Spinal Muscular Atrophy

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Introduction

Neuromuscular disorders and what people commonly call muscular dystrophies are very complex and often devastating conditions. Some strike children, others do not display symptoms until well into adult life. Most are progressively disabling, getting worse over time and some are fatal, often in childhood. Some affect primarily muscles, others can affect a wide spectrum of health, including; personality and intellectual functioning, the eyes, the bones, digestion and diabetes to list just a few. There are over 100 different types of disorders and variations listed under this umbrella. Many disorders have genetic causes but in many cases, just how these genetic mutations cause the symptoms we see is not yet understood. Every day, medicine is making progress in understanding these disorders, but at the present time, there are more theories than facts. Sadly there are no direct treatments yet.

Usually thousands of pages of information can be found on each disorder on the internet. This synopsis is yet another contribution to the public knowledge base. The reader is cautioned that no overview can be comprehensive and cover every question or situation. While a given type of disorder shares the same basic mechanisms and patterns, one of the features of these illnesses is that they are quite variable in how they affect people and no two people will have quite the same symptoms or experiences of the condition. For a given disorder, there is often wide variation between patients concerning how “big” the mutations are and this causes wide differences in how the disorder affects different people. The main aspects that differ are at what age the disorder strikes, how severe the symptoms are in an individual and exactly what is affected.

This is general information and should not be seen as medical advice. The best advice for you and your family is obtained from the doctor and the team of health care specialists who are diagnosing and following your case or that of your child.

The biggest impact of a muscular disorder is on lifestyle. Be it a child who is affected or an adult, the lifestyle of the whole family will be impacted. Yet, ironically, lifestyle is barely covered here. Why? Because the psychological and lifestyle impacts of these disorders are quite unique and evolve over time as the condition emerges, is diagnosed and progresses. It is not practical to offer advice on these complex and individual experiences on a general page like this. There are excellent peer support groups and discussion groups for all disorders on the internet. For even the rarest conditions, there are many others like you and it is usually helpful to discuss your feelings and questions with others who "are in your shoes."

Please feel free to contact Muscular Dystrophy Canada if you have suggestions or questions about this page. Our website is: http://www.muscle.ca/ or e-mail us at info@muscle.ca Thank you.

1). GENERAL OVERVIEW

1-A). What is Spinal Muscular Atrophy?

Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder that is characterized by the degeneration of motor neurons in the anterior horn of the spinal cord (it is a type of motor neuron disease). This loss of lower motor neurons leads to progressive symmetrical muscle weakness and wasting of voluntary muscles, as well as, dysphagia (problems swallowing), dyspnea (problems breathing), and in severe cases, to death. Spinal muscular atrophy usually affects the muscles closer to the center of the body (proximal muscles) more than the muscles farther from the center (the distal muscles). Sensation and the ability to feel are not affected. Intellectual ability is normal and it is often observed that children with SMA are unusually bright and sociable.

Research led to the identification of a gene on chromosome 5 named ''survival of motor neurons'' (SMN1) as the root cause for SMA. Mutations of the SMN1 gene cause reduced levels of the SMN1 protein. Without sufficient SMN protein, motor neurons shrink and die and as they do, the ability of the brain to control muscles diminishes. With less nerve control and use, muscles weaken and waste away. In general, the severity of SMA corresponds to the amount of SMN protein available in cells. Why low levels of the SMN protein lead to the specific loss of motor neurons is a central question in SMA research.

1-B). Quick Facts about Spinal Muscular Atrophy.

What: Spinal Muscular Atrophy, three main "childhood" types: I, II and III and one type that affects adults.
Who: Anyone

When: At any age
Where: Primarily proximal muscles (the torso)
Why: Muscle weakness caused by a genetic mutation leading to a protein abnormality

1-C). How common is Spinal Muscular Atrophy?

SMA affects approximately 1 in 6000 to 1 in 10,000 live births and is the leading genetic cause of infant mortality. It is the second most common lethal, autosomal recessive disease in Caucasians (after cystic fibrosis).

1-D). Are there different types of Spinal Muscular Atrophy?

There have been several types of SMA identified that are classified based upon their varying clinical presentations. The SMA type is generally determined from the clinical examination, evaluating the child's degree of weakness and the ability to achieve major developmental motor milestones such as the age when the baby first sits alone, takes a step, holds a toy, rolls, crawls, or walks. For example, when placed in a sitting position, the typical six-month-old child is able to use his or her arms as props to keep balanced and upright. Within another month or two, he or she is able to get into and out of the sitting position without any help.

Spinal Muscular Atrophy I (SMA I): (severe) Onset from birth to 6 months, child is severely affected (cannot sit without help) and with rapid mortality due to respiratory complications. Life expectancy is less than 2 years (death may occur in the womb). Over 50% of SMA patients have this most severe form of the disease.

Spinal Muscular Atrophy II (SMA II): (intermediate) Onset from 6 to 18 months, child is seriously affected (but can sit without help) and shows varying degrees of muscle weakness. Life expectancy is variable.

Spinal Muscular Atrophy III (SMA III): (mild) Onset after 18 months, these children have less weakness and usually have a normal life expectancy. The disorder progresses slowly, with the ability to walk usually lasting until into adolescence. A wheelchair is often required later in life.

Spinal Muscular Atrophy Type IV: (adult onset) Onset after age 35, much less common than the other forms, it is characterized by a gradual onset and very slow progression.

The same genetic abnormality, but of varying degrees of severity, is thought to cause all four types of SMA.

1-E). What other names do people use for Spinal Muscular Atrophy?

