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Spinal Muscular Atrophy: An Inherited Neuromuscular Disorder with a Potentially Optimistic Future

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Abstract

Spinal muscular atrophy (SMA) is a rare "orphan" genetic neuromuscular disorder that kills more babies than any other genetic disorder. SMA is often associated with progressive, severe physical disability that manifests before or after the age of 18, though not with cognitive impairment. Not considered a developmental disability in Ontario or Canada, SMA is so classified in certain other jurisdictions. Since discovery of the genetic basis of SMA in 1996, there have been substantial advances in its understanding. These provide optimism for development of an effective treatment of SMA or even a cure. This paper provides a multidisciplinary introduction to SMA, its management, potential treatments, research advances, and ethical dilemmas. Lessons learned from experiences with SMA are generally relevant to disabilities with a genetic basis or severe physical disability. Information learned about the aberrant molecular and physiological processes in SMA may provide important clues about causes of certain other neurological disorders such as fragile X syndrome. Readers should note that unlike the U.S. and some other countries, Canada does not have an "orphan" drug policy to facilitate the development of promising treatments for rare debilitating disorders, including SMA. It also does not have provision for ensuring access to such treatments even if these exist. As rare disorders collectively affect as many as 1 person in 10 in the general population, communities should unite and lobby governments at all levels for policy changes to ensure that persons affected with rare disorders will have access to life-saving treatments and drugs and a program to cover the costs of such treatments.

Spinal muscular atrophy (SMA) is an inherited neuromuscular disorder which kills more babies than any other genetic disorder. (The term "neuromuscular disorders" is a general one that refers to diseases that affect any part of the nerve and muscle.) It affects cells inside the spinal column that are responsible for generating nerve signals that move muscle (Figure 1). Survivors of SMA do not have significant cognitive disability, but they often have significant, progressive physical disability that affects their ability to manage on a day to day basis.

Since the genetic basis of SMA was first discovered in 1996, there have been substantial advances in its understanding, and the prospect of having an effective treatment or even cure for SMA within the next five years is high. Our understanding of approaches to treating SMA is changing rapidly with advances in technology, and advances in technology are resulting in complex ethical dilemmas. Hence, it is timely and appropriate to review issues relating to the cause and treatment of SMA.

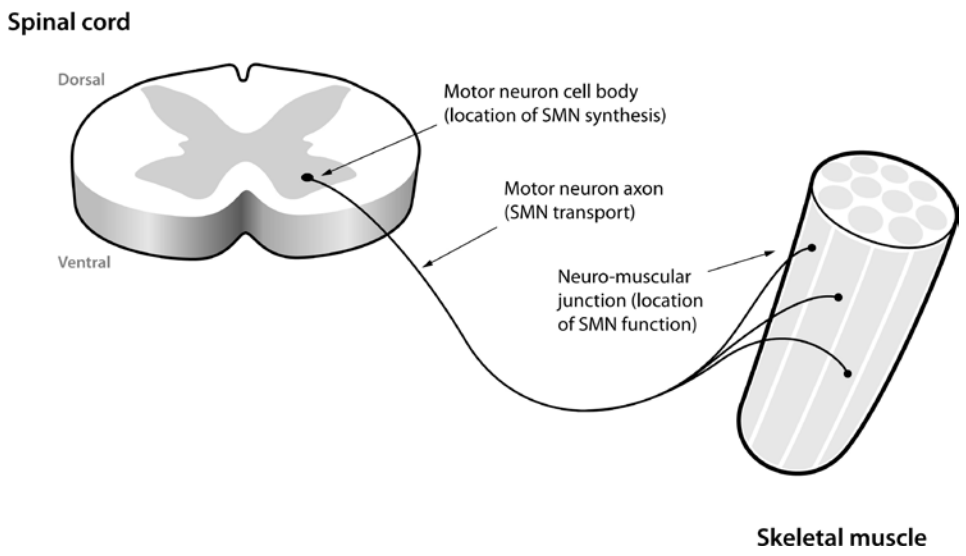

Figure 1. Diagram of a motor neuron

The spinal cord contains white matter (mostly myelinated axons) and gray matter (which contains cell bodies and unmyelinated axons). Myelin is an electrically insulating material that forms a layer usually around only the axon of a neuron enabling it to conduct electrical impulses quickly. An axon is the long, slender projection of a nerve cell, or neuron, that conducts electrical impulses away from the body of the neuron. The gray matter is divided into regions called dorsal and ventral horns. The dorsal and ventral horns also are called posterior or anterior horns, respectively. The dorsal horns are located at the back of the spinal cord whereas the ventral horns are at the front. Motor neurons located in the ventral horns and brainstem are affected in spinal muscular atrophy. The brainstem is the lower part of the brain which connects with the spinal cord. The solid line in diagram traces the axon of one motor neuron from the ventral horn of the spinal cord (left) to the neuromuscular junction (right) where it makes contact with a skeletal muscle. The total length of a single motor neuron (from spinal cord to muscle) can be of the order of 1–3 feet. Survival motor neuron protein (SMN) is synthesized in the cell body of the motor neuron and transported towards the skeletal muscle. In spinal muscular atrophy, there is a deficiency of SMN in cells. See also information in the text.

