's degrees, and now am in private practice as a licensed mental health counselor. My wife, Sheryl, and I have two great kids, and I also enjoy such hobbies as computer technology and music composition (including the publication of two songs in Nashville).

And I'm in no way an exception to the rule. People with SMA are involved in all areas of society: the arts, science, law, management, teaching — you name it. Children with SMA tend to be highly intelligent, creative and adaptable individuals who contribute much to the world despite their challenges.

As you'll learn from this pamphlet, great progress is being made in treating SMA and moving toward a cure. Medical, computer and assistive technologies

enable even very young children to compensate for weak muscles. While some forms of SMA still shorten life span, new approaches to ventilation and feeding have expanded what's possible. And the search for cures is making steady, encouraging progress.

The Muscular Dystrophy Association is the leading sponsor of SMA research. The Association also provides a full program of services for individuals and families coping with SMA, and up-to-date information about research progress. See "MDA Is Here to Help You" on page 13 for more details.

When I was a baby more than half a century ago, the world was much more discouraging for people with disabilities. Today, medical science, technology, health care services and laws such as the Americans with Disabilities Act help us to stretch to reach our full potential.

If I were to share any words of advice, it would be to let your own experience, rather than a medical label, determine what your life's limitations and potentials are going to be. Build on your personal strengths, determination and faith — or encourage your child to do so. And remember that the extended family of MDA is there to help when needed. You're not in this alone.

Throughout my life I've been called a dreamer, and I've found much joy in fulfilling those dreams. May this also be true for you and your family.



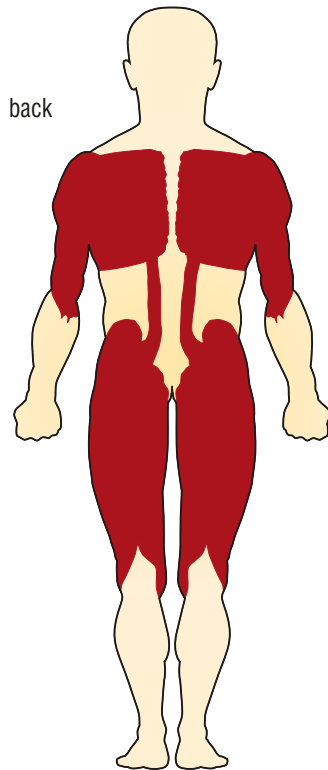
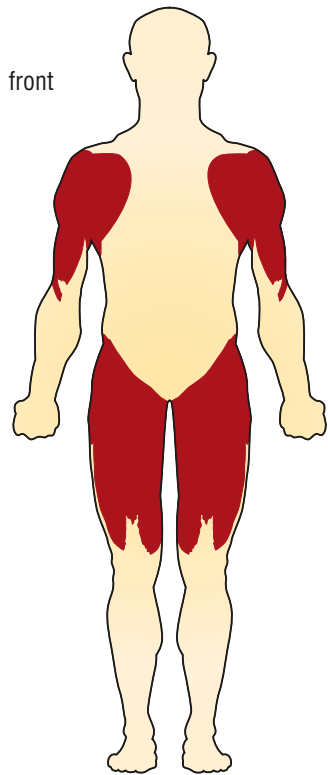
Jerry Ferro
Casselberry, Florida



Jerry Ferro



Jerry Ferro, with his wife, Sheryl, and children Jacob and Sheri in 1999



The muscles closer to the center of the body (proximal muscles) are usually more affected in spinal muscular atrophy than are the muscles farther from the center (distal muscles).

What Is Spinal Muscular Atrophy?

Spinal muscular atrophy (SMA) is a genetic disease affecting the part of the nervous system that controls voluntary muscle movement.

Most of the nerve cells that control muscles are located in the spinal cord, which accounts for the word *spinal* in the name of the disease. SMA is *muscular*, because its primary effect is on muscles, which don't receive signals from these nerve cells. *Atrophy* is the medical term for wasting or shrinkage, which is what generally happens to muscles when they're not active.

SMA involves the loss of nerve cells called *motor neurons* in the spinal cord and is classified as a *motor neuron disease*.

There's a great deal of variation in the scope and severity of SMA in different people.

What causes SMA?

Most cases of SMA are caused by a deficiency of a motor neuron protein called *SMN*, for *survival of motor neurons*.

This protein, as its name implies, seems to be necessary for normal motor neuron function. Recent evidence suggests that a lack of SMN might also directly affect muscle cells.