Spinal Muscular Atrophy, type I, SMA1, SMA I
-Werdnig-Hoffmann disease, infantile acute form

Spinal Muscular Atrophy, type II, SMA2, SMA II
-Spinal muscular atrophy, intermediate type
-Spinal muscular atrophy, infantile chronic form

Spinal Muscular Atrophy, type III, SMA3, SMA III
-Kugelberg-Welander disease
-Juvenile Spinal Muscular Atrophy

Spinal Muscular Atrophy Type IV, SMA4, SMA IV
-spinal muscular atrophy, adult form
-spinal muscular atrophy, proximal, adult, autosomal recessive

1-F). Are there other disorders related to Spinal Muscular Atrophy?

Disorders of a similar type: SMA is a motor neuron disorder. There are several other disorders in this category:

- Spinal muscular atrophy with respiratory distress type I (SMARD I):
SMARD I has been linked to a mutations in the gene encoding the immunoglobulin micro-binding protein 2 (IGHMBP2) on chromosome 11. This rare form presents symptoms from age of 1 to 6 months with respiratory distress due to paralysis of the diaphragm and progressive muscle weakness with predominantly distal lower limb muscle involvement (ankles and feet). Sensory and autonomic nerves are also affected.

- Spinal and bulbar muscular atrophy (SBMA):
A rare, adult-onset form of motor neuron disease that is less common than childhood-onset SMA type I, II and III. This form only occurs in males and has a genetic cause, linked to a mutation on the X chromosome. It is associated with CAG repeat mutations that affect a protein called androgen receptor protein, apparently making it toxic to neurons. It often causes weakness of the muscles of the mouth, throat, face and limbs. Symptoms related to abnormal processing of androgens (male hormones), such as breast enlargement and reduced fertility, may also occur.

- Amyotrophic Lateral Sclerosis (ALS), Lou Gehrig's disease. The cause is generally unknown, although several genetic factors are thought to play a role. About 15 - 20 percent of cases are linked to a mutation on chromosome number 21. Symptoms include rapidly progressive loss of motor function with predominantly lower motor neuron manifestations, generalized weakness and muscle wasting with cramps and muscle twitches. ALS first affects the legs, arms and/or throat and mouth muscles but ultimately affects all voluntary muscles, resulting in paralysis. ALS has an average age of onset of 55 and usually progresses rapidly with a 3 to 5 year average survival after diagnosis.

2). SYMPTOMS

2-A). What are the symptoms of Spinal Muscular Atrophy?

The different types of SMA display different symptoms; please refer to the section on types (1-D) for details.

ANESTHESIA WARNING: A higher rate of complications is associated with general anesthesia in patients with neuromuscular disorders. Even mildly affected patients may have complications. Patients with SMA or a family history of SMA need to discuss this with their surgeons.

2-B). What is the age of onset of Spinal Muscular Atrophy?

The different types of SMA display different age of onset; please refer to the section on types (1-D) for details.

2-C). Are different age-groups affected differently?

Yes. The different types of SMA affect different age groups differently; please refer to the section on types (1-D) for details.

2-D). Who can be affected by Spinal Muscular Atrophy?

Spinal Muscular Atrophy affects both males and females.

2-E). How does Spinal Muscular Atrophy progress and what is the prognosis?

SMA is a progressive disorder, which means the symptoms worsen over time. How rapidly the disability progresses and the extent of muscle loss depend upon the levels of SMN protein available in the cell. Most doctors view SMA as a continuum of severity and do not want to make predictions about progress, prognosis, weakness or life expectancy.

2-F). Are there non-neuromuscular problems associated with Spinal Muscular Atrophy?

As the body develops and muscles atrophy, a number of secondary physical issues may arise, notably, bone and spinal deformities. As well, typically children with SMA have inborn errors of fatty acid and protein metabolism and many benefit from a special diet.

2-G). How “serious” or disabling is Spinal Muscular Atrophy?

SMA causes a varying degree of muscle weakness that becomes progressively more disabling over time. Again, the severity of SMA depends upon the level of protein that is being produced. This is not measured directly but is usually implied by the age of onset

and the severity of the symptoms observed. If the protein shortage is major, the disorder is severe and disabling, in the most severe cases, with death occurring before age two.

2-H). Does Spinal Muscular Atrophy affect thinking or behaviour?

There has been no documented link of SMA to learning disabilities or mental impairment. In fact, it is often observed that children with SMA are unusually bright and sociable.

3). DIAGNOSIS

3-A). How do I know if I have Spinal Muscular Atrophy?

Because Spinal Muscular Atrophy is a genetic disorder, the defect related to SMA is present at birth. However, the symptoms of SMA are variable and may emerge at different points throughout childhood or adulthood. Parents would note unusual weakness in children and an inability to meet expected developmental milestones as described above.

3-B). How is Spinal Muscular Atrophy diagnosed and what tests are performed?

There are three main diagnostic approaches:

- Clinical diagnosis: the doctor looks at you and notes your pattern of symptoms.
- Diagnostic tests: These can include blood tests, x-rays and other types of scans, tests of muscle and nerve function and different types of biopsies.
- Molecular (genetic) testing: This method looks at your cells and genetic material to see if there is a genetic problem. This is usually done through looking at blood samples.

Diagnostic approaches for SMA involve clinical diagnosis, diagnostic testing and molecular (genetic) diagnosis.

Clinical diagnosis involves a doctor or neurologist looking for key symptoms to identify the distinctive pattern of muscle involvement.

Diagnostic testing includes doing studies of the electrical pattern of the muscles using electromyography (EMG). Tiny needles are placed in a muscle and hooked up to a computer to measure the electrical activity of the muscle as it contracts and relaxes. In addition, the physician will do a blood test called a creatine kinase (CK) level (also known as a phosphocreatine kinase (CPK) level) to test the health of the muscles. If muscles are abnormally breaking down, they release elevated levels of the enzyme creatine kinase into the blood. Other tests may include a Nerve Conduction Velocity (NCV) test to measure how fast electrical signals are moving along the nerves.

