Spinal Muscular Atrophy (SMA) is an autosomal recessive disease characterized by the loss or mutation of spinal cord and brain stem motor neurons. SMA is a progressive, degenerative disease of the muscles. SMA results in muscle weakness, atrophy, and in the worst cases, the inability to breathe. The brain is not affected by degeneration, therefore, cognitive development is normal. SMA has a continuous spectrum of symptoms that ranges from very severe to mild. The incidence of spinal SMA is approximately 5-7 per 100,000 live births, affecting males twice as often as females. SMA is the second most common disease inherited in an autosomal recessive pattern – cystic fibrosis is the leading. SMA kills more babies than any other genetic disorder and is the leading genetic cause of death of children under the age of two years old.

This newsletter will discuss the transmission and the basic defect associated with SMA. The three childhood types of SMA will be described, including clinical manifestations and ages of onset.

**Transmission**

To have SMA, a child must inherit two abnormal SMA genes from each parent. Both parents are carriers, identified in the Punnett square as Nn. The parents have just one abnormal gene, and are asymptomatic. Each time two carriers for SMA have a child, there is a 25% chance the baby will have SMA (nn), 50% chance the baby will be a carrier (Nn), and a 25% chance the baby will have not abnormal genes (NN).

One in 40 Americans is a carrier of the gene that causes SMA. It is only when a person has a child with a partner that carries the same recessive gene mutation, that there is a chance of having a child with a recessive disorder, such as SMA, as well as cystic fibrosis and sickle cell anemia.

The birth of a child with SMA is often a surprise to the parents, since in most cases there is no previous family history of SMA. Many autosomal recessive conditions occur this way. A referral for genetic counseling is indicated. Many parents of a child with SMA will decide not to have further children or will pursue adoption. Although quite expensive, in vitro fertilization, with testing of the embryos using pre-implantation genetic screening (PGS) is also an option, as well as using donor sperm or eggs.

**The Basic Defect With SMA**

SMA is characterized by progressive degeneration of certain lower neurons within the spinal cord, the anterior horn cells, as well as the motor neurons in the lowest region of the brain, the brainstem. Motor neurons are nerve cells within the central nervous system that send out messages to muscle fibers. Normally, messages from 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 there to particular muscles. Lower motor neurons control muscles in the arms, legs, chest, face, throat, and tongue. Loss or damage of lower motor neurons results in weakness, wasting, and atrophy of these muscles, universal to SMA. As a result, movement of these muscles is significantly impaired, resulting in hypotonia of the legs and arms, as well as problems with breathing, swallowing, sucking, and controlling secretions.

The mutated or absent gene responsible for SMA is the Survival Motor Neuron (SMN), specifically the gene, SMN1. SMN1 is located on chromosome 5 and is a protein critical for the survival and health of lower motor neurons. Normally, each cell has two copies of the SMN1 gene. About 95 percent of individuals with SMA have mutations that delete a section, called exon 7, in both copies of this gene. In about 5 percent of people with this disorder, one copy of the SMN1 gene has a deletion of exon 7, and the other copy has a different mutation that disrupts the production or function of the SMN1 protein.

SMN1 is normally inactive during the fetal period and allows normal apoptosis (cell death) necessary in the developing fetus. This protein normally becomes active in the healthy mature fetus so that programmed cell death doesn’t persist. With SMA, in the mutation or absence of this gene, programmed cell death persists. The mechanism and timing of abnormal motor neuron death remain unknown.

There is another gene, SMN2, which also provides instructions for the survival motor neuron (SMN) protein.
The SMN2 gene is similar to SMN1, but does not produce as much protein, or the right kind of protein, as the SMN1 gene. One determination of the type of SMA the child has, and therefore, the prognosis, is the number of copies of the SMN2 gene. The greater the number of SMN2 copies, the more SMN protein is produced and the greater likelihood that more motor neurons remain healthy and productive. Individuals with only 1 or 2 copies of the SMN2 gene will typically have the most severe form of SMA, Type I.

**TYPES OF SMA**

There are three types of SMA in childhood – Type I, II, and III, which are determined by the age of onset and the severity of symptoms.

**Type I**, also known as infantile onset SMA and Werdnig-Hoffman disease, is the most severe form of SMA. Approximately 80 percent of children with SMA fall into the severe category. Type I develops within the first 6 months of life, and in the majority of cases the diagnosis is made before 3 months of age. Many mothers of babies with Type 1 SMA report a reduction in fetal movement in the final months of pregnancy. In general, the earlier the symptoms appear, the shorter the child’s lifespan. The onset is usually sudden and dramatic. Once symptoms appear the motor neuron cells quickly deteriorate.

Muscle weakness, poor muscle tone, and lack of motor development, are the major clinical manifestations of Type I SMA. The infant is often described as “floppy”. There is little spontaneous movement and marked hypotonia in the legs, arms, neck, and chest is present. Weakness is often most severe in the legs. The infant typically lies in a frog position, with hips abducted and knees flexed. Movement of the arms from the elbows down only is common. Their hands commonly remain fistled with their hands/wrists turned the "wrong" way. Extremities are areflexive, meaning there are no adjacent movements, restraint, or hesitation, when the arms and legs are raised and allowed to fall. The infant’s head is often tilted to one side, even when lying down, because of lack of neck muscles.

There is weakness of the intercostal muscles, the muscles between the ribs that normally help expand the chest during inspiration. Due to this weakness, the diaphragm, the muscle between the chest and abdomen, and muscles around the abdominal area are used to breathe. Consequently, children with Type 1 SMA typically have bell-shaped bodies, with a smaller, often concave, chest, and a protruding abdomen. Due to this type of breathing, the lungs may not fully develop, and it may be difficult to take deep enough breaths while sleeping to maintain normal oxygen and carbon dioxide levels. Weakness of the chest muscles also results in a weak cry and cough, as well as accumulation of secretions in the lungs and/or throat and, therefore, an increased susceptibility to respiratory tract infections. Pneumonia is the most common cause of death, which often occurs prior to the first birthday. Most affected children die before 2 years of age, but survival may be dependent on the degree of respiratory function and respiratory support. Parents have difficult decisions to make for their baby, such as the use of mechanical ventilation to prolong life.

Respiratory compromise causes difficulty with sucking and/or swallowing, resulting in feeding difficulties. Tongue atrophy, as well as fasciculations (quivering) of the tongue, commonly occurs with Type 1 SMA, further adding to feeding difficulties. A gastrostomy feeding tube often becomes necessary early on. The infant’s weight is often lower than normal, falling below the 5th percentile. Additionally, developmental milestones, such as lifting the head or sitting up aren’t reached. Infants with Type 1 SMA have poor head control, and may not kick their legs.

**Type II**, also known as chronic infantile or intermediate SMA, is a disease affecting children before 2 years of age. The onset of weakness is usually recognized sometime between 6 and 15 months. Infants with SMA Type II have less severe symptoms during early infancy, but they become progressively weaker with time. These children are usually able to be in a sitting position without support, but often cannot get there by themselves. They can sometimes crawl with bracing and therapy, and on occasion may stand with braces, but are typically unable to walk. Children with Type II SMA also commonly have tongue fasciculations and often have fine tremors in outstretched fingers. Like with Type 1 SMA, weak intercostals muscles cause predominantly diaphragmatic breathing. Scoliosis is almost uniformly present as these children grow, as a result of weak back muscles. Spinal surgery and/or bracing is often needed at some point in their life.

The lifespan of a child with Type II SMA varies, but is greater than those with Type I. As with all forms of SMA, weakness increases over time. The prognosis and lifespan depends on how early symptoms were first experienced. Some children live into adolescence or early adulthood.

**Type III**, also known as Kugelberg-Welander disease and Juvenile SMA, is much more variable in the age of onset, occurring from one year of age to as late as adolescence. However, diagnosis prior to age 3 years is typical. Type III is the least severe form of SMA in childhood. In the beginning these children have normal development, including being able to stand alone and walk. However, as with all forms of SMA, weakness gets progressively worse and a wheelchair often eventually required. Early motor milestones are often normal. However, once they begin walking, they may fall more frequently, have difficulty in getting up from sitting on the floor or a bent over position, and may be unable to run. They typically have a normal lifespan.

There is no cure for SMA. As with any terminal disease, families with babies with Type 1 SMA, as well as other types, must grieve for the loss of a normal child, and ultimately the child’s death. Offering support, being non-judgmental as they face difficult decisions related to their infant, as well as future pregnancies, and keeping the parents informed, are key implications for the healthcare provider.
1. SMA is characterized by all of the following EXCEPT:
   a. mental retardation.
   b. muscle weakness.
   c. atrophy of the arms, legs, neck, and chest muscles
   d. hypotonia.

2. In SMA, the basic defect is mutated or absent:
   a. SMN2.
   b. exon 7.
   c. link on Chromosome 5.

3. SMA is what kind of genetic trait?
   a. Chromosomal
   b. Autosomal dominant
   c. Autosomal recessive
   d. Y-linked

4. Samantha, 2 months old, has Type 1 SMA. When assessing Samantha, which of the following findings is not commonly associated with Type 1 SMA?
   a. A frog-legged position
   b. Scoliosis
   c. A bell-shaped body
   d. Diaphragmatic breathing

5. Which of the following statements made by Samantha’s mother’s pregnancy is often associated with Type 1 SMA?
   a. “I had nausea for most of my pregnancy. A couple of times I needed IV fluids.”
   b. “I didn’t feel her move very often during the last couple of months of my pregnancy.”
   c. “I had gestational diabetes. She was a big baby and I had to have a c-section.”
   d. “They couldn’t tell her sex on the ultrasound I had.”
6. Samantha’s mother asks, “How could this have happened? We have no history of SMA in our families. We have another child, Matt. He’s 4 years old and healthy and so are we.” The healthcare provider appropriately responds:

a. “SMA tends to only affect females, so that’s why your son doesn’t have it.”
b. “With SMA both parents are carriers for it. I’ll be glad to go over that with you.”
c. “DNA testing will probably be done to insure your husband is Samantha’s father.”
d. “Since there’s no family history, I’ll have to check with Samantha’s doctor.”

7. Samantha’s father says, “We were planning on having four children. Since Samantha has SMA, and Matt doesn’t, that means our others will only be carriers, right?” The healthcare provider responds:

a. “That’s exactly right. If you have 4 children, 1, or 25%, will have SMA.”
b. “Yes, they won’t have SMA, but there’s a 50% chance they’ll be carriers.”
c. “Your chances are about the same as for anybody else.”
d. “Your risk for having a child with SMA is 25% for each pregnancy.”

8. Samantha’s mother asks, “Does that mean we shouldn’t have more children?” The correct response is to say:

a. “A genetic counselor can best help you with the risks and options. I’ll see about getting a referral if that’s something you’d like to do.”
b. “Your next child, if they have SMA, may have Type II or Type III, and they’re not as severe as the type Samantha has.”
c. “Since you are both carriers for SMA, I certainly wouldn’t take my chances, but that’s certainly up to you both.”
d. “I think you should consider adopting right away, so Matt will have a brother or sister.”

9. The SMA type is determined by the severity of clinical manifestations, as well as the age of onset.

a. True
b. False

10. With Type II SMA, the child, with or without bracing, is usually unable to:

a. hold head up.
b. sit up without support.
c. crawl.
d. walk.