

Nutrition issues associated with spinal muscular atrophy. (Review).

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Sarah Leighton

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Abstract

Spinal muscular atrophy (SMA) is one of the more common genetic conditions, with one in 40 people being carriers of the gene. Much research has been conducted into genetic identification and classification of this group of neuromuscular disorders, yet very little information is available with regard to nutrition for those affected. Spinal muscular atrophy varies in severity according to the area of gene involved. This review of recent literature gives an overview of some of the genetics of spinal muscular atrophy, as genetic influences may affect metabolism for some people with this condition. Recent research relating to nutrition for people with SMA is presented, with consideration as to how nutrition may affect quality of life for those affected with SMA.

Key words: spinal muscular atrophy, SMA, nutrition, diet

Spinal muscular atrophy

Spinal muscular atrophy (SMA) encompasses a large group of mostly inherited disorders that affect the spinal motor neurons, causing degeneration of the anterior horn cells of the spinal cord. The population incidence for SMA has been measured consistently at one in 6000 to 10 000. One in 40 people are carriers of the gene, making this condition one of the more common genetic diseases and one of the most significant causes of infantile death and disability (1).

Spinal muscular atrophy is a symmetrical process with a predilection for the proximal musculature. Presenting symptoms can include symmetric weakness, hypotonia, hyporeflexia or areflexia, muscle atrophy (which may not be obvious due to overlying fatty tissue) and fasciculations of the tongue. The facial muscles and diaphragm are usually unaffected, and there is no abnormality of sensory function. Classification of SMA types has so far presented difficulties, but is becoming clearer as the genetic bases of the different syndromes are identified (2).

There are three types of childhood SMA, reflecting a continuum in the severity of the condition:

* Type 1 (previously called Werdnig-Hoffmann disease): Mothers occasionally describe the cessation of fetal movements in the third trimester, implying that in severe cases the motor neuron loss may begin in utero. Most cases manifest by six months of age, either as severe weakness which may require intubation at birth, or inability to gain head control. These children never achieve the ability to sit or roll unaided. The condition is rapidly progressive, and children have a prognosis of death or full-time ventilator dependence before the second birthday (1).

* Type 2 (intermediate, juvenile or chronic): These infants may have normal milestones up to six to eight months of age, but are hypotonic, with the onset of symptoms occurring in the first 18 months of life (3). They are able to sit unaided, but never stand, and are thus severely disabled. The life expectancy is extremely variable, depending on the degree of respiratory muscle involvement, and problems due to kyphoscoliosis, which may appear in infancy. A study of 240 patients with Type 2 SMA showed a survival rate of 98.5% at five years, and 68.5% at 25 years (1).

* Type 3 (Kugelberg-Welander or mild): These people have a normal life expectancy, and have independent ambulation for part of their life. A further division has been made within Type 3. If onset is before three years of age (Type 3a), the probability of being able to walk at ten years is 70.3%, and at 40 years, 22.0%. Type 3b, where onset is after three years of age, the probability is 96.7% walking at ten years, and 58.7% walking at 40 years (1). SMA Type 3 patients have a waddling gait, lumbar lordosis, genu recurvatum and a protuberant abdomen. They may appear to be very thin.

Genetics of SMA

As human gene mapping develops, the complicated picture of the genetic identity of SMA becomes clearer. Talbot and Davies (1) have adopted a classification based on patterns of inheritance, including some relatively rare syndromes. The proximal SMA of childhood (Types 1, 2 and 3) is an autosomal recessive condition.

The SMA locus is a complicated region of the genome with both large- and small-scale repetitive elements and instability. This has made it difficult to map the region, and may also explain the frequency of SMA and the genetic basis of clinical heterogeneity. In 1995, two candidate genes were identified—the survival motor neuron (SMN) gene, and the neuronal inhibitor of apoptosis protein (NAIP) gene (1). Only recently has it been recognised that all three types of childhood autosomal recessive SMA are due to mutations in the SMN gene on chromosome 5.

Chromosomes carrying an SMA mutation may contain either:

* Several large-scale deletions in the NAIP gene (a 'severe' allele)

* Gene conversion events affecting the SMN gene due to a failure of DNA repair mechanisms (a 'mild' allele)

* Mis-sense or other small intragenic mutations in SMN.