A muscle biopsy may be suggested at this stage. A small piece of muscle is surgically removed and examined in the laboratory.

Once a clinical diagnosis has been suggested, the patient and doctor can discuss genetic testing. Molecular (genetic) diagnosis is often used to confirm the clinical diagnosis.

Molecular (genetic) diagnosis involves a much more accurate test than clinical diagnosis and is often used to confirm clinical suspicions. Molecular diagnosis involves a genetic understanding of the disorder and the ability to test the DNA (or RNA) in the blood for specific mutations as compared to a healthy sample.

In the case of SMA, the first diagnosis is based on clinical observations and this is usually confirmed through a blood test, which looks for problems with, or absence of, the SMN1 gene. Since the genetic blood test for SMA became available, a muscle biopsy is seldom indicated and is valuable mainly in cases where the genetic test is ambiguous or negative.

3-C). Is there a genetic test for it?

Yes, there is a widely available test that is both very specific and very accurate for SMA that detects problems with the SMN1 gene.

DNA, the body's genetic information, is found in most cells and a sample of the patient's DNA can be obtained from the white blood cells found in a sample of blood. The DNA sample is analyzed to look for the specific mutation associated with the disorder.

The genetic test looks for a piece of code called exon 7 on the SMN1 gene. An absence of this piece of DNA code is diagnostic of SMA in about 95% of cases. This approach is complicated due to a very similar piece of code on the SMN2 gene (exon 7 in the SMN2 gene differs by only one letter from the SMN1 exon 7 section).

A prenatal test and preimplantation genetic diagnosis (PGD) for SMA are also available, please see this site for more information: http://www.fsma.org/genetics.shtml

Gene Tests SMA testing:
http://www.genetests.org/servlet/access?prg=j&db=genetests&site=gt&id=8888892&fcn=c&qry=2256&res=&key=QdWQCjF3V0QCL&show_flag=c

3-D). Should other members of the family be tested for Spinal Muscular Atrophy?

As SMA is a genetic disorder, it is possible that parents, siblings, or children may also carry variations of the mutation responsible for the disorder. Given that it is an autosomal recessive disorder, a person could carry a copy of the mutated gene yet, not show any symptoms, and pass the gene on to a child (the individual is a carrier). Family members may choose to have a simple blood test involving quantitative analysis of the SMN1 gene

to determine whether they are SMA carriers or not. The results of this test will provide critical information for genetic counselling. However, testing for any genetic disorder is a personal choice and, when done on a seemingly healthy individual, that choice should not be made lightly. This question should be discussed with your family, your doctor, or a genetic counselor.

3-E). How can we be confident in the diagnosis?

Modern diagnostic procedures are generally very accurate. However, if you feel unsure about your diagnosis, it is important that you discuss your concerns with your doctor and ask about options for further testing or for a second opinion.

4). CAUSES and PATHOLOGY

4-A). What causes Spinal Muscular Atrophy?

Typically, genetic disorders involve mutations in a specific gene. Genes are used by the cell to make proteins, therefore a mutation usually disrupts a specific protein and this causes the disorder. In the case of SMA, a genetic mutation causes a protein called SMN1 to be disrupted and there is not enough of this protein in the nerve cells for them to operate properly. As a consequence, the motor neurons die off and this affects the transmission of nerve signals from the brain to the muscles. Without proper signals, the muscles cannot function properly and they eventually shrink and die.

4-B). How does a person get Spinal Muscular Atrophy?

As an inherited genetic disorder, SMA is passed from generation to generation. Parents who carry the mutated gene (known as SMA carriers) can pass the mutated gene to their children at conception.

It is also known that SMA can arise as a new or spontaneous mutation. In the development of new cells after conception, the DNA is copied over and over and, in this copying process, a mistake can occur and the child's DNA suffers a new mutation. About 2% of SMA cases fall into this category. In these cases, the DNA that is passed on by one parent is healthy (and becomes mutated after conception), the DNA from the other parent already carries a mutation (new mutations in two healthy parents would be possible but very very unlikely). Most new mutations are seen in the gene copy inherited from the father.

4-C). Is Spinal Muscular Atrophy anyone's fault? Is it contagious?

No. The mutations that cause SMA occur by chance and are passed from generation to generation or arise as a new genetic mutation, again by chance. SMA is not something that is routinely screened for but if SMA is suspected or if there is a family history of the disorder, a prenatal test for SMA is available.

Is it contagious? SMA is not contagious. SMA is a genetic disorder and therefore cannot be passed from person to person by any sort of physical contact. Genetic disorders can only be passed on through reproduction.

5). GENETICS

5-A). Does genetics play a role in Spinal Muscular Atrophy?

Yes. Spinal Muscular Atrophy is a genetic disorder caused by a genetic mutation. This mutation is either a new, spontaneous mutation or has been passed down from generation to generation.

5-B). What genes are related to Spinal Muscular Atrophy?