There are other forms of SMA not related to the SMN protein (see page 5).

What are the forms of SMA?

SMN-related SMA

SMN-related SMA is usually broken down into three categories. Type 1 is the most severe with the earliest age of onset, and type 3 is the least severe, with the latest age of onset. Some doctors add a type 4 for moderate or mild SMA that begins in adulthood.

All these types are related to genetic flaws (the scientific term is *mutations*) on chro-

mosome 5 that affect the amount of SMN protein that can be produced. In general, a higher level of SMN protein lessens the severity of SMA. See "Does It Run in the Family?" on page 11 for more about how these mutations lead to SMA.

Non-SMN SMA

There are also forms of SMA that aren't related to SMN and don't stem from chromosome 5 mutations. For more about these disorders, see page 5.

Spinal-bulbar muscular atrophy

A type of SMA that's usually called *SBMA*, for *spinal-bulbar muscular atrophy*, stems from a gene defect on the X chromosome. This type of SMA, also known as *Kennedy's disease*, is quite different from the chromosome 5 type. See page 9 for more information.

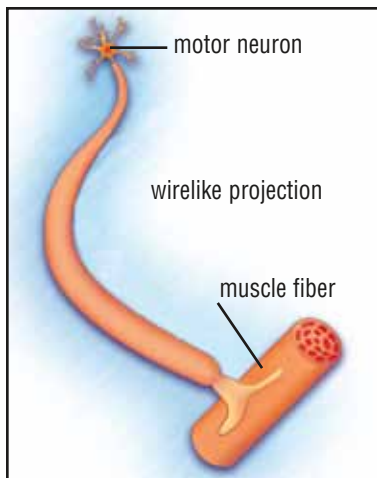
What happens to someone with SMN-related SMA?

The severity of SMN-related SMA is roughly correlated with how early symptoms begin, which in turn is roughly correlated with how much SMN protein there is in the motor neurons. The later the symptoms begin and the more SMN protein there is, the milder the course of the disease is likely to be.

Most doctors, however, now consider SMN-related SMA to be a continuum of severity and prefer not to make rigid predictions about life expectancy or weakness based strictly on age of onset. Recent research has supported this flexibility.

Type 1 SMA (Werdnig-Hoffmann Disease)

Children with SMA who are very weak in the early months of life and have breathing, sucking and swallowing difficulties in infancy aren't likely to have a good prognosis. In the past, it was said that such children weren't likely to survive more



Muscle-controlling nerve cells (motor neurons) are located mostly in the spinal cord. Long, wirelike projections connect the motor neurons to muscles in the limbs and trunk. Normally, signals from the neurons to the muscles cause muscles to contract. In SMA, motor neurons are lost, and muscles can't function.



Many children with SMA can benefit greatly from physical therapy and assistive technology.

than two years. Today, this is still often true.

However, with technology to take the place of natural breathing and eating functions, such children can often survive several years. Mechanical ventilation (today's ventilators are portable, in contrast to the "iron lungs" and heavy machinery of former decades) and feeding tubes that go directly into the stomach (not down the throat) can prolong life.

Mental and emotional development and sensation are entirely normal in SMA.

Type 2 SMA (Intermediate SMA)

A diagnosis of type 2 SMA allows parents and children to plan for a future, even if life span may be shorter than normal. This type of SMA begins in childhood but generally after infancy. Some sources say the onset has to be between 6 and 18 months to be type 2. Others say that any child who has been able to sit without support after being placed in a sitting position can be classified as type 2.

The muscles closer to the center of the body (*proximal* muscles) are usually more affected, or at least affected much sooner, than the muscles farther away from the center in SMA type 2. For example, the muscles of the thighs are weaker than the muscles of the lower legs and feet.

Also, legs tend to weaken before arms. Hands may get weak eventually, but they usually stay strongest the longest, and, even if they do weaken, they usually remain strong enough for typing on a computer keyboard and other basic functions of modern life.

Children with type 2 SMA benefit greatly from physical therapy and assistive technology of all kinds. Aids to walking and standing, such as lightweight braces (*orthoses*) and standing frames, allow for more mobility today than in the past.

Many children can handle a power wheelchair or other type of powered vehicle very early, even at age 3 or so, depending on the child's maturity and general outlook. Many professionals have observed that children with SMA seem unusually intelligent, and a small body of research supports this observation.