Furthermore, lessons learned from discoveries and experiences in the SMA field are likely to be relevant to many other disorders. In this paper, SMA has been reviewed as an educational and inspirational tool, and to encourage analogous activity and discovery in developmental and intellectual disabilities generally.

What is Spinal Muscular Atrophy?

Spinal muscular atrophy (SMA) is an umbrella term used to describe a spectrum of genetic neuromuscular disorders that are characterized by symmetrical muscle weakness and shrinkage (atrophy). SMA results in degeneration of the lower motor neurons (also called motoneurons) located in the ventral horns of the spinal cord and the brainstem. It does not involve the upper motor neurons located in the motor region of the cerebral cortex or brainstem. Healthy motor neurons are critical because they control muscle movement. Motor neurons carry signals out of the spinal cord and synapse with muscle fibres to facilitate muscle contraction and with muscle spindles to modify sensitivity to stimuli originating outside of the body. Without proper input from motor neurons, muscle cells become much smaller, causing muscle weakness. Motor neurons control voluntary muscles which are important for activities such as sitting, crawling, walking, controlling the head and neck, and swallowing. In SMA, muscles that are closest to the trunk of the body are more affected

than those farther from the trunk of the body. For additional information see: Families of Spinal Muscular Atrophy Canada (FMSA), n.d.; Herrera-Soto, Crawford, & Mehlman, 2008; Lamb & Peden, 2008; Lunn & Wang, 2008; Mahadevan, Korneluk, Roy, MacKenzie, & Ikeda, 1995; National Institute of Neurological Disorders and Stroke (NINDS) Spinal Muscular Atrophy Information Page, 2008; Official Parent's Sourcebook on Spinal Muscular Atrophy, n.d.; Oskoui et al., 2007; Oskoui & Kaufmann, 2008; Tsao & Armon, 2009).

The severest form of SMA is associated with autosomal recessive inheritance (in which one defective gene is inherited from each parent), and is the commonest cause of death in early childhood (Online Mendelian Inheritance in Man (OMIM), n.d.). SMA is often associated with progressive severe physical disability that persists for life, though not with cognitive dysfunction. Individuals with SMA often have above average IQ, and are highly social (Sieratzki & Woll, 2002 & 2005; von Gontard et al., 2002). In certain jurisdictions, SMA is classified as a developmental disability (The Developmental Disabilities Assistance and Bill of Rights Act of 2000, 2008). However, it is not considered a developmental disability in Ontario, since the definition of developmental disability requires significant deficits in both adaptive function and cognitive function (Developmental Services Act, n.d.; Ontario Ministry of Children and Youth Services, 2008).

The international birth incidence (number of births annually) of SMA is approximately 1 in 10,000, similar to that of cystic fibrosis and Duchene muscular dystrophy. The frequency of SMA carriers (persons who carry one gene causing SMA but who never develop it) is approximately 1 in 50 (Tsao & Armon, 2009).

Because there presently is no cure for SMA, management of clinical symptoms is key for improving the quality of life of persons who are affected. For these reasons, a diagnosis of SMA is very important for ascertaining an appropriate classification of the disorder as this relates to its prognosis. Accordingly, we begin our discussion with an introduction to the clinical features, classification and management of SMA patients.

Clinical Aspects

SMA Subtypes

In SMA, histopathological changes (changes in the appearance of cells under the microscope) occur in motor neurons at all levels of the spinal cord with a marked loss of large anterior horn cells, and in the motor nuclei of cranial nerves V through XII (Dubowitz, 1995; Merlini, Granata, & Dubowitz, 1989; Simic, 2008). The extent of these changes correlates with the degree of muscle weakness, the age at onset of the disorder, and survivorship. SMA onset ranges from before birth to adolescence or young adulthood. A scheme for classifying SMA subtypes is outlined in Table 1 (National Human Genome Research Institute, 2009; Kostova et al., 2007; OMIM, 2009). Not every case of SMA falls into a distinct subtype, however. A fifth type, denoted as 0, has been proposed for severe SMA that is expressed prena-

