ARCHIVES OF DISEASE IN CHILDHOOD

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Annotation

L-Carnitine

L-Carnitine (β-hydroxy-γ-trimethylaminobutyric acid) is a small water soluble molecule important in mammalian metabolism; it is essential for the normal oxidation of fats by the mitochondria and is involved in the transesterification and excretion of acyl-CoA esters, the oxidation of branched chain α-ketoacids, and removal of potentially toxic acylcarnitine esters from within mitochondria. L-Carnitine is found in both plasma and tissue as free carnitine or bound to fatty acids as acylcarnitine derivatives. Quantitative reductions in total and/or acylcarnitine concentrations and changes in the concentration of different acylcarnitine species are known to occur in a number of inherited and acquired disorders. The measurement of free and acylcarnitine is now a standard method for the investigation of children with certain inherited metabolic disorders of intermediary metabolism. More recently the identification of abnormal acylcarnitines by tandem mass spectrometry is being used for the purposes of newborn screening. Treatment with exogenous L-carnitine has been advocated for a number of inherited and acquired disorders. It is the purpose of this article to review conditions effecting infants and children that involve L-carnitine metabolism and to discuss the efficacy of L-carnitine in their treatment.

Primary disorders

L-Carnitine can be synthesised in the liver from methionine and protein bound lysine but the majority of the requirement for L-carnitine is supplied by the diet, particularly from red meat and dairy products.[1 2] To date no inherited disorders of carnitine synthesis have been described, although there is evidence that in newborn babies, particularly those born prematurely, synthetic pathways are immature. Plasma and tissue concentrations of L-carnitine are low in newborn infants compared with older children,[3 4] possibly related to a lower renal threshold combined with reduced synthesis.[5–7] Both human milk and whey based formula feeds contain L-carnitine but soya preparations and parenteral nutrition solutions usually do not.[8–14] Consequently sick preterm infants requiring long term treatment with intravenous feeding or those being given soya preparations may be at risk of L-carnitine deficiency. Reduced concentrations of ketone bodies have been reported in preterm infants suggesting that lipolysis and/or ketogenesis may be limited, although this may be due to causes other than carnitine deficiency.[8 9 15 16] In theory any reduction in the ability of infants to oxidise fats could have a deleterious effect upon energy dependent processes with an increased risk of hypothermia, hypoglycaemia, respiratory distress, infection, and delayed growth.

Primary genetic disorders of L-carnitine metabolism are due to inherited enzyme deficiencies involved either in the transfer of L-carnitine across cellular membranes or of long chain fats into mitochondria. All of these are rare and show autosomal recessive inheritance. They include a defect of L-carnitine uptake across plasma membranes (carnitine transport defect), and three disorders affecting the transfer of long chain fatty acids from the cytoplasm into mitochondria namely carnitine palmitoyltransferase (CPT) I deficiency, CPT II deficiency, and carnitine/acylcarnitine translocase. The clinical presentation of these disorders is varied and includes non-ketotic hypoglycaemia, encephalopathy, myopathy with myoglobinuria, or cardiomyopathy.[17–28]

Secondary disorders

A number of genetic conditions affecting intermediary metabolism result in a reduction in total plasma concentrations and/or an increase in the acyl:free L-carnitine ratio. In the organic acidaemias such as propionic acidaemia and methylmalonic acidaemia there is an accumulation within the mitochondria of short chain acyl-CoA derivatives.[29 30] L-Carnitine facilitates their removal into the cytoplasm and also their excretion by the kidneys as acylcarnitine derivatives. The loss of acylcarnitine by the kidneys is, at least in part, responsible for the reduction in total L-carnitine that is commonly seen in the organic acidaemias.[31 32] Inherited fatty acid oxidation disorders due to enzyme deficiencies involved in mitochondrial β-oxidation, also cause a similar disturbance in L-carnitine concentration.[33 34] Medium chain acyl-CoA dehydrogenase (MCAD) deficiency is the most common of these with an incidence in the white