The most serious danger in type 2 SMA comes from the weakness of muscles necessary for breathing. Careful attention to respiratory function is needed throughout life, with prompt attention to infections. Your doctor can help you with details of maintaining respiratory health, including clearance of secretions and perhaps assisted ventilation (not necessarily around the clock). See page 5 for more.

Another major problem in type 2 SMA is spinal curvature, usually a side-to-side type of curvature called *scoliosis*. Scoliosis occurs because of weakness of the muscles that normally support the spine, which is a flexible column. Scoliosis can be very uncomfortable, interfere with position and mobility, and damage a child's (or adult's) body image. Some studies have shown that spinal curvatures, if they're severe, can interfere with breathing.

Many children with SMA start to show a scoliotic curve early in life, which is often treated with a brace until the right time for surgery is reached. Surgeons generally like to wait until growth is complete or nearly so before surgically straightening and fusing the spine. They also take into account the child's pulmonary function and how fast the curve is likely to progress.

At this time, life expectancy in childhood-onset SMA varies. Survival into young adulthood or even later can be expected.



Scoliosis (spinal curvature) is a common problem in SMA and should be corrected.



People with SMA type 3 often retain some ability to walk well into adulthood.



In adult-onset SMA, tools such as reachers can help make up for muscle weakness.

Type 3 SMA (Kugelberg-Welander disease or mild SMA)

Some sources describe type 3 SMA as a type of SMA that begins any time after 18 months of age, while others prefer to describe it as SMA that begins after the child has started walking or has taken at least five independent steps.

Many people with this type of SMA walk until their 30s or 40s, although some stop walking in adolescence.

Careful attention to respiratory matters and potential spinal curvature remain important. Adaptive equipment, such as power wheelchairs, tools for using a computer, etc., are usually essential in type 3 SMA. Some people need only a cane and perhaps a portable seat, with a wheelchair for going longer distances, as in airports and malls.

People with this milder type of SMA can survive long into adulthood, and academic and workplace achievements are common.

Type 4 SMA (adult-onset SMA)

This is a still milder type of SMA on the continuum. By definition, it begins in adulthood. Some physicians lump types 3 and 4 or types 2 and 3 together.

What happens to people with other forms of SMA?

Other types of SMA, not related to the SMN deficiency, vary greatly in severity and in the muscles most affected. Some forms of SMA, like the SMN-related type, affect mostly the proximal muscles, while others affect mostly the *distal* muscles, those farther away from the body's center, at least at the beginning. The hands and feet are typically affected early in the disease.

Sometimes, in adults with a disorder of uncertain origin that affects only the motor neurons in the spinal cord and lower part of the brain, the condition is referred to as

progressive muscular atrophy. This condition sometimes progresses to involve motor neurons in the upper part of the brain, and it's then referred to as *amyotrophic lateral sclerosis (ALS)*. It doesn't always become ALS.

Special aspects of SBMA are discussed beginning on page 9.

While all known forms of SMA are apparently genetic, they result from defects in different genes and have different inheritance patterns and implications for family planning.

If you or your child has been told the diagnosis is SMA but it's not the SMN-related type, you'll need to talk with your doctor and perhaps a genetic counselor to find out more about the genetics and prognosis for the particular SMA involved.

How is SMA treated?

The biggest potential problems in SMA, especially the chromosome 5 type, are, in approximate order of seriousness:

- respiratory muscle weakness
- swallowing muscle weakness
- back muscle weakness with progressive spinal curvature
- abnormal reactions to muscle-relaxing medications

These problems can be, and need to be, treated or prevented.

Respiratory muscle weakness

In the more severe forms of SMN-related SMA, and in some other forms of SMA, respiratory muscle weakness is an enormous problem. It's the usual cause of death in types 1 and 2 SMA. When the respiratory muscles weaken, air doesn't move into and out of the lungs very well, with subsequent adverse effects on general health. Signs of weakening respiratory



Respiratory muscle weakness in this baby with type 1 SMA requires assisted ventilation through a mask much of the time.



Noninvasive ventilation can be delivered through a mask or mouthpiece. Photo courtesy of Respirationics



A device that assists with coughing can help clear respiratory secretions. Photo courtesy of Respirationics

muscles are headaches, difficulty sleeping at night, excess sleepiness during the day, poor concentration, chest infections, and eventually, possible heart damage and respiratory failure.

