SPOTLIGHT
on **CARNITINE**

Clinical benefits of **L-carnitine in Pediatrics**

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Summary

Introduction

DEFECTIVE FATTY ACID OXIDATION AND METABOLIC IMPAIRMENT: AN OVERVIEW

Under normal physiological conditions, in cardiac and skeletal muscle, oxidation of fatty acids accounts for the vast majority of adenosine triphosphate (ATP) generation. In particular, cardiac muscle cells meet 90% of their ATP demands by oxidizing fatty acids[1].

Carnitine, a hydrophilic amino acid derivative, plays an essential role in energy metabolism through four key activities, strictly linked to cell metabolic life. Besides its primary role in the translocation of long-chain fatty acids from cytoplasm into mitochondria where their oxidation occurs, carnitine performs a second key metabolic function: the removal from the mitochondria of short and medium-chain fatty acids (acetyl groups) formed as products of β-oxidation and bound to coenzyme A as acetyl-coenzyme A.

Mitochondrial accumulation of this product is toxic, inhibiting pyruvate dehydrogenase activity and glucose oxidation, and it has been implicated in the development of insulin resistance[2].

The involvement of fatty acids in atherosclerosis is supported by observations of an increased risk for cardiovascular disease (CVD) associated with high levels of fatty acids.

Carnitine also participates in metabolism of branched chain aminoacids and stabilizes cellular membranes (**Table 1**)[3].

Table 1. Main physiological functions of carnitine. (Adapted from [3]).

Long-chain fatty acids mitochondrial transport and β-oxidation with ATP production
Removal of toxic compounds of fatty acid metabolism from the mitochondria and eventual excretion in the urine
Modulation of the mitochondrial acetyl-CoA/free CoA ratio
Stabilization of cell membranes and prevention of apoptosis

CoA = coenzyme A

Therefore, any deficiency in carnitine availability or in the carnitine-dependent transport system of mitochondria results in the curtailment of fatty acids oxidation. When the oxidation of fatty acids is defective, the inability to use long-chain fatty acids as main fuel results in their release from adipose tissue, with an associated reduced production of ketones by the liver. These events lead to energy deficiency and to accumulation of fats inside organs, such as liver, heart, skeletal muscle and brain, impairing their function (**Figure 1**): in fact, the lack of usable supplies of energy can cause hepatic steatosis, muscle weakness, cardiomyopathy with congestive heart failure and loss of consciousness[4,5]. The free long-chain fatty acids can also alter the electrical activity of cardiac cells resulting in arrhythmia (**Figure 1**).

Since skeletal and particularly cardiac muscles depend on fatty acid oxidation for most of their energy expenditure, these tissues can be expected to be the most severely affected by carnitine deficiency paving the way to life-threatening alterations[6].

Although carnitine is supplied exogenously as a component of the diet and can also be synthesized endogenously from two essential amino acids, lysine and methionine mostly in liver and kidney[7], evidence shows that both primary and secondary carnitine deficiencies do occur, the latter can be acquired or a result of inborn errors of metabolism. Irrespective of the cause, carnitine supplementation should be recommended.

IMPORTANCE OF FATTY ACIDS FOR ENERGY METABOLISM IN CHILDREN'S HEART

Shortly after birth, the heart rapidly develops the ability to metabolize fatty acids, while dramatically decreasing glycolytic rates[8].

As the newborn matures, oxidation of fatty acids increases and they become the dominant oxidative substrates; the increasing work requirement and high growth rate of the heart create the necessity for increasing energy production[9]. Thus, fat oxidation relative to total caloric expenditure is higher in prepubescent children than in adults[10].

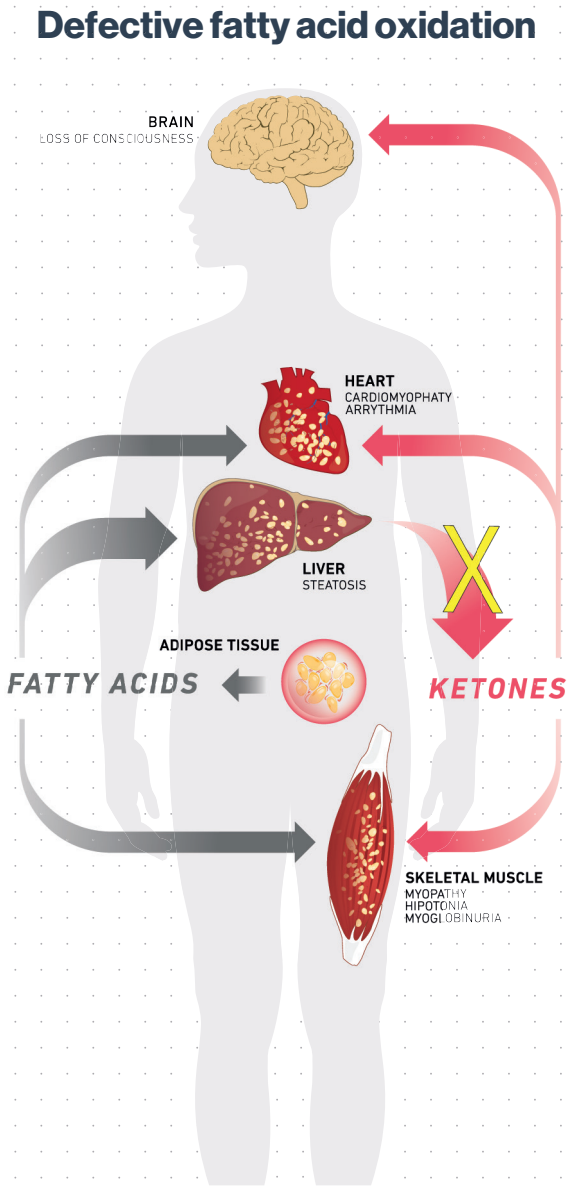


Figure 1. Chain of abnormal events resulting from carnitine deficiency and subsequent metabolic impairment. Fatty acids released from the adipose tissue cannot be converted to ketones by the liver, causing energy deficiency and fat accumulation inside organs compromising their function. (Depicted from [4]).

Systemic primary carnitine deficiency (SPCD)

Systemic primary carnitine deficiency (usually abbreviated as SPCD) is a rare autosomal recessive disorder of carnitine transportation, related to fatty acids oxidation[5,7]. According to the World Health Organization (WHO) definition, a disease is considered rare when it affects one person out of 2000 or less[11]. Unfortunately, epidemiological data on systemic primary carnitine deficiency is very fragmented: prevalence rates tend to range between 1:20,000 and 1:120,000[5,12], with one notable exception being the Faroe Islands, an isolated archipelago in the North Atlantic Ocean, where prevalence of systemic primary carnitine deficiency is 1:297[13] (**Figure 2**). The undefined and fragmented picture of systemic primary carnitine deficiency epidemiology can be attributed to the fact that incidence varies with ethnicity, to the broad clinical spectrum of the disease, and to its tendency to remain asymptomatic observed in some subjects, who may go undiagnosed throughout their entire life[5,12]. Furthermore, in most cases this rare condition manifests during childhood and results in premature death of the affected children: therefore, the incidence of systemic primary carnitine deficiency drastically decreases with aging[11]. This suggests that the prevalence of this deficiency in the general population is difficult to determine and may well be much higher or different than previously indicated[5,12]. According to the European definition, to be identified as rare, a pathology should be also recognized as a life-threatening or chronically debilitating condition[11]. This is the case with systemic primary carnitine deficiency, which, if left untreated, can cause irreversible and fatal organ damage[5,12]. Applying 'evidence-based medicine' (EBM) criteria is very challenging in the study of rare disorders in general and of systemic primary carnitine deficiency in particular[14], since there are many obstacles to implementing randomized controlled trials, which represent the 'gold standard' in evidence-based medicine (**Table 2**).

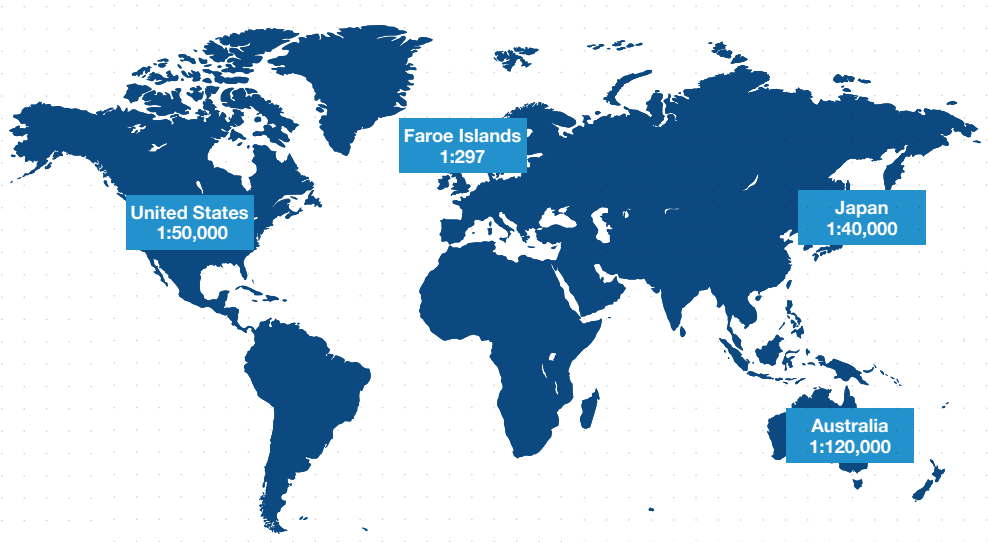


Figure 2. Average prevalence estimates available for systemic primary carnitine deficiency (SPCD) in different countries. (Adapted from [5,12,13]).

The factors listed in **Table 2** significantly reduce the ability of healthcare practitioners to both diagnose and treat systemic primary carnitine deficiency. Full-size randomized controlled trials in rare diseases are difficult to develop; however, limited data

Table 2. Key factors limiting the application of 'evidence-based medicine' principles to systemic primary carnitine deficiency (SPCD) (Adapted from [5,11]).

Limited and not fully reliable epidemiological data
Patients disseminated across different countries
Lack of information and disease understanding
Scarce awareness within the medical community
Clinical manifestations widely variable with respect to age of onset, organ involvement, and severity of symptoms

CoA = coenzyme A

is better than no data so case series and case reports are considered of scientific value for these conditions[14]. Most of the information we have about systemic primary carnitine deficiency has emerged from clinical experience, creating a body of diagnostic methods and therapeutic approaches that to date represent the standard to effectively address this condition.

ROLE OF CARNITINE IN LONG-CHAIN FATTY ACIDS β-OXIDATION AND PATHOPHYSIOLOGY OF SYSTEMIC PRIMARY CARNITINE DEFICIENCY

To understand the etiology of systemic primary carnitine deficiency, it can be helpful to analyze the β-oxidation process of long-chain fatty acids and the abnormalities in carnitine regulation underlying the disorder.