population of between one in 9000 to one in 15 000. [35–37] Patients with this disorder usually first become ill after 9 months of age with profound hypoketotic hypoglycaemia often with a Reye-like illness, although presentation in newborn infants and asymptomatic adults is described. [38–42] Although in organic acidaemias and fatty acid oxidation disorders plasma carnitine concentrations are often reduced, with an abnormal acyl:free ratio, a normal L-carnitine profile using standard assays does not exclude these defects. More sensitive methods using tandem mass spectrometry, which quantifies different acylcarnitines, demonstrate persistent abnormalities even when patients are well.[43] Genetic disorders, such as cystinosis or Lowe's syndrome, which cause a renal tubular Fanconi's syndrome, result in increased urinary loss of L-carnitine and subsequent reduction in total plasma concentrations.[44 45] L-Carnitine deficiency has also been reported in other inborn errors of metabolism including mitochondrial myopathies, and disorders of the urea cycle.[46 47] In addition a number of non-genetic conditions have been implemented as a cause of reduced plasma L-carnitine including AIDS, chronic haemodialysis, chronic fatigue syndrome, and treatment with sodium valproate or antibiotics that contain pivalic acid (pivampicillin and pivmecillinam).[48–57]

Therapeutic role of L-carnitine

Carnitine treatment has been advocated in a large number of inherited and acquired disorders, both to restore low concentrations in conditions associated with deficiency states, but also as a means of removal of toxic metabolites even when plasma and tissue carnitine concentrations are normal. Both oral and intravenous preparations are available. However despite the widespread use of L-carnitine the rarity of most of the individual disorders for which it is used has meant that reports of its efficacy has been largely anecdotal and there have been few controlled studies. Fortunately adverse effects from L-carnitine treatment are infrequent and not severe. Large oral doses may cause diarrhoea and an unpleasant fishy smell but these are usually stopped by a reduction in dose.

PRIMARY DISORDERS OF L-CARNITINE METABOLISM

The necessity for L-carnitine supplements in preterm infants has not been proved. In some studies of newborn infants fat oxidation or ketogenesis has been shown to be enhanced by additional L-carnitine,[9 16 58–61] but a beneficial effect has not been demonstrated in others. [62–64] A large double blind placebo controlled trial failed to show any beneficial effect on growth or morbidity in premature infants from birth to 3 months,[65] and this suggests that the effects of L-carnitine supplementation on fat oxidation may not be of any significant clinical benefit. Premature infants who are particularly at risk from L-carnitine deficiency, such as those on long term parenteral nutrition,[9 16 58 59 66] should probably be given supplements but there is little evidence to support this in other infants.[11 65]

Treatment of carnitine transport defect with oral L-carnitine (100 mg/kg/day) is dramatic; it results in resolution of cardiomyopathy and prevents further episodes of hypoketotic hypoglycaemia. [24–26 28 67 68] Although the plasma concentration of L-carnitine can be brought within the normal range, muscle levels remain less than 5% of control values despite treatment, but this appears to be sufficient for normal fat oxidation within muscle. As there is continued loss of L-carnitine in the urine, treatment needs to be continued indefinitely.

L-Carnitine has also been used in the treatment of carnitine-acylcarnitine translocase deficiency and CPT II deficiency. In the former the outcome for the small number of patients described has been poor with the majority dying within infancy.[20] Treatment with L-carnitine and medium chain triglycerides in these children does not appear to have significantly altered the course of their disease. However one child with carnitine-acylcarnitine translocase deficiency, who presented with neonatal hypoglycaemia and subsequently developed severe hypotonia, cardiomyopathy, and hepatomegaly, had shown considerable improvement by 10 months after treatment with a low fat diet, propanolol, and L-carnitine.[69]

SECONDARY DISORDERS

In disorders of fatty acid β-oxidation and organic acid metabolism the use of L-carnitine treatment is based on its ability to remove toxic acyl-CoA intermediates from within the mitochondria. The efficacy of giving L-carnitine in fat oxidation disorders has been questioned, [70 71] and there are concerns that it might increase the uptake of long chain fatty acids into the mitochondria, place an additional load on the β-oxidation pathway, and lead to an increase rather than a decrease in acyl-CoA intermediates. However an increase in fatty acid oxidation after intravenous L-carnitine was not shown in one patient with MCAD deficiency,[72] and there are advocates for its use in this condition and in other disorders of fatty acid oxidation, particularly if plasma L-carnitine concentrations are very low. [73–75] In our experience patients with MCAD deficiency remain well without specific treatment provided fasting stress can be avoided. In view of the possible detrimental effects we do not, at present, use L-carnitine in fatty acid β-oxidation disorders but there is little clinical data to either support or refute its use in these conditions.