This gives a model of disease severity where alleles with large-scale deletions are more likely to give more severe phenotypes, combinations of severe and mild alleles an intermediate phenotype, and combinations of mild alleles, a mild phenotype (1).

Functions of survival motor neuron (SMN) protein

Lower motor neurons consist of a cell body within the central nervous system and a long axon projecting into the periphery that can be up to a metre long in adult humans. Mutations in the SMN gene in SMA are completely clinically specific for lower motor neuron loss, through either degeneration or enhanced programmed cell death in development. Loss of lower motor neurons results in weakness and wasting of skeletal muscles (4).

The severity of muscle weakness corresponds to the amount of full length SMN protein produced (4). SMN protein appears to play a critical role in RNA (ribonucleic acid) processing, influencing pre-mRNA splicing (1).

The SMN gene is expressed in most tissues. The SMN mutation is apparently specific for motor neuron dysfunction. Talbot suggests that either motor neurons have intrinsic vulnerability to defects in mRNA metabolism, or that SMN directs post-transcriptional processing of special subclasses of mRNA that will be translated into motor-neuron specific proteins (4). RNA metabolism may proceed in a cell-specific way in neurons.

Other functions potentially relevant to motor neuron survival that have been recently demonstrated for SMN, include an interaction with a protein ('bcl-2') that negatively regulates cell death. SMN enhances bcl-2 action and therefore promotes cell survival, in vitro. SMN has also been shown to interact with other proteins (profilins) that regulate actin dynamics, and therefore maintain cytoskeletal integrity. It is not yet known whether either of these pathways is relevant to SMA pathogenesis (1).

A recent study by Friesen et al. (5) has demonstrated that the activity of SMN depends on folate and vitamin B12, both necessary for the methylation of proteins. SMN binds the arginine- and glycine-rich domains of certain proteins. Specific arginines are modified to dimethylarginine, and SMN binds preferentially to these. The binding of other SMN-interacting proteins is also strongly enhanced by methylation. Insufficient intake of folate and vitamin B12 may result in protein

hypomethylation, and contribute to the severity of SMA. Clinical trials are planned to determine whether dietary intake of these vitamins does influence the course of SMA.

Recent research by Chang et al. reports the treatment of SMA-like mice with sodium butyrate (6). Oral sodium butyrate treatment of the mice resulted in increased expression of SMN protein in motor neurons of the spinal cord, and significant improvement of clinical symptoms. These researchers consider that sodium butyrate may be effective for the treatment of human SMA patients.

Metabolic abnormalities in SMA

A variety of metabolic abnormalities has been described in isolated cases of SMA and other diseases with comparable involvement of motor neurons. A number of studies has shown that children with SMA are likely to have metabolic defects involving fatty acid metabolism.

Plasma

Children with severe SMA, in the fasting state, have increased plasma levels of the medium chain fatty acid, dodecanoic (lauric) acid. A study by Crawford et al. reported normal plasma acylcarnitine profiles in ten infants with severe SMA (7). However, an earlier study by Tein et al. (8) found that the serum total:free carnitine ratio showed a higher esterified fraction--from 35 to 58% of total carnitine (normal is 25 to 30%) in children with severe SMA (three subjects) and in their two youngest SMA Type 2 patients.

Urine

Many studies have found a distinctive and marked dicarboxylic aciduria in the fasting state in children with severe SMA (Type 1 only), similar to that of children with primary defects of fatty acid 13-oxidation, as well as moderate ketonuria (unlike infants with known defects of [beta]-oxidation) (7,8). The ability to mount a fasting ketosis reflects normal fatty acid utilisation by the liver, and suggests a muscle-specific defect in [beta]-oxidation (8).

Urinary analyses by Tein et al. (8) found evidence of short and medium chain fatty acid metabolites--mostly in patients with SMA Type 1, less in patients with SMA Type 2, and normal urinary profile in those with SMA Type 3.

