ND30471

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

ELSEVIER

Brain & Development 28 (2006) 358–365

www.elsevier.com/locate/braindev

Original article

Plasma free carnitine in epilepsy children, adolescents and young adults treated with old and new antiepileptic drugs with or without ketogenic diet

Giangennaro Coppola *, Giuseppina Epifanio, Gianfranca Auricchio, Rosario Romualdo Federico, Gianluca Resicato, Antonio Pascotto

Department of Psychiatry, Clinic of Child Neuropsychiatry, Second University of Naples, Via Pansini, 5 80131 Naples, Italy

Received 10 April 2005; received in revised form 22 September 2005; accepted 10 November 2005

Abstract

This study was performed to evaluate carnitine deficiency in a large series of epilepsy children and adolescents treated with old and new antiepileptic drugs with or without ketogenic diet. Plasma free carnitine was determined in 164 epilepsy patients aged between 7 months and 30 years (mean 10.8 years) treated for a mean period of 7.5 years (range 1 month-26 years) with old and new antiepileptic drugs as mono or add-on therapy. In 16 patients on topiramate or lamotrigine and in 11 on ketogenic diet, plasma free carnitine was prospectively evaluated before starting treatment and after 3 and 12 months, respectively. Overall, low plasma levels of free carnitine were found in 41 patients (25%); by single subgroups, 32 out of 84 patients (38%) taking valproic acid and 13 of 54 (24%) on carbamazepine, both as monotherapy or in combination, showed low free carnitine levels. A higher though not statistically significant risk of hypocarnitinemia resulted to be linked to polytherapy (31.5%) versus monotherapy (17.3%) ($P = .0573$). Female sex, psychomotor or mental retardation and abnormal neurological examination appeared to be significantly related with hypocarnitinemia, as well. As to monotherapy, valproic acid was associated with a higher risk of hypocarnitinemia (27.3%) compared with carbamazepine group (14.3%). Neither one of the patients on topiramate (10), lamotrigine (5) or ketogenic diet (11) developed hypocarnitinemia during the first 12 months of treatment. Carnitine deficiency is not uncommon among epilepsy children and adolescents and is mainly linked to valproate therapy; further studies are needed to better understand the clinical significance of serum carnitine decline.

Keywords: Plasma free carnitine; Epilepsy children; Ketogenic diet; Topiramate; Lamotrigine

1. Introduction

Carnitine (beta-hydroxy-gamma-trimethylaminobutyric acid) is a water-soluble quaternary amine with important intracellular functions [1,2] and only biologically active in the L isoform [1,3]. It acts as cofactor for mitochondrial fatty acid oxidation by transferring long-chain fatty acids as acylcarnitine esters across the inner mitochondrial membrane; facilitates branched-chain alfa-ketoacid oxidation; shuttles acyl-CoA products of peroxisomal beta-oxidation to mitochondrial matrix in the liver; modulates the acyl-CoA-to-CoA ratio in mammalian cells; esterifies potentially toxic acyl-CoA metabolites that impair the citric acid cycle, urea cycle, gluconeogenesis and fatty acid oxidation during acute clinical crises [4]. In omnivores, approximately 75% of carnitine comes from the diet and 25% from endogenous biosynthesis [5]. Human skeletal muscle (the major tissue reservoir of carnitine), heart, liver, kidney and brain are capable of carnitine biosynthesis [6].

Carnitine deficiency was defined as a plasma free concentration of ≤ 20 μM/L at an age older than 1 week after term or a plasma esterified-to-free ratio of ≥ 0.4 at an age older than 1 week after term [7]. A subnormal concentration of total carnitine may result from decreased biosynthesis, inadequate dietary intake, inadequate absorption, defective tissue transport, excessive renal excretion, inborn errors of metabolism. Carnitine deficiency may be classified as primary or secondary. The criteria for diagnosis of primary syndromes are: severe reduction of plasma or tissue carnitine levels, evidence that the low carnitine levels impairs fatty acid oxidation, correction of the disorder when carnitine levels are restored and exclusion of other primary

* Corresponding author. Tel.: +39 081 5666695 fax: +39 081 5666694.
E-mail address: giangennaro.coppola@unina2.it (G. Coppola).