In organic acidaemias the theoretical basis for treatment with L-carnitine is less controversial and an increase in the urine excretion of fatty acyl-CoA esters has been demonstrated.[31 76–78] Clinical benefit has been claimed after treatment in a number of organic acidaemias including propionic acidaemia,[78 79] methylmalonic acidaemia,[80] isovaleric acidaemia, [81–84] and glutaryl-CoA dehydrogenase deficiency.[85] There are, however, no large scale studies to confirm significant clinical benefit. Despite the lack of strong evidence to support the efficacy of treatment most units give oral L-carnitine as a regular medication for children with organic acidaemias and intravenous L-carnitine during periods of metabolic decompensation. Although not widely used, L-carnitine has also been advocated in disorders of the urea cycle where it may protect the brain from some of the toxic effects of hyperammonaemia.[46 86 87]

There are a number of reports of L-carnitine deficiency in patients on treatment with sodium valproate,[88 89] some of which detail disturbances in mitochondrial β-oxidation. [90–92] The clinical significance of such abnormalities is not clear. One child taking sodium valproate who developed a cardiomyopathy, improved after L-carnitine treatment but may have had a primary deficiency of L-carnitine metabolism. L-Carnitine given with sodium valproate did not prevent the development of fatal liver disease in another child,[93] and a double blind crossover study of children on either sodium valproate or carbamazepine failed to show any benefit in terms of patients wellbeing compared with placebo.[94]

Significant loss of L-carnitine occurs during haemodialysis and L-carnitine deficiency has been suggested as a cause, or at least a contributory factor, in the hyperlipidaemia and muscle weakness associated with chronic haemodialysis. Although total L-carnitine concentrations in plasma may be normal, low free carnitine and raised acylcarnitine have been reported.[95] Infusions of L-carnitine after dialysis failed to have any significant effect upon blood lipid profiles in a multicentre, double blinded, placebo controlled trial.[95] However the same study found a

reduction in muscle cramps and hypotension during dialysis, an improvement in exercise capacity, reduction in serum urea nitrogen, creatinine, and phosphorous, and sense of wellbeing in the L-carnitine treated patients. A beneficial effect upon muscle function was also found in another placebo controlled trial[96] but not in two others.[97 98]

Conclusions

The measurement of plasma and occasionally tissue L-carnitine should be considered in children with hypoketotic hypoglycaemia, cardiomyopathy, or skeletal myopathy where very low concentrations are indicative of carnitine transport defect. Low concentrations of L-carnitine may also be associated with a number of other disorders. Apart from carnitine transport defect the case for treatment with L-carnitine is not clearly established, although there are good theoretical reasons for using L-carnitine in patients with organic acidaemias. Placebo controlled trials are necessary to confirm whether there is a real clinical benefit in these and in other disorders but, as many are individually rare, such studies will be difficult to undertake unless they involve a number of centres. Some clinicians are already convinced of the efficacy of treatment with L-carnitine and may find such studies unethical but others remain more sceptical.[99] Without properly conducted trials treatment with L-carnitine will not be based on robust evidence.