Normally, people have two genes called Survival Motor Neuron 1 (SMN1) and Survival Motor Neuron 2 (SMN2) on chromosome 5. Both genes make SMN protein. The SMN1 gene produces the normal SMN protein that nerve cells need, this protein is often referred to as full-length SMN. The SMN2 gene mostly produces a slightly smaller SMN protein that the nerve cells cannot fully use, this protein is often referred to as delta7-SMN or Δ7-SMN. SMN2 also makes a little bit of the normal full-length SMN1 protein (10 to 30% of what is needed) but this is not enough SMN1 protein to allow nerve cells to function properly. Therefore, when the SMN1 gene is mutated or absent, the SMN2 gene cannot make enough full-length SMN to compensate for the loss of the SMN1 gene. In about 95% of SMA patients, the SMN1 gene is either deleted (absent) or rearranged. Mutations that “rearrange” the SMN1 gene usually convert the SMN1 gene into a SMN2 gene. The consequence of this “rearrangement” or “gene conversion” is that the converted SMN1 can no longer make the amounts of full-length SMN protein needed by the nerve cells. The severity of symptoms (or type of SMA) is correlated to the status of the SMN1 gene as well as the number of functional SMN2 genes. If SMN1 is deleted (absent) but there are several SMN2 genes making some full-length SMN protein, the symptoms will be milder (SMAII or SMA III).

- SMN1 mutations are present in 95% of SMA patients
- The number of SMN1 gene copies sometimes varies in normal people (most have two copies – one on each chromosome # 5 of the pair of autosomes). (Autosomes are the 22 pairs of chromosomes that are identical in males and females. The remaining pair of chromosomes are the sex chromosomes, namely the X and Y chromosomes that distinguish females (XX) from males (XY). Each cell has 23 chromosomes inherited from the mother and 23 chromosomes inherited from the father, for a total of 46 chromosomes.)
- The number of SMN2 copies also varies:
    - Normal people: No SMN2 copy 9%; 1 SMN2 copy 42%; 2 SMN2 copies 46%; 3 SMN2 copies 3%

- SMA carriers: No SMN2 copy 1%; 1 SMN2 copy 18%; 2 SMN2 copies 47%; 3 SMN2 copies 31%; 4 SMN2 copies 3%
- SMA patients:
  - SMA I: 80% have one or two copies of the SMN2 gene,
  - SMA II: 82% have three copies of the SMN2 gene,
  - SMA III: 96% have three or four copies of the SMN2 gene.
- These variations complicate testing.
- SMN1 & SMN2 genes are both correlated with disease severity

  - Absence of both SMN1 & SMN2 genes = Lethal
  - No SMN1 gene & 1 copy of SMN2 = Fetal death or soon after birth
  - Milder disease (SMA II or III) = Three or more SMN2 gene copies present

Summary:
SMA type I
-Mostly SMN1 deletions (more severe)
-A few missense point mutations in SMN1 (less severe)
-SMN2 gene copy number: Often just 2
SMA type II
-Mutations convert the SMN1 gene to SMN2
-SMN2 gene copy number: $\geq$ 3
-A few missense point mutations in SMN1 (less severe)
SMA type III
-Mutations convert the SMN1 gene to SMN2
-SMN2 gene copy number: $\geq$ 3
-A few missense point mutations in SMN1 (less severe)

For more detail, please see:
http://www.neuro.wustl.edu/neuromuscular/synmot.html#sma5q

5-C). Is Spinal Muscular Atrophy inherited and if so, how?

Yes, SMA is inherited – it is passed from generation to generation in an autosomal recessive manner. Typically autosomal recessive diseases are inherited from both parents who are unknowingly genetic carriers. In order for a child to be affected by SMA, both parents must be carriers of the abnormal gene and both must pass the mutated gene on to their child. About 1 in every 30 to 1 in 60 Caucasians (many quote 1 in 40) appear to be carriers of the SMA mutation. Each parent has one healthy gene and one defective gene and each will contribute one of these genes to the child's DNA. The parents do not show symptoms because their one healthy gene is able to make enough protein to keep things working (the defective gene is recessive, so it just sits there in the background doing nothing). If both parents are carriers, the likelihood of a child inheriting the disorder is 25%, or 1 in 4 – the child needs to receive two defective copies for SMA to be present.

Summary:

Inheritance from two diseased parents odds: 100%. In this rare case, two people who have an autosomal recessive disease (not just carriers), carry 4 copies of the bad gene and so the child will get 2 bad copies and will have SMA.

If two carriers have a child, that child randomly gets one gene from each parent. There are three possible outcomes:
- the child may inherit two healthy genes and be normal (a 25% likelihood)
- the child may inherit two mutated genes and have SMA (a 25% likelihood)
- the child may inherit one healthy gene and one mutated gene and be a carrier (a 50% likelihood)

If parents have a child with SMA, this almost always means that they are both carriers. The chances a second child will also have the disease are the same as for two parent carriers, listed above. Genetic testing can often detect rare cases where a child gets a sporadic genetic disease without both parents being carriers (perhaps only one is a carrier and the child had one spontaneous mutation, coincidentally mutating exactly the same gene as in the carrier parent).

Inheritance from one SMA parent: Usually the child will not have SMA but will be a genetic carrier. The affected parent has two bad copies of the gene, so the child gets a bad gene from that parent, but usually a good second copy is received from the other unaffected parent (who is not a carrier). However, if the spouse is an SMA carrier, their children may inherit two mutated genes and have SMA (a 50% likelihood) or one healthy gene and one mutated gene and be a carrier (a 50% likelihood). The spouse of an SMA individual can have a quantitative PCR test that will assess whether he/she is an SMA carrier. The results of this test will provide critical information for risk assessments.

Inheritance if one parent is a carrier and the other is not: Generally, both parents must be genetic carriers of an autosomal recessive disease for a child to get the disease. If only one parent is a carrier (and the other unaffected), the child cannot get an autosomal recessive disease, but might still be a carrier (typically 50% chance of being a genetic carrier of the autosomal recessive disease).

Inheritance patterns for autosomal recessive diseases tend to be "horizontal," with a generation being affected – many siblings of the same parents are affected, but not their parents and not their own children. Parents and next-generation children will usually be carriers.