Table 1. Main subtypes of SMA

Type	*Onset*	*Course*	*Age at death*
I (severe infantile, acute)	Birth to 6 months	Never sit	Usually <2 years
II (intermediate; infantile chronic)	<18 months	Never stand	>2 years
III (mild; juvenile)	>18 months	Stand alone	Adult
IV (adult)	Age 15–50 years	Stand alone	Normal lifespan

From: Online Mendelian Inheritance in Man (2009)

Type I accounts for 70% of SMA, other forms for 30%.

tally. Other rare forms of SMA also occur. In SMA, a predominance of the male gender has been reported, though the reason for this is not known (Jędrzejowska et al., 2009).

Type I or severe SMA (Werdnig-Hoffman Disease) is characterized by generalized hypotonia (the amount of tension or resistance to movement in a muscle), with an almost general paralysis of limbs and trunk, particularly in the lower limbs. Some infants are usually unable to move their shoulders or arms against gravity. In addition, there is marked weakness of the axial (skeletal) muscles in the head. Tendon reflexes in these patients are always absent. Of primary concern in these infants are respiratory difficulties. Frequently difficulty in sucking and swallowing is seen with associated mucous accumulation in the pharynx (the part of the throat that begins from behind the nose to the beginning of the voice box and the esophagus). Further to this problem is the severe weakness of the intercostal muscles (those that run between the ribs, and help form and move the chest wall) leading to breathing which relies almost exclusively on motion of the diaphragm (the sheet of muscle extending across the bottom of the rib cage). These difficulties in respiration are complicated by recurrent respiratory tract infections and consequently these infants rarely survive beyond two years.

Type II or intermediate SMA is usually characterized by a normal history for the first six months of life. Infants with this form of SMA then develop some degree of weakness in the upper limbs and tendon reflexes are depressed or absent. Intercostal muscle weakness is less severe than in Type I SMA which gives a better prognosis with regards to overall respiratory function. Fasciculations (involuntary twitching of muscles) of the tongue are a common feature as well as hand tremors both of which aid in diagnosis. In these patients respiratory function determines their prognosis. This should be closely monitored and maintained as some patients survive into adulthood.

Type III or mild SMA (Kugelberg-Welander Disease) is associated with the attaining of normal milestones in the first year of life including the ability to walk. Children eventually begin to show evidence of mild muscle weakness; the muscles of the pelvic girdle are mainly affected, but the muscles of the arms may also be.

SMA Type IV begins later in life, usually between the ages of 15 and 50. The degree of disability is often mild and life expectancy is not usually affected. Type IV is the least common form of SMA and it is less clearly understood at the present time than the three childhood forms.

Although somewhat subjective in nature, this classification system aids in providing a functional assessment of a patient's status and also allows for some indication of disease progression. It also provides a guide for multidisciplinary management strategies to improve and maintain the quality of life and minimize disability.

Management

SMA management currently involves managing symptoms and preventing complications (Burnett, Crawford, & Sumner, 2009: Wang et al., 2007). The biggest potential problems are: respiratory muscle weakness, swallowing muscle weakness, back muscle weakness with progressive spinal curvature, and abnormal reactions to muscle-relaxing medications. Common complications include poor weight gain, sleep difficulties, pneumonia, scoliosis, and joint contractures.

Patients are typically regularly assessed for nutritional state, respiratory function, and orthopedic status. Treatment is usually supportive, with the goals being to improve the patients' quality of life and to minimize disability. Examples of possible treatments, depending on type and severity of condition, include: dietary assessment (i.e., recommendations for dealing with swallowing issues) and/or nutritional support via tube feeding; physical therapy to improve or maintain mobility and flexibility; wheelchair assistance for independent mobility; splints, braces and orthoses to prevent/minimize spinal curvature and/or to support walking; spinal fusion surgery; respiratory therapies (e.g., tracheotomy or non-invasive respiratory support including supplementary oxygen, mechanical ventilation, and chest physiotherapy; positive airway masks for sleep apnea); occupational and speech therapy.

Before the genetic aspects of SMA were known, SMA was diagnosed using clinical criteria. However, it is now possible to identify SMA using genetic analysis (Sick Kids, n.d.). In particular, genetic analysis enables SMA often

to be distinguished from amyotrophic lateral sclerosis (ALS, or Lou Gherig's disease, a rapidly progressing neuromuscular disorder that involves upper and lower motor neurons and is inevitably fatal) and quite a number of other neuromuscular disorders that mask as SMA. With the clinical aspects of SMA in mind, we now move to what is known of the genetic/molecular basis of the disorder.