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1 Rebouche CJ. Carnitine function and requirements during the life cycle. *FASEB J* 1992; **6:** 3379-86.
2 Bieber LL. Carnitine. *Annu Rev Biochem* 1988; **57:** 261-83.
3 Shenai JP, Borum PR, Mohan P, Donlevy SC. Carnitine status at birth of newborn infants of varying gestation. *Pediatr Res* 1983; **17:** 579-82.
4 Shenai JP, Borum PR. Tissue carnitine reserves of newborn infants. *Pediatr Res* 1984; **18:** 679-82.
5 Olson AL, Rebouche CJ. Renal conservation of carnitine by infants and adults: no evidence of developmental regulation. *Early Hum Dev* 1989; **19:** 29-38.
6 Melegh B, Szucs L, Kerner J, Sandor A. Changes of plasma free amino acids and renal clearances of carnitines in premature infants during L-carnitine-supplemented human milk feeding. *J Pediatr Gastroenterol Nutr* 1988; **7:** 424-9.
7 Olson AL, Rebouche CJ. Gamma-butyrobetaine hydroxylase activity is not rate limiting for carnitine biosynthesis in the human infant. *J Nutr* 1987; **117:** 1024-31.
8 Melegh B, Kerner J, Sandor A, Vinceller M, Kispal G. Effects of oral L-carnitine supplementation in low-birth-weight premature infants maintained on human milk. *Biol Neonate* 1987; **51:**185-93.
9 Melegh B, Kerner J, Sandor A, Vinceller M, Kispal G. Oral L-carnitine supplementation in low-birth-weight newborns: a study on neonates requiring combined parenteral and enteral nutrition. *Acta Paediatr Hung* 1986; **27:** 253-8.
10 Rovamo LM, Salmenpera L, Arjomaa P, Raivio KO. Carnitine during prolonged breast feeding. *Pediatr Res* 1986; **20:** 806-9.
11 Cederblad G, Svenningsen N. Plasma carnitine and breast milk carnitine intake in premature infants. *J Pediatr Gastroenterol Nutr* 1986; **5:** 616-21.
12 Rubaltelli FF, Orzali A, Rinaldo P, Donzelli F, Carnielli V. Carnitine and the premature. *Biol Neonate* 1987; **52** (suppl 1):65-77.
13 Warshaw JB, Curry E. Comparison of serum carnitine and ketone body concentrations in breast- and in formula-fed newborn infants. *J Pediatr* 1980; **97:** 122-5.
14 Penn D, Dolderer M, Schmidt Sommerfeld E. Carnitine concentrations in the milk of different species and infant formulas. *Biol Neonate* 1987; **52:** 70-9.
15 Orzali A, Donzelli F, Enzi G, Rubaltelli FF. Effect of carnitine on lipid metabolism in the newborn. I. Carnitine supplementation during total parenteral nutrition in the first 48 hours of life. *Biol Neonate* 1983; **43:** 186-90.
16 Bonner CM, DeBrie KL, Hug G, Landrigan E, Taylor BJ. Effects of parenteral L-carnitine supplementation on fat metabolism and nutrition in premature neonates. *J Pediatr* 1995; **126:** 287-92.
17 Demaugre F, Bonnefont JP, Colonna M, Cepanec C, Leroux JP, Saudubray JM. Infantile form of carnitine palmitoyltransferase II deficiency with hepatomuscular symptoms and sudden death. Physiopathological approach to carnitine palmitoyltransferase II deficiencies. *J Clin Invest* 1991; **87:** 859-64.
18 Demaugre F, Bonnefont JP, Mitchell G, *et al.* Hepatic and muscular presentations of carnitine palmitoyl transferase deficiency: two distinct entities. *Pediatr Res* 1988; **24:** 308-11.
19 Falik Borenstein ZC, Jordan SC, Saudubray JM, *et al.* Brief report: renal tubular acidosis in carnitine palmitoyltransferase type 1 deficiency. *N Engl J Med* 1992; **327:** 24-7.