Carnitine (β-hydroxy-γ-N-trimethylaminobutyric acid) is a naturally occurring hydrophilic amino acid derivative. In humans, it is synthetized endogenously from lysine and methionine in the kidneys, liver and brain or obtained exogenously from meat and dairy products in the diet. The primary function of carnitine is to promote the translocation of long-chain fatty acids from the cytoplasm into the mitochondria for the subsequent β-oxidation cycle. This essential process provides most of the energy required for skeletal and cardiac muscle activity[4,5,7,15].

Systemic primary carnitine deficiency is caused by recessive mutations in the SLC22A5 gene encoding high-affinity carnitine transporter OCTN2 which is expressed in the plasma membrane of myocardium, skeletal muscle, renal tubules, fibroblasts, intestine and placental tissue cells. OCTN2 normally transfers carnitine across the cell membrane in a sodium-dependent manner and is essential in maintaining high intracellular carnitine concentrations. If OCTN2 is not functioning properly, the transportation of carnitine across the cell membrane is compromised, resulting in a decrease of intracellular carnitine accumulation. This intracellular carnitine deficiency impairs long-chain fatty acid β-oxidation: in this condition the energy metabolism becomes almost completely dependent on carbohydrates, determining the consumption of glucose as a predominant energy source and a consequent hypoglycemic state[5,12].

CLINICAL DESCRIPTION AND CARDIAC INVOLVEMENT

The clinical manifestations of systemic primary carnitine deficiency can vary widely and range from metabolic decompensation in infancy and cardiomyopathy in childhood, to fatigability or absence of symptoms in adulthood[4,5,12,15]. The most common phenotype associated with this deficiency condition includes progressive cardiomyopathy with or without skeletal muscle weakness beginning at 1-4 years of age, with a 62.3% of reported cases characterized by an exclusive cardiac manifestation[15] **Table 3** illustrates the predominant disease features observed in the different age groups.

As previously outlined, cardiomyopathy is the most common clinical manifestation in children with systemic primary carnitine deficiency, including dilated cardiomyopathy

Table 3. Main clinical features of systemic primary carnitine deficiency (SPCD) in relation to age of occurrence. (Adapted from [4,5,12,15]).

Age group	Main disease presentation	Further less common clinical manifestations
Infancy: 3 months-2.5 years	Metabolic decompensation triggered by fasting or common illnesses such as upper respiratory tract infections or gastroenteritis: episodes of hypoketotic hypoglycemia, hyperammonemia, elevated transaminases, hepatic encephalopathy (poor feeding, irritability, lethargy)	In older patients: cardiomyopathy, skeletal muscle weakness, and mildly elevated creatine kinase values
Childhood: 1-7 years	Myopathic manifestations: dilated cardiomyopathy, hypotonia, skeletal muscle weakness, and elevated creatine kinase	Anemia, proximal muscle weakness, developmental delay, respiratory distress, arrhythmias and electrocardiogram abnormalities
Adulthood: including women diagnosed with systemic primary carnitine deficiency after positive results obtained in newborn screening on their infants	Absence of symptoms or mild symptoms including decreased stamina or easy fatigability	Dilated cardiomyopathy and arrhytmias

and hypertrophic cardiomyopathy[15]. The first case of this deficiency was described in a 3-year-old boy in 1980. The initial presentations were hypoketotic hypoglycemic encephalopathy, hepatomegaly, and cardiomegaly when he was 3 months old. Pierpont and colleagues reported the cases of 3 children who had carnitine transporter defect, two of whom had severe dilated cardiomyopathy and extremely low plasma and skeletal muscle carnitine concentration. The third child had hypoglycemia and coma and presented mild left ventricular hypertrophy but no cardiac failure. The prognosis for long-term survival in pediatric dilated cardiomyopathy is poor, if the underlying condition is not detected early and treated medically[16].

Cardiac arrhythmia, although rare, is another clinical manifestation in patients with systemic primary carnitine deficiency. In a literature review of 42 adult patients, cardiac arrhythmias were present in five of them (12%). Bradycardia and atrial arrhythmias are also possible in these patients. Furthermore, three children with systemic primary carnitine deficiency and cardiomyopathy had strikingly peaked T waves on the electrocardiogram[15]. If systemic primary carnitine deficiency is not correctly diagnosed and an appropriate treatment is not promptly initiated, this condition can be progressive and eventually lead to very serious and fatal outcomes. In particular, children with untreated metabolic decompensation may fall into a coma and die; progressive cardiomyopathy may determine irreversible heart failure followed by death; finally, in asymptomatic adult individuals, the first clinical manifestation could be a sudden and unexpected death[5]. All children with dilated cardiomyopathy or hypoglycemia and coma should be evaluated for systemic primary carnitine deficiency because it is readily amenable to therapy that results in prolonged prevention of cardiac failure[16].

MANAGEMENT OF SYSTEMIC PRIMARY CARNITINE DEFICIENCY

As previously observed, the infantile metabolic and childhood myopathic manifestations of systemic primary carnitine deficiency can be fatal if not treated early, therefore it is crucial to start treatment for this deficiency before organ damage becomes irreversible[5,12].

The Food and Drug Administration first approved the use of L-carnitine for the treatment of systemic primary carnitine deficiency in 1985[15]. The treatment of metabolic decompensation and skeletal and cardiac muscle dysfunctions is based on 100-400 mg/kg/day of levocarnitine (L-carnitine) supplementation, orally administered in three daily doses: the exact dosage of L-carnitine should be adapted to an individual's plasma carnitine level. This pharmacological approach has shown to be highly effective in infants with systemic primary carnitine deficiency, resulting in slow normalization of the plasma carnitine concentration[5,12]. Oral L-carnitine supplementation has demonstrated the ability to revert childhood cardiomyopathy, which has disappeared in one year without sequelae: a few weeks of therapy with oral L-carnitine resulted in an impressive resolution of severe congestive heart failure and myopathy in all treated patients[15]. Recurrent hypoglycemic attacks and sudden death from cardiac arrhythmia have been reported in cases of carnitine supplementation discontinuation: it is strictly necessary in the treatment of systemic primary carnitine deficiency patients that carnitine supplementation be lifelong[5]. Newborn screening programmes for primary carnitine deficiency can identify affected patients at risk for this condition before irreversible damage occurs. Diagnosis of primary carnitine deficiency can be biochemically confirmed by demonstrating low free carnitine levels in plasma (< 8 μM, normal 25-50 μM) with reduced renal reabsorption (< 90%) and normal renal function with no abnormalities in urine organic acids. A recent study by Therrell et al. found that the frequency of primary carnitine deficiency among newborn screening programs in the USA is 1:142,000. However, the frequency of mutations (nonsense, splicing and expressed missense only) in 60,000 normal individuals (carriers) in the exac browser is 1:141, with an extrapolated frequency of affected individuals (homozygous or compound heterozygous) of 1 in 79,910. Since the reported frequency is 1 in 142,236, this would suggest that many cases are missed by newborn screening. The possibility that newborn screening might miss cases of carnitine transporter deficiency should be considered in patients with persistent low or borderline levels of carnitine or who show a decrease in carnitine levels after stopping supplementation. Such individuals should be investigated for primary carnitine deficiency[17].

Also asymptomatic individuals and all pregnant women with systemic primary carnitine deficiency, although asymptomatic, need to be closely monitored for plasma carnitine levels and receive appropriate L-carnitine supplementation dosage to maintain a normal plasma carnitine concentration[5,12].

There was general consensus that future trials on the effect of carnitine in disorders of fatty acid oxidation should be randomized, double-blinded, multicentered and minimally include the following diagnoses: medium-chain acyl coenzyme A (CoA) dehydrogenase deficiency, very long-chain acyl-CoA dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and mitochondrial trifunctional protein deficiency[18].

There are different strategies for newborn screening that vary among states in the USA. In Utah, we perform 2 screenings, the first within about 48 h after birth, and the second at 7-21 days of life. Carnitine is transferred from the mother to the child via the placenta and levels of carnitine can be normal in an infant if the sample is collected shortly after birth. In this case, carnitine levels may decline over time. A two step screening might allow better detection of infants with primary carnitine deficiency. On the other hand, maternal primary carnitine deficiency is better identified with very low carnitine levels on the first screening. In such cases, most mothers are symptomatic, but are at risk of sudden death. Carnitine supplementation in asymptomatic mothers can increase plasma carnitine levels and prevent cardiac arrhythmia[18].

This life-saving strategy should also be adopted to prevent primary and secondary manifestations of systemic primary carnitine deficiency, thus avoiding the risk of metabolic, hepatic, cardiac, and muscular complications occurring[5,12]. Obviously, treatment for systemic primary carnitine deficiency should also include supportive and other therapies related to the patient's condition[15].

Unfortunately, there is little correlation between the type of mutation and timing or type (metabolic versus cardiomyopathy) of presentation in children with primary carnitine deficiency. Moreover, even within the same family, there is variability in clinical presentation, with some children presenting early with hepatic encephalopathy and

others presenting later with cardiac dysfunction. This lack of genotype-phenotype correlation has been demonstrated in several studies[17].

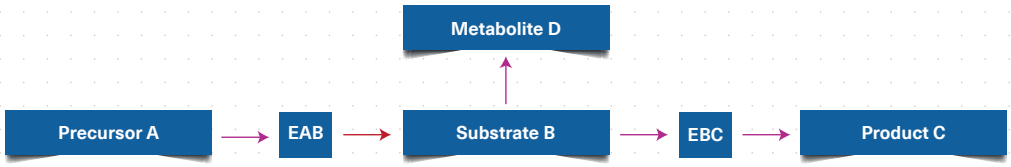
L-carnitine therapy is well tolerated and is associated with relatively few side effects: high doses of oral L-carnitine can cause increased gastrointestinal motility, diarrhea, and intestinal discomfort and the production of trimethylamine, which can result in a fishy odor. In these cases, a decrease in the L-carnitine dose is indicated, together with a cycle of oral metronidazole at a dose of 10 mg/kg/day for 7-10 days to improve the odor[4,5,12]. Although carnitine crosses the placenta during pregnancy, animal and human studies have reported no teratogenic effects[5].

It is important to note that, due to the absence of targeted randomized controlled trials, all these evidences are derived from clinical experience as reported in case series and expert opinions, which recommend the essential and life-saving use of L-carnitine supplements in the management of systemic primary carnitine deficiency. Thus, clinical practice represents so far the most reliable source of knowledge about the dramatic responsiveness of systemic primary carnitine deficiency patients to this therapy and its extraordinary benefits for the treatment of such a rare disease.

Inborn errors of metabolism

Inborn errors of metabolism comprise a large and heterogeneous group of genetic disorders in which a single gene defect causes the loss of function of a single enzyme, leading to altered synthesis or catabolism of proteins, carbohydrates or fats and, consequently, to a clinically significant block in a metabolic pathway[19,20]. The underlying mechanism common to all the different metabolic conditions is depicted in **Figure 3**.

Figure 3. Mechanism of metabolic disorders. (Adaped from [19]).



