Primary and Secondary Alterations of Neonatal Carnitine Metabolism

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Carnitine plays an essential role in the transfer of long-chain fatty acids across the inner mitochondrial membrane, in the detoxification of acyl moieties, and in maintaining normal levels of free coenzyme A. Although carnitine can be synthesized in liver and kidney, normal adults obtain the majority of carnitine from the diet. Preterm newborns have a reduced capacity to synthesize carnitine. Total parenteral nutrition lacks carnitine and exposes very low birth weight infants to carnitine deficiency, with decreased production of ketones from long-chain fatty acids. Supplementation with low doses of carnitine improves nitrogen balance and growth in these infants. Carnitine deficiency can be part of a number of inherited and acquired diseases. Primary carnitine deficiency is an autosomal recessive disorder characterized by increased losses of carnitine in the urine and decreased accumulation in the heart and skeletal muscle caused by defective carnitine transport. This condition is corrected by high-dose carnitine supplementation. Secondary carnitine deficiency can be caused by increased losses, pharmacological therapy, or a number of inherited metabolic disorders that must be correctly diagnosed before initiating carnitine supplementation.

Carnitine (β-hydroxy-γ-trimethylammonium butyrate) is a hydrophilic molecule that plays an essential role in the transfer of long-chain fatty acid inside mitochondria for β-oxidation. Carnitine binds acyl residues and helps in their elimination. This decreases the number of acyl residues conjugated with coenzyme A (CoA) and increases the ratio between free and acylated CoA.[1] Less-defined functions of carnitine include the shuttling of fatty acids between different intracellular organelles (peroxisomes, microsomes, mitochondria) involved in fatty acid metabolism. Carnitine deficiency has been known for several years in humans, but only in recent years the difference between primary and secondary carnitine deficiency has been fully defined.

Carnitine can be synthesized by the human body or assumed by diet. Carnitine is not metabolized by humans and is excreted in free or conjugated form in urine and bile. Newborns are at risk for carnitine deficiency for the immaturity of their carnitine synthesizing enzymes and of their mechanisms devoted to carnitine conservation.[2] In addition, infants can be affected by rare inherited disorders causing alterations in carnitine levels. This review discusses the biosynthesis and the function of carnitine and describes how to identify and treat infants who have carnitine deficiency. Additional general information about carnitine deficiency can be found in recent reviews.[3-5]

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0146-0005/99/2302-0005$10.00/0

Carnitine Biosynthesis and Dietary Sources

Carnitine can be obtained from the diet or synthesized by the liver and the kidney, and in smaller amounts by the brain from methionine and protein bound lysine.[1,6] Several cofactors, such as pyridoxal phosphate, niacin, vitamin C, and iron are required for carnitine biosynthesis as shown in Fig 1. Mammals cannot synthesize carnitine from free lysine, but from post-translational modification of lysyl residues in proteins, which are methylated by protein-dependent methyl transferases using *S*-adenosylmethionine as the methyl donor.[6,7] When proteins are degraded in the lysosome, 6-*N*-trimethyllysine is released via proteolysis. Free trimethyllysine is converted in mitochondria to 3-hydroxy-6-*N*-trimethyllysine by the action of a dioxygenase, which requires vitamin C and iron as cofactors.