20 Pande SV, Murthy MS. Carnitine-acylcarnitine translocase deficiency: implications in human pathology. *Biochim Biophys Acta* 1994; **1226:** 269-76.
21 Pande SV, Brivet M, Slama A, Demaugre F, Aufrant C, Saudubray JM. Carnitine-acylcarnitine translocase deficiency with severe hypoglycemia and auriculo ventricular block. Translocase assay in permeabilized fibroblasts. *J Clin Invest* 1993; **91:** 1247-52.
22 Stanley CA, Hale DE, Berry GT, Deleeuw S, Boxer J, Bonnefont JP. Brief report: a deficiency of carnitine-acylcarnitine translocase in the inner mitochondrial membrane. *N Engl J Med* 1992; **327:** 19-23.
23 Stanley CA, Sunaryo F, Hale DE, Bonnefont JP, Demaugre F, Saudubray JM. Elevated plasma carnitine in the hepatic form of carnitine palmitoyltransferase-1 deficiency. *J Inherit Metab Dis* 1992; **15:** 785-9.
24 Stanley CA, Deleeuw S, Coates PM, *et al.* Chronic cardiomyopathy and weakness or acute coma in children with a defect in carnitine uptake. *Ann Neurol* 1991; **30:** 709-16.
25 Tein I, De Vivo DC, Bierman F, *et al.* Impaired skin fibroblast carnitine uptake in primary systemic carnitine deficiency manifested by childhood carnitine-responsive cardiomyopathy. *Pediatr Res* 1990; **28:** 247-55.
26 Treem WR, Stanley CA, Finegold DN, Hale DE, Coates PM. Primary carnitine deficiency due to a failure of carnitine transport in kidney, muscle, and fibroblasts. *N Engl J Med* 1988; **319:** 1331-6.
27 Vianey Saban C, Mousson B, Bertrand C, *et al.* Carnitine palmitoyl transferase I deficiency presenting as a Reye-like syndrome without hypoglycaemia. *Eur J Pediatr* 1993; **152:** 334-8.
28 Waber LJ, Valle D, Neill C, DiMauro S, Shug A. Carnitine deficiency presenting as familial cardiomyopathy: a treatable defect in carnitine transport. *J Pediatr* 1982; **101:** 700-5.
29 Chalmers RA, Stacey TE, Tracey BM, *et al.* L-Carnitine insufficiency in disorders of organic acid metabolism: response to L-carnitine by patients with methylmalonic aciduria and 3-hydroxy-3-methylglutaric aciduria. *J Inherit Metab Dis* 1984; 7(suppl 2):109-10.
30 Mandel H, Africk D, Blitzer M, Shapira E. The importance of recognizing secondary carnitine deficiency in organic acidaemias: case report in glutaric acidaemia type II. *J Inherit Metab Dis* 1988; **11:** 397-402.
31 Di Donato S, Rimoldi M, Garavaglia B, Uziel G. Propionylcarnitine excretion in propionic and methylmalonic acidurias: a cause of carnitine deficiency. *Clin Chim Acta* 1984; **139:** 13-21.
32 Stanley CA, Berry GT, Bennett MJ, Willi SM, Treem WR, Hale DE. Renal handling of carnitine in secondary carnitine deficiency disorders. *Pediatr Res* 1993; **34:** 89-97.
33 Touma EH, Charpentier C. Medium chain acyl-CoA dehydrogenase deficiency. *Arch Dis Child* 1992; **67:** 142-5.
34 Coates PM, Hale DE, Finocchiaro G, Tanaka K, Winter SC. Genetic deficiency of short-chain acyl-coenzyme A dehydrogenase in cultured fibroblasts from a patient with muscle carnitine deficiency and severe skeletal muscle weakness. *J Clin Invest* 1988; **81:** 171-5.
35 Seddon HR, Green A, Gray RG, Leonard JV, Pollitt RJ. Regional variations in medium-chain acyl-CoA dehydrogenase deficiency. *Lancet* 1995; **345:** 135-6.
36 Ziadeh R, Hoffman EP, Finegold DN, *et al.* Medium chain acyl-CoA dehydrogenase deficiency in Pennsylvania: neonatal screening shows high incidence and unexpected mutation frequencies. *Pediatr Res* 1995; **37:** 675-8.