EAB: enzyme converting A into B; EBC: enzyme converting B into C

The Figure illustrates a conventional metabolic pathway where EAB is the enzyme converting A into B and EBC is the enzyme converting B into C. If EBC is absent due to a defect in the corresponding gene, then Substrate B will build up in abnormally high concentrations. The consequences of this altered process are the toxic accumulation of Substrate B before the block of Metabolite D obtained from an alternative pathway, a deficiency of Product C and/or defects in energy production and utilization[19,20]. Therefore, the lack of a single component of a pathway is the factor that compromises the entire process and causes the development of metabolic anomalies. All inborn errors of metabolism are genetically transmitted, typically in an autosomal recessive or X-linked recessive fashion, and although individually rare, they are collectively numerous and not uncommon[19-21]: over 200 of these disorders have been characterized and have a collective incidence of 1 per 1,500 people[22]. Occurrence is not limited to the neonatal period or infancy (< 3 months), as the term 'inborn' could lead to believe: late-onset inborn errors of metabolism (from late infancy to adulthood) are now recognized. Unlike neonatal forms, that are characterized by non specific symptoms or associated with protein intolerance[21], the late-onset forms of inborn errors of metabolism often display psychiatric or neurological presentations[23].

Table 4. Classification of inborn errors of metabolism into three different groups. (Adapted from [20,24]).

Disease groups	Disease subcategories	Common features
Group 1 Disorders of energy production/utilization	Fatty acid oxidation defects Mitochondrial disorders Cytoplasmic energy defects	Effects on cytoplasmic and mitochondrial energetic processes Mitochondrial defects: the most severe and generally untreatable
Group 2 Disorders that result in toxic accumulation	Disorders of protein metabolism including aminoacidopathies, most organic acidurias, congenital urea cycle defects Disorders of carbohydrate intolerance Metal intoxication Porphyrias	Alternate acute or chronic intoxication with a symptom-free interval No interference with embryo-fetal development Mostly treatable with a nutritional approach
Group 3 Disorders involving complex molecules	Lysosomal storage disorders Peroxisomal disorders Disorders of intracellular trafficking processing Mucolipidoses Disorders of cholesterol synthesis	Permanent and progressive symptoms Independent of intercurrent events and unrelated to food intake Several lysosomal disorders treatable with enzyme replacement therapy

CLASSIFICATION OF INBORN ERRORS OF METABOLISM

Due to the high number and variety of inborn errors of metabolism, different methods of classification have been proposed. One simplified classification defines distinct categories of metabolic disorders based on their pathophysiological effects and on the potential availability of treatment, identifying three disease groups[20,24]:

- **Group 1**, consisting of mostly untreatable inborn errors of metabolism with symptoms due at least partly to a deficiency in energy production or utilization;
- **Group 2**, including mostly treatable inborn errors of intermediary metabolism that lead to an acute or progressive intoxication from the accumulation of toxic compounds proximal to the metabolic block;
- **Group 3**, involving cellular organelles and including partially treatable diseases that affect the synthesis or the catabolism of complex molecules.

The subcategories included in each disease group are reported in **Table 4**.

Nearly every metabolic disease presents in several forms that vary in age of onset and clinical severity[20,24] making identification often uncertain and delayed. Diagnosis relies on the physician's suspicion, the study of personal and family history, a physical examination, plasma, urine and cerebrospinal fluid analyses and, finally, advanced screening tests based on biochemical and genetic investigations[20,24]. **Table 5** reports the specific inborn errors of metabolism related to disorders of carnitine transportation that share a treatment approach based on a common nutritional therapy.

CLINICAL PRESENTATION: SIGNS AND SYMPTOMS

Fatty acid oxidation defects

In fatty acid oxidation disorders, the body cells are unable to break down fatty acids to produce energy. Therefore, a common pathological factor of fatty acid oxidation disorders is decreased energy production[25].

Table 5. Inborn errors of metabolism related to disorders of carnitine transportation.

Disease groups	Disease subcategories	Common features
Group 1 Disorders of energy production/utilization	Fatty acid oxidation defects	Systemic primary carnitine deficiency Carnitine-acylcarnitine translocase deficiency
Group 2 Disorders that result in toxic accumulation	Hyperhomocysteinemia Organic acidurias Urea cycle disorders	Methylenetetrahydrofolate reductase deficiency Isovaleric acidemia Glutaric acidemia type I Propionic acidemia 3-Methylcrotonyl glycinuria 3-Methylglutaconic aciduria type

Systemic primary carnitine deficiency. As discussed in the previous chapter, systemic primary carnitine deficiency is an autosomal recessive disorder of carnitine transportation. Intracellular carnitine deficiency prevents the β-oxidation of long-chain fatty acids with a consequent impairment of energy metabolism[5,12].

The main clinical features of this condition are metabolic and cardiac. The metabolic presentation is more typically observed in pediatric patients of < 2 years and progressively encompasses upper respiratory tract infection, acute gastroenteritis, lethargy, hepatomegaly, coma and death. Cardiac symptoms are more frequently reported in older patients, wherein cardiomyopathy is the hallmark symptom. This condition is also associated with an increased loss of carnitine in the urine, low serum carnitine levels (0-5 μM, normal 25-50 μM) and decreased carnitine accumulation in tissues[4,25].

Carnitine-acylcarnitine translocase deficiency. Carnitine-acylcarnitine translocase (CACT) is located in the inner mitochondrial membrane triggering the carnitine/acylcarnitine exchange across it (**Figure 4**).

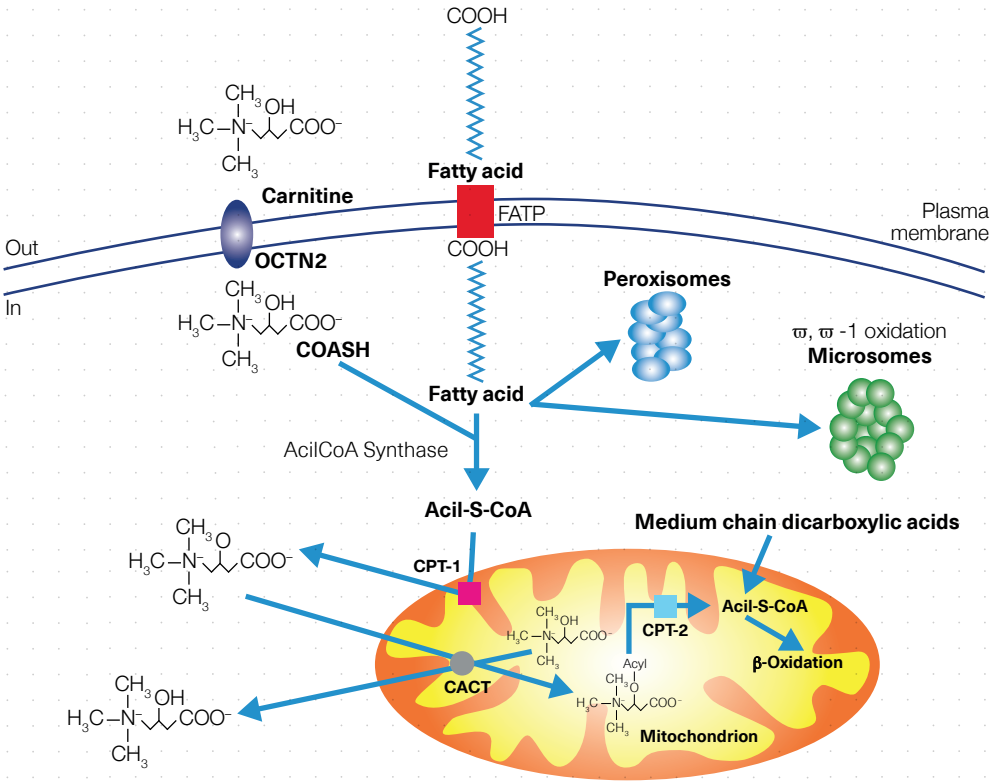


Figure 4. The carnitine cycle in fatty acid oxidation and the role of carnitine-acylcarnitine translocase (CACT). CPT-1: carnitine palmitoyl tansferase-1; CPT-2: carnitine palmitoyl transferase-2; FATP: fatty acid transporter protein; OCTN2: carnitine transporter. (Adapted from [4]).

Two forms of carnitine-acylcarnitine translocase deficiency are known, one with neonatal onset and the other with a later occurrence in infancy or early childhood. When it presents in the neonatal period, carnitine-acylcarnitine translocase deficiency is associated with metabolic crises – seizures, irregular heartbeat, and apnea – often culminating with death from cardiopulmonary complications and/or liver failure. This is the most prevalent type. When carnitine-acylcarnitine translocase deficiency occurs later in infancy or early childhood, it is predominantly characterized by hypoglycemia without cardiomyopathy. The main signs and symptoms common in the two forms include clinical encephalopathy, hepatomegaly, arrhythmias, hyperammonemia, elevation of creatine kinase levels, extremely reduced carnitine levels (< 5 μM), a relevant increase in long-chain acylcarnitines and a drop in levels of free carnitine[4,25].

Hyperhomocysteinemia and methylenetetrahydrofolate reductase deficiency

Homocysteine, a sulfur-containing amino acid, is an intermediate product in methionine metabolism. Methionine obtained by diet is converted to S-adenosylmethionine and then to S-adenosylhomocysteine[26]. Carnitine is also involved in this metabolic pathway: it is derived from trimethyllysine, whose synthesis is catalyzed by S-adenosylmethionine methyltransferase enzyme, yielding S-adenosylhomocysteine[27]. The hydrolysis of this latter compound produces adenosine and homocysteine. If the pathway to methionine is impaired, then homocysteine levels may increase. Homocysteine metabolism depends on the presence of adequate enzyme levels; in particular, the methylenetetrahydrofolate reductase enzyme (MTHFR) catalyses the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. A deficiency in this enzyme determines hyperhomocysteinemia, responsible for neurologic abnormalities, mental retardation, atherosclerosis and thrombosis. Furthermore, some mutations in methylenetetrahydrofolate reductase related to high levels of homocysteine have been recognized: one of these leads to a thermolabile form of methylenetetrahydrofolate reductase and is associated with a higher risk of developing cardiovascular disease. Hyperhomocysteinemia may cause premature vascular diseases and thromboembolic vascular lesions[28].

Organic acidurias

Organic acidurias form a large and diverse group of disorders caused by abnormal metabolism of proteins, fats or carbohydrates and characterized by the excretion of nonamino organic acids in urine, metabolic acidosis with ketosis, often with elevated lactate and mild to moderate hyperammonemia. Most organic acidurias result from the dysfunction of a specific stage in amino acid catabolism caused by a deficient enzyme activity and leading to the accumulation of toxic precursors and deficiency of products. The effect of the altered metabolic pathways is the toxicity of small molecules for the brain, liver, kidney pancreas, retina, and other organs[28]. A newborn with an organic aciduria usually appears normal at birth and for the first few days of life. Subsequently, he/she develops toxic encephalopathy with vomiting, poor feeding, neurologic symptoms such as seizures and abnormal tone, and lethargy progressing to coma. Although adequately treated, patients with organic acidurias have a greater risk of infection and a higher incidence of life-threatening pancreatitis[28]. In these conditions, some of the coenzyme A derivatives of the organic acids may be in excess and form a complex with carnitine, therefore, carnitine deficiency may develop and contribute to disordered homeostasis[28].