In type 1 SMA, the muscles between the ribs are very weak, while the diaphragm muscle stays fairly strong. This leads to children who appear to be breathing by moving their bellies rather than their chests and to a pear-shaped body in these infants.

Parents of newborns with type 1 SMA may face the question of whether to prolong the lives of their children, who weren't expected to survive more than two years. In recent years, the availability of more portable and effective ventilation devices has given parents more choices. Some of these children have surprised their families and physicians by living many years. Some are in their teens today.

For children and adults with SMA who are less severely affected, various types of ventilatory assistance can help. Many physicians advise starting out with *noninvasive ventilation*, which generally means air (usually room air, not enriched with oxygen) delivered under pressure through a mask or mouthpiece.

This kind of system comes in many forms and can be used as many hours of the day and/or night as necessary. It can easily be removed for eating, drinking, talking or, when possible, breathing normally without it. Some people prefer to use *negative-pressure* ventilation systems, which create an intermittent vacuum around the chest or body to help the lungs expand and contract. These work on the same principle as the old "iron lungs" of decades ago, but they're far less cumbersome.

For severely affected children and adults, ventilatory assistance delivered through a *tracheostomy* — a surgical hole in the trachea, or windpipe — is often recom-

mended. Air under pressure is then delivered through a tube in the tracheostomy site. It's usually possible for people to eat, drink and talk with a tracheostomy tube, but these processes may take some adjustment. There's some concern that children who undergo a tracheostomy before they begin to talk may have difficulty learning to speak.

Other necessary aspects of respiratory care in SMA include clearance of respiratory secretions, sometimes also achieved with a mechanical device, and prevention of infection as far as possible.

Your MDA clinic staff can advise you about these needs.

Swallowing muscle weakness

Weakness of the muscles of the mouth and throat cause problems in swallowing, especially in the more severe forms of SMA. Babies with type 1 SMA usually have trouble swallowing and sucking, and in the past, this in itself often brought an end to their lives. Sucking weakness led to dehydration and poor nutrition, while swallowing weakness led either to obstruction of the airway by inhaled food or liquids or to respiratory infections from them. The medical term for this kind of inhalation is *aspiration*.

Nowadays, babies who can't swallow can be fed with alternative methods, such as a *gastrostomy tube* (g tube). Modern systems are often constructed so that the tube can be detached from a "button" on the abdomen when it's not in use. Liquid food, readily available in stores, is put into the tube either with a syringe or via a feeding pump. Some people grind up their own food.

Some g tube users also eat and drink through the mouth, in addition to using the tube. If the main problem is weakness of the chewing muscles, making eating laborious and time-consuming, then it's fine to eat for pleasure and extra nutrition



Because SMA affects the swallowing muscles, this baby is fed through a gastrostomy tube.



This girl with SMA type 2 used a back brace as a toddler. At 9, she underwent surgery to correct a spinal curvature, and wore a temporary brace while recovering from surgery.

and use the g tube for basic calories. If, on the other hand, the main reason for the tube is constant inhaling of food and liquid, then it's probably not safe to eat and drink through the mouth.

In SBMA (see page 9), swallowing and chewing muscle weakness pose a choking hazard. A swallowing specialist should be consulted to determine the safest ways of swallowing and altering food consistency. A feeding tube can be considered in cases of extreme weakness.

Back muscle weakness

Weakness of the muscles of the back that normally support the flexible, growing spine is a major problem in childhood-onset SMA. If it's not corrected, the child may develop scoliosis — a side-to-side curvature of the spine (see page 4) — or *kyphosis*, a forward curvature of the spine, or both. Some may even end up with “pretzel” types of curvatures that make it impossible to sit or lie down with comfort.

Many physicians believe that severe spinal curvatures also compromise respiratory function, since the curved spine often compresses a lung. In severe SMA, it's hard to say how much respiratory decline would have occurred even without the curvature, so its contribution is uncertain.

Bracing with a back brace or corset to support the child in a certain position is often prescribed to try to direct the spine as it's growing. (This isn't unlike bracing a young tree with a support.) These appliances don't solve the problem, although they may slow the progression of a curve, which is desirable.

The permanent solution to spinal curvature is almost always spine-straightening surgery (*spinal fusion*), which can be done if the child's respiratory status is good enough to withstand the surgery. Doctors generally like to wait until maximum spinal growth has been achieved, so a simpler surgical technique can be used. On the

other hand, they often can't wait until growth is complete, because respiratory status may be deteriorating at the same time. The timing of back surgery is tricky. Here again, your MDA clinic can help you decide.