Somatic and Germline (gonadal) mosaicism:

The above description assumes that, if there is a mutation, all of the cells will have it. This does not always happen, sometimes a few cells will have the mutation and other cells will be healthy. This complicated scenario is called mosaicism and the individual is referred to as a mosaic. Think of the pattern of tiles on a black and white mosaic floor – the white tiles are healthy and the black ones are mutated – this is the type of pattern seen in the cells, some are healthy and some carry the mutation.

How does this happen? As described above, genetic mutations are not always inherited from a parent (through an egg or sperm cell), some may occur spontaneously as a new mutation after conception and during the early days of embryonic development. Very early in the development of an embryo, ancestor cells that are the child's future sperm or egg cells separate from the rest of the developing cells. This batch of cells that are set aside – eggs in a female and sperm in a male – are called the germline.

Germline cells divide and multiply in the developing embryo and this division continues after the child's birth. For males, sperm cells don't complete their development until the child becomes an adolescent. A female's egg cells complete part of their development during fetal life and part at puberty. New mutations can occur in the genes of these cells at any stage during this process. If mutations occur early in development, they often affect many of the subsequent sperm or egg daughter cells. If they occur later, mutations may affect very few cells, or maybe even just one cell.

[We should mention here that new mutations are not uncommon and geneticists estimate that about 30 negative mutations occur during an average lifetime. These mutations accumulate as we age and increase in frequency as we age, this is one of the reasons why birth defects become much more common when the parents are 35 and older.]

When mutations occur after the germline has separated, there's a good chance they'll affect many sperm or egg cells but not the other cells in the body, such as blood or skin cells – these are the cells commonly used in genetic testing. A genetic test of these cells will not suggest any problems. Even if a sample of sperm or egg cells is tested and shows no mutations, other egg or sperm cells could still carry the mutation. Just one mutated cell is all it takes. Once a mutation has been inherited by a child, it becomes part of his or her DNA and can be passed on to future generations if he or she subsequently has children – the children would have the mutation in every cell.

[During a person's lifetime, new mutations are also occurring in the somatic (body) cells. These mutations cannot be passed on to future children (because they are not in sperm or egg cells), but they can cause illness in the person's lifetime. Common examples are mutations in skin cells causing skin cancer or in breast cells causing breast cancer.]

In summary, these mutations often affect only some cells, leaving others healthy and leading to mosaicism in the individual. In SMA, it's ~~not~~ uncommon but not impossible to

find that only some of a person's egg or sperm cells (the germline cells) have the SMA mutation. About 1 in 50 SMA patients have a de novo (new) mutation. Thus, 1 in 100 parents of SMA children have germinal mosaicism.

~~Mosaicism greatly complicates making predictions about inheritance or the severity of a disorder in children of mosaic parents. A parent who has the mutation in only some of his or her cells may have very mild, undetectable SMA symptoms. But that person's child could acquire the mutation through a germline cell (an egg or a sperm) and thus have it present in all cells starting at conception. Such a child would be more severely affected than his or her mosaic, partially affected parent. Thus, if a parent has SMA diagnosed but his or her mosaic status isn't recognized, by assuming the severity of the disorder will be like that of the parent, the severity in the offspring may be underestimated.~~

If all germline cells have the mutation, the risk of passing on a recessive disease like SMA is 25 percent. However, germinal mosaicism greatly complicates making predictions about inheritance. In individuals who are germline mosaics, only some of the cells carry the mutation and the risk of passing on the disorder falls below 25 percent – it would reflect the ratio of healthy cells to mutated cells in the mosaic parent – a ratio that can not be calculated. There are several scenarios for this recessive disorder when a parent has a mixture of mutated and healthy germ cells (either eggs or sperm).

- If one mutated egg or sperm cell from the mosaic parent becomes part of the fertilization, the child will be a carrier of SMA.
- If a mutated egg is received from mom and a mutated sperm cell is received from dad, the child will have SMA (both could be mosaics or one parent could be a full carrier and the other a mosaic)
- If a healthy egg is received from mom and a healthy sperm cell is received from dad, the child will be SMA free and will not be a carrier.

Once an SMA child has been identified as carrying a de novo mutation, prenatal diagnosis is available to determine if future children of an parent with germinal mosaicism will have SMA or not.

~~In summary, if a parent has SMA diagnosed but his or her mosaic status isn't recognized, the chances of passing on the SMA mutation to a child are often overestimated.~~

~~In patients who display mild SMA symptoms but whose genetic testing suggests a more severe type of mutation, mosaicism should be suspected. In these cases, special genetic testing should be done to reveal the mosaicism.~~

6). TREATMENT and MEDICAL MANAGEMENT

6-A). How can we cope with this diagnosis?

A diagnosis of SMA comes as a shock, and in the most severe cases, is a devastating realization. SMA brings challenges and very difficult adjustments and decisions for the parents of an affected child. It is common to experience many mixed emotions, especially

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Comment [S1]: I have trouble with these sentences (highlighted in yellow) because, to my knowledge, there is no evidence that germline mosaic parents have any symptoms of SMA. If we say that they do, then the 1 in 100 SMA parents may begin to worry uncessarily. Also, this paragraph reads as if the SMA patient is mosaic, I am not sure such cases have been reported. However, I am not a neurologist and it might be worthwhile getting some feedback from either Brenda or Bernard. In my mind, this paragraph could be dropped without losing critical information. As also for the two final paragraphs.

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grief, anger, and fear. Giving yourself time to adjust, talking to family, friends and professionals, and reading about SMA, may help as you deal with this diagnosis. Talking to other people coping with this disorder, parents of children with SMA, or health professionals may also be helpful.