0387-7604/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.braindev.2005.11.005

Table 1
General characteristics of the sample (164 pts)

N° AEDS	N° PTS	Sex		Age range	BMI range	PMD/IQ		NE		Type of epilepsy		Duration of epilepsy range	Total time of treatment range	Hypocarnit. N° PTS
		F	M	(mean, years)	(mean)	N (%)	P (%)	N (%)	P (%)	GE	PE	(mean, years)	(mean, years)	
1	75	31	44	7 months–26 years (10.1)	12.5–31.7 (21.24)	47 (62.6)	28 (37.3)	50 (66.6)	25 (33.3)	30	45	2 months–19 years (5.6)	1 month–10 years 6 months (5.5)	13 (17.3)
2	44	20	24	1 year 6 months–27 years (11.9)	10.41–33.78 (19.98)	22 (50)	22 (50)	26 (59.1)	18 (40.9)	21	23	8 months–26 years (9.2)	7 months–26 years (9)	12 (27.3)
3	31	17	14	1 years 4 months–30 years (11)	9.2–27.54 (18.83)	10 (32.2)	21 (67.7)	13 (41.9)	18 (58.1)	19	12	9 months–23 years 6 months (9.1)	8 months–23 years 4 months (9)	12 (38.7)
4	13	5	8	3 years 8 months–21 years 6 months (11.4)	14.2–26.79 (20.39)	2 (15.4)	11 (84.6)	3 (23.1)	10 (76.9)	8	5	2 years 4 months–21 years 3 months (10.1)	2 years 2 months–21 years 2 months (9.10)	4 (30.7)
5	1	0	1	2 years	18.3	0	1	1	0	0	1	1 years 4 months	1 year 3 months	0

N° AEDs, number of antiepileptic drugs; N° PTS, number of patients; Sex F/M, female and male sex; BMI: body mass index; PMD/IQ N P, psychomotor; development/intelligence quotient, normal or pathological; NE N P, neurological examination, normal or pathological. Type of epilepsy, GE, PE, FC, generalized epilepsy, partial epilepsy, feverish convulsions. Hypocarnit. N° PTS (%), number and percentage of patients with hypocarnitinemia at the first sample of blood (P0).

defects in fatty acid oxidation [8]. Much more common are secondary syndromes, which produce a decrease in the levels of carnitine in plasma (<20 μM/L) or tissues or increased ratio (>0.4) of esterified to free carnitine or both. They may be associated with genetically determined metabolic errors, acquired medical conditions or iatrogenic factors such as drug administration [7].

Carnitine deficiency is not uncommon in patients with epilepsy. Risk factors for carnitine deficiency include young age (less than 10 years old), neurologic disabilities (mental retardation, cerebral palsy, microcefaly, blindness), diet low in meat and dairy products, on tube feeding or intravenous hyperalimentation, therapy with multiple anticonvulsant drugs including valproate, hyperammonemia, hypoglycemia, metabolic acidosis and evidence of an underlying inborn error of metabolism [9].

Numerous studies have shown that the total or free plasma carnitine concentrations, or both, are significantly lower in patients taking multiple AEDs, including VPA or VPA alone [10–16]. Some studies report hypocarnitinemia in patients taking anticonvulsant drugs other than valproate, such as carbamazepine, phenytoin or phenobarbital [15,17,18]; other studies have found no difference [19]. No data are available relative to the more recently introduced AEDs.

In the present study levels of free carnitine were evaluated in a large series of epilepsy children, adolescents and young adults treated with old and new AEDs, in monotherapy or in combination, in order to better understand the clinical significance of carnitine deficiency, and which of the old drugs other than valproate or which of the new drugs as topiramate and lamotrigine can cause carnitine deficiency. Moreover, a subset of patients was administered ketogenic diet in addition to their baseline AEDs.

2. Material and methods

Patients were recruited among those followed in the Epilepsy Unit of the Clinic of Child Neuropsychiatry from January 2002 to June 2003.

Inclusion criteria were: (1) epilepsy patients on mono or polytherapy from 3 months and over; or (2) patients who started topiramate or lamotrigine as mono or add-on therapy; or (3) patients who started ketogenic diet in combination to their baseline antiepileptic drugs.

Exclusion criteria were the following: (1) primary carnitine deficiency; (2) chronic assumption of drugs other than antiepileptic therapy; (3) progressive degenerative or metabolic diseases.