Genetic and Molecular Aspects of SMA

SMA Inheritance

Most cases of SMA have an autosomal recessive pattern of inheritance (Sick Kids, n.d.). This means that a defective gene is inherited from each of two parents. If two individuals are carriers, there is a 25 per cent chance they will have an affected child. There is a 75 per cent chance their children will be unaffected. De novo (new) mutational events occur in approximately two per cent of patients with SMA, meaning that only one parent is a carrier and a new mutation in the offspring resulted in SMA.

Chromosomal Localization of the SMA Gene

SMA was mapped to chromosome 5q11.2-13.3 beginning with work started in the late 1980s. The SMA gene, known as Survival of Motor Neuron gene (SMN), was identified in 1994 (Lefebvre et al., 1995; Roy et al., 1995a; 1995b). The region on human chromosome 5 that harbours SMN contains a large inverted duplication. This duplicated region also contains repetitive elements that make it prone to genomic

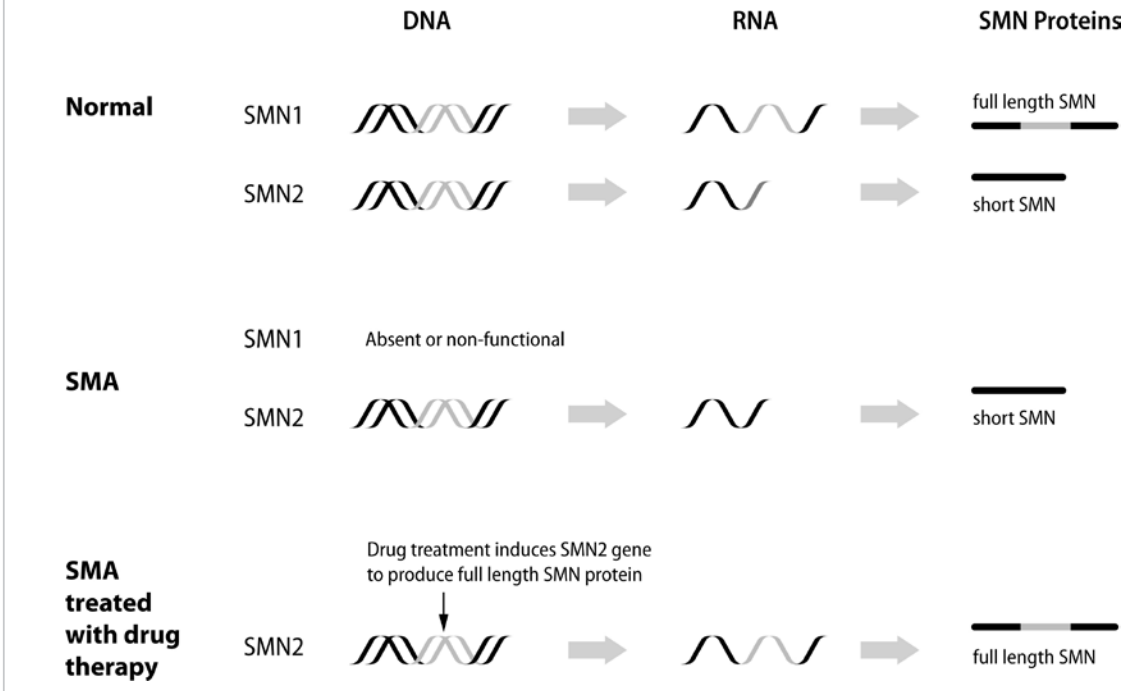

Figure 2. Genetic basis of SMA

Most people have Survival of Motor Neuron 1 (SMN1) and Survival of Motor Neuron 2 (SMN2) genes. Full-length SMN protein is the main product of the SMN1 gene, while short SMN protein is the main product of the SMN2 gene, but both types of protein can be made from either gene. In SMA, the two SMN1 genes are nonfunctional, usually as the result of deletions, vastly decreasing the amount of full-length SMN protein. However, the remaining SMN2 genes still produce some full-length protein. See also information in the text.

rearrangements and deletions. Genes located in this region occur twice, once within each of the duplicated regions. Thus, there are two copies of the SMN gene; these are named Survival of Motor Neuron 1 (SMN1) and Survival of Motor Neuron 2 (SMN2). Because SMN1 is located nearer the end of the chromosome, and ends of chromosomes harbour repetitive sequences called telomeres, it is referred to as "telomeric." SMN2 is referred to as "centromeric" because it is nearer the centromere (the most condensed and constricted region of a chromosome) (Burglen et al., 1996) (Figure 2).