Fatty acid oxidation

Similarities between patients with severe SMA Type 1 and those with primary metabolic defects of mitochondrial [beta]-oxidation include:

* excretion of abnormally large amounts of dicarboxylic acids during catabolism when free fatty acids are mobilised from fat stores, and

* elevation in plasma C-12 fatty acids (7).

When plasma free fatty acid concentrations are high, dicarboxylic acids are formed in the liver and kidney, more often than in muscle. Some

infants with severe SMA have fatty vacuolisation of the liver, characteristic of most disorders of fatty acid oxidation (7).

There are some differences between patients with severe SMA and people with genetic defects of fatty acid metabolism. Fasting patients with defects in fatty acid metabolism have markedly diminished production of ketone bodies. Infants with severe SMA however, have a normal or only slightly reduced ketone body production, despite a marked dicarboxylic aciduria. This suggests that mitochondrial fatty acid transport, [beta]-oxidation, and ketogenesis in the liver are not greatly impaired (7).

Muscle

Spinal motor neurons affect the growth and metabolism of both red (oxidative) and white (glycolytic) muscle fibres. They govern the rate of protein synthesis, morphological differentiation, and cholinesterase activity. Denervation leads to complex changes in muscle cell composition affecting responsiveness to circulating hormones, and possibly contributing to altered rates of metabolism. The effect is due to more than simply disuse atrophy (8).

In animal models, reduced muscle carnitine and fatty acid oxidation has been seen following denervation of muscle. Treatment with L-carnitine reversed the loss of free carnitine in red muscle fibres only, with no effect on the total carnitine concentration in white muscle fibres. It was suggested that the motor neuron possibly has an effect on the transport of carnitine and fatty acid oxidation in red muscle fibres, which are primarily dependant on mitochondrial fatty acid oxidation for energy during mild to moderate prolonged (aerobic) exercise (8).

However, with regard to muscle intramitochondrial [beta]-oxidation, there appears to be some research disagreement:

* Tein et al. report multiple significant deficiencies, described as a marked increase in activity ratio of crotonase to other enzymes for both short chain and long chain fatty acids (8). These combined deficiencies were considered to point to a significant defect in the mitochondrial multifunctional enzyme complex.

* Tein et al. also reported reduced muscle carnitine and reduced carnitine palmityl-transferase activity in SMA Type 1 (only) compared with controls (8).

This is compared with boys with Duchenne muscular dystrophy, (a myogenic condition, whereas SMA is neurogenic) who have increased carnitine palmityltransferase activity, but reduced or normal muscle carnitine. Urinary carnitine is increased in SMA but normal in dystrophies. A selective renal loss of carnitine is reported in severe SMA, distinguishing SMA from other conditions causing muscular atrophy. Secondary carnitine deficiency occurs in other intramitochondrial [beta]-oxidation disorders, with increased renal excretion of free carnitine.

* Harpey et al. found decreased muscle carnitine in six out of ten children with SMA Type 2, and muscle coenzyme Q10 was decreased in the two patients studied for this (9). These researchers consider the carnitine deficiency may be due in part to intramitochondrial accumulation of acylcarnitines, followed by renal excretion. Reduced availability of acetyl Co-A could aggravate the already reduced muscle function in SMA Type 2.

* Crawford et al. (7) report that acylcarnitine profiles are normal, challenging a major block of mitochondrial [beta]-oxidation in denervated muscle. It is suggested that the significant abnormalities in levels of fatty acid metabolites found only in infants with severe SMA are directly attributable to the loss of survival motor neuron function, or that of a contiguous gene, rather than an indirect physiological consequence of muscle denervation. Age-matched disease control infants, i.e. infants with other neuromuscular conditions, not SMA, and older children with chronic SMA had normal fatty acid profiles by urinary assay.

Children with milder forms of SMA have neither the elevated plasma C12:C14 ratios, nor the dicarboxylic aciduria. Reasons for this may include that the condition normalises with development, or that the magnitude of the abnormality is directly proportional to the severity of SMA (7).