37 Matsubara Y, Narisawa K, Tada K, *et al.* Prevalence of K329E mutation in medium-chain acyl-CoA dehydrogenase gene determined from Guthrie cards. *Lancet* 1991; **338:** 552-3.
38 Treem WR, Stanley CA, Hale DE, Leopold HB, Hyams JS. Hypoglycemia, hypotonia, and cardiomyopathy: the evolving clinical picture of long-chain acyl-CoA dehydrogenase deficiency. *Pediatrics* 1991; **87:** 328-33.
39 Catzeflis C, Bachmann C, Hale DE, *et al.* Early diagnosis and treatment of neonatal medium-chain acyl-CoA dehydrogenase deficiency: report of two siblings. *Eur J Pediatr* 1990; **149:** 577-81.
40 Roe CR, Millington DS, Maltby DA, Kinnebrew P. Recognition of medium-chain acyl-CoA dehydrogenase deficiency in asymptomatic siblings of children dying of sudden infant death or Reye-like syndromes. *J Pediatr* 1986; **108:** 13-8.
41 Christodoulou J, Hoare J, Hammond J, Ip WC, Wilcken B. Neonatal onset of medium-chain acyl-coenzyme A dehydrogenase deficiency with confusing biochemical features. *J Pediatr* 1995; **126:** 65-8.
42 Heptinstall LE, Till J, Wraith JE, Besley GTN. Common MCAD mutation in a healthy parent of two affected siblings. *J Inherit Metab Dis* 1995; **15:** 638-9.
43 Van Hove JL, Zhang W, Kahler SG, *et al.* Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency: diagnosis by acylcarnitine analysis in blood. *Am J Hum Genet* 1993; **52:** 958-66.
44 Charnas LR, Bernardini I, Rader D, Hoeg JM, Gahl WA. Clinical and laboratory findings in the oculocerebrorenal syndrome of Lowe, with special reference to growth and renal function. *N Engl J Med* 1991; **324:** 1318-25.
45 Bernardini I, Rizzo WB, Dalakas M, Bernar J, Gahl WA. Plasma and muscle free carnitine deficiency due to renal Fanconi syndrome. *J Clin Invest* 1985; **75:** 1124-30.
46 Mayatepek E, Kurczynski TW, Hoppel CL, Gunning WT. Carnitine deficiency associated with ornithine transcarbamylase deficiency. *Pediatr Neurol* 1991; **7:** 196-9.
47 Ohtani Y, Ohyanagi K, Yamamoto S, Matsuda I. Secondary carnitine deficiency in hyperammonemic attacks of ornithine transcarbamylase deficiency. *J Pediatr* 1988; **112:** 409-14.
48 Campos Y, Arenas J. Muscle carnitine deficiency associated with zidovudine-induced mitochondrial myopathy. *Ann Neurol* 1994; **36:** 680-1.
49 Dalakas MC, Leon Monzon ME, Bernardini I, Gahl WA, Jay CA. Zidovudine-induced mitochondrial myopathy is associated with muscle carnitine deficiency and lipid storage. *Ann Neurol* 1994; **35:** 482-7.
50 Bohmer T, Bergrem H, Eiklid K. Carnitine deficiency induced during intermittent haemodialysis for renal failure. *Lancet* 1978; **i:** 126-8.
51 Leschke M, Rumpf KW, Eisenhauer T, *et al.* Quantitative assessment of carnitine loss during hemodialysis and hemofiltration. *Kidney Int Suppl* 1983; **16:** S143-6.
52 Rodriguez Segade S, Alonso de la Pena C, Paz JM, *et al.* Carnitine deficiency in haemodialysed patients. *Clin Chim Acta* 1986; **159:** 249-56.
53 Kuratsune H, Yamaguti K, Takahashi M, Misaki H, Tagawa S, Kitani T. Acylcarnitine deficiency in chronic fatigue syndrome. *Clin Infect Dis* 1994;**18** (suppl 1):S62-7.
54 Ohtani Y, Endo F, Matsuda I. Carnitine deficiency and hyperammonemia associated with valproic acid therapy. *J Pediatr* 1982; **101:** 782-5.
55 Laub MC, Paetzke Brunner I, Jaeger G. Serum carnitine during valproic acid therapy. *Epilepsia* 1986; **27:** 559-62.