Genetic Basis of SMA

Most cases of SMA result from a deficiency of SMN protein caused by a deletion in the SMN1 gene on each of the two copies of chromosome 5 (Lefebvre et al., 1997; Sick Kids, 2009; Sumner, 2007). Normally, each cell has two copies of the SMN1 gene. About 95 percent of persons with SMA have mutations that delete all or some of the DNA in both copies of this gene. As a result, little or no SMN protein is made. In about 5 percent of people with SMA, one copy of the SMN1 gene has a deletion, and the other copy has a mutation that affects the amino acids used to make the SMN protein. Most SMN protein is produced by SMN1. SMN2 mainly produces a short version of SMN lacking regions called exons 6 and 7, although it produces some full-length SMN protein. (Exons are regions of DNA that get transcribed into mature RNA and then translated into protein.)

Functions of SMN Protein

The SMN protein is found throughout the body, with high levels in the spinal cord. It is located in the cytoplasm of cells, and in some cells also is found in distinct nuclear structures called "gems." Gems are closely associated with nuclear coiled bodies called Cajal bodies (CBs). CBs are characteristic of cells that are rapidly dividing or rapidly metabolizing, such as neurons (Young, Le, thi Man, Burghes, & Morris, 2000). In cells, the SMN protein plays an important role in processing messenger RNA (mRNA) molecules, which provide the genetic information for making proteins. The mRNA begins as pre-mRNA (a rough draft) and undergoes splicing (processing) to become mature mRNA. The SMN protein helps to assemble the cellular machinery needed to process pre-mRNA. It does this via interaction with several other proteins. High levels of SMN may be needed in motor neurons because they are very large and long (Fischer, Liu, & Dreyfuss, 1997; Gubitz, Feng, & Dreyfuss, 2004; Kolb, Battle, & Dreyfuss, 2007). The description of the molecular machinery underlying SMA is a very important advance that is enabling scientists to develop effective therapies (see Rossoll & Bassell, 2009; Ymlahi-Ouazzani et al., 2009).

Exactly how SMN protein deficiency leads to motor neuron loss is not clear, however. SMN protein may be important in both neuron and muscle cells (Burghes & Beattie, 2009; Farrar, Johnston, Grattan-Smith, Turner, & Kiernan, 2009; Kerr, Nery, Traystman, Chau, & Hardwick, 2000; Parker et al., 2008; van Bergeijk, Rydel-Könecke, Grothe, & Claus, 2007).

Other Genes Involved in the SMA Phenotype

Siblings who have lost both copies of SMN1 can have variable SMA phenotypes (very different observable physical or biochemical characteristics) (Capon et al., 1996). This suggests that the clinical expression of SMA is modified by other factors in addition to the loss of full length SMN protein. The SMN2 gene has been shown to modulate SMN severity. Increased copy numbers of SMN2 are associated with better functional status in SMA. Defects in another gene localized to the SMN region called Neuronal Apoptosis Inhibitory protein Gene (NAIP) also modulate SMA severity, especially in Type 1 SMA (Salahshourifar, Shafeghati, Golkar, & Najmabadi, 2007; Simard, Rochette, Semionov, Morgan, & Vanasse, 1997; Somerville et al., 1997). Severity may also be modulated by deletions in p44, a subunit of the basal transcription factor TFIIH that is duplicated in the SMA region (Carter et al., 1997). SMN protein interacts tightly with another protein called Survival Motor Neuron Interacting Protein 1 (SIP1) located on chromosome 14. In SMA, two splice variants of SIP1 have been found to be expressed aberrantly, suggesting their involvement in SMA pathogenesis (Aerbajinai et al., 2002). (Pathogenesis refers to the series of changes in the structure and /or function of cells and tissues in persons with SMA.)

Some types of SMA result from mutations on other chromosomes. For example, spinal bulbar muscular atrophy (SBMA or Kennedy's disease) is an X-linked recessive disorder. In such disorders, mutation in a gene on the X chromosome causes the phenotype to be expressed in males who are necessarily hemizygous for the gene mutation because they have only one X chromosome. Females are less severely affected because they have two X chromosomes of which one is inactivated. SMBA results from amplification of the glutamine repeat region in the androgen receptor gene. Males with SBMA also may be more severely affected than females because of the involvement of androgen in this disorder (Finsterer, 2009). Finkel type SMA is an autosomal dominant disorder caused by a mutation in the vesicle-associated membrane protein-associated protein B or C (VAPB) genes (Nishimura et al., 2004). In autosomal dominant disorders only one defective gene inherited from either parent is sufficient to cause the disorder.