In patients selected following criteria (1), a blood sample for the dosage of free carnitine was drawn; patients selected by criteria (2) and (3) were followed prospectively and each of them underwent a blood evaluation for free carnitine before starting the new treatment (T_0) and after 3 and 12 months (T_3 and T_{12}).

In the same day the following biochemical parameters were measured: a full blood count, glucose, iron, uric acid, urea, creatinine, serum alanine aminotransferase (ALT), aspartate amino-transferase (AST), gammaglutamyl transferase (GGT), and AED blood level.

For each patient data were evaluated based on sex, age, psychomotor development/intelligence quotient, body mass index, neurological examination, type and duration of epilepsy, type and duration of treatment, daily dose/Kg of body weight, previous antiepileptic treatments and their length, adverse drug reactions.

A fasting blood sample was drawn and sent to the Sigma-tau Central Laboratory for measurement of the free carnitine in a TBA-80PR (Toshiba Co, Japan) automatic analyser by enzyme cycling method.

Based on the statements from Committee on Carnitine and Seizures [20], carnitine deficiency was defined as: (1) a plasma free concentration of $<$ or $=$ 20 Micromoles/dl at an age older than 1 week after term or (2) a plasma esterified-to-free-ratio of $\geq$0.4 at an age older than 1 week after term.

Clinical and laboratory data were processed using a computer statistical package (SPSS). Data were analysed statistically using chi-square test.

3. Results

The study group is composed by 164 patients (73 females and 91 males), aged between 7 months and 30 years (mean 10.8 years), with generalised (78 pts; 47.6%) or partial (86 pts; 52.4%) epilepsies. The overall duration of epilepsy ranged from 2 months and 26 years (mean 7.6 years), and the time on antiepileptic drug therapy was comprised between 1 month and 26 years (mean 7.5 years). At the time of enrolment, the patients were assuming 1 (75; 45.7%), 2 (44; 26.8%), 3 (31; 18.9%), 4 (13; 7.9%), 5 (1; 0.6%) antiepileptic drugs. Eleven out of 164 (6.7%) patients were started on ketogenic diet.

Overall, low plasma levels of free carnitine were found in 41 patients (25%); by single subgroups, 32 out of 84 patients (38%) taking VPA and 13 of 54 (24%) on carbamazepine, both on monotherapy or in combination, showed low free carnitine levels. Table 1 summarises the data relative to each subgroup, based on the number of antiepileptic drugs. A higher though not statistically significant risk of hypocarnitinemia results to be linked to polytherapy (31.5%) compared with monotherapy (17.3%) ($P=.0573$). In addition, risk factors significantly associated with polytherapy were an abnormal neurological examination and a psychomotor delay or mental retardation ($P<0.05$, at chi-square test).Table 2 shows data regarding monotherapy; it is noteworthy that valproic acid is associated with a higher risk of hypocarnitinemia (27.3%) compared with carbamazepine group (14.3%); none of the patients on phenobarbitone (9), lamotrigine (6) and topiramate (4) developed low serum levels of carnitinemia.

Table 2
General characteristics of the patients with monotherapy (75 pts)

AEDs	N° PTS	Sex		Age	BMI	PMD/IQ		NE		Type of epilepsy		Duration of epilepsy	Time of last treat	Hypocarnit. N° PTS (%)
		F	M	Range (mean, years)	Range (mean)	N	P	N	P	GE	PE	Range (mean, years)	Range (mean, years)	
VPA	33	13	20	1 year 6 months–26 years (10.7)	15.6-31.7 (22.24)	20	13	22	11	19	14	2 months–19 years (6.3)	2 months–19 years (3.5)	9 (27.3)
CBZ	21	9	12	3years 4 months–23 years (10.4)	17.3-27.3 (21.10)	14	7	14	7	2	19	2 months–26 years (5.5)	1 month–12 years 6 months (3.9)	3 (14.3)
PB	9	1	8	7 months–15 years (7.7)	12.5-19.87 (15.91)	4	5	4	5	4	5	7 months–14 years (5.3)	7months–7years 2 months (3.4)	0
LTG	6	5	1	8 years–13 years (10.10)	17.95-28. 61 (22.21)	5	1	6	0	4	2	2 months–12 years (2.9)	1 month–2 years (0.9)	0
TPM	4	1	3	4 years–16 years (8.6)	15.68-20. 11 (17.57)	4	0	4	0	0	4	2 months–13 years (6.1)	1month–1 year 6 months (0.9)	0
ESM	1	1	0	7 years	26.8	0	1	0	1	1	0	6 years	3 years–7 months	1 (100)
ACTH	1	1	0	3 years 10 months	21.27	0	1	0	1	0	1	5 months	5 months	0

VPA, valproate; CBZ, carbamazepine; PB, phenobarbital; LTG, lamotrigine; TPM, topiramate; ESM, ethosuximide; ACTH, Time of last treat, time of the last treatment.

