

To Whom It May Concern:

Spinal Muscular Atrophy is a disorder of muscle and of fatty acid metabolism. Within 3 hours of a normal meal, blood amino acid levels of children with SMA decrease to levels that would not be reached until after at least 8 hours of fasting in normal children. In addition, infants with SMA type 1 do not efficiently metabolize fatty acids, a major source of energy during fasting. These children can have high levels of fatty acid byproducts in their urine and blood after overnight fasting.

In addition to metabolic aberration associated with immobility, systemic illness, muscle denervation, and muscle atrophy, SMA patients have inborn metabolic abnormalities in mitochondrial fatty acid oxidation and carnitine metabolism. Any process that increases cytoplasmic free fatty acid levels, such as fasting or defects of fatty acid transport or beta-oxidation, would be expected to increase the liver and kidney's production and excretion of dicarboxylic acids. Fasting ketosis reflects normal ketogenesis by utilization of free fatty acids by the livers of SMA patients, but defective beta-oxidation of fatty acids by muscle causes fatty acid metabolites like dicarboxylic acids to spill into the blood. Dicarboxylic acid levels are elevated in the urine of infants with SMA. The extent of dicarboxylic aciduria is a function of SMA severity such that SMA type 1 patients tolerate the briefest fasting without ketosis and dicarboxylic aciduria whereas SMA type 3 patients express these abnormalities only during prolonged fasting, illness and periods of physiologic stress.

With relatively minor fasting infantile SMA patients develop dicarboxylic aciduria similarly to patients with primary defects of mitochondrial fatty acid beta-oxidation. (1) Metabolic analyses including the appearance of relatively early ketosis and selective renal loss of carnitine (2) and fatty vacuolization of the liver, suggest that the abnormalities are caused by changes in the cellular physiology related to the molecular defects of the SMA pathogenic Survival Motor Neuron gene or neighboring genes. thus, the defect may be epigenic to the molecular pathogenesis of SMA itself or related to another function of the primary genetic defect. It may also contribute to the development of SMA. (1) Abnormal fatty acid metabolism also appears to resolve with age independent of disease severity. (1)

Very often before 10 years of age or during periods of physiologic stress, SMA patients suddenly lose muscle strength at a high rate. (3) Loss of strength is often triggered by respiratory tract infections and other episodes of physiologic stress and undernutrition and tends to become progressive and is most severe in infants. It is very likely that the muscle weakening in SMA infants is due to the inborn errors in fatty acid oxidation rather than to primary SMA denervation and that the weakening can be abated or averted with dietary manipulation. Diets high in carbohydrate, amino acids and polypeptides, and low in fat provide muscle with utilizable energy substrates thereby decreasing dependence on fatty acid oxidation and decreasing excessive accumulation of potentially toxic free fatty acids which can further damage muscle. (2)

This diet maintains more normal blood glucose levels during fasting, delays fasting associated ketoacidosis, and has been noted to normalize liver function enzyme

levels. Provision of amino acids and short chained peptides instead of complex dairy proteins facilitates gluconeogenesis and also appears to have a beneficial effect on decreasing airway secretion production for some children.

Harpey et al. felt that there was a significant improvement in strength and function for 13 patients treated with modified diets that provide high carbohydrate and elemental amino acids and small chained polypeptides, such as Tolorex and Pediatric Vivonex (Novartis, Minneapolis). (4) Although 90% of SMA type 1 patients have been reported to die by 1 year of age, none of our 30 SMA type 1 patients using this diet have died and the oldest are now 8 years of age. Therefore, I recommend prescription of Pediatric Vivonex for infants with a diagnosis of SMA Type 1.

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1. Crawford TO, Sladky JT, Hurk O, Besner-Johnston A, Kelley RI. Abnormal fatty acid metabolism in childhood spinal muscular atrophy. *Ann Neurol* 1999; 45: 337-343
2. Tein I, Sloan AE, Donner EJ, Lehotay DC, Millington DS, Kelley RI. Fatty acid oxidation abnormalities in childhood-onset spinal muscular atrophy: primary or secondary defects? *Pediatr Neurol* 1995; 12: 21-30
3. Iannaccone ST, Russman BS, Browne RH, Buncher CR, White M, Samaha FJ. Prospective analysis of strength in spinal muscular atrophy. DCN/Spinal Muscular Atrophy Group. *J Child Neurol* 2000; 15: 97-101
4. Harpey JP, Charpentier C, Paturneau-Jonas M, Renault F, Romero N, Fardeau M. Secondary metabolic defects in spinal muscular atrophy type II. *Lancet* 1990; 336: 629-630