Genetic diagnosis for autosomal recessive SMA is presently available in a number of countries. Because genetic counselling for families is an obligatory component of genetic diagnosis, genetic testing and counseling are discussed next.

Genetic Testing and Counselling

As of 2009, genetic testing for autosomal recessive SMA in Canada identifies about 95% of patients with SMA who have deletions in the SMN1 gene, and about 85% of carriers (Sick Kids, 2009). This provides individuals and families with information on the nature, inheritance, and implications of SMA. Genetic counselling is an integral aspect of genetic testing. This refers to the process by which patients or relatives, at risk of an inherited disorder, are advised of the consequences and nature of the disorder, the probability of developing or transmitting it, and the options open to them in management and family planning in order to prevent or avoid it, or to lessen its effects.

At the Hospital for Sick Children in Toronto, genetic testing for SMA is offered to individuals suspected of being affected with SMA

> … who wish to upgrade their existing skills; to individuals with a family history of SMA and their spouses to determine the carrier status of unaffected individuals; and to individuals whose pregnancies are at risk due to a family history of SMA. Testing identifies persons who have deletions on both copies of SMN1 and those who have a deletion in one copy of SMN2. (Sick Kids, 2009)

As mentioned above, genetic testing identifies deletions in the SMN1 gene. Persons who have point mutations in the SMN1 gene or who carry two SMN2 genes are not identified by present testing methods. When there is clinical evidence of SMA in the family, but there is no detectable deletion in the SMN1 gene, or when prenatal assessment is requested, linkage analysis can be used to compare DNA markers associated with the SMN1 gene in affected and unaffected family members. This family history is used to calculate the likelihood that a person is a carrier or is affected, and the risk of recurrence (Sick Kids, 2009).

Prenatal testing for SMA can be done using chorionic villus sampling (CVS), or amniocentesis. CVS involves getting a sample of the chorionic villus (placental tissue); Amniocentesis involves analysis of a small amount of amniotic fluid (which contains fetal tissues) from the amniotic sac surrounding a developing fetus. CVS is performed as early as the 8th–11th week of pregnancy. Amniocentesis is most safely performed after the 14th–16th week of pregnancy. Persons at risk of having a baby with SMA also have the option of having in vitro fertilization with preimplantation genetic analysis in order to have a healthy baby. Genetic detection of SMA meets criteria necessary for the implementation of screening for all newborns, a program that would help babies with SMA to get the best start in life and to stay healthy (American College of Obstetrics & Gynaecology, 2009). To date, such a program has not been introduced in any country (Norrgard, 2008a).

The facts that SMA is essentially a monogenic disorder caused by too little SMN protein, and that the biological function of SMN protein is beginning to be understood, has stimulated research directed at treatment of SMA. This is discussed next.

Current Research

Overview of Research Priorities Directed at Treatment

There is much hope that pharmacological strategies, gene therapy or cell transplants may be developed to alleviate motor neuron loss and progressive muscular atrophy in SMA. Research priorities presently include:

Basic research. Major strides have been made in SMA research with the identification of the SMN gene and the development of models for SMA in yeast, nematode, fly, zebra fish, and mouse (Schmid & DiDonato, 2007). Basic research efforts are now focusing on determining how genetic defects in SMN1 actually cause SMA, and identifying functions of specific regions (domains) of SMN protein in different types of cells (Chari, Paknia, & Fischer, 2009; Gavrilina et al., 2008).

Pre-clinical drug discovery. Activities in this strategy aim to develop SMA drugs that increase SMN protein levels, enhance residual SMN protein function, compensate for loss of SMN protein, or protect SMN deficient neurons. Approaches for increasing SMN protein levels include induction of SMN2 gene expression, modulation of the processing of RNA transcribed from SMN2 to produce more full-length SMN protein, stabilization of existing SMN protein, and enhancement of residual SMN function (see Hastings et al., 2009). Other functions of potentially therapeutic drugs include the prevention of motor neuron death, enhancement of the space occupied by existing motor neurons, and alteration of pathways that affect muscle maintenance and growth (Hauke et al., 2009; Oskoui & Kaufmann, 2008).

Gene therapy. This term refers to an intervention based on modification of the genetic material of living cells including DNA and RNA (see Horne & Young, 2009). Cells may be modified in vitro for subsequent administration to humans, or may be altered in vivo. When the genetic manipulation is performed in vitro on cells which are then administered to the patient, this is a form of *somatic cell therapy*. Gene therapy is complex and involves repairing the right cells, ensuring that the protein product of a mutated gene functions properly, and that the introduced gene continues to work in the targeted cells without resulting in harmful side effects. The term *germ-line therapy* refers to treatment that modifies all cells in an organism so that the changes are heritable (DiDonato, Parks, & Kothary, 2003; Wirth, Brichta, & Hahnen, 2006).