Isovaleric acidemia is due to a deficiency of isovaleryl-CoA dehydrogenase, an enzyme catalysing the third stage of leucine catabolism[29], that occurs in acute and chronic intermittent forms. It is characterized by periodic vomiting, lethargy, coma, ketoacidosis and a 'sweaty feet' odor[30].

Glutaric acidemia type I is caused by inadequate levels of glutaryl-CoA dehydrogenase, an enzyme contributing to the breakdown of amino acids lysine, hydroxylysine, and tryptophan. Excessive levels of these amino acids and the accumulation of their intermediate breakdown products lead to severe brain damage. Cortical atrophy and progressive neuronal loss and gliosis are particularly evident in the basal ganglia, with

a resultant extrapyramidal movement disorder associated with spasms, jerking, rigidity, or decreased muscle tone. Intellectual disability, cerebral and intraretinal hemorrhages may also occur[28,31,32].

Propionic acidemia is caused by a deficiency of propionyl-CoA carboxylase, which converts propionyl-CoA, derived from the catabolism of isoleucine, valine, methionine, threonine and odd-chain fatty acids, to methylmalonyl-CoA[29,33]. A neonatal-onset, most common form can be phenotypically differentiated from a lateronset form, as reported in **Table 6**.

Table 6. Clinical phenotypes of propionic acidemia. (Adapted from [29,33]).

Onset	Clinical features
Neonatal-onset	Food refusal Vomiting Progressive weight loss Irritability Generalized hypotonia Abnormal posturing and movements Lethargy Progressive encephalopathy Seizures Coma Respiratory failure
Late-onset	Acute and intermittent: encephalopathy, coma and/or seizures precipitated by catabolic stressors (e.g. intermittent illness, surgery) Chronic and progressive: vomiting, protein intolerance, failure to thrive, developmental regression, neurodevelopmental delay Isolated cardiomyopathy

This condition is generally associated with metabolic acidosis with anion gap, ketonuria, hypoglycemia, hyperammonemia, and cytopenias[29,33].

3-Methylcrotonyl glycinuria is caused by the impairment of leucine catabolism resulting from the deficiency of the 3-methylcrotonyl-CoA carboxylase enzyme. Most of the accumulated acyl-CoA is conjugated with glycine, whereas 3-methylcrotonyl-CoA is acylated with carnitine. The spectrum of this condition ranges from neonatal-onset, characterized by severe neurological involvement and even death, to late-onset disease including muscular hypotonia, seizures, psychomotor delay and even an asymptomatic adult phenotype. Laboratory signs include hypoglycemia, ketoacidosis, hyperammonemia and very low plasma carnitine[34].

3-Methylglutaconic aciduria type I derives from a defective activity of the 3-methylglutaconyl-CoA hydratase enzyme which normally promotes the conversion of 3-methylglutaconyl-CoA to 3-hydroxy-3-methylglutaryl-CoA. Its main laboratory signs include urinary excretion of 3-methylglutaconyl and 3-methylglutaric acids. The clinical manifestations of this very rare disorder vary from absence of symptoms (at 2 years of age), to mild neurological impairment, severe encephalopathy with basal-ganglia involvement, quadriplegia, athetoid movement disorder, severe psychomotor retardation, and leukoencephalopathy in late forms[34].

Urea cycle disorders

Urea cycle disorders occur as a consequence of a mutation affecting one of the six enzymes involved in nitrogen detoxification/arginine synthesis and leading to enzyme deficiencies. In normal conditions, these enzymes promote the clearance of excess ammonia derived from the breakdown of amino acids and other nitrogenated compounds and contribute to the conversion of the waste nitrogen to urea that is transferred into the urine. In pathological conditions, disturbances of the urea cycle in the liver lead to

higher ammonia levels in blood producing hyperammonemia. Urea cycle disorders vary in onset and severity depending on the specific mutated enzyme[35-37]. A few days after birth, the complete deficiency of all six enzymes typically results in cerebral edema and the related signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, abnormal posturing, culminating in hyperammonemic coma with about 50% mortality. In survivors, severe developmental delay and recurrent hyperammonemic crises are observed. In later ages, patients with partial urea cycle defects experience feeding difficulties, vomiting, lethargy, irritability, tachypnea, convulsive crises and behavioral changes and may also develop acute encephalopathy with coma. These symptoms may be triggered by illness or stressing circumstances at almost any time of life. A hyperammonemic coma occurs when serum ammonia concentrations are greater than 300 μmol/L and, if not promptly managed, it may cause irreversible brain damage[35-37].

MANAGEMENT: CARNITINE SUPPLEMENTATION FOR TREATABLE INBORN METABOLIC DISEASES

Most of the inborn errors of metabolism described are treatable through an appropriate therapy aimed at removing toxin substances, replenishing body stores and/ or improving mitochondrial energy metabolism[24,25]. One of the agents specifically used for this purpose is L-carnitine. As previously reported, secondary carnitine deficiency is a common condition to many inborn errors of metabolism; hence, oral carnitine supplementation has been included in the management of inborn errors of metabolism, demonstrating beneficial effects in many different disorders[19,25]. Pediatric patients with primary carnitine deficiency are effectively treated with dietary carnitine supplementation (100-400 mg/kg/day), if initiated before irreversible organ damage has occurred. The long-term prognosis is favorable as long as children remain on carnitine supplements. L-carnitine has variously shown to be an effective cardioprotective agent[4,23]. L-carnitine supplementation in CACT deficiency has also demonstrated therapeutic benefits by improving the acylcarnitine profile and preventing further attacks of hypoglycemia and arrhythmia[4,25]. The effect of carnitine supplementation on these diseases is dramatic, improving cardiomyopathy and preventing further episodes of hypoketotic hypoglycemia[36].

The therapeutic approach considered for the management of hyperhomocysteinemia related to methylenetetrahydrofolate reductase deficiency is also based on the use of carnitine[38]. Some preclinical and clinical studies have investigated the effect of exogenous administration of L-carnitine on plasma levels of homocysteine in chronic renal failure patients on hemodialysis[27], in hemodialysis patients with peripheral arterial disease[39], and in murine models of Alzheimer disease, with very promising results[40].

The aim of therapy for organic acidurias is the recovery of biochemical and physiologic homeostasis[28]. Although not yet confirmed by randomized and controlled trials, L-carnitine has proven its efficacy for the treatment of several organic acidurias, by promoting the formation of organic acylcarnitines that will re-establish the coenzyme A levels and by binding to free organic acids so that they can be filtered and excreted effectively by the kidneys. Therefore, L-carnitine is recommended for both long-term treatment and initial management of a patient in a decompensation crisis with a definite diagnosis of organic aciduria; in patients with isovaleric or propionic acidemias, it is also suggested for prevention of primary manifestations[29,33,34,36,38]. **Table 7** reports the therapeutic strategies including carnitine recommended for the management of fatty acid oxidation defects, methylenetetrahydrofolate reductase deficiency, and several organic acidurias.

To date, studies investigating the effect of L-carnitine in human hyperammonemic syndromes, clearly shown that L-carnitine is able to counteract the neurotoxic effects of ammonia, increase energy metabolism and decrease mortality (**Table 8**).

Patients with urea cycle disorders lead to higher ammonia levels in blood; they may also exhibit carnitine deficiency because low protein diets can be low in carnitine and nitrogen scavengers also conjugate with carnitine. In these patients, plasma carnitine should be monitored and severe carnitine deficiency treated with carnitine supplementation[35].

The treatment of the acute manifestations of urea cycle defects is also based on the intravenous administration of L-carnitine at dosages of 100 mg/kg/day, even if the enzyme defect is undefined[36].

Table 7. Therapeutic approaches to inborn errors of metabolism (Adapted from [4,38]).

Systemic primary carnitine deficiency (SPCD)	Carnitine supplements, avoid fasting, sick day management
Carnitine-acylcarnitine translocase (CACT) deficiency	Carnitine supplements, avoid fasting, sick day management
Late-onset methylenetetrahydrofolate reductase (MTHFR) deficiency	Betaine supplements, ± folate, carnitine, methionine supplements
Late-onset glutaric acidemia type I	Lysine restriction, carnitine supplements
Glutaric acidemia type II	Carnitine, riboflavin, β-hydroxybutyrate supplements, sick day management
Late-onset isovaleric acidemia	Dietary protein restriction, carnitine supplements, avoid fasting, sick day management
Late-onset propionic acidemia	Dietary protein restriction, carnitine supplements, avoid fasting, sick day management
Late-onset methylmalonic acidemia	Dietary protein restriction, carnitine supplements, avoid fasting, sick day management
3-Methylcrotonyl glycinuria	Dietary protein restriction, carnitine, glycine, biotin supplements avoid fasting, sick day management
3-Methylglutaconic aciduria type I	Carnitine supplements, avoid fasting, sick day management

Table 8. Hyperammonemia triggers requiring carnitine supplementation. (Adapted from [35]).

Infections
Fever
Vomiting
Gastrointestinal or internal bleeding
Decreased energy or protein intake (e.g. fasting pre-surgery, major weight loss in neonates)
Catabolism and involution of the uterus during the postpartum period (mostly ornithine transcarbamylase)
Chemotherapy, high-dose glucocorticoids
Prolonged or intense physical exercise
Surgery under general anesthesia
Unusual protein load (e.g. a barbecue, parenteral nutrition)
Drugs: mainly valproate and L-asparaginase/pegaspargase. Topiramate, carbamazepine, phenobarbitone, phenytoin, primidone, furosemide, hydrochlorothiazide and salicylates have also been associated with hyperammonemic decompensation

Other potential carnitine deficiency conditions in children and adolescents

This section examines the relationship between carnitine deficiency and specific conditions, mostly concerning the pediatric population, and outlines the benefits of administering exogenous carnitine for these conditions.

CANCER TREATMENT AND FATIGUE

Clinical presentation

Fatigue is the most frequent adverse effect experienced by young oncology patients undergoing chemotherapy and is usually described as a reduced capacity to carry out normal daily activities, slow physical recovery from tasks, and diminished concentration[41,42]. This condition significantly affects an already declined quality of life in children and adolescents with cancer and undergoing cytotoxic treatments[42].

Until recently, the pathogenetic mechanisms underlying the fatigue associated with cancer and chemotherapy were poorly understood and many hypothetical factors had been suggested, including neurophysiologic changes of skeletal muscles, chronic stress response and hormonal changes. In the light of recent biochemical investigations, it is now ascertained that one of the phenomena contributing to cancer-related fatigue is an abnormality of energy metabolism associated with carnitine deficiency[43].

Pathophysiology of chemotherapy-induced fatigue

Carnitine exerts an essential function in energy metabolism leading to the synthesis of adenosine triphosphate (ATP). This amino acid derivative is required for the transportation of long-chain fatty acids from the cytoplasm to the mitochondrial matrix for oxidation, which represents the primary energy source in heart and skeletal muscles (**Figure 5**)[4,41,44,45]. A carnitine depletion results in a reduced ATP production and, as a consequence, in a decline in energy levels and increased muscular weakness[41,43].

In normal conditions, carnitine homeostasis is preserved through absorption, synthesis, and renal resorption; however, it has been demonstrated that specific chemotherapeutic agents disrupt the carnitine system through different mechanisms[41,43].