Tein et al. (8) consider that there is a lower percentage of atrophied muscle fibres in SMA Type 3 than in types 1 or 2, so that fewer fatty acid metabolites are generated, and these can be taken up by the liver and metabolised. They postulate that in more severe SMA, the absolute levels of these metabolites are higher or the capacity of the liver is saturated, hence excess fatty acid metabolites are detected in urine and serum. During times of acute illness with fasting and metabolic decompensation, the urinary acid profile may become abnormal in SMA Type 3, similar to several disorders of fatty acid oxidation which remain clinically silent until times of acute stress, such as fasting, cold exposure, infection, or emotional stress.

Complications of SMA and management

There is no cure for SMA, so treatment consists of preventing or treating the complications. Restrictive lung disease, poor nutrition, orthopedic deformities, immobility and psychosocial problems are common complications of SMA.

Respiratory compromise is a major complication of SMA. It is caused by the involvement of the respiratory musculature as well as concomitant scoliosis, and can be monitored by pulmonary function testing as forced vital capacity falls over time. Recurrent respiratory infections are frequently a problem from accumulation of respiratory secretions (8).

Physiotherapy is an integral part of care for people with SMA. As pulmonary function decreases, positive pressure ventilation (often used at night only) is useful to maintain oxygen saturation levels. Scoliosis is slowed, and its subsequent problems reduced, by early orthopaedic intervention in the form of bracing or surgery, and a correctly fitted wheelchair (10).

Granger et al. studied masticatory muscle function in patients with spinal muscular atrophy, and found that bite force in patients with SMA was only half as great, and fatigue times of patients with SMA were reduced by 30% compared with controls (11). Mandibular movements of these patients are more limited than in unaffected people. Weakened and easily fatigued masticatory muscles will further impact on the nutritional status of people with SMA.

Hypoglycaemia has been described in patients with SMA. Bruce et al. (12) observed repeated episodes of hypoglycaemia in two females (aged 14 and 20 years) with SMA Type 2. The girls were admitted to hospital several times over a two-year period with this condition, one girl also developed ketonuria. The authors consider that reduced gluconeogenesis, due to low muscle mass (about 10% of bodyweight, compared to normal 30 to 40%) was probably the cause of the hypoglycaemia. Despite their low muscle mass, the patients had normal to high rates of protein oxidation. The authors recommend regular meals of mainly carbohydrates and proteins, with a late evening meal included for patients with recurrent hypoglycaemia.

Commonly reported psychosocial problems are those also common to families with a chronically ill child--financial stress, marital discord and depression among siblings. Iannaccone reports that the SMA child is rarely depressed (3). She considers that this is due to the child having no discernable loss of function after mid-childhood. SMA children have high cognitive function; often being described as 'gifted' intellectually (3). Von Gontard et al. have studied intelligence and cognitive function in children and adolescents with SMA (13). They conclude that these children have a general intelligence in the normal range, but that by adolescence environmentally mediated aspects of intelligence are higher in people with SMA, The researchers speculate that the development of cognitive skills and knowledge may be a compensation for the physical restrictions faced by these people.

Nutritional therapy

General nutritional concerns for people with reduced mobility include the increased likelihood of osteoporosis (an adequate calcium intake and sunlight exposure for vitamin D is recommended), and weight gain due to inability to exercise (10). However, undernutrition rather than overnutrition appears to be the greater problem for people with SMA. Constipation is frequently found in people with reduced mobility, but responds well to increasing intake of fluids and fibre (especially soluble fibre) (3). Daily routine and planning for a regular bowel habit is important to reduce toileting problems which may lead to delayed bowel actions and subsequent constipation.

Harpey et al. (9) conducted a therapeutic trial of a high carbohydrate, low fat diet with supplements of riboflavin to stimulate acyl Co-A dehydrogenase activity, coenzyme Q10, and L-carnitine given to 13 children for three to 30 months. Tein et al. state that although significant motor improvement had apparently occurred in the majority of treated patients, the outcome was obscured by controversial methods (8).

Where known defects of mitochondrial [beta]-oxidation exist, dietary changes are recommended, but the role of fatty acid metabolism in SMA is not yet clear. Children with diminished muscle mass have limited capacity for muscle buffering of various dietary components and limited supply of muscle protein for gluconeogenesis. Crawford et al. (7) recommend that dietary changes are not advised until the role of fatty acid metabolism in SMA has been clarified, in order to avoid unintended and potentially serious adverse consequences.