Stem cell therapy. Stem cells are the master cells of the human body. They can divide to produce copies of themselves and many other types of cell. They are found in various parts of the human body at every stage of development from embryo to adult. Transplantation of high purity motor neuron populations derived from human stem cells holds great promise for patients with SMA (Hedlund, Hefferan, Marsala, & Isacson, 2007). This approach has been used successfully in proof-of-concept efficacy and preliminary safety studies. Partnerships already have been established to obtain formal efficacy and safety data necessary for movement towards human testing (Families of Spinal Muscular Atrophy, 2009).

Other research priorities. Despite many important advances, however, very little is known about the natural history or cellular mechanisms resulting in motor neuron loss in SMA. Answers to these questions are crucial for the rational design of therapeutics, and also to establish the developmental window during which such therapeutics are likely to be most effective.

Human Clinical Trial Initiatives

Pharmacological treatments are currently favored for the first clinical trials in SMA, as these are considered to be safer than those involving gene alteration of the structure or function of existing genes, or transplants of normal cells into the spinal canal. Some drugs that increase the amount of full-length SMN protein and that currently are under investigation include valproic acid, levocarnitine, hydroxyurea, leuprolide, testosterone, riluzole, somatotropin, and levetiracetam. As well, tetracyclines have been found to promote SMN2 exon 7 splicing (Hastings et al., 2009). Although no published study has documented significant benefits to persons with SMA from drug treatments as of June, 2009, it is clear that the carrying out of clinical trials in SMA is feasible (Bosboom, Vrancken, van den Berg, Wokke, & Iannaccone, 2009a; 2009b). To note are reports

that a thyrotropin-releasing hormone analogue has benefited individuals with SMA (Kato et al., 2009)

Descriptions of clinical trials completed, underway or planned with NIH funding in the U.S. are available from the National Institutes of Health (NIH) Clinical Trials website (2009). See also websites for Families of Spinal Muscular Atrophy (2009), the International Spinal Muscular Atrophy Patient Registry (2008), and the Spinal Muscular Atrophy Foundation (2009).

Serious Ethical Dilemmas

Advancing technology is leading to better management of SMA, the prospects for an effective treatment or even a cure, and approaches for SMA prevention. Yet, with these advances, some serious ethical dilemmas are arising in different areas, as outlined below.

Management. Survival in spinal muscular atrophy type 1 patients has increased in recent years, in relation to the growing trend toward more proactive clinical care (Oskoui et al., 2007). Increased survival has been attributed to use of a mechanical insufflation–exsufflation device for aiding respiration, and gastrostomy tube feeding. However, recent progress in the understanding of the molecular pathogenesis of spinal muscular atrophy and advances in medical technology have not been matched by similar developments in the care for persons with SMA generally (Wang et al., 2007). Guidelines for standards of care are urgently needed in this field, and development of such is underway (Family Guide to the Consensus Statement for Standard of Care in Spinal Muscular Atrophy, 2009). Other dilemmas include the issues of who should bear the costs of management, and who should decide to provide or withhold life supports.

Accessibility of new treatments. As explained above, effective new drug treatments for SMA are envisioned within a few years. Since SMA is by definition a rare disorder, there presently is concern that industry may not be motivated to develop these treatments, or if they do, will the costs of these treatments be out of reach for most individuals. Another concern is which SMA subtype should have highest priority in clinical trials.

Barriers to stem cell therapy. Stem cell therapy is a very promising potential form of treatment (Brignier & Gewirtz, 2010). Prior to 2009, stem cell research has been forbidden in some U.S. states. However, this state of affairs may improve in the near future. Most stem cell research in Canada is on adult stem cells. Not known is if stem cells need to be embryonic in origin or if stem cells from adults might be effective in SMA. Safety is still a primary concern in stem cell therapy. Researchers still do not know how to keep stem cells unspecialized, and they do not know what signals are needed to cause them to specialize. In animal models, stem cell transplants generally are associated with a high frequency of tumour formation.

Newborn screening programs. These are feasible, but are being debated because there currently is not an effective treatment for SMA. Early identification of SMA will lead to optimum management, however (Norrgard, 2008a).