As to bitherapy (44 patients), nine of 18 patients (50%) on valproic acid plus one other AED, two out of 15 patients (13.3%) assuming carbamazepine plus one other AED, and 1 of 3 patients (33.3%) on carbamazepine plus valproate resulted hypocarnitinemic. None of the 8 patients on other antiepileptic combinations developed low free carnitine levels.

As to tritherapy (31 patients), hypocarnitinemia was found in 2 out of 6 patients (33.3%) on carbamazepine plus two AEDS other than VPA, in 7 of 16 (43.7%) on VPA plus two AEDs other than CBZ, and 2 of 5 (40%) on CBZ plus VPA and another AED. One of 4 children on combination not including CBZ and VPA was hypocarnitinemic.

Among patients on four antiepileptic drugs (13), one of six (16.7%) on AED combination including VPA and three of six (50%) including CBZ plus VPA were found hypocarnitinemic. One other patient on CBZ plus other drugs other than VPA disclosed normal blood values.

Table 3 summarises the main clinical features of patients with hypocarnitinemia (41 patients) compared with normal values group (123 patients). Factors that appear to be significantly related with hypocarnitinemia, are gender (females 63.4 vs 38.2% of normocarnitinemic; $P<0.05$; OR = .356; 95% Cl = .160 and .786), abnormal neurological examination (mostly tetraparesis, diplegia, and dystonia) ($P<0.05$; OR = .438; 95% Cl = .200 and .953).

Thirty-two out of 84 children (38.1%) on valproate both as mono or add-on therapy (Table 4), showed low free carnitine levels. In this group too, hypocarnitinemia resulted significantly related to female sex ($P<0.05$; OR = .301; 95% Cl = 1.07 and .382) and abnormal neurological examination ($P<0.05$; OR = .375; 95% Cl = .136 and 1.01). Thirteen out of 54 children on carbamazepine as mono or add-on therapy (24%) resulted hypocarnitinemic (Table 5); none of the aforementioned risk factors was significant in this group.

Table 6 shows the effect on plasma levels of free carnitine in 16 patients who had been assuming an antiepileptic drug as first-line or add-on treatment to their baseline therapy. Neither one of the patients on TPM (10) or LTG (5) developed hypocarnitinemia during the first 12 months of treatment.

Eleven out of 164 patients were prospectively treated with ketogenic diet as add-on therapy to their baseline AEDs. In all children, the diet was started at the classic 4: 1 ratio (ratio of grams of fat to protein and carbohydrate). No one patient received liquid formula for the ketogenic diet or was fed by tube feeding or intravenously. Clinical features and free carnitine values are summarized in Table 7. Blood samples were drawn before starting the diet and after 3 and 12 months, respectively. None of the patients developed abnormal levels of plasma free carnitine.

Table 3
Pts hypocarnitinemic vs pts normocarnitinemic

(Carnitinemia)	N° PTS (%)	Sex		Age	BMI	PMD/IQ		NE		Type of epilepsy		Duration of epilepsy	Time of last treat	Total time of treatment
		F (%)	M (%)	Range (mean, years)	Range (mean)	N (%)	P (%)	N (%)	P (%)	GE	PE	Range (mean, years)	Range (mean, years)	Range (mean, years)
<20	41 (25)	26* (63.4)	15 (36.6)	1 year 6 months–30 years (11.2)	12.06–32.8 (20.27)	16 (39.1)	25 (60.9)	17 (41.5)	24** (58.5)	23	18	6 months–25 years (8.7)	2 months–10 years (1.9)	2 months–25 years (8.6)
>20	123 (75)	47* (38.2)	76 (61.8)	7 months–29 years (10.8)	9.2–33.78 (20.28)	65 (52.8)	58 (47.2)	76 (61.8)	47** (38.2)	55	68	2 months–26 years (7.3)	1 month–19 years (2.7)	1 month–26 years (7.10)

(Carnitinemia), plasma free carnitine concentration. *(χ^2) $P<0.05$; OR = 0.356; 95% CI = 0.160 and .786. **(χ^2) $P<0.05$; OR = 0.438; 95% CI = 0.200 and .953.