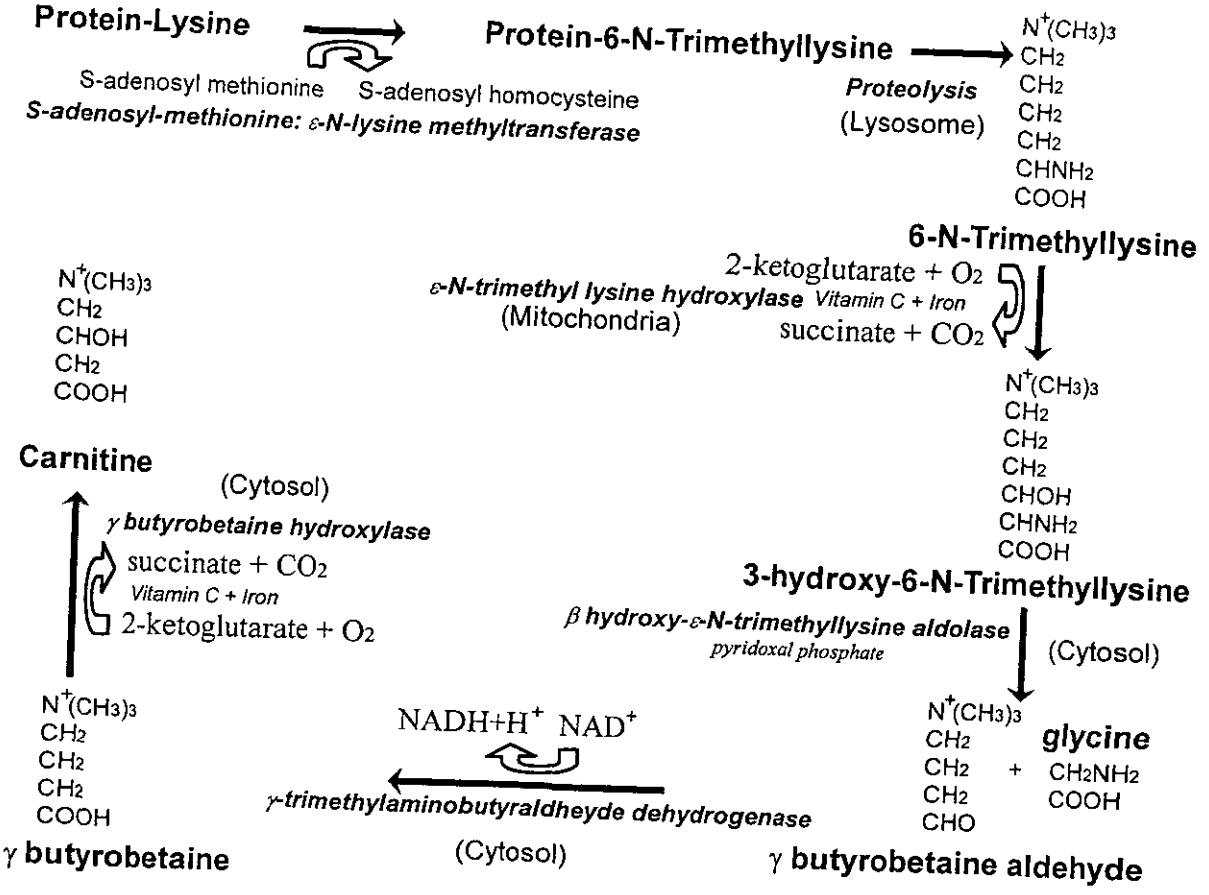

Figure 1. Carnitine biosynthesis.

A cytosolic aldolase (β-hydroxy-ε-*N*-trimethyllysine aldolase) then generates glycine and γ-butyrobetaine aldehyde, which is converted to γ-butyrobetaine by γ-trimethylaminobutyraldehyde dehydrogenase. Gamma-Butyrobetaine hydroxylase, a cytosolic dioxygenase, adds the hydroxyl group that carnitine uses to form esters with acyl moieties. This latter enzyme is not present in heart or skeletal muscle, which cannot synthesize carnitine and depends on carnitine transport for long-chain fatty acid oxidation.[8] This enzyme also is developmentally regulated, and newborns have only about 12% of the adult enzyme activity.[9] However, this low activity is not rate limiting for carnitine production in the normal neonate.[9] By contrast, generation of 3-hydroxy-6-*N*-trimethyllysine limits the generation of carnitine in the premature infant.[10] It is not known whether the rate-limiting step is in the transport of 6-*N*-trimethyllysine by cells or mitochondria or its hydroxylation by ε-*N*-trimethyllysine hydroxylase.[10]

In animal models, the availability of ε-*N*-trimethyllysine from lysosomal degradation of muscle actin and myosin controls the rate of carnitine biosynthesis.[11] In humans, carnitine levels are reduced in patients with Batten disease, an autosomal recessive neuronal ceroid lipofucsinosis characterized by defective lysosomal degradation of proteins containing trimethyllysine.[12] Interestingly, carnitine therapy slows disease progression in an animal model of hereditary ceroid lipofucsinosis.[13] The gene for this conditions has been identified, but its function and relationship to trimethyllysine degradation remains unclear.