Iannaccone reports that failure to thrive in infants and older children with SMA may occur as a result of a weak suck, unprotected airway, or easy fatigability (3). Weakness and tiredness may be further exacerbated as the result of a negative nitrogen balance. Chronic malnutrition may manifest as easy fatigability and reduced reserve. Some reports of organic aciduria in SMA may have been caused by inadequate nutrition. A thorough assessment and review by a speech pathologist, occupational therapist and dietitian is recommended so that the feeding schedule, positioning during feeding and food textures can be organised to maximise nutrient value and energy intake, particularly for those with more severe SMA. In some cases, a gastrostomy may be recommended for either full or supplementary feedings, particularly if there is a risk of aspiration (3).

Nutrition is important in respiratory function. Undernutrition can cause deleterious changes in the structure and function of the diaphragm muscle. Respiratory muscle strength and endurance are reduced in proportion to reduced body weight. Diaphragm strength may be improved by correcting nutritional deficiencies (14). However, in treating patients with respiratory failure due to atrophied respiratory muscles, caution must be used. Aldrich (15) states that abrupt increases in nutritional support, particularly with high percentages of carbohydrates, will increase carbon dioxide production, potentially worsening respiratory failure.

Conclusion

Research continues into the genetic nature of SMA with a view to treatment or prevention. In the meantime, in addition to regular physiotherapy and monitoring of respiratory status, certain dietary measures can be taken to optimise each individual's state of health within their own genetic boundaries.

Children with severe SMA Type 1 may have a lower dietary fat tolerance due to disturbances in fatty acid metabolism. Further research is needed to determine whether certain types of fats are better tolerated than others. A high carbohydrate diet (the implicit result of a low fat diet) may place additional stress on the respiratory system by increasing carbon dioxide production, so should be approached with caution. Current recommendations for the general population are that around 55% of dietary energy should be derived from carbohydrates, and that not more than 30% of dietary energy should be derived from fat. This may be a good starting point to adhere to for those with SMA, as many 'average' diets are of a higher fat and lower carbohydrate proportion than these recommendations. Younger children (under five years of age) are advised to have a higher proportion of fat in their diet.

As those severely affected with SMA Type 1 (and thus having greater disturbances in fatty acid metabolism) may not survive beyond their first few years, the issue becomes more complicated. Given the sensitive nature of a condition where children die in infancy and feeding can often be difficult anyway, perhaps observation and monitoring of urinary acids and respiratory function in response to preferred diets may help to plan and optimise individual dietary intake.

Basics of optimum nutrition for people with SMA include:

- * ensuring adequate folate intake (plenty of fresh vegetables and fruit)
- * ensuring adequate vitamin B 12 intake (meat products, dairy foods, eggs)
- * ensuring daily energy and protein requirements are met
- * utilising 'low glycaemic index' or slow release type carbohydrates, (recommendations for carbohydrate proportion in the diet for those with SMA are yet to be determined)
- * avoiding foods with high fat content, although ensure sufficient fat (or oil) intake for fat-soluble vitamin provision, and sufficient to reduce stress on the respiratory system
- * food texture and consistency may need to be modified according to ability to chew and swallow, and positioning during mealtimes must be considered,

* if adequate nutrition is unable to be taken orally, a gastrostomy should be considered.

* ensuring adequate calcium and vitamin D intake to avoid osteoporosis

* ensuring adequate fibre (especially soluble fibre) intake and sufficient daily fluids to avoid constipation.

Optimum nutrition will not cure SMA, but may modify the process by preventing unnecessary muscle breakdown, and improving the function of faulty SMN protein. Further research is required to determine ideal recommendations for fat, protein and carbohydrate intakes in response to metabolic differences observed across the spectrum of the three types of childhood SMA.

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Rocky Bay, Western Australia

S. Leighton, GradDipDiet, Dietitian

Correspondence: S. Leighton, Rocky Bay Inc, PO Box 53, Mosman Park, WA 6912. Email: sarahl@rockybay.org.au

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