6-B). How can I best manage my life with my symptoms?

In most cases, this question will be “How can we best manage our child’s symptoms?” You need to manage the symptoms in close liaison with your medical team. If the symptoms present very early (SMA 1) then it will be necessary to make some critical and very complicated decisions about the way you want the medical team to handle your child. The basic challenges involve issues related to breathing and eating.

Respiration

There are three basic options depending upon the decisions you make:

- Palliative Care: This is the least invasive option. A child with SMA Type 1, with no intervention, has a life expectancy of approximately 8 months, with 80% expected to pass away by 1 year. In palliative care, parents usually choose to use oxygen and pain medications such as morphine to help keep the child as comfortable as possible until they pass away.

- “NIV Protocol:” This technique is used in muscular disorders that affect respiration like SMA and Duchenne muscular dystrophy. It was developed by Dr. John R. Bach and is also known as “noninvasive intermittent positive pressure ventilation (IPPV) or often as “Dr. Bach’s Non-Invasive Protocol.” This is a respiratory protocol using machines to help the child breath. One machine is called a "Bipap" (Bi-level Positive Airway Pressure) and another machine that helps the child cough is called a "Cough Assist" (mechanically assisted coughing (MAC)). These machines help the child breath and generally increase the length and quality of life. Usually, a Bipap machine is used with a non-invasive face mask. The machine adjusts air pressure as the child breathes in and out.

- Tracheotomy: This surgical procedure allows insertion of a tube into the throat to connect to a permanent ventilation machine that breathes for the child all the time.

Feeding

Many believe that a special diet is required for SMA children. Often feeding tubes must be used, either a nasal gastric tube that goes through the nose down to the stomach or a more permanent type of tube, a gastric tube that goes directly into the stomach.

Children with SMA II or SMA III usually do not present with such life threatening or urgent problems. There is a wide range of challenges and needs as these children grow.

6-C). How can doctors and specialists (like neurologists) help?

Neurologists are doctors who specialize in disorders affecting the nervous system and the muscles. They are often consulted for patients who may have Spinal Muscular Atrophy. Where your family doctor may not be able to offer specialized advice about SMA, they should be able to recommend you to a neurologist in a neuromuscular clinic who is better equipped to diagnose your disorder and answer questions about possible management options. There are neuromuscular clinics and hospitals across Canada that are equipped to do the necessary diagnostic testing and to offer advice and support regarding the ongoing management of SMA.

6-D). Are there treatments or medications for Spinal Muscular Atrophy?

There are no specific treatments for SMA, treatments are focused on dealing with symptoms as they arise.

A major research project is trying to develop methods to treat SMA:
The National Institute of Neurological Disorders and Stroke (NINDS) has established the SMA Project: A Collaborative Program to Accelerate Therapeutics Development for Spinal Muscular Atrophy (SMA). http://www.smaproject.org/

For the most recent review (2005) of SMA and its potential treatments, please see: http://www.smafoundation.org/pdf/White_Paper.pdf This review is published by the SMA Foundation (http://www.smafoundation.org/).

There are a number of on-going clinical trials and additional trials possible in the near future. For routine updates of these, please see: http://clinicaltrials.gov/ and Section 8-B.

6-E). Can surgery help?

People living with SMA might be recommended for certain surgical procedures to help stabilize the bones in the spinal column.

6-F). Can physiotherapy help?

Once a diagnosis is confirmed, a person living with SMA may be assessed in physiotherapy in order to evaluate their joint mobility, test their facility to move from one position to another, test their ability to walk, and to evaluate their capacities in activities involving gross motor skills (jumping, running, or climbing stairs). A regular or standardized monitoring may be suggested and, depending on each person's needs, done in conjunction with a program of activities to practice at home. These programs are aimed at strengthening or maintaining range of motion, coordination, and balance.

6-G). How can occupational therapy help?

The role of the occupational therapist is to foster fine motor skills development and lessen the impact of the disorder on lifestyle. Accessible transportation is often a

requirement. Physical education (for children) or ongoing physical activities need to be adjusted to each person's capacities as soon as possible.

An occupational therapist can also recommend braces, girdles, or special belts to help compensate for weakened muscles. Muscular Dystrophy Canada's equipment loan program relies on the expertise of occupational therapists to recommend equipment required by people living with disorders such as SMA.

People with SMA III or one of the adult onset forms may lead productive lives and go on to have their own families.

In the work environment, it is the responsibility of adults living with SMA to negotiate employment conditions with their superiors and co-workers.

6-H). How can a nurse help?

The nurse may provide additional information about SMA and available services and resources. A nurse may offer support to help the individual and family members cope with the disorder, provide guidance with the administrative processes when required, and liaise with the various health care professionals from the clinic and other external services.

6-I). How can a genetic counselor help?

Geneticists, doctors who specialize in medical genetics, molecular geneticists, and genetic counselors are employed in major hospitals across Canada and are available to people and their families for the purpose of diagnosis and counselling. Genetic specialists can inform the person living with SMA and their family members about the specific inheritance processes involved, the genetic testing available, as well as family planning alternatives they may wish to consider. The information provided by a genetic counselor can be specifically tailored to an individual's family history and this knowledge might be very useful in further understanding how the disorder has affected him or her and his or her family.

6-J). How can a dietician help?

Diet appears to be a major concern for the parents of SMA children. Many parents circulate "unofficial" diets in SMA support groups and believe that these specialized diets are crucial to the health of the child. There is a good deal of controversy over whether supplements and elemental formulas are of benefit.