One of these chemotherapy drugs is cisplatin, which can cause impairment in glomerular filtration and damage to the renal tubule, where carnitine is absorbed. Therefore, cisplatin administration may increase the urinary excretion of carnitine and cause a drop in its plasma levels[41,43]. Another relevant function of carnitine is the detoxification and removal of toxic metabolites. The antineoplastic agent ifosfamide promotes the formation of chloroacetyl-CoA and a related reduction in concentrations of coenzyme A, an activator involved in energy production. Carnitine binds to the chloracetyl-CoA and detoxifies it, allowing for urinary elimination of this toxic substance. Binding of carnitine to chloracetyl-CoA can cause more carnitine to be excreted, leading to a deficiency of it in the plasma.

One of the most serious undesirable events associated with long-term doxorubicin therapy is cardiotoxicity[46]. While carnitine administration has been shown to improve cardiomyopathy in patients receiving doxorubicin, this agent has been observed to influence a decrease in heart concentration of free carnitine and a reduction of free fatty acid oxidation[41,46]. In a study conducted on 15 previously untreated patients with non-Hodgkin lymphoma and an age of 4-15 years, during treatment with doxorubicin, the serum carnitine levels were monitored to determine a relationship between serum carnitine levels and cardiac dysfunction. The results reported a trend towards lower serum carnitine levels with higher cumulative doses of doxorubicin[46].

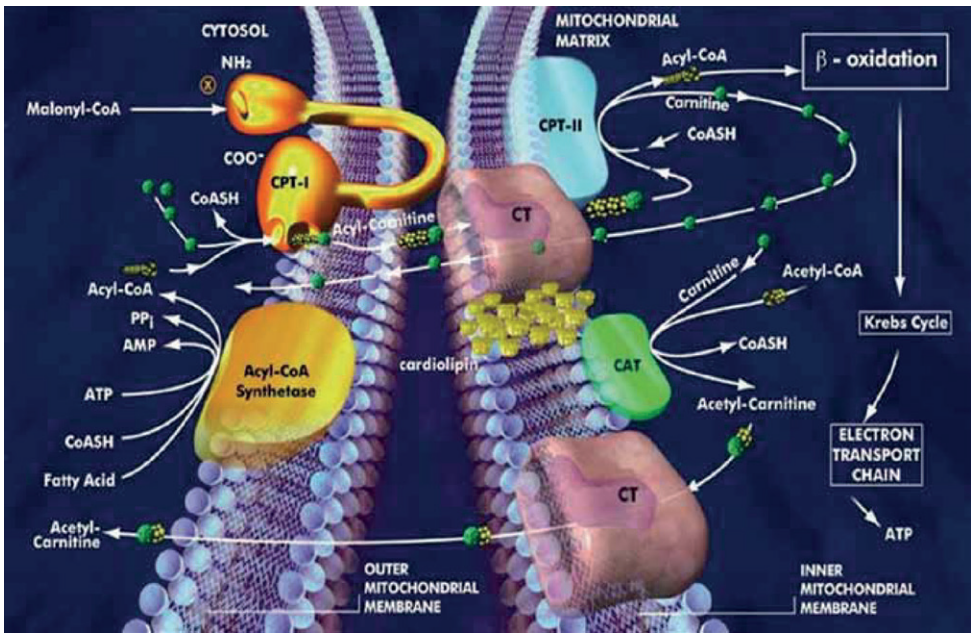


Figure 5. Fatty acid transportation and oxidation with energy production. ATP: adenosine triphosphate; CAT: carnitine-acetyltransferase; CoASH: coenzyme A; CPT-I: carnitine palmitoyltransferase I; CPT-II: carnitine palmitoyltransferase II; CT: carnitine translocase. (Adapted from [45]).

Evidence-based relationship between carnitine and fatigue in young cancer patients

One significant study has observed a correlation between fatigue and carnitine in children/adolescents with cancer[41]. This trial enrolled 67 young oncology patients (43.3% with leukemia/lymphoma and 56.7% with solid tumors) of 7-18 years of age receiving their first or second course of cisplatin, ifosfamide or doxorubicin chemotherapy. Fatigue status and carnitine levels were evaluated before chemotherapy administration and one week later for the two groups, one which has undergone a previous cycle of the drugs and one that has not. The study reported an initial increase in carnitine for the group that was having chemotherapy for the first time: this phenomenon is due to the rapid release of carnitine from tissues into the bloodstream to replace the carnitine lost through renal excretion. Subsequently, after 1-2 courses of chemotherapy, a decrease in carnitine and an increase in fatigue were observed (**Figure 6**)[41].

Furthermore, all patients showed an increase in fatigue and lower carnitine levels when they were treated using doxorubicin compared to the other 2 drugs used in the study[41].

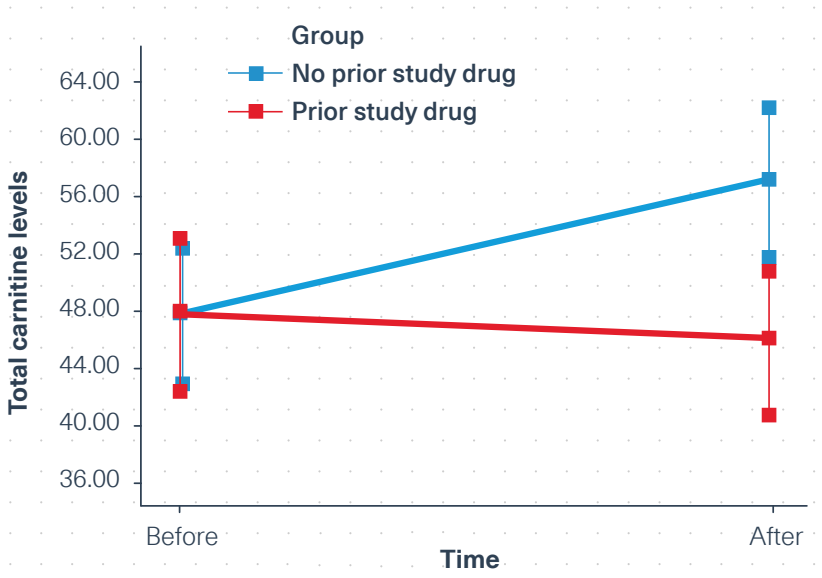
Management: carnitine supplementation

Some trials have evaluated the role of exogenous L-carnitine in improving fatigue and increasing plasma carnitine concentrations in cancer patients with low plasma carnitine levels[43,44]. Patients reported a reduction in fatigue and an improvement in functional well-being[43,44]. Furthermore, L-carnitine supplementation has been shown to restore normal plasma carnitine levels and solve symptomatic deficiencies with a very good tolerability profile and without interfering with the efficacy of antineoplastic drugs[43,44]. The pediatric oral dosage for a primary carnitine deficiency is 50 to 100 mg/kg/day, divided over 2 to 3 times per day, with a maximum dose of 3 g/day[41].

VALPROATE-INDUCED HEPATOTOXICITY

Clinical presentation

Valproate, or valproic acid, is a carboxylic acid derivative indicated for the treatment of epilepsy and also used for several other neurological and psychiatric conditions in children and adolescents. It seems to work by raising cerebral concentrations of gamma aminobutyric acid (GABA), a major inhibitory neurotransmitter in the human central nervous system[47]. Although highly effective, valproate-based therapy can produce several adverse effects, including skin reactions, hematologic conditions,



	No prior study drug mean (95% CI)	Prior study drug mean (95% CI)
Before chemotherapy	47.70 (42.88-52.51)	47.52 (42.05-52.98)
One week after chemotherapy	57.12 (51.71-62.59)	46.00 (40.53-51.47)

Figure 6. Total carnitine levels (mean and 95% CI) before and one week after receiving chemotherapy for newly diagnosed patients and patients who received prior chemotherapy. CI: confidence interval. (Adapted from [41]).

reproductive defects and hepatotoxicity. Further and related undesirable events reported in patients treated with valproate are metabolic disorders in the common form of hyperammonemia, also observed in acute valproate overdose together with other manifestations, such as central nervous system depression and hepatic failure[47]. Most frequent symptoms of valproate-induced hepatotoxicity are acute hepatocellular injury with hyperammonemia, progressive jaundice, nausea and vomiting, hepatic synthetic dysfunction, worsening seizures, confusion, stupor and lethargy, that can progress to coma and death. Children and adolescents are exposed to a higher risk of liver damage and its life-threatening consequences[47,48].

Pathophysiology of valproate-induced hepatotoxicity

The mechanism underlying valproate-induced hepatotoxicity appears to be related to a drug-induced carnitine deficiency[46]. Valproic acid is metabolized by the liver through mitochondrial β-oxidation, cytosolic β-oxidation, and glucuronic acid conjugation[45,47] and is excreted in urine. It has been proposed that valproate could determine a mitochondrial toxicity, perhaps from inhibition of β-oxidation, and a reduction in the process of carnitine biosynthesis, contributing to carnitine deficiency and impairing mitochondrial function. The subsequent production of toxic metabolites can cause liver toxicity and hyperammonaemia[47].

Management: carnitine supplementation

On the basis of the postulated damage mechanism, it has been hypothesized that L-carnitine supplementation may increase the β-oxidation of valproate, thereby limiting cytosolic β-oxidation and the production of toxic metabolites responsible for liver complications[47,49]. Carnitine may promote a detoxification process of valproate maintaining the mitochondrial metabolism (**Figure 7**)[48,49].

These considerations have prompted several studies investigating the effects of L-carnitine supplementation on valproate-induced hepatotoxicity in a pediatric population and results have demonstrated the life-saving benefit of this treatment[47-50].

A 1996 study investigated the effect of carnitine supplementation in 69 valproate treated patients of 1-24 years. A total of 24 patients were hyperammonemic and 48 patients reported carnitine deficiency. In all the 15 patients supplemented with carnitine, a decrease of plasma ammonia concentrations and a raise of plasma carnitine

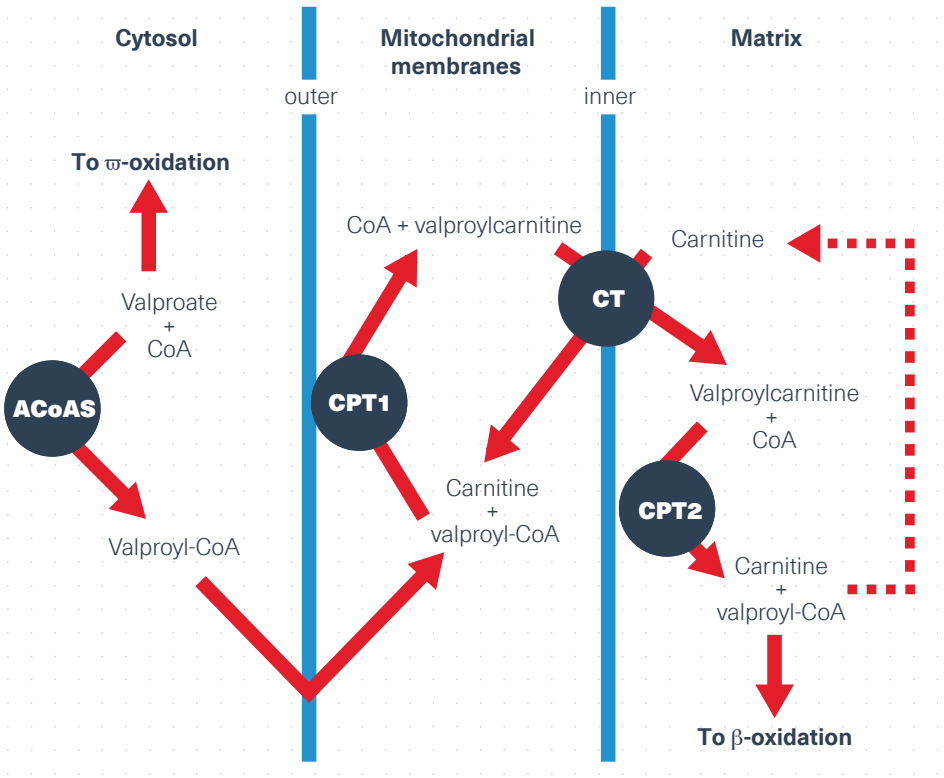


Figure 7. Detoxification of valproate toxic metabolites by carnitine. CoA: co-enzyme A; ACoAS: acetyl-CoA synthase; CPT1: carnitine palmitoyltransfe-rase I; CPT2: carnitine palmitoyltransferase II; CT: carnitine translocase. (Adapted from [47]).

levels were observed. These results support the protective effect of L-carnitine supplementation against hyperammonemia and confirm the benefits of this intervention in valproate-treated patients[50].