Anesthesia concerns

A child or adult with SMA who must undergo surgery (for example, to correct scoliosis) needs to take special precautions. The surgical team, particularly the anesthesiologist, must thoroughly understand SMA.

Sometimes, especially in the early stages of SMA, the muscle cells that aren't receiving nerve signals develop certain abnormalities as they try to “reach out” to nerves. These abnormalities can lead to dangerous reactions to muscle-relaxing drugs often used during surgery. Doctors can get around this problem if they're aware of it, by using different drugs.

What about diet?

Many people wonder whether feeding their child or themselves in a special way will affect the course of SMA. So far, there's little evidence to suggest that any particular type of diet is useful in SMA.

It seems to make sense to many parents that a high-protein diet or some sort of special nutritional formula will help their child's muscles get stronger. While it's certainly true that children with SMA need good nutrition, there's no evidence that any particular type of diet is necessary, and, in fact, some may be harmful.

For example, special formulas made up of broken-down protein components called amino acids — so-called “elemental diets” — may actually cause problems for children with SMA who have little muscle tissue. Some experts say these amino acids can rise to too high a level in the blood if there isn't enough muscle tissue to properly use them.



People with SMA must take special precautions when undergoing anesthesia.



Physical therapy is an important part of preserving joint flexibility in SMA.

Some children may do better with small, frequent feedings than with three large meals a day.

Some children and many adults with SMA become overweight, probably because they can't exercise effectively and are taking in too many calories for their level of activity. With the guidance of a physician or nutritionist, it should be possible to keep weight under control, which is important for health, appearance and the backs of caregivers who must often help with lifting and transferring every day.

Some physicians recommend over-the-counter supplements, including creatine and/or coenzyme Q10, to meet nutritional needs. Creatine is being studied in SMA.

Your MDA clinic physician and other staff members at the clinic can help you with nutritional issues for yourself or your child.

What kind of exercise is best?

Most physicians advise people with SMA and parents of children with SMA that doing as much physical activity as is comfortable without going to extremes is a good idea, for general physical and psychological health and well-being.

It's important to protect joints from stiffness or injury, preserve range of motion (flexibility in the joints), maintain circulation and, especially for children, allow enough mobility for exploration of the environment.

Exercising in a warm pool (85 to 90 degrees) may be particularly beneficial. A person with SMA shouldn't swim alone, and appropriate safety precautions should be provided.

Some physical therapy experts have raised questions about whether it's wise to put too much demand on a gradually decreasing number of motor neurons, which have to do the work that would normally be done by many more such cells. Research

is needed to determine whether this theoretical issue should actually be considered in designing an exercise plan. Some experts believe it's impossible to overdo it, while others believe exercising to exhaustion can "burn out" remaining motor neurons before their time. It seems sensible to exercise with discretion and stop before reaching the point of exhaustion.

Physical therapy and *occupational therapy* programs can help both children and adults learn the best ways to use the muscle function they have and to come up with the most effective ways to accomplish activities of daily living. You can obtain a referral to a physical or occupational therapist through your MDA clinic.

Today, an array of assistive technology products can help even very young children explore the world despite having very weak muscles. Strollers, walkers, various kinds of powered and manual wheeled vehicles, and braces (the medical term is *orthoses*) can help with standing and moving around. Therapists also can help teachers and parents find the best physical solutions for the school environment.

Some families have even designed and built their own vehicles with special capabilities, such as adjustable heights that allow children to explore things at floor level or sit at tables and desks.

Special aids for writing, painting, using a computer or telephone, and electronically controlling the environment (for example, temperature, lighting, television and so forth) are helpful to adults and children with SMA-related weakness.

How is SMA diagnosed?

The first steps in diagnosis of a neuromuscular disease are usually an in-office physical examination and family history, with some nonpainful tests to distinguish SMA from similar conditions (such as muscular dystrophy).



A physical exam is a key part of diagnosing SMA.



Occupational therapy can help people with SMA learn to write, use a computer and do other daily tasks.

The doctor may order a simple blood test for an enzyme called *creatin kinase (CK)*. This enzyme leaks out of muscles that are deteriorating. It's a nonspecific test, since CK levels are elevated in many neuromuscular diseases, but it's often useful anyway. High blood CK levels aren't harmful; they're just an indicator of muscle damage.

The doctor will probably recommend genetic testing if SMA is suspected, since this is the least painful and most accurate way to diagnose SMN-related SMA or SBMA.