A balanced, nutritional diet is essential to achieve the maximum function of muscles. It is often a challenge for the average person to keep fit and keep their weight from rising as the years go by. This is especially true in patients who have muscle disorders because their ability to exercise and burn off calories is usually greatly impaired. Excessive

weight gain by people living with SMA is not recommended. The extra work that weakened muscles must do to lift excess weight adds to the challenge.

A dietician can offer advice in building a balanced diet for anyone living with a neuromuscular disorder. Some specific advantages to working with a dietician may include weight control and finding a proper balance of food that will keep the body healthy. Parents may need to provide their child with support and information about healthy nutrition based on work with a dietician. The ongoing support and understanding of family where nutrition is concerned is very important.

6-K). What is ventilation and will I need it?

In SMA, the muscles that control breathing are often weakened. In these cases, machines may be used to help air move in and out of the lungs. Assisted ventilation is an extreme measure and a significant decision in the lives of many people living with a neuromuscular disorder.

Sadly, respiratory complications usually eventually cause death in SMA. Please see item 6-B, above for more information.

7). LIFESTYLE IMPACTS

7-A). How will Spinal Muscular Atrophy affect my lifestyle?

It is very difficult to answer this question due to the wide range of severity seen in SMA. Perhaps the most honest answer is “it depends.” Lifestyle impacts will depend upon the type and severity of symptoms you, or your child, experience. When symptoms emerge will also be a big factor.

Neuromuscular disorders may have wide impacts on many different aspects of our lifestyle. These may include physical aspects like impacts on breathing, swallowing, bathroom habits, one’s sex-life and other day-to-day activities. In addition, there are major psychological impacts on the patient and on the rest of the family as the disorder progresses and adaptations have to be made. Progressive disorders involve progressive changes and progressive impacts. As you adjust to things, things often change again. Lifestyle impacts and psychological adaptations are therefore an unfolding process that mirrors the progression of the disorder.

8). RESEARCH

8-A). What research is being done on Spinal Muscular Atrophy?

One of the keys to treating SMA will be to better understand the gene(s) affected by the SMA mutation and how to get more SMN protein functioning within the cell. Someday, perhaps the genes involved in SMA will be manipulated to reverse the symptoms seen.

Muscular Dystrophy Canada funds an active and broad research agenda. You can find out more information about recent SMA research funded by Muscular Dystrophy Canada at: http://www.muscle.ca/content/index.php?id=90

8-B). Are there clinical trials for this disorder?

As of November 2005, the following North American trials are active:
-Valproic Acid and Carnitine in Patients with Spinal Muscular Atrophy Condition: Spinal Muscular Atrophy Recruiting
-Measuring Levels of SMN in Blood Samples of SMA Patients Condition: Spinal Muscular Atrophy Recruiting
-A Pilot Therapeutic Trial Using Hydroxyurea in Type II and III Spinal Muscular Atrophy Patients Condition: Spinal Muscular Atrophy Recruiting
-A Pilot Therapeutic Trial Using Hydroxyurea in Type I Spinal Muscular Atrophy Condition: Spinal Muscular Atrophy Recruiting
-Quantitative Analysis of SMN1 and SMN2 Gene Based on DHPLC System Condition: Spinal Muscular Atrophy Recruiting
-Establishing Novel Detection Techniques for Various Genetic-Related Diseases by Applying DHPLC Platform. Conditions: Spinal Muscular Atrophy; Neonatal Hyperbilirubinemia; Colon Cancer Recruiting

You can search for the latest clinical trials by entering the term SMA at: http://clinicaltrials.gov/

9). MUSCULAR DYSTROPHY CANADA SUPPORTS

9-A). How can organizations like MDC help?

Muscular Dystrophy Canada provides a number of services to people registered with our association, including: Information and Education, Equipment, Peer Support, Chapter Support, Referral, Social Action.

9-B). What kind of information is available?

Muscular Dystrophy Canada provides information to people registered with us, their families, community professionals, and the general public about neuromuscular disorders and related issues. Information is available in the form of disorder specific information sheets, research updates, brochures, videos, and books. An extensive and dynamic website (www.muscle.ca) provides access to electronic copies of all our publications, plus links to news and in depth coverage of our research funding. Muscular Dystrophy Canada publishes a national newsmagazine, Connections, available in both French and English. The magazine features information on a variety of neuromuscular disorders as well as related topics such as research, genetics, parenting, and quality of life. Regional offices may also keep people registered in their area up to date through regional

newsletters. Services staff in our regional offices will respond to any request for information that you may have, or they will help you find the information that you need.

9-C). What kind of assistance is available for medical equipment?

The Muscular Dystrophy Canada equipment loan program provides basic medical equipment, on loan, from a stock of recycled devices such as scooters, manual and electric wheelchairs, and hospital beds. Some funding assistance may be available for the purchase of new equipment. If a request is made for a device that MDC does not cover, or only partially covers, Muscular Dystrophy Canada staff may be able to suggest other sources of funding. For more information about equipment funding, call the regional office nearest you.

9-D). What is peer support and how can it help?

Peer support means getting help or advice from, or just plain talking to other people who have experience with SMA. Often others who have the same disorder are good people to ask questions and to get advice from, especially in terms of how to manage the small day-to-day frustrations that come up.

Support comes in many forms and is dependent on individual needs. Some people already have strong support systems in place through family, community, and church and their needs are minimal. Other people are facing stresses such as financial difficulties or family problems, in addition to the day-to-day reality of life with a neuromuscular disorder. Life can become difficult at particular times, such as when the diagnosis is made or when symptoms seem to get suddenly worse.

The Muscular Dystrophy Canada Peer Support Program offers those facing challenges the chance to talk to someone who has gone through a similar experience. People registered with MDC, family members, and close friends -- trained by Muscular Dystrophy Canada staff – offer information about resources, tips on coping, and an "understanding ear" to people who are looking for support.