In a 2001 study, 92 young patients aged 3.4-5.1 years and affected by severe, symptomatic, valproate-induced hepatotoxicity were analysed to verify the potential association between carnitine treatment and hepatic survival[48]. Forty-two patients were treated with carnitine supplementation: of these, 21 received intravenous treatment and the remainder received an enteral treatment. Fifty control patients received only aggressive supportive care. Survival was reported for 45% of the 42 patients treated with L-carnitine supplementation, whereas only 10% of the 50 patients treated with only aggressive supportive care survived ($P < 0.001$). Survival was more prevalent in the subgroup of patients treated with intravenous carnitine. Early intervention with valproate discontinuation and intravenous carnitine administration (< 5 days) were associated with the greatest hepatic survival (**Figure 8**)[48].

These dramatic results suggest that an early recognition of hepatotoxicity and an early treatment with L-carnitine, particularly using the intravenous formulation, are the two main determinants for the hepatic survival of patients: consequently, if L-carnitine treatment is not promptly administered to reverse hepatotoxicity, liver failure could be fatal[48].

A 2010 review of seven published articles examined evidence-based data supporting the efficacy and safety of L-carnitine in the management of acute valproate overdose in adult and young patients. All patients involved in the analysed studies reported achieving complete recovery with carnitine supplementation without adverse events.

The therapeutic recommendation for significant valproate toxicity emerging from this review indicates a preferential use of intravenous carnitine at a loading dose of 100 mg/ kg and a maintenance dose of 50 mg/kg[47].

METABOLIC ABNORMALITIES IN CHILDREN AND ADOLESCENTS WITH PRIMARY HYPERTENSION

Clinical presentation and aetiology of primary hypertension

In recent years a trend towards an increased prevalence of hypertension in the pediatric population has been observed. This seems to be related to metabolic disorders,

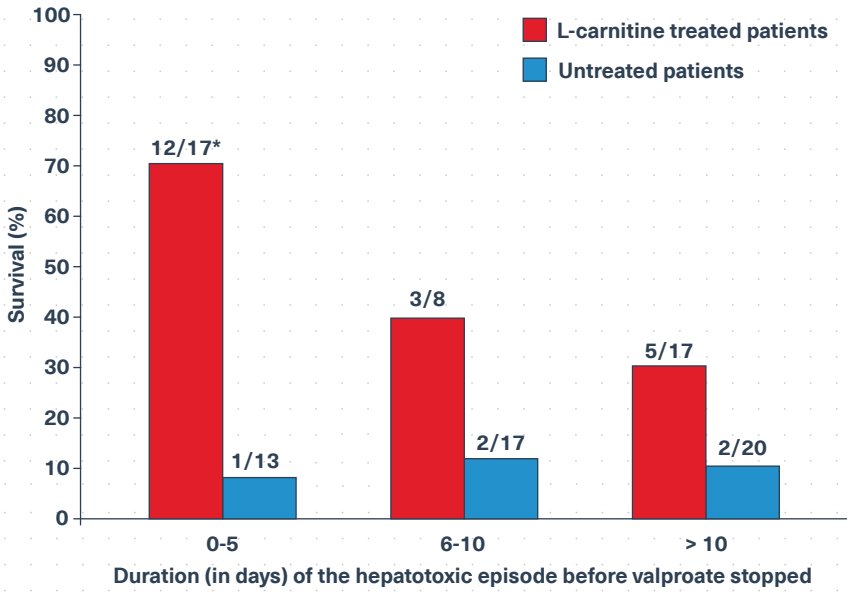
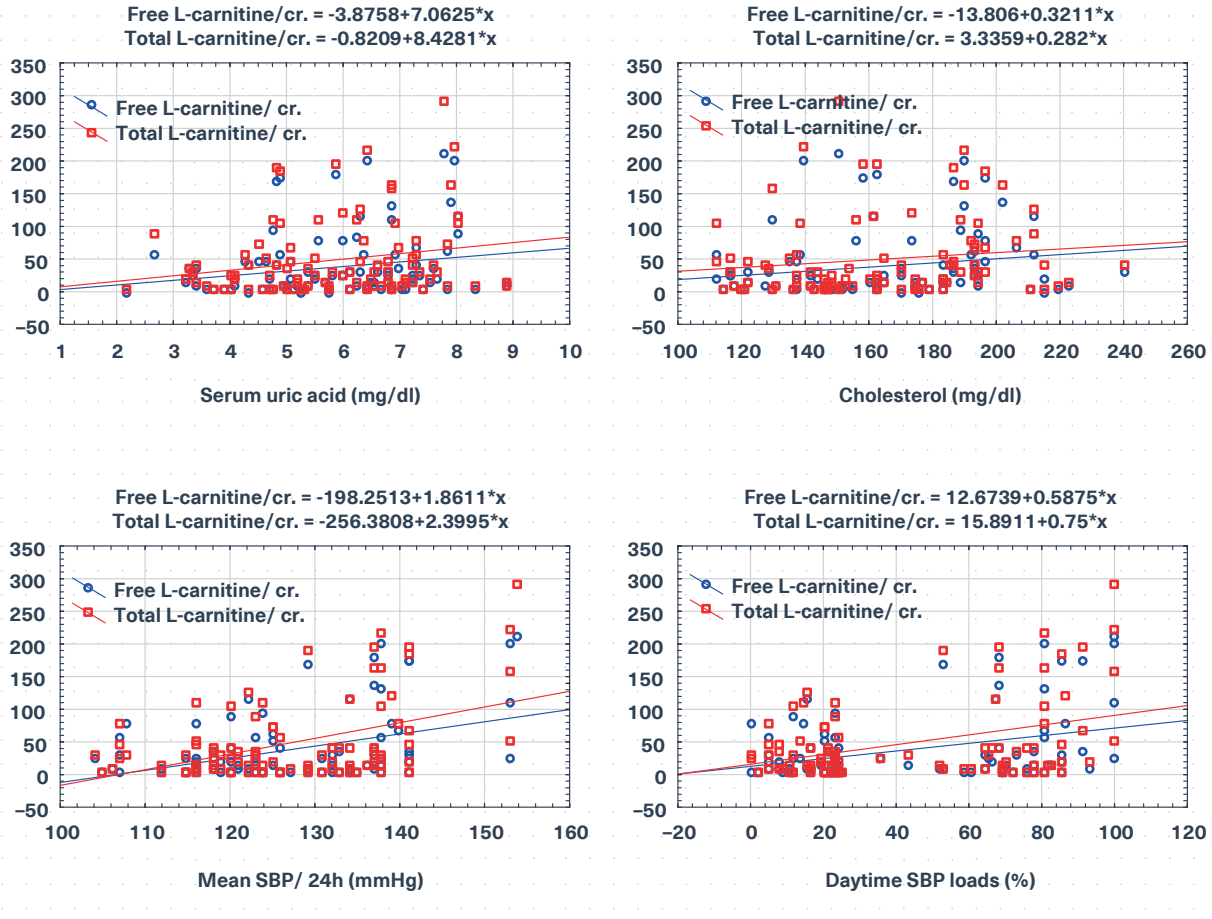


Figure 8. Effect on survival of the duration of hepatotoxicity before stopping valproate treatment: comparison of L-carnitine treated patients and untreated patients. *P < 0.001 for the association of intravenous treatment with survival for patients with valproate treatment stopped within the first 5 days of the hepatotoxic event. (Adapted from [48]).

Figure 9. Relationship between free L-carnitine/creatinine, total L-carnitine/creatinine ratio and serum uric acid level, serum cholesterol level, mean systolic blood pressure (SBP) during 24 h, and daytime systolic blood pressure loads. (Adapted from [51]).



particularly involving serum uric acid: several trials have suggested a correlation between the rise of values for this parameter and primary hypertension in children and adolescents[51]. In turn, hypertension acts as a crucial determinant in the occurrence and progression of renal abnormalities, leading to a disruption in carnitine metabolism[51]: a preclinical study conducted on spontaneously hypertensive rats has reported an elevation in serum carnitine and a concurrent increase in urine carnitine excretion. It has been hypothesized that hypertension could promote a higher carnitine synthesis by the liver associated with a decreased resorption by the proximal tubule[52]. The kidney dysfunction responsible for the altered urinary excretion of carnitine seems to be caused by hypertension through the activation of the renin-angiotensin system (RAS)[51].

A cross-sectional study was carried out by Kepka et al. (2014) to evaluate the rise in urinary levels of carnitine and its derivatives in children and adolescents with hypertension (**Figure 9**)[51]. The study included 112 subjects (45 girls and 67 boys) aged 10-18 years: 64 were hypertensive and 48 were control subjects who had whitecoat hypertension. All participants were not receiving any medication and did not have a family history of hypertension or other cardiovascular diseases. The urinary excretion of total and free L-carnitine was significantly higher in the hypertensive adolescents compared to the control patients. Furthermore, significant and positive correlations between free L-carnitine/creatinine, total L- carnitine/creatinine ratio and serum uric acid level, serum cholesterol level and systolic blood pressure were reported (**Figure 9**).

Management: carnitine supplementation

Multiple pre-clinical and clinical studies have reported the beneficial effects of L-carnitine supplementation in reducing blood pressure in hypertensive subjects and in attenuating the inflammatory process associated with hypertension[53-55]. Mate et al. (2010) observed that carnitine exerts an antihypertensive effect similar to captopril, a widely used and effective antihypertensive drug[55]. A possible mechanism to explain these favourable effects could be related to the antioxidant action of carnitine: it has been hypothesized that oxidative stress may be a factor involved in the development of arterial hypertension. Therefore, the antioxidant capacity of carnitine may inhibit hypertensive conditions by reducing the oxidative process[53,55].