4. Discussion

In the present study a large series of epilepsy children, adolescents and young adults, assuming old and new antiepileptic drugs both in mono or add-on therapy, has been reported. In addition, a few patients were administered ketogenic diet as adjunctive treatment to their own baseline drugs.

The overall data show carnitine deficiency in about 25% of our patients, to be mainly linked to valproate assumption both as mono or add-on. Literature data show a carnitine deficiency in patients taking valproate ranging from 4 to 76% [11,14–17,21,22].

According with Castro-Gago et al. [15], carnitine deficiency was also found in 24% of our patients assuming carbamazepine as mono or add-on therapy. Carnitine deficiency occurring in patients treated with drugs other than VPA is also worth noting, and it probably suggests that an impairment of carnitine metabolism is part of a more general biochemical effect of AED therapy on lipid metabolism.

Persisting normal plasma free carnitine in all children treated with topiramate or lamotrigine as mono or in combination over a 12 months period, are also noteworthy. To our knowledge, these are the first available data relative to two of the most prescribed new antiepileptic drugs.

In our series, other possible risk factors resulted to be female sex, psychomotor delay or mental retardation and an abnormal neurological examination

Prevalence of carnitine deficiency among females treated with valproic acid was first reported by Beghi et al. [17]. Consequently, this author assumed that carnitine requirements might differ according to sex. Thus, this variable should be considered when the risk of carnitine deficiency and subsequent liver failure, is being assessed in patients receiving AED therapy with or without valproic acid.

In our sample, cerebral palsy appeared to be significantly associated with low free carnitine levels; this issue appears indirectly confirmed by the absence of carnitine deficiency in epilepsy children without severe neurologic problems being treated with valproate [23].

In our children on ketogenic diet, carnitine levels remained substantially unchanged at least in the short period, accordingly with Berry-Kravis et al. [24] who confirm that most patients on KD do not require carnitine supplementation.

All our children with low carnitine levels were apparently asymptomatic, according with other reports [9,10,12] in which there was no clear correlation between carnitine deficiency and clinical symptoms. Further, carnitine supplementation in such patients may be followed by an increase of the carnitine levels to ‘normal’ without a noticeable change in their clinical status [25].

Based on the fact that in asymptomatic patients low plasma carnitine levels may not reflect the actual muscle tissue concentrations of carnitine, ‘low’ carnitine levels

Table 4
Patients on valproate as mono or add-on therapy (84 pts)

(Carnitinemia)	N° PTS	Sex		Age	BMI	PMD/IQ		NE		Duration of epilepsy	Time of last treat	Total time of treatment	VPA as Mg/kg/day	[Carnitinemia]
		F	M	Range (mean, years)	Range (mean)	N	P	N	P	Range (mean, years)	Range (mean, years)	Range (mean, years)	Mean (±SD)	Mean (±SD)
<20	32	21*	11	1 year 6 months–30 years (11.5)	12.06–32.8 (20.53)	11	21	12	20**	6 month–25 years (9.9)	2 months–10 years (1.9)	2 months–25 years (9.2)	19.83 (±9.01)	14.60 (±4.74)
>20	52	19*	33	1 year 4 months–26 years (10.6)	9.2–33.78 (21.27)	25	27	32	20**	8 months–21 years 3 months (6.9)	1 month–19 years (2.8)	7 months–21 years 3 months (6.8)	18.02 (±7.78)	33.83 (±8.89)

(Carnitinemia), plasma free carnitine concentration. *(χ^2) $P<0.05$; OR = 0.301; 95% Cl = 1.07 and 0.382. **(χ^2) $P<0.05$; OR = 0.375; 95% Cl = 0.136 and 1.01.