The majority of carnitine is supplied to the organism by exogenous supplementation. In utero, carnitine is transferred across the placenta and provides significant carnitine stores to

Table 1. Carnitine Content of Milk, Formula, and Nutritional Supplements

	Carnitine Content	
	(nmol/mL)	μmol/g Powder
Human milk	60-70	
Cow milk	250	
Similac, Enfamil	62	
Prosobee	66	
Alimentum	93	
ProPhree		1.6
Provimin		2.5
Phenex-2, Tyrex-2		2.5
Ketonex-1, Propimex-1		6.2
Ketonex-2, Propimex-2		12.4
Glutarex-1, I-Valex-1		55.8
Glutarex-2, I-Valex-2		111.6

NOTE. The carnitine content of individual formulas was obtained from the manufacturer's information and from Acosta and Yannicelli.[50]

the growing human.[14] Pregnant women have decreased plasma carnitine levels (average, 17.4 ± 1.3 μmol/L at delivery) compared with nonpregnant women.[15,16] There is a correlation between carnitine levels in maternal and newborn blood, with values in the neonate (25.9 ± 2.7 μmol/L) being higher than in the mother.[15,17] Carnitine levels are higher in preterm than in full-term neonates (5 to 10 μmol/L).[18,19]

Glucose is the major metabolic fuel for the fetus, and the newborn must adapt to the use of lipids after birth. The newborn must also adapt to discontinuous feedings in contrast to the continuous supply of calories provided by the placenta. Preterm and full-term infants depend on exogenous sources of carnitine to use fat effectively as fuel. Table 1 lists carnitine content in milk, formula, and nutritional supplements used in normal children and children with inherited metabolic disorders. Human milk contains an average of 60 to 70 nmol/mL of carnitine.[2] The dietary carnitine intake for the full-term breastfed neonate is approximately 1.7 to 4 mg/kg daily. Carnitine is present in milk from all species, with cow milk providing at least twice the concentration of human milk. Common formula, prepared from cow milk, has approximately the carnitine concentration of human milk. Soy-based formulas do not have endogenous carnitine, but, since a few years ago, carnitine is routinely added to achieve a concentration similar to that of human milk.[2] Formula used for the treatment of inborn errors of metabolism associated with increased formation of acylcarnitine and carnitine wasting in the urine contain high amounts of carnitine (Table 1).

Plasma and red blood cell carnitine levels of full-term neonates who receive either breast milk or formula containing carnitine increase progressively after birth, reaching adult levels at 3 to 6 months of life.[2,18] Once adult plasma levels are reached, they are maintained throughout lifetime, with values in girls (51.5 ± 11.6 μmol/L) being slightly lower than those in boys (59.3 ± 11.9 μmol/L).[20] In contrast to enteral formula, none of the parenteral nutrition solutions contain carnitine.[2] Plasma carnitine levels decline in preterm neonates who receive carnitine-free total parenteral nutrition,[2,14] indicating that their carnitine stores and biosynthesis are not adequate to provide sufficient amounts of carnitine.[2]

The average adult diet provides about 75% of daily carnitine requirements.[2] Carnitine is provided mainly from beef (5.5 μmol/g), with reduced amounts in pork (1.5 μmol/g) and chicken (0.2 μmol/g). Dairy products contain carnitine (0.2 μmol/mL in whole milk), whereas fruits and vegetables (excluding asparagus) contain negligible amounts (<0.005 μmol/g).[21] Strict vegetarians maintain normal carnitine levels,[22] indicating that humans not only synthesize carnitine, but can also conserve it effectively. Normal infants of vegetarian mothers do not have problems with carnitine deficiency. However, a fulminant course in the neonatal period has been described in a child with primary carnitine deficiency born to a vegetarian mother.[22] Carnitine is lost in urine and is also secreted in the bile, where millimolar concentrations of carnitine conjugates are present and are clinically useful for the postmortem diagnosis of infants with sudden infant death caused by inherited disorders of fatty acid oxidation.[23] The quantitative contribution of biliary excretion to total carnitine losses in humans remains unclear. Measurement of biliary excretion through the measurement of stool carnitine is complicated by the metabolic conversion of carnitine by intestinal bacteria, which, unlike mammalian cells, can use carnitine as a nitrogen or carbon source.[24] Kidney losses are likely to represent the major route of carnitine elimination, because

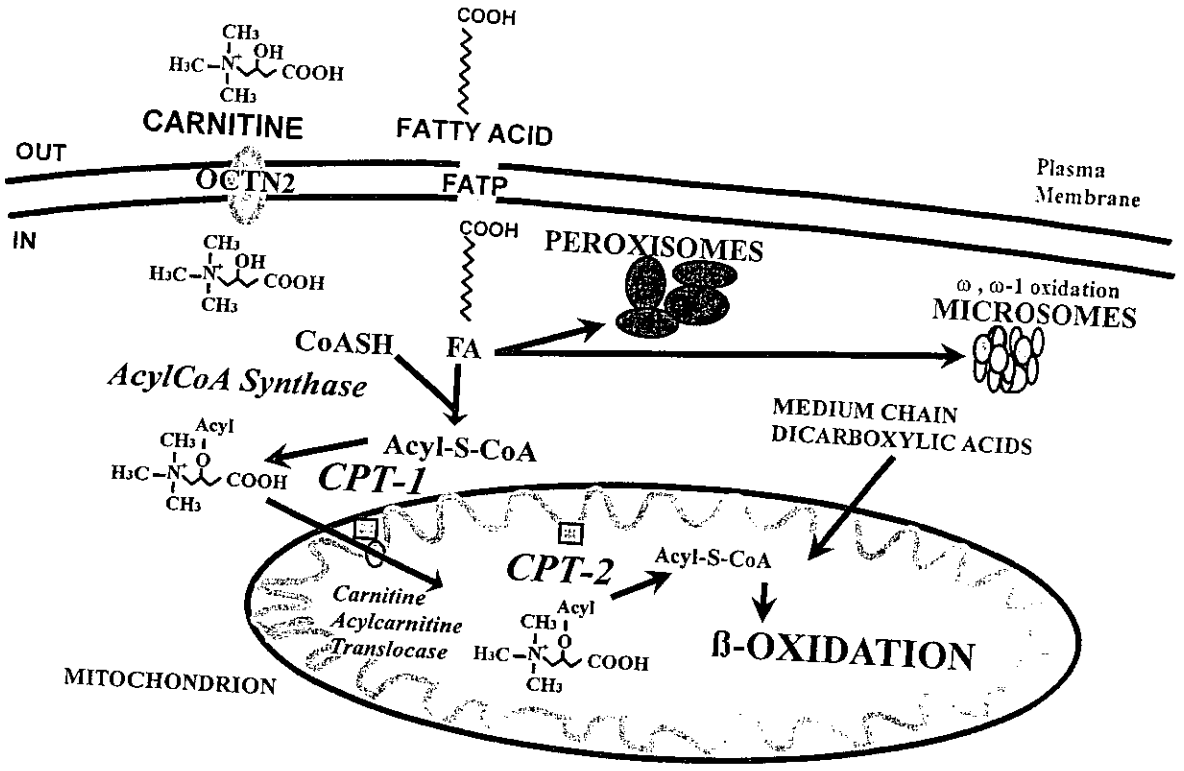

Figure 2. The carnitine cycle in fatty acid oxidation.

patients with acute renal failure have elevated carnitine levels,[25] and heterozygotes for primary carnitine deficiency, with limited increases in urinary carnitine wasting, have significantly decreased plasma carnitine levels.[26] The combination of biosynthesis and effective conservation help maintain plasma carnitine levels within a relatively narrow range in normal adults. Preterm neonates have impaired reabsorption of carnitine and acylcarnitine at the level of the proximal renal tubule, which matures with advancing gestational age in preterm infants.[27] The combination of immature kidneys with the immature carnitine biosynthesis[10] renders preterm newborns strictly dependent on exogenous supplies to maintain normal plasma carnitine levels.[28,29]

Carnitine Deficiency and Fatty Acid Oxidation

Carnitine is required for the transfer of long-chain fatty acids to the mitochondrial matrix for their oxidation.[30] During periods of fasting, fatty acids turn into the predominant substrate for energy production via oxidation in the liver, cardiac muscle, and skeletal muscle. During prolonged aerobic exercise, fatty acid oxidation accounts for 60% of muscle oxygen consumption. The brain does not directly use fatty acids for oxidative metabolism but oxidizes ketone bodies derived from acetyl CoA and acetoacetyl CoA produced by β-oxidation of fatty acids in the liver.

Fatty acids are mobilized from adipose tissue stores and transported in the circulation primarily bound to albumin. After their entry into the cells by a specific membrane transporter, fatty acids are conjugated to CoA by acyl CoA synthase (Fig 2). Fatty acids then must be conjugated to carnitine to enter mitochondria. Carnitine is accumulated inside the cell by a high-affinity membrane transporter in the heart, muscle, and kidney. The liver has a different low-affinity, high-capacity transporter. Carnitine forms a high-energy ester bond with long-chain carboxylic acids at its β-hydroxyl position by the action of carnitine palmitoyl transferase 1 (CPT-1), located in the inner aspect of the outer mitochondrial membrane. Acylcarnitine is then

translocated across the inner mitochondrial membrane by a translocase and cleaved by CPT-2 in the inner aspect of the inner mitochondrial membrane. Carnitine is released in the mitochondrial matrix and can then return to the cytoplasm for another cycle, whereas the fatty acid is conjugated back to CoA in the mitochondrial matrix and can enter (in aerobic conditions and in the presence of low levels of adenosine triphosphate [ATP]) β-oxidation with production of acetyl-CoA for oxidative phosphorylation or production of ketone bodies in the liver.

Inherited defects of all these steps, transmitted as autosomal recessive traits, have been reported in humans,[30] and some of these result in abnormal carnitine levels. A defect in the plasma membrane carnitine transporter in kidney and muscle causes primary carnitine deficiency (OMIM 212140 [On-Line Mendelian Inheritance In Man]). Primary defects in carnitine biosynthesis have not yet been identified. The lack of the plasma membrane carnitine transporter results in urinary carnitine wasting and decreased intracellular carnitine accumulation. Patients with this condition can present before 1 year of age with hypoketotic hypoglycemia, liver failure, and an acute encephalopathy often diagnosed as Reye's syndrome. Older patients present with skeletal or cardiac myopathy. Plasma carnitine levels (free and acylated fraction) are extremely reduced (less than 10% of normal), and urine organic acids do not show any consistent anomaly. Diagnosis is confirmed by demonstrating reduced carnitine transport in fibroblasts, which express the defective transporter. All patients respond to dietary carnitine supplementation (100 to 400 mg/kg/d), if started before irreversible damage occurs. Supplemental carnitine normalizes carnitine levels in the liver, but not in the heart or skeletal muscle, which share the defective transporter with the kidney. The long-term prognosis appears favorable as long as children remain on carnitine supplements. The gene for this condition (*OCTN2*) encodes a protein of 557 amino acids[31] and maps to chromosome 5q.[32] Causative nonsense mutations in this gene have recently been identified.[33,34]

Carnitine deficiency limited to the muscle is observed in myopathic carnitine deficiency (OMIM 212160). Affected patients present usually in the second or third decade with progressive proximal muscular weakness, myalgia, exercise intolerance, myoglobinuria, and occasionally cardiomyopathy.[3] They have reduced levels of carnitine in the muscle and normal levels in plasma. There is variable response to carnitine therapy. The basic biochemical defect has not been defined, and it is debated whether muscle carnitine deficiency is secondary to undiagnosed fatty acid oxidation defects, as demonstrated in some patients who initially received this diagnosis.[3]

Carnitine palmitoyl transferase I (CPT-1) deficiency (OMIM 255120) is triggered by mild viral illnesses. Affected children present, usually between 8 and 18 months of age, with altered mental status and hepatomegaly. Laboratory evaluation indicates nonketotic hypoglycemia, mild hyperammonemia, elevated liver function test results, and elevated free fatty acid levels. In this disease, plasma carnitine levels are not decreased, but are either increased or normal. No abnormal organic acids are detected in urine. Diagnosis is confirmed by assay of CPT-1 in fibroblasts. Children with severe episodes may have delays secondary to the initial brain insult. Therapy consists of avoidance of fasting and a diet rich in medium chain triglycerides, which do not need the carnitine cycle to enter β-oxidation in lever mitochondria. The gene for this condition maps to 11q13,[35] and the causative mutation has now been identified in one affected patient.[36]

Defects in the carnitine-acylcarnitine translocase (OMIM 212138) cause neonatal onset of seizures, irregular heart beat, and apnea. Many times these episodes are triggered by fasting. Laboratory examination findings show nonketotic hypoglycemia and hyperammonemia. Carnitine levels usually are reduced, with an increase in the long-chain acyl carnitine fraction. Dicarboxylic aciduria has also been reported. The episodes repeat over time with progressive neurological, cardiac, and hepatic deterioration. Diagnosis is confirmed by assay of carnitine-acylcarnitine translocase in fibroblasts. Complete deficiency of this transporter is associated with rapidly progressive disease. Residual activity has been associated with a milder phenotype and near-normal development when the child is kept on a frequent feeding schedule with a diet rich

in carbohydrates, low in fat, and supplemented with carnitine. The gene for this condition maps to 3p21,[37] and a 1 basepair (bp) insertion, causing a frame-shift that extends the reading frame by 21 amino acids, has been demonstrated in an infant with *neonatal* presentation.[38]

Carnitine palmitoyl transferase 2 (CPT-2) deficiency presents frequently in adolescents or young adults (OMIM 255110) with predominant muscular involvement, but can also present in the neonatal period (OMIM 600649). The neonatal form causes a generalized disease with seizures, altered mental status, hepatomegaly, cardiomegaly, cardiac arrhythmia, skeletal muscle involvement, and, in some cases, renal dysgenesis. The laboratory indicates hypoketotic hypoglycemia with elevated levels of creatine kinase and absence of dicarboxylic aciduria. Carnitine levels are reduced, with an increase in the long-chain acylcarnitine fraction. Diagnosis is confirmed by enzyme assay in fibroblasts. This disorder responds poorly to therapy. By contrast, the myopathic form of CPT-2 deficiency presents in young adults with muscle aching and myoglobinuria with elevation of *serum creatine* kinase precipitate by strenuous exercise or prolonged fasting. Unlike patients with phosphorylase and phosphofructokinase deficiency, these patients have a normal rise in lactic acid during muscle exercise. The late onset CPT-2 deficiency responds to restriction of fat and long-chain fatty acids, avoidance of fasting, and strenuous exercise. The gene for CPT-2 maps to 1p32,[39] and different missense mutations have been identified in patients with the infantile and late onset forms. Mutations in the infantile form reduce enzyme activity below a critical threshold, which prevents long-chain fatty acid oxidation in all tissues, whereas the S113L mutation (which accounts for about 60% of mutations in patients with late-onset CPT-2 deficiency [40]) allows residual fatty acid oxidation at least in fibroblasts.[41]

Disorders of fatty acid β-oxidation are described in a separate chapter. In general, these *present with* episodic hypoketotic hypoglycemia with Reye's syndrome–like episodes or prevalent involvement of the cardiac or skeletal muscle.[30] Urine organic acids, obtained during acute episodes, can provide clues to the specific diagnosis that can be confirmed by enzyme assay or, in some cases, molecular studies. Carnitine depletion can be severe in these disorders, and some of the patients initially reported with systemic carnitine deficiency indeed had carnitine deficiency secondary to defects in fatty acid β-oxidation.[30] In most of these conditions, carnitine deficiency is accompanied to an increase in the acylcarnitine component. Study of the acylcarnitine profile can indicate the level of the enzymatic block.

Impairment of fatty acid oxidation results in the accumulation of metabolities proximal to the block and failure to produce energy. Fatty acids that do not undergo mitochondrial β-oxidation can be used for triacylglycerol synthesis, explaining lipid accumulation in muscle, heart, and liver, or diverted to the endoplasmic reticulum for ω and ω-1 oxidation with generation of dicarboxylic and hydroxymonocarboxylic acids. Hydroxymonocarboxylic acids can be further oxidized to dicarboxilic acids, which can undergo β-oxidation in peroxisomes. Fatty acids that accumulate in defects of mitochondrial β-oxidation are toxic in free form and are usually conjugated to carnitine and glycine as a mechanism of detoxification. However, long-chain acyl carnitines are also toxic and can have an arrhythmogenic affect, causing sudden cardiac arrest. Thus, the accumulation of substrates proximal to the metabolic block can explain fatty degeneration of tissues, secondary carnitine deficiency, dicarboxilic aciduria, cardiac and skeletal myopathy, and sudden death. Other manifestations are explained by the hypoketotic hypoglycemia, which is a sign of defective energy production.

Diagnosis of Carnitine Deficiency

Fatty acid oxidation defects and carnitine deficiency become evident when the body must use fat to provide sufficient energy to meet physiological requirements. Breast-fed infants may experience a catabolic state shortly after birth (1 to 4 days of life), *when milk* production is not yet adequate to meet their nutritional requirements. Later in life, fatty acid oxidation defects can present at 1 to 3 months of age, when children start sleeping through the night, or at any age during times of increased energy demands, such as fever, sepsis, or prolonged fasting. If the system is not stressed, fatty acid oxidation defect may remain completely silent and be diagnosed

in asymptomatic adults for a positive family history.

Signs and symptoms related to carnitine deficiency are incompletely defined in the newborn. Apnea, irregular breathing, cardiac arrest, failure to thrive, recurrent infections, hypotonia, encephalopathy, cardiomyopathy, nonketotic hypoglycemia, and sudden infant death syndrome have been reported in infants with reduced carnitine concentration without a defined metabolic disorder.[42-44] It is unclear whether these presentations are the result of carnitine deficiency or of an underlaying metabolic defect associated with carnitine deficiency, because most fatty acid oxidation defects present in the same way. Given the paucity and the lack of specificity of clinical symptoms pointing to carnitine deficiency, measurement of carnitine levels is the key to diagnosis. Plasma values are commonly used to diagnose carnitine deficiency, although these values do not always reflect tissue carnitine concentrations. Radiochemical methods can determine the levels of carnitine and the acylated fraction. Analysis of the plasma acylcarnitine profile by fast atom bombardment (FAB) or electrospray-MS-MS can identify the type of fatty acid conjugated with carnitine, aiding (with the study of urinary organic acids and acylglycine profile, plasma amino acids, and free fatty acids) in determining the level of the metabolic block.

Carnitine levels should be evaluated in infants at risk for carnitine deficiency. Risk factors include extreme prematurity, infections, need for parenteral nutrition, and the suspicion of inherited metabolic conditions that increase carnitine requirements (Table 2). Carnitine deficiency also should be excluded in neonates being evaluated for incompletely defined syndromes such as acute life-threatening events or a family history of sudden infant death syndrome.[42]

When carnitine deficiency is confirmed, the underlaying mechanism should be investigated. A careful history will determine whether the mother had adequate carnitine intake during pregnancy, and if the infant is receiving dietary carnitine or drugs that affect free carnitine levels. A history of apnea, seizures, skeletal or cardiac myopathy, hypoglycemia, or metabolic acidosis should direct the attention toward possible inherited metabolic disorders. Study of urinary carnitine and a urine metabolic screen can determine if there is selective or generalized tubular dysfunction, although in our experience, Fanconi's syndrome rarely causes severe carnitine deficiency in the neonatal period. Urine organic acids, plasma amino acids, and the analysis of the plasma acylcarnitine profile can indicate the level of the metabolic block that can be confirmed by specific enzymatic analysis or DNA studies. In the typical premature newborn, in

Table 2. Secondary Carnitine Deficiency

Fatty acid oxidation defects
Defects of the carnitine cycle
Carnitine-acylcarnitine translocase
Carnitine palmitoyl transferase 2
Defects of the β-oxidation cycle
Short-chain acyl-CoA dehydrogenase (SCAD)
Medium-chain acyl-CoA dehydrogenase (MCAD)
Long-chain acyl-CoA dehydrogenase (LCAD)
Very long-chain acyl-CoA dehydrogenase (VLCAD)
Short-chain 3-hydroxyacyl-CoA dehydrogenase (SCHAD)
Trifunctional protein (including LCHAD)
Defects of amino acid metabolism
Branched chain amino acids
Isovaleric acidemia
Propionic acidemia
Methylmalonic acidemia
3-Methylcrotonyl-CoA-carboxylase
3-Hydroxybutyric aciduria
3-Hydroxymethylglutaryl-CoA lyase
2-Methylacetoacetyl-CoA thiolase
Other amino acids
Glutaric acidemia type I
Ornithine transcarbamylase
Carbamyl phosphate synthase
Defects of mitochondrial energy transfer
Defects of the respiratory chain due to mtDNA mutations
Cytochrome C oxidase deficiency
Glutaric acidemia type 2
Decreased intake/or biosynthesis
Total parenteral nutrition
Malabsorption
Malnutrition
Acquired Immunodeficiency Syndrome
Extreme prematurity
Chronic liver or renal disease
Chronic illness
Increased losses
Renal Fanconi's syndrome
Dialysis
Medical therapy
Ketogenic diet
Drugs (benzoate, emetine, pivampicillin, valproate, zidovudine)

whom carnitine deficiency is not caused by an inherited disorder but results from prematurity, total carnitine levels are reduced, and the urine organic acid screen does not show any primary metabolic abnormality.

Therapy of Carnitine Deficiency

Low plasma levels of free carnitine in infants are associated with impaired ability to use long-chain fatty acids from intravenous lipid solutions, with reduced formation of ketones.[2,45] Because lipids provide a substantial amount of calories to the growing newborn, it is not surprising that supplementation of total parenteral nutrition solutions with carnitine improves growth and nitrogen balance in infants.[46] Some studies have also suggested a beneficial effect of supplemental oral carnitine in preterm infants fed human milk.[47] Supplementation of carnitine in preterm newborns who receive total parenteral nutrition can start while the results of carnitine testing are pending and adjusted after the results are received. A dose of carnitine of 2 to 10 mg/kg (as continuous infusion or divided into four daily doses) prevents carnitine deficiency and improves ketogenesis in very low birth weight infants.[45] Intravenous carnitine administration has very few, if any, side effects. This level of supplementation should be maintained until enteral feedings do not represent at least 50% of caloric intake.

Carnitine supplementation in newborns who do not receive total parenteral nutrition should be started only if there is demonstrated carnitine deficiency or high suspicion of a metabolic disorder associated with carnitine deficiency. In addition to primary carnitine deficiency and disorders of fatty acid oxidation (Table 2), carnitine supplementation is given routinely to infants who have disorders of branched chain amino acid metabolism such as propionic acidemia, methylmalonic acidemia, isovaleric acidemia, and other more rare disorders (3-methylcrotonyl-CoA carboxylase deficiency, 2-methylacetoacetyl-CoA thiolase deficiency, 3-hydroxy-3-methylglutaryl-CoA lyase deficiency, 3-hydroxybutyric aciduria). In these conditions, carnitine is conjugated with abnormal metabolites and excreted in urine. The starting dose of carnitine is 100 mg/kg/d, which should be adjusted based on plasma levels. In all of these diseases, carnitine supplementation is only one aspect of therapy and should be provided with adequate nutritional intervention.

Carnitine supplements at the doses reported above have also been given to patients with defects of the mitochondrial respiratory chain caused by mtDNA or nDNA mutations with variable benefit. In these diseases, there is both increased formation or short-chain acylcarnitine esters, increased urinary losses caused by generalized tubular dysfunction, and decreased synthesis caused by abnormally high NADH to NAD^+ ratio.

Carnitine deficiency has been observed in children with the urea cycle defects ornithine transcarbamylase and carbamyl phosphate synthase deficiency.[48] It is unclear whether carnitine deficiency is related to the primary metabolic defect, to the concomitant liver disease observed during the initial presentation, or to benzoate therapy.

Carnitine deficiency can develop in children with renal Fanconi's tubulopathy. This can be acquired (heavy metals or drug exposure, dysproteinemias, immunologic disorders) or be part of an inherited condition. These include cystinosis; tyrosinemia type I; hereditary fructose intolerance; glycogen storage disease type 1; galactosemia; vitamin D dependency; mitochondrial defects; Lowe, Wilson's, and Fanconi-Bickel syndrome; in addition to idiopathic Fanconi's syndrome. In most cases, the tubulopathy disappears after correction of the basic metabolic defect, but persists in patients with cystinosis, which requires carnitine supplementation at 50 to 100 mg/kg/d.

Finally, carnitine supplementation can be considered in children with chronic diseases (AIDS, cystic fibrosis, chronic renal failure in hemodialysis), on ketogenic diet, or on medications (valproic acid, zidovudine, pivampicillin) known to cause carnitine depletion. In these cases, carnitine depletion is not automatic and may require additional contributing factors.[49]

There are several conditions that cause carnitine deficiency in children. Carnitine therapy of these conditions can be effective only after the underlaying mechanism producing carnitine deficiency has been identified and corrected. In these cases, carnitine supplementation is part of a comprehensive therapeutic plan. Carnitine therapy is started immediately in primary carnitine deficiency, defects of fatty acid oxidation,

and organic acidemias. In other conditions, plasma carnitine levels should be serially monitored and supplementation initiated only when free carnitine levels are reduced.

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