In conclusion, the beneficial effects of carnitine supplementation have been observed in a wide and diversified spectrum of diseases. As reported, there is evidence of its high efficacy based on findings from many trials, which suggest that carnitine can be a life-saving strategy to be adopted in different and serious pathological conditions.

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01

Historical perspective on clinical trials of carnitine in children and adults

Buist NR

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HISTORICAL ASPECTS

- The metabolic roles of carnitine have been greatly clarified over the past 50 years, and it is now well established that carnitine is a key player in mitochondrial generation of energy and metabolism of acetyl coenzyme A.
- The first report of a potential therapeutic role for carnitine was in 1958 in treatment of nutritional deficiencies in infants and children using synthetic DL-carnitine. The first known inborn error of carnitine metabolism was reported in 1975, whereas in 1992 was identified the carnitine translocase deficiency.
- Carnitine was approved by the US Food and Drug Administration in 1985 for treatment of 'primary carnitine deficiency', and later in 1992 for treatment of 'secondary carnitine deficiency', a definition that included the majority of relevant metabolic disorders associated with low or abnormal plasma carnitine levels.
- Since the first reports, the number of PubMed citations related to carnitine has increased dramatically from 142 in 1965 to 7,439 in 2002. As of November 2015, there were more than 14,500 with 2,873 related to carnitine deficiency and 1,667 on its use in treatment. The total number of known inborn errors of metabolism has increased from 70 in the 1st edition of "Metabolic and Molecular Bases of Inherited Metbolic Diseases" to around 900 actually.

SYMPTOMS OF PEDIATRIC CARNITINE DEPLETION

- The most common symptom of carnitine depletion in children were hypotonia/gross motor delay, recurrent infections and failure to thrive (**Table**).
- Following treatment with carnitine, it is observed improvement in muscle tone and acceleration of acceleration of growth, while the frequency of infections appeared to decrease in majority of patients. After therapy, the echocardiograms of all patients with cardiomyopathy also normalized.

THE NEED FOR ADDITIONAL DATA

- The lack of randomized, controlled clinical data on the use of carnitine in inborn errors of metabolism was emphasized in a Cochrane review from 2012. It was stated that there are no published or ongoing relevant randomized controlled clinical trials in this area.
- Importantly, it is noted that in the absence of any high level evidence, clinicians should base their decisions regarding the use of carnitine on clinical experience and that the lack of randomized data does not mean that carnitine is ineffective.
- There is a major need for rigorously controlled clinical trials with carnitine, although in many inborn errors of metabolism ethical issues may preclude such efforts.
- There is also an objective need for greater awareness and education on the role of carnitine in intermediary metabolism and associated primary and secondary deficiencies.

key points

Today, carnitine treatment of inborn errors of metabolism is a safe and integral part of many treatment protocols, and a growing interest in carnitine has resulted in greater recognition of many causes of carnitine depletion.

TABLE Frequency of symptoms associated with carnitine depletion.

Symptom	Frequency, %
Hypotonia/gross motor delay	85
Recurrent infections with metabolic decompensation	85
Failure to thrive	75
Mental retardation	40
Cardiomyopathy	30
Encephalopathy	5

02

Primary carnitine deficiency and newborn screening for disorders of the carnitine cycle

Longo N

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THE CARNITINE CYCLE AND CARNITINE DEFICIENCY IN NEWBORNS

- Genetic defects in the OCTN2 carnitine transporter encoded by the SLC22A5 gene result in primary carnitine deficiency, which is associated with decreased accumulation of intracellular carnitine, increased loss of carnitine in urine and low levels of carnitine in serum.
- Affected individuals can present with hypoketotic hypoglycemia and hepatic encephalopathy early in life, or with skeletal and cardiac myopathy or sudden death from cardiac arrhythmia later in life, usually triggered by fasting or catabolic state.
- Other conditions have also been identified that can cause carnitine deficiency in newborns: dietary carnitine deficiency, total parenteral nutrition without added carnitine, maternal glutaric acidemia type I, maternal medium chain acyl coenzyme A (CoA) dehydrogenase deficiency, 3-methyl-crotonyl-CoA carboxylase deficiency. Another conditions that may warrant treatment with carnitine comprise deletions in the trimethyllysine hydroxylase (TMLHE) gene on Xq28 encoding for ε-N-TMLHE, a risk factor for non-syndromic autism-spectrum disorders in males.

SCRENING AND TREATMENT OF PRIMARY CARNITINE DEFICIENCY

- Primary carnitine deficiency responds to oral carnitine that, at pharmacological doses, enters cells using the amino acid transporter $B^{0,+}$. Key aspects of carnitine transporter deficiency are shown in **Table**.
- Decreased intracellular carnitine accumulation results in impaired fatty acid oxidation, and if carnitine supplements are not initiated, patients with primary carnitine deficiency can present with early acute metabolic decompensation, or later in life with skeletal and cardiac myopathy or sudden death from arrhythmia.
- Newborn screening programmes for primary carnitine deficiency can identify affected patients at risk for this condition before irreversible damage occurs. Diagnosis of primary carnitine deficiency can be biochemically confirmed by demonstrating low free carnitine levels in plasma (< 8 μM, normal 25-50 μM) with reduced renal reabsorption (< 90%) and normal renal function with no abnormalities in urine organic acids. The diagnosis is definitively confirmed by molecular testing of the SLC22A5 gene or by studying carnitine transport in fibroblasts (< 20% of normal controls).
- It is important to emphasize that there is little correlation between the type of mutation and timing or type (metabolic versus cardiomyopathy) of presentation in children with primary carnitine deficiency. Moreover, even within the same family, there is variability in clinical presentation, with some children presenting early with hepatic encephalopathy and others presenting later with cardiac dysfunction.

key points

Defects in carnitine biosynthesis have been identified in humans, which result in low-normal carnitine levels and accumulation of intermediates before metabolic bloc.

OCTN2 carnitine transporter deficiency causes a spectrum of diseases, from hepatic encephalopathy to cardiomyopathy and sudden death.

Newborn screening can miss infants with primary carnitine deficiency, in part due to the timing of the screening.

TABLE Key features of primary carnitine deficiency.

Carnitine transporter deficiency (Primary carnitine deficiency MIM 212140)
Frequency: 1:142,000 (USA), 1:40,000 (Japan), 1:300 (Faroe Islands)
Cause: Carnitine transporter (OCTN2) defect (SLC22A5 gene)
Pathogenesis: Loss of carnitine in urine reduces availability of carnitine in liver, muscle and heart, impairing fatty acid oxidation
Presentation: Hepatic encephalopathy, hypoglycemia, cardiomyopathy in childhood, arrhythmia in adults, sudden death in children and adults
Diagnosis: Plasma carnitine levels (very low, usually < 5 μM, can be higher in newborns), decreased urinary carnitine reabsorption, confirmed by transport studies in fibroblasts or DNA testing. Can be detected by newborn screening
Therapy: Carnitine 100-150 mg/kg up to 3 g per day PO divided into 3-4 daily doses
Monitoring: Plasma carnitine free and total
Prognosis: Excellent with treatment

ABSTRACT

03

Carnitine deficiency disorders in pediatrics – Round Table Discussion

Winter S, Buist NR, Longo N, et al.

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INTRODUCTION

- Here we report the main topics of discussion that emerged in the 1st International Carnitine Working Group concluded with a round table discussion addressing several areas of relevance.
- These included the design of future studies that could increase the amount of evidence-based data about the role of carnitine in the treatment of fatty acid oxidation defects, for which substantial controversy still exists.

MAIN TOPICS OF DISCUSSION

- There was general consensus that future trials on the effect of carnitine in disorders of fatty acid oxidation should be randomized, double-blinded, multicentered and minimally include the following diagnoses: medium-chain acyl coenzyme A (CoA) dehydrogenase deficiency, very long-chain acyl-CoA dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency and mitochondrial trifunctional protein deficiency.
- Another area that generated interest was trials of carnitine in cardiomyopathy and, especially, the use of biomarkers to identify patients at greater risk of cardiotoxicity following treatment with anthracyclines. There are a growing number of inborn errors of metabolism that are known to be associated with cardiomyopathy, many of which relate to the generation and maintenance of energy in the heart.
- The possibility that carnitine treatment may lead to improvements in autistic behaviors was also discussed, given a possible mechanism of carnitine's role in autism due to a mutation in trimethyllysine hydroxylase epsilon (TMLHE), an enzyme involved in the initial step in carnitine synthesis in both muscle and brain. The evidence, however, is still not sufficient to make any firm conclusions in this regard.
- Preliminary data on carnitine levels in children and adolescents with primary hypertension, low birth weight and nephrotic syndrome was also presented. All participants agreed that further studies examining concurrent plasma and urine concentration of L-carnitine and correlation with proximal tubular markers.

key points

There are still several controversies and uncertainties regarding the treatment of primary and secondary carnitine deficiency, and many topics have been studied and debated for decades.

Additional areas of further interest have subsequently arisen, including the role of carnitine in disorders of fatty acid oxidation, in cardiomyopathy (anthracycline-included cardiotoxicity) and the relation of carnitine with insulin resistance and associated disorders such as primary hypertension, low birth weight and nephrotic syndrome.

04

Metabolic aspects of myocardial disease and a role for L-carnitine in the treatment of childhood cardiomyopathy

Helton E, Darragh R, Francis P, et al.

Pediatrics 2000;105(6):1260-70

BACKGROUND AND AIM

- Cardiomyopathy is an associated symptom in metabolic disorders, where the intra-mitochondrial accumulation of toxic organic acid intermediates leads to the depletion of L-carnitine.
- The aim of this study was to investigate the possible metabolic causes of pediatric cardiomyopathy and evaluate the outcome of patients treated with L-carnitine.

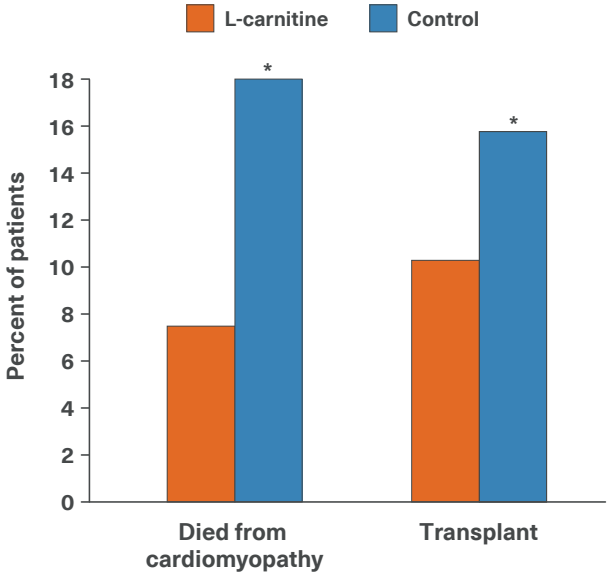
MATERIALS AND METHODS

- In this multicenter retrospective study, 76 patients diagnosed with cardiomyopathy were treated with L-carnitine (mean dose of 96 mg/kg/day) in addition to conventional cardiac treatment and 145 patients were treated with conventional treatment only (control group).
- The duration of L-carnitine treatment ranged from 2 weeks to > 1 year. Information was collected on length of survival (time-to-event), clinical outcome, echocardiogram parameters and clinical assessments.