56 Holme E, Greter J, Jacobson CE, *et al.* Carnitine deficiency induced by pivampicillin and pivmecillinam therapy [see comments]. *Lancet* 1989; **ii:** 469-73.
57 Abrahamsson K, Eriksson BO, Holme E, Jodal U, Lindstedt S, Nordin I. Impaired ketogenesis in carnitine depletion caused by short-term administration of pivalic acid prodrug. *Biochem Med Metab Biol* 1994; **52:** 18-21.
58 Larsson LE, Olegard R, Ljung BM, Niklasson A, Rubensson A, Cederblad G. Parenteral nutrition in preterm neonates with and without carnitine supplementation. *Acta Anaesthesiol Scand* 1990; **34:** 501-5.
59 Helms RA, Mauer EC, Hay WW Jr, Christensen ML, Storm MC. Effect of intravenous L-carnitine on growth parameters and fat metabolism during parenteral nutrition in neonates. *J Parenter Enteral Nutr* 1990; **14:** 448-53.
60 Schmidt Sommerfeld E, Penn D, Wolf H. Carnitine deficiency in premature infants receiving total parenteral nutrition: effect of L-carnitine supplementation. *J Pediatr* 1983; **102:** 931-5.
61 Olson AL, Nelson SE, Rebouche CJ. Low carnitine intake and altered lipid metabolism in infants. *Am J Clin Nutr* 1989; **49:** 624-8.
62 Orzali A, Maetzke G, Donzelli F, Rubaltelli FF. Effect of carnitine on lipid metabolism in the neonate. II. Carnitine addition to lipid infusion during prolonged total parenteral nutrition. *J Pediatr* 1984; **104:** 436-40.
63 Sulkers EJ, Lafeber HN, Degenhart HJ, Przyrembel H, Schlotzer E, Sauer PJ. Effects of high carnitine supplementation on substrate utilization in low-birth-weight infants receiving total parenteral nutrition. *Am J Clin Nutr* 1990; **52:** 889-94.
64 Melegh B, Kerner J, Szucs L, Porpaczy Z. Feeding preterm infants with L-carnitine supplemented formula. *Acta Paediatr Hung* 1990; **30:** 27-41.
65 Shortland GJ, Walter JH, Stroud C, Speidel BD, Fleming PJ, Marlow N. L-Carnitine: effects of nutritional supplementation in preterm infants. *Arch Dis Child* (in press).
66 Tibboel D, Delemarre FM, Przyrembel H, Bos AP, Affourtit MJ, Molenaar JC. Carnitine deficiency in surgical neonates receiving total parenteral nutrition. *J Pediatr Surg* 1990; **25:** 418-21.
67 Stanley CA, Treem WR, Hale DE, Coates PM. A genetic defect in carnitine transport causing primary carnitine deficiency. *Prog Clin Biol Res* 1990;**321:** 457-64.
68 Eriksson BO, Gustafson B, Lindstedt S, Nordin I. Transport of carnitine into cells in hereditary carnitine deficiency. *J Inherit Metab Dis* 1989; **12:** 108-11.
69 Parini R, Garavaglia B, Melotti D, *et al.* Carnitine-acylcarnitine translocase deficiency (CACTD): severe hypotonia and liver enlargement at 4 months. *Proceedings of the SSIEM 33rd Annual Symposium* 1995:P102 (abstract).
70 Treem WR, Stanley CA, Goodman SI. Medium-chain acyl-CoA dehydrogenase deficiency: metabolic effects and therapeutic efficacy of long-term L-carnitine supplementation. *J Inherit Metab Dis* 1989; **12:** 112-9.
71 Rinaldo P, Schmidt Sommerfeld E, Posca AP, Heales SJ, Woolf DA, Leonard JV. Effect of treatment with glycine and L-carnitine in medium-chain acyl-coenzyme A dehydrogenase deficiency. *J Pediatr* 1993; **122:** 580-4.
72 Van Hove JL, Kahler SG, Millington DS, *et al.* Intravenous L-carnitine and acetyl-L-carnitine in medium-chain acyl-coenzyme A dehydrogenase deficiency and isovaleric acidemia. *Pediatr Res* 1994; **35:** 96-101.
73 Haller RG, Lewis SF. Pathophysiology of exercise performance in muscle disease. *Med Sci Sports Exerc* 1984; **16:** 456-9.
74 Schmidt Sommerfeld E, Penn D, Kerner J, Bieber LL, Rossi TM, Lebenthal E. Quantitation of urinary carnitine esters in a patient with medium-chain acyl-coenzyme A dehydrogenase deficiency: effect of metabolic state and L-carnitine therapy. *J Pediatr* 1989; **115:** 577-82.
75 Marsden D, Sege Petersen K, Nyhan WL, Roeschinger W, Sweetman L. An unusual presentation of medium-chain acyl coenzyme A dehydrogenase deficiency. *Am J Dis Child* 1992; **146:** 1459-62.
76 Roe CR, Hoppel CL, Stacey TE, Chalmers RA, Tracey BM, Millington DS. Metabolic response to carnitine in methylmalonic aciduria. An effective strategy for elimination of propionyl groups. *Arch Dis Child* 1983; **58:** 916-20.