Genetic testing requires only a blood sample. However, it has implications for the whole family that must be considered (see "Does It Run in the Family?" on page 11).

Genetic tests are readily available for SMN-related SMA and SBMA, while genetic tests for the rarer forms of SMA are generally available only as part of a research study. However, such tests are improving and expanding rapidly, as knowledge and technology improve. In the near future, highly detailed genetic tests for SMN-related SMA will likely be used to predict the course of the disease with greater accuracy than is now possible.

It's a good idea to talk with a genetic counselor when someone in the family is found to have a genetic disease or when testing is undertaken. Your MDA clinic can help you find one.

The age distribution and symptoms of SBMA and adult-onset SMA overlap with those of another motor neuron disease, ALS, so the two are sometimes confused early in the diagnostic workup. It's very much worth knowing which disorder affects you or your family members, since ALS is a much more severe and rapidly progressive condition than are SBMA or adult-onset SMA.

In rare cases, doctors want the person suspected of having SMA to have a *muscle biopsy*, which involves taking a small sample of muscle tissue, usually from the thigh, and looking at it under a microscope.

Other tests that may be requested are those that measure *nerve conduction velocity* — the speed with which signals travel along nerves — and the electrical activity in muscle. The latter is called an *electromyogram*, or *EMG*. Nerve conduction velocity tests involve sensations that feel like mild electric shocks, and EMGs require that short needles be inserted in the muscles.

What is spinal-bulbar muscular atrophy?

Spinal-bulbar muscular atrophy, or SBMA, is sometimes called Kennedy's disease, after William Kennedy, the physician who originally described the disease in 1968. It's also sometimes called *bulbospatial muscular atrophy*.

This disease is a variant of spinal muscular atrophy. The adjective *bulbar* refers to a bulblike structure in the lower part of the brain that contains nerve cells controlling muscles in the face, mouth and throat.

SBMA also involves weakness and atrophy of the arm and leg muscles, particularly those nearest the center of the body. Twitching or cramping of muscles also can occur.

What happens to someone with SBMA?

SBMA mostly affects men and usually begins between the ages of 30 and 50, although symptoms have begun in boys as young as 15 or men as old as 60. In those few women who have the disease, the symptoms are usually mild.

SBMA is different from other forms of late-onset SMA. In contrast to most forms



Adults with SMA are often able to drive with specialized hand controls.



A nerve conduction velocity test may be part of the diagnostic process in SMA.



SBMA usually affects men between ages 30 and 50.

of SMA that begin in adulthood, the bulbar muscle involvement in SBMA can be significant, affecting speech, chewing and swallowing. The swallowing muscle weakness can lead to choking on food or liquids or inhaling them into the lungs. This kind of inhalation can lead to obstruction of airways or infection.

Weakness in the throat muscles also can make breathing during sleep difficult. Ventilation aids, which push air in under pressure, can help with this.

Facial muscle weakness can occur, making it hard to smile or convey emotion through facial expressions.

SBMA is *like* other forms of adult-onset SMA in that it causes weakness of the limbs. This weakness is often first noticed as trouble with stairs or difficulty walking long distances, such as through malls or parking lots. It progresses very slowly, over decades. As time goes by, a cane may be sufficient help for short distances, while a scooter or wheelchair may be needed for longer ones.

One aspect of SBMA that doesn't apply to any other form of SMA is that men with the disease can develop enlarged breasts (*gynecomastia*) and may have reduced fertility and atrophy (shrinkage) of the testicles. These symptoms, which became important clues to the cause of the disease, are related to the way the body's cells fail to process male hormones, known as *androgens*.

The usual form of SBMA is inherited in an *X-linked* pattern (see "Does It Run in the Family?" on page 11).

What is the root cause of SBMA?

The genetic flaw in X-chromosome SBMA is an expanded section of DNA called a *trinucleotide repeat* in a gene that carries instructions for a protein known as the *androgen receptor*.

The normal function of the androgen receptor is to help cells process androgens (male hormones). When the androgen receptor has extra DNA, it's longer than it's supposed to be and may be sticky. The flawed androgen receptor can't transport male hormones in the right way, and it may "gum up the works" of motor neurons in other ways that keep them from performing their usual functions.

Can women develop SBMA?

Because SBMA is an X-linked disease, it usually affects men. However, in some cases, women can have the disease, although it's almost always a very mild case.