For people registered with Muscular Dystrophy Canada who might prefer support in a group setting, Association staff can refer you to a local network or support, or even help you to create a new one.

Also see: http://muscle.ca/content/index.php?id=145

9-E). How can Chapters help?

Muscular Dystrophy Canada Chapters form a nationwide network of people registered with MDC, their families, and volunteers. They actively help Muscular Dystrophy Canada to achieve our common objectives especially at a local level. Chapter activities can include support, social events, and fund raising.

Chapter members are often people registered with MDC and their families. However, anyone who is interested in furthering the aims and objectives of Muscular Dystrophy Canada is welcome to join. In communities across Canada, dedicated Chapter members provide valuable time, energy, and experience that ultimately benefit people with neuromuscular disorders and the communities they live in. For the location of the Chapter nearest you, call your regional or community office.

9-F). What kinds of referrals are made?

Staff can provide referrals and contact information to neuromuscular clinics, agencies, and other community resources, to help people registered with Muscular Dystrophy Canada find solutions to problems they face in their daily lives.

9-G). What is Muscular Dystrophy Canada's Social Action Plan?

Muscular Dystrophy Canada engages in social action to ensure that people with neuromuscular disorders can participate fully in all aspects of daily living. It aims to do this by working with other organizations to bring about policy changes in provincial and federal governments and providing volunteers in local Chapters and communities with tools they need to participate in local and community advocacy efforts.

9-H). How can I receive Muscular Dystrophy Canada services?

If you wish to receive more information about one or more of the neuromuscular disorders under the Muscular Dystrophy Canada service umbrella, or about MDC itself, please contact the regional office nearest you. Services staff can provide you with general information in response to your needs, or help you in registering with Muscular Dystrophy Canada to receive direct services.

9-I). What is the mission of Muscular Dystrophy Canada?

Muscular Dystrophy Canada supports the independence and full participation of Canadians with neuromuscular disorders. We assist individuals to participate in the decisions that affect them and collaborate with others for social change. We fund research to improve the quality of life of people with neuromuscular disorders and to find a cure.

9-J). How can I help?

Muscular Dystrophy Canada conducts year-round fund raising campaigns to support our diverse programs. Your gift will help MDC provide the dollars necessary to assist individuals living with neuromuscular disorders, and fund much-needed medical research and educational information. Please make a gift through our National office or any Regional or Community Muscular Dystrophy Canada office.

9-K). How can family and friends help?

Family support is a critical part of any illness, especially a chronic and progressive one like SMA. Sometimes family will also need to go through a period of adjustment and "getting used to" a new diagnosis. Over time, family members can learn about SMA and how they can best help you meet your particular challenges. Family can also play an important role in looking out for symptoms and in helping deal with the health care system.

Friendships are important to everyone. Regular interaction with friends and social groups can encourage positive attitudes and a positive sense of worth for both children and adults. Regular interaction and playtime with siblings and children in the neighborhood and at school help a child learn necessary social and problem-solving skills. Adults also benefit from a social network that is satisfying to them and that understands their needs. Friends play an integral role in the emotional well-being of those living with any neuromuscular disorder.

Family and friends also play a critical role in helping the person liaise with Muscular Dystrophy Canada and with other persons with disorders. Muscular Dystrophy Canada also thanks family and friends for their tremendous efforts in fund raising and the many other activities they become involved with, including raising awareness and in advocacy of persons with muscular dystrophy.

10). OTHER RESOURCES

10-A). What other resources are available to people living with Spinal Muscular Atrophy?

AmSMART (American Spinal Muscular Atrophy Randomized Trials): http://www.amsmart.org/

Families of Spinal Muscular Atrophy: http://www.fsma.org/

Families of Spinal Muscular Atrophy Canada: http://www.fsma.org/canada/default.shtml

Fight SMA: http://www.fightsma.com/

Genetics Home Reference (National Library of Medicine): http://ghr.nlm.nih.gov/condition=spinalmuscularatrophy

Gene Reviews SMA Review: http://www.genetests.org/profiles/sma

Muscular Dystrophy Association USA: www.mdausa.org

Online Mendelian Inheritance in Man (OMIM). This database is a catalog of human genes and genetic disorders authored and edited by Dr. Victor A. McKusick and his colleagues at Johns Hopkins and elsewhere, and developed for the World Wide Web by

NCBI, the National Center for Biotechnology Information, National Institutes of Health (NIH):
Page on SMA I: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=253300
Page on SMA II: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=253550
Page on SMA III: http://www.ncbi.nlm.nih.gov/entrez/dispomim.cgi?id=253400

SMA Support Inc; http://www.smasupport.com/

Spinal Muscular Atrophy Foundation http://www.smafoundation.org/
A Review of Spinal Muscular Atrophy Literature:
http://www.smafoundation.org/pdf/White_Paper.pdf

Spinal Muscular Atrophy Net: http://www.affari.com/smanet/

10-B). References used in this paper.

Crawford T. O. (2003) in *Neuromuscular Disorders of Infancy, Childhood and Adolescence: A Clinician's Approach.* (Jones, H. R., De Vivo, D. C., and Darras, B. T., eds) pp. 145-166, Butterworth-Heinemann, Philadelphia.

Please feel free to search for specific terms on the internet. A number of excellent medical and genetic dictionaries are now online.

For example:
http://www.nlm.nih.gov/medlineplus/mplusdictionary.html

http://cancerweb.ncl.ac.uk/omd/

http://www.stedmans.com/

http://www.dorlands.com/wsearch.jsp

http://www.onelook.com/

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