77 Kurczynski TW, Hoppel CL, Goldblatt PJ, Gunning WT. Metabolic studies of carnitine in a child with propionic acidemia. *Pediatr Res* 1989; **26:** 63-6.
78 Davies SE, Iles RA, Stacey TE, De Sousa C, Chalmers RA. Carnitine therapy and metabolism in the disorders of propionyl-CoA metabolism studied using 1H-NMR spectroscopy. *Clin Chim Acta* 1991; **204:** 263-77.
79 Shigematsu Y, Mori I, Nakai A, *et al.* Acute infantile hemiplegia in a patient with propionic acidaemia. *Eur J Pediatr* 1990; **149:** 659-60.
80 Penn D, Schmidt H, Otten A, Schmidt Sommerfeld E. [Carnitine in the treatment of methylmalonic aciduria (MMA)] Carnitin in der Behandlung der Methylmalonazidurie (MMA). *Monatsschr Kinderheilkd* 1986; **134:** 758-61.
81 De Sousa C, Chalmers RA, Stacey TE, Tracey BM, Weaver CM, Bradley D. The response to L-carnitine and glycine therapy in isovaleric acidaemia. *Eur J Pediatr* 1986; **144:** 451-6.
82 Roe CR, Millington DS, Maltby DA, Kahler SG, Bohan TP. L-Carnitine therapy in isovaleric acidemia. *J Clin Invest* 1984; **74:** 2290-5.
83 Mayatepek E, Kurczynski TW, Hoppel CL. Long-term L-carnitine treatment in isovaleric acidemia. *Pediatr Neurol* 1991; **7:** 137-40.
84 Berry GT, Yudkoff M, Segal S. Isovaleric acidemia: medical and neurodevelopmental effects of long-term therapy. *J Pediatr* 1988; **113:** 58-64.
85 Hoffmann GF, Trefz FK, Barth PG, *et al.* Glutaryl-coenzyme A dehydrogenase deficiency: a distinct encephalopathy. *Pediatrics* 1991; **88:** 1194-203.
86 Matsuda I, Ohtani Y, Ohyanagi K, Yamamoto S. Hyperammonemia related to carnitine metabolism with particular emphasis on ornithine transcarbamylase deficiency. *Enzyme* 1987; **38:** 251-5.
87 Mori T, Tsuchiyama A, Nagai K, Nagao M, Oyanagi K, Tsugawa S. A case of carbamylphosphate synthetase-I deficiency associated with secondary carnitine deficiency–L-carnitine treatment of CPS-I deficiency. *Eur J Pediatr* 1990; **149:** 272-4.
88 Opala G, Winter S, Vance C, Vance H, Hutchison HT, Linn LS. The effect of valproic acid on plasma carnitine levels. *Am J Dis Child* 1991;**145**:999-1001.
89 Melegh B, Kerner J, Acsadi G, Lakatos J, Sandor A. L-Carnitine replacement therapy in chronic valproate treatment. *Neuropediatrics* 1990; **21:** 40-3.
90 Kossak BD, Schmidt Sommerfeld E, Schoeller DA, Rinaldo P, Penn D, Tonsgard JH. Impaired fatty acid oxidation in children on valproic acid and the effect of L-carnitine. *Neurology* 1993; **43:** 2362-8.
91 Melegh B, Pap M, Morava E, Molnar D, Dani M, Kurucz J. Carnitine-dependent changes of metabolic fuel consumption during long-term treatment with valproic acid. *J Pediatr* 1994; **125:** 317-21.
92 Murakami K, Sugimoto T, Nishida N, Kobayashi Y, Kuhara T, Matsumoto I. Abnormal metabolism of carnitine and valproate in a case of acute encephalopathy during chronic valproate therapy. *Brain Dev* 1992; **14:** 178-81.
93 Murphy JV, Groover RV, Hodge C. Hepatotoxic effects in a child receiving valproate and carnitine [see comments]. *J Pediatr* 1993; **123:** 318-20.
94 Freeman JM, Vining EP, Cost S, Singhi P. Does carnitine administration improve the symptoms attributed to anticonvulsant medications? A double-blinded, crossover study [see comments]. *Pediatrics* 1994; **93:** 893-5.
95 Golper TA, Wolfson M, Ahmad S, *et al.* Multicenter trial of L-carnitine in maintenance hemodialysis patients. I. Carnitine concentrations and lipid effects. *Kidney Int* 1990; **38:** 904-11.
96 Siami G, Clinton ME, Mrak R, Griffis J, Stone W. Evaluation of the effect of intravenous L-carnitine therapy on function, structure and fatty acid metabolism of skeletal muscle in patients receiving chronic hemodialysis. *Nephron* 1991; **57:** 306-13.
97 Fagher B, Cederblad G, Eriksson M, *et al.* L-Carnitine and haemodialysis: double blind study on muscle function and metabolism and peripheral nerve function. *Scand J Clin Lab Invest* 1985; **45:** 169-78.
98 Rogerson ME, Rylance PB, Wilson R, *et al.* Carnitine and weakness in haemodialysis patients. *Nephrol Dial Transplant* 1989; **4:** 366-71.
99 Anonymous. Carnitine deficiency. *Lancet* 1990; **335:** 631-3.