The second X chromosome that females have is usually enough to protect them from most aspects of the disease. However, females (who also produce and use androgens, although less so than males) carrying the androgen receptor gene defect on one X chromosome (*carriers* of SBMA) can have muscle cramps and twitches, particularly as they get into their 60s or 70s. The hormonal differences between men and women also may contribute to the less severe course in women.

Does It Run in the Family?

When people learn that a family member has a genetic disorder, they often wonder how this could be the case if it doesn't "run in the family."

The chromosome 5 type of SMA (the most common type) follows an inheritance pattern known as *autosomal recessive*, which often takes families by surprise. Diseases that are *recessive* require two gene flaws — usually one from each parent, but occasionally one from one parent and one that occurs as a fetus is being formed — before the disease shows itself. People who have only one gene flaw for a recessive disease are said to be *carriers* and usually show no symptoms. Often, a family has no idea that some members are carriers until a child is born with a recessive disorder.

The *autosomes* are the numbered chromosomes, that is, all the chromosomes except the X and the Y, which determine gender.

If both parents are carriers of SMN-related SMA, the risk of each pregnancy producing a child with the disease is 25 percent. This risk doesn't change no matter how many children in the family have been affected previously. The "dice are rolled" with each new conception.

Genetic testing for chromosome 5 SMA is widely available for those suspected of having the disease, including unborn babies. However, as of 2003, carrier testing for SMA is more difficult and *not* widely available.

Genetic testing is expanding and changing rapidly, but its implications can be complex. It's best to talk with a genetic counselor (you can obtain a referral through your MDA clinic) before embarking on testing.

In contrast to chromosome 5 (SMN-related) SMA, the gene flaw causing most cases of spinal-bulbar muscular atrophy (SBMA) is on the X chromosome, leading to an X-linked inheritance pattern.

Females have two X chromosomes, and males have an X and a Y chromosome. Females who have a gene flaw on one X chromosome are usually considered carriers of an X-linked disease (although sometimes they can have a mild form of the disease). Males, in contrast, have no second X to protect them from the full effects of a gene flaw on the X chromosome and show the full effects of such a flaw.

Males who inherit an X-linked gene flaw generally have the disease. Each son of a woman who carries an X-linked disease has a 50 percent chance of inheriting the gene flaw and developing the disease. Each daughter has a 50 percent chance of inheriting the gene flaw and being a carrier herself.

Genetic testing via a blood test is available for SBMA.

For more on genetics and genetic testing, see MDA's pamphlet "Facts About Genetics and Neuromuscular Diseases."



In this family, two of the six children have SMA because they each inherited a flawed gene from each parent. The other children may be SMA carriers, able to pass a flawed gene to their children.



SMA can occur even when there's no family history.

MDA's Search for Treatments and Cures

The MDA website is constantly updated with the latest information about the neuromuscular diseases in its program. See the latest research news at www.mda.org.

The research picture has brightened considerably for chromosome 5-linked SMA in the last decade.

There are some special circumstances that pertain to the genetics of SMN-related, chromosome 5 SMA, and these have provided researchers with some special opportunities for intervention.

Since 1995, scientists have known that the main gene that determines whether someone develops SMA is a gene for the SMN protein (see page 3). The SMN gene comes in two slightly different versions, called *SMN1* (also known as *SMN-T*) and *SMN2* (also known as *SMN-C*).

The protein molecules made from the *SMN1* gene's instructions are longer than most of those made from the *SMN2* gene. These longer ("full-length") SMN protein molecules appear to be necessary for the proper survival and function of the motor neurons.

The *SMN2* gene can provide a certain amount of full-length SMN protein, but not enough. Fortunately, many people have multiple copies of the *SMN2* gene on one or both of their chromosome 5s. These "extra" *SMN2* genes can lessen the impact of a flaw in both *SMN1* genes. In general, the more *SMN2* genes a person has, the milder the course of his or her chromosome 5 SMA is likely to be.

Many research strategies to treat SMA are based on increasing production of full-length SMN from the *SMN2* gene.

Other approaches include less specific methods of helping motor neurons to survive in adverse circumstances.

Drugs that are based on *neurotrophic factors* (natural body chemicals that have a positive effect on nerve cells) and *anabolic* (tissue-building) chemicals are under consideration.

Also being studied is *creatine*, a substance that may help muscle or nerve cells produce energy more readily.

In SBMA, research has focused largely on strategies to block the formation of abnormal clumps found inside cells in this condition; ways to interfere with some of the actions of male hormones; and methods to influence how genetic instructions are "read" by cells. (See "What is spinal-bulbar muscular atrophy?" on page 9 for more on SBMA.)

Scientists funded through MDA's worldwide research program lead the search for potential treatments for SMA.



MDA Is Here to Help You

The Muscular Dystrophy Association offers a vast array of services to help you and your family deal with SMA or SBMA. The staff at your local MDA office is there to assist you in many ways. The Association's services include:

- nationwide network of clinics staffed by top neuromuscular disease specialists
- MDA summer camps for kids with neuromuscular diseases
- help with locating durable medical equipment through its national equipment program
- financial assistance with repairs or modifications to all types of durable medical equipment
- annual occupational, physical, respiratory or speech therapy consultations
- annual flu shots
- support groups for those affected, spouses, parents or other caregivers
- online support services through the e-community *myMDA* and through *myMuscleTeam*, a program that helps recruit and coordinate in-home help

MDA's public health education program helps you stay abreast of research news, medical findings and disability information through magazines, publications, educational speakers, seminars, videos and newsletters.

MDA's website at www.mda.org contains thousands of pages of valuable information, including disease specifics, research findings, clinical trials and past magazine articles.

Everyone registered with MDA automatically receives *Quest*, MDA's award-winning quarterly magazine. *Quest* publishes detailed articles about research findings, medical and day-to-day care, helpful products and devices, social and family issues, and much more. Other MDA publications can be found at www.mda.org/publications; many booklets are available in Spanish. Ask your local office for "MDA Services for the Individual, Family and Community" and for help with obtaining copies of other publications.

If you have any questions about SMA or SBMA, someone at MDA will help you find the answer. To reach your local MDA office, call (800) 572-1717.



On the cover:
Alexis, born in 1995, has type 3 SMA. She uses leg braces most of the time, and occasionally a wheelchair for longer distances. She loves going to MDA summer camp and is seen regularly at an MDA clinic.

MDA's Purpose and Programs

The Muscular Dystrophy Association fights neuromuscular diseases through an unparalleled worldwide research effort. The following diseases are included in MDA's program:

Muscular Dystrophies

Myotonic dystrophy (*Steinert disease*)
Duchenne muscular dystrophy
Becker muscular dystrophy
Limb-girdle muscular dystrophy
Facioscapulohumeral muscular dystrophy
Congenital muscular dystrophy
Oculopharyngeal muscular dystrophy
Distal muscular dystrophy
Emery-Dreifuss muscular dystrophy

Motor Neuron Diseases

Amyotrophic lateral sclerosis (*ALS*)
Infantile progressive spinal muscular atrophy
(*Type 1, Werdnig-Hoffmann disease*)
Intermediate spinal muscular atrophy
(*Type 2*)
Juvenile spinal muscular atrophy
(*Type 3, Kugelberg-Welander disease*)
Adult spinal muscular atrophy (*Type 4*)
Spinal-bulbar muscular atrophy
(*Kennedy disease*)

Inflammatory Myopathies

Polymyositis
Dermatomyositis
Inclusion-body myositis

Diseases of Neuromuscular Junction

Myasthenia gravis
Lambert-Eaton (myasthenic) syndrome
Congenital myasthenic syndromes

Diseases of Peripheral Nerve

Charcot-Marie-Tooth disease
Friedreich's ataxia
Dejerine-Sottas disease

Metabolic Diseases of Muscle

Phosphorylase deficiency (*McArdle disease*)
Acid maltase deficiency (*Pompe disease*)
Phosphofructokinase deficiency
(*Tarui disease*)
Debrancher enzyme deficiency
(*Cori or Forbes disease*)
Mitochondrial myopathy
Carnitine deficiency
Carnitine palmityl transferase deficiency
Phosphoglycerate kinase deficiency
Phosphoglycerate mutase deficiency
Lactate dehydrogenase deficiency
Myoadenylate deaminase deficiency

Myopathies Due to Endocrine Abnormalities

Hyperthyroid myopathy
Hypothyroid myopathy

Other Myopathies

Myotonia congenita
Paramyotonia congenita
Central core disease
Nemaline myopathy
Myotubular myopathy
Periodic paralysis



MDA's website, mda.org, is constantly updated with the latest research news and information about the diseases in its program. Follow MDA on Facebook, Twitter and YouTube.



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P-181W 7/11