Genetic testing and counselling. As in other genetic disorders associated with significant burden, the questions of whether genetic information should be shared within families and healthy children be tested are being debated. As for other inherited disorders, there has been ethical outcry about SMA prevention by therapeutic abortion or preimplantation genetic analysis. This is of peculiar relevance in SMA families, because expression of the disorder within families is very variable, and because SMA is not associated with intellectual disability. With genetic testing also comes the risk of genetic discrimination. Persons at high risk of developing a genetic disorder may face discrimination in the work place and not be hired or retained. As well, they may have difficulty obtaining medical insurance (Norrgard, 2008b). In the U.S., a new federal law, the Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, protects Americans from being treated unfairly because of differences in their DNA that may affect their health. Many other countries also have such protection. Canada lacks such laws.

Future Research Considerations

The rapid advances in the understanding of the genetic and molecular basis of SMA in the past 15 years is truly impressive. Not only do they serve to further our understanding of the disorder itself, but also of the development and maintenance of the nervous system in general. A better understanding of SMA and its complexities will benefit understanding of other neurodegenerative diseases and developmental and intellectual disabilities. Because there is a deficiency of FMR1 protein in persons with fragile X syndrome, and the FMR1 and SMN proteins interact, fragile X is one developmental disability that will benefit from basic research studies of SMA (Piazzon et al., 2008). It also follows that SMA genetic research may well provide novel insights into potential ways to treat many other disorders with neuron deterioration including Tay-Sachs disease, amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's disease.

Of interest is the fact that, generally, SMA patients are noted for their intelligence. They typically are early to speak and have reported intelligence quotients significantly higher than the average of the normal population (Merlini et al., 1989; Sieratzki & Woll, 2002; 2005). These findings raise a number of important questions. First, is there a molecular correlation between the events that occur in SMA and neural mechanisms of processing centrally? Second, are there larger issues to be considered in the prenatal diagnosis and potential termination of SMA fetuses? Finally, does the expression of altered NAIP or p44 proteins in persons with SMA affect intelligence?

If SMA mutations do, in fact, confer increased intelligence, it might be possible that SMN protein(s) regulate neuron-target feedback mechanisms. Motor neurons send axonal projections to reach target muscle fibres by a process regulated in part by neurotrophic factors that are released by the target muscle fibres. Neurotrophic factors also ensure that each muscle fiber is innervated by the appropriate number motor neurons. As with most types of neurons in the nervous system, motor neurons are more numerous in early development than in adulthood. Muscle fibres secrete a limited amount of neurotrophic factors capable of sustaining only a fraction of the motor neurons that initially project to the muscle fibre. Those that do not receive sufficient neurotrophic factors undergo apoptosis, a form of programmed cell death (Gould & Enomoto, 2009). Centrally, neuron-neuron interactions are strengthened in a similar manner. Conceivably, neuronal alterations which in the periphery confer neuronal loss may, in fact, add an extra degree of plasticity in the brain. The issue of increased intelligence in persons with SMA deserves to be a topic of further research.

Also of note is the fact that in all forms of SMA, several muscles are spared, including the diaphragm, the involuntary muscles of the gastrointestinal system, the heart, and the sphincters Herrera-Soto, Crawford, & Mehlman, 2008; Novelli et al., 1997). The reasons for this are unclear and deserve investigation. Is there some common neurophysiological characteristic amongst these locations that makes them resistant to mechanisms resulting in apoptosis (programmed cell death)? Or is there some developmental aspect which is at play in either strengthening cell-cell interactions such that programmed cell death is not induced or involves a less selective pruning of neuronal input as is seen in other locations? Beyond the clinical fascination with the sparing of these organs, there may be a wealth of information to be uncovered through investigation of the underlying neurology.

Need for Heightened Advocacy

The recent knowledge gained in the understanding of SMA has given new hope in the anticipation of better treatments. As detailed in this report, this optimistic state of affairs has resulted, in part, as the result of the monogenic nature of SMA, dedication on the part of researchers, and the power of education and advocacy, especially in the U.S. For example, the Spinal Muscular Atrophy Treatment Acceleration Act of 2009 is now being considered in the U.S. Congress. SMA is one of more than a thousand disorders classified as rare or orphan that nevertheless together affect as many as 1 in 10 persons in the general population (Bain, 2006; Orphan drugs, n.d.). Unlike the U.S. and some other countries, Canada does not have an orphan drug policy to facili-

tate development of treatments for uncommon diseases. Furthermore, Ontario and Canada do not have policies in place to ensure that persons affected with rare disorders will have access to life-saving treatments and drugs and a program to cover the costs of such treatments (Best Medicines Coalition, 2007).. Advocates for rare disorders should unite and lobby governments to change these states of affairs (Canadian Association for Rare Disorders (CORD), 2009; Wong-Rieger, 2009).

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