RESULTS

- L-carnitine treated patients showed lower mortality from cardiomyopathy (6.8% *vs* 17.9%) and less transplantation (9.6% *vs* 15.0%) than control patients (**Figure**). The distribution of clinical outcomes was significantly different (p = 0.010) in an overall sense.
- Unexpectedly, the patients treated with ACE inhibitors (40%) revealed significantly poorer survival versus who did not receive ACE inhibitors (p = 0.0001).
- A significant improvement in survival was observed for L-carnitine treated patients who did not receive ACE inhibitors versus control patients (p = 0.046).

FIGURE Cardiomyopathy-related death and transplantation in L-carnitine and control patients (*p = 0.010).



key points

L-carnitine supplementation in pediatric myopathy showed a significant improvement in clinical severity and functioning in myocardial disease.

05

L-carnitine in children with idiopathic dilated cardiomyopathy

Kothari SS, Sharma M

Indian Heart Journal 1998;50:59-61

BACKGROUND AND AIM

- The utility of L-carnitine in the rare disorder of dilated cardiomyopathy secondary to carnitine deficiency in children has been reported; however, no systematic studies have been conducted.
- The aim of this study was to evaluate the effects of L-carnitine in children with idiopathic dilated cardio-myopathy.

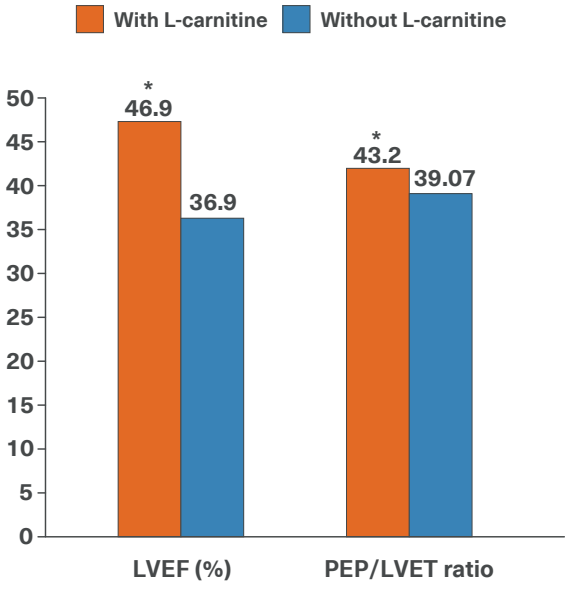
MATERIALS AND METHODS

- 13 children (8 males, 5 females; mean age 3.29 years) who presented with idiopathic dilated cardiomyopathy over a 1-year period were included in this prospective study. All patients had NYHA (New York Heart Association) class III 50 or IV congestive heart failure. Mean duration of symptoms was 9.7 months and mean left ventricular ejection fraction (LVEF) was 36.9%. Symptoms, LVEF and the pre-ejection period/left ventricular ejection time ratio (PEP/LVET) were assessed. In group 1, these parameters were recorded after patients had been receiving L-carnitine (50 mg/kg/day) for 3 weeks, and again 3 weeks after stopping L-carnitine. In group 2, parameters were recorded prior to initiation of L-carnitine and after 3 weeks' therapy with L-carnitine.

RESULTS

- The two objective myocardial function parameters that significantly improved during L-carnitine therapy were LVEF and PEP/LVET (**Figure**).
- There was a symptomatic improvement noticed by parents in patient's appetite, wellbeing and social interaction while on L-carnitine treatment. NYHA class improved overall in both groups while on carnitine treatment.

FIGURE Myocardial function parameters improved during L-carnitine therapy (*p < 0.01 *vs* without L-carnitine). LVEF = left ventricular ejection fraction; PEP/LVET = pre-ejection period/left ventricular ejection time.



key points

L-carnitine therapy is beneficial for children with idiopathic dilated cardiomyopathy and leads to an improvement in myocardial function.

06

Myocardial protection by L-carnitine in children treated with Adriamycin®

Anselmi Chávez G, Machado Hernández I, Febres Ollarve C, et al.

Revista Latino-Americana Cardiología 1997;18:208-4

BACKGROUND AND AIM

- The major risk in using doxorubicin hydrochloride (Adriamycin®) to treat neoplastic diseases is cardiotoxicity, which is dose-dependent. Early detection of myocardial damage is of the utmost importance for discontinuing chemotherapy.
- L-carnitine has demonstrated to be really effective in preventing cardiotoxicity, both experimentally and clinical trials in adults.
- The aim of this study was to evaluate the possible cardioprotective effects of L-carnitine used in children treated with Adriamycin® for the treatment of several types of tumors.

MATERIALS AND METHODS

- Adriamycin® cardiotoxicity was compared in 2 groups of patients: one group (n = 20), non-protected group, was treated only with Adriamycin®, and a second group (n = 108), protected group, was treated with Adriamycin® plus L-carnitine (1-2 g i.v. on the same day the children received Adriamycin®, and 175 mg/kg/day up to one year after the end of Adriamycin® treatment).
- Clinical and laboratory heart function testing were performed at baseline and periodically throughout the study and included ECG, echocardiography and cardiac enzyme level assessment.

RESULTS

- In the non-protected group, 2 patients developed marked myocardial toxicity necessitating the withdraw-al of doxorubicin, one of them also developing a severe congestive heart failure (NYHA IV) which did not responded to standard treatment. This child recovered to NYHA I after 3 months of L-carnitine treatment.
- There was no evidence of doxorubicin-induced cardiotoxicity in any patient who received L-carnitine plus chemotherapy.

key points

The protective effect of L-carnitine against doxorubicin cardiotoxicity, showed for the first time in children in a clinical setting, appears to be very encouraging.

07

Carnitine and cardiac dysfunction in childhood cancer survivors treated with anthracyclines

Armenian SH, Gelehrter SK, Vase T, et al.

Cancer Epidemiol Biomarkers Prev 2014;23(6):1109-14

BACKGROUND AND AIM

- Anthracyclines are widely used in the treatment of childhood cancer. Unfortunately, their use is limited by the occurrence of cardiac damage by their strong dose-dependent association with late-onset congestive heart failure (CHF).
- As the precise mechanism underlying is still not fully understood, metabolomic profiling of asymptomatic childhood cancer survivors could help to identify molecular pathways involved in the pathogenesis of anthracycline-related CHF and help identify druggable targets.
- The aim of this study was to describe how metabolomic profiling of anthracycline-exposed survivors may provide new information for the development of targeted primary or secondary prevention strategies.

MATERIALS AND METHODS

- 150 asymptomatic childhood cancer survivors (age 2.6-37.9 [mean 12.4] years; 65 female and 85 male) previously treated with anthracyclines (mean dose 350 mg/m^2 [range 25-642 mg/m^2]) were included in this cross sectional study between October 2010 and September 2012.
- Study participants underwent a detailed cardiac evaluation with echocardiographic assessment. For metabolomic profile, blood samples were collected on the same day of the echocardiographic assessment, and plasma was extracted within 1 hour of sample collection. Plasma samples were stored at -80°C and shipped to Metabolon, Inc. (Research Triangle, NC) for batched analytic studies.

RESULTS

- Thirty-five (23%) participants had cardiac dysfunction, defined as left ventricular end-systolic wall stress > 2SD by echocardiogram.
- Plasma levels of 15 compounds in three metabolic pathways (carbohydrate, amino acid, and lipid metabolism) were significantly different between individuals with cardiac dysfunction and those with normal systolic function.
- Individuals with cardiac dysfunction had significantly lower plasma carnitine levels (relative ratio [RR] 0.89, p < 0.01) when compared to those with normal function.

key points

Childhood cancer survivors with cardiac dysfunction occurring years following completion of cardiotoxic therapy showed significantly lower plasma carnitine levels compared to those with normal function.

Treatment of carnitine deficiency prior to/during anthracycline administration may facilitate the primary prevention in patients at highest risk for congestive heart failure.

08

L-carnitine supplementation and EPO requirement in children on chronic hemodialysis

Aoun B, Bérard E, Vitkevic R, et al.

Pediatr Nephrol 2010; 25(3):557-60

BACKGROUND AND AIM

- It has been suggested that excess free fatty acids secondary to L-carnitine deficiency leads to altered function of the erythrocyte sodium-potassium pump in chronic renal failure and thereby reduces erythrocyte survival time.
- It is a common finding in chronic dialysis patients to have deficiency in carnitine such patients are on a low protein diet and this molecule is easily dialyzed. L-carnitine deficiency has been correlated to the duration of dialysis.
- The aim of this study was to evaluate the effects of L-carnitine supplementation on the use of erythropoietin (EPO) requirement in pediatric hemodialysis (HD) patients.

MATERIALS AND METHODS

- This was a prospective study that included six children (three girls) without residual renal function who were on regular HD (three 4-h sessions per week) on high-flux membranes. All patients were started on intravenous L-carnitine supplementation at the same time.
- All patients received L-carnitine intravenously (2.5 g per session for patients > 30 kg and 1 g for those < 30 kg, with an average dose of 50 mg/kg per session) for a total duration of 9 months. The whole observation period was 16 months: 3 months before L-carnitine (phase 1), 9 months on L-carnitine (phase 2), and 4 months after L-carnitine withdrawal (phase 3).
- Carnitine levels (free and total) were measured by mass spectrometry, and the EPO dosage was adjusted to maintain a hemoglobin (Hb) level between 11 and 13 g/dl.

RESULTS

- Free carnitine blood level values were 40.4 ± 4.9 μmol/l before supplementation, 378.5 ± 77.3 μmol/l immediately after the 9-month supplementation period, and 95.6 ± 4.0 μmol/l 4 months after L-carnitine withdrawal.
- The EPO requirement before L-carnitine was 1.15 ± 0.22 (0.37-1.75) μg/kg darbepoetin alpha. During the intravenous L-carnitine supplementation period of 9 months, the EPO dose was decreased stepwise and reached 50% of the initial dose after 9 months (0.47 ± 0.10 μg/kg; $p < 0.001$) (**Figure, panel A**). All patients experienced an important reduction in EPO requirement during L-carnitine supplementation (**Figure, panel B**).
- The mean Hb level before L-carnitine supplementation was 12.9 ± 0.50 g/dl, and after the 9-month supplementation period the Hb level was unchanged. However, there was a significant increase during the first 2 months (12.2 ± 0.97 to 14.0 ± 0.54 g/dl; $p < 0.05$).

key points

Following intravenous carnitine supplementation, FC levels were higher and persisted longer than expected: this rise was associated with increased Hb levels and decreased EPO requirement.

Prospective long-term multicenter studies on a large number of patients are required to provide solid answers to the controversial question of L-carnitine supplementation in hemodialyzed children.

FIGURE A Erythropoietin (EPO) requirement before, during, and after intravenous L-carnitine supplementation in six hemodialyzed children. **B** Erythropoetin requirement before and at the end of the L-carnitine supplementation. Patients with a higher EPO dose had a relatively higher benefit in terms of EPO dose reduction.