Table 5
Patients on carbamazepine as mono or add-on therapy (54 pts)

(Carnitinemia)	N° PTS	Sex		Age	BMI	PMD/IQ		NE		Duration of epilepsy	Time of last treat	Total time of treatment	CBZ as Mg/kg/day	[Carnitinemia]
		F	M	Range (mean, years)	Range (mean)	N	P	N	P	Range (mean, years)	Range (mean, years)	Range (mean, years)	Mean (±SD)	Mean (±SD)
<20	13	6	7	2 years 7 months–25 years (10.2)	13.84–32.8 (19.85)	5	8	5	8	1 years 4 months–25 years (7.9)	3 month–10 years (2.5)	1 year 2 months–25 years (7.76)	15.94 (±7.25)	15.29 (±4.95)
>20	41	16	25	3 years 4 months–29 years (12.4)	12.3–33.08 (19.62)	22	19	26	15	3 months–26 years (9.5)	1 month–16 years (3.2)	1 month–26 years (9.3)	14.84 (±6.69)	32.21 (±5.62)

Table 6
Prospective serum levels of free carnitine in 16 patients who assumed topiramate or lamotrigine as monotherapy or add-on

N° of bas. AEDs	N° PTS	Sex		Age	BMI	PMD/IQ		NE		Type of epilepsy		Duration of epilepsy	AED AS	TO	T3	T12
		F	M	Range (mean, years)	Range (mean)	N	P	N	P	GE	PE	Range (mean, years)	Monoth. or add-on	Mean (± SD)	Mean (± SD)	Mean (± SD)
0	4	2	2	6–10 years (8.4)	15.68–21. 32 (18.4)	3	0	3	0	3	1	2 months–8 months (4)	2LTG 2TPM	41.41 (±11.15)	38.27 (±16.65)	37.55 (±7.72)
1	8	4	4	1 year 6 months–15 years (9.7)	10.41–19. 86 (16.2)	3	5	4	4	3	5	8 months–13 years (6.1)	1 LTG 7 TPM	32.93 (±5.71)	35.64 (±10.99)	39.24 (±10.37)
2	3	1	2	1 year 4 months–6 years (3.9)	16–18.75 (17.6)	1	2	2	1	1	2	9 months–6 years (2.1)	3 TPM	35.67 (±13.34)	34.12 (±9.85)	31.20 (±14.06)
4	1	0	1	2 years	18.3	0	1	1	0	0	1	1 year 4 months	1 LTG	41.14	33.15	50.79

N° of bas. AEDs, number of baseline AEDs.

Table 7
Prospective serum values of free carnitinemia in 11 patients on ketogenic diet

N° PTS	Sex		Age	BMI	PMD/IQ		NE		Type of epilepsy		Duration of epilepsy	Duration of KD	N° BAS. AEDs (pts)	[Free carnitinemia] TO	T3	T12
	F	M	Range (mean, years)	Range (mean)	N	P	N	P	GE	PE	Range (mean, years)	Range (mean, years)		Mean (±SD)	Mean (±SD)	Mean (±SD)
11	7	4	2 years 7 months–23 years 7 months (10.3)	9.2-27.29 (18.46)	5	6	5	6	8	3	2 years 4 months–23 years 6 months (8. 7)	1 month–2 years (0.6)	3 (8) 4 (2) 2 (1)	21.17 (±8.69)	22.03 (±9.65)	20.17 (±9.40)

Duration OF KD, duration of ketogenic diet. N° BAS. AEDs (pts), number of baseline AEDs per patients (pts).

should be interpreted with caution. Nonetheless, there is evidence for carnitine supplementation to decrease a VPA-induced asymptomatic hyperammonemia [26], that appears otherwise transient and reversible in most patients [16].

If carnitine treatment is not likely to benefit low-risk, asymptomatic patients, it may benefit those showing clearcut clinical symptoms such as apathy, constipation, nausea, vomiting, weakness or hypotonia [9,20].

In conclusion, our data confirm carnitine deficiency to be not uncommon among epilepsy children and adolescents. It is mainly linked to VPA as mono or add-on therapy though other drugs as carbamazepine are not irrelevant. Other major risk factors are represented by female sex and multiple neurological abnormalities. Preliminary data seem to rule out any significant role of lamotrigine, topiramate and ketogenic diet.

Further prospective, long-term follow-up studies comparing low and normal carnitine level groups are needed to better understand the clinical significance of serum carnitine decline, given carnitine supplementation doesn't always prevent the emergence of serious hepatotoxicity [27]. Thus far, carnitine therapy seems only justified in high risk symptomatic patients.

References

[1] Bremer J. Carnitine-metabolism and functions. Physiol Rev 1983;63:1420–80.

[2] Bieber LL. Carnitine. Annu Rev Biochem 1988;57:261–83.

[3] Rebouche CJ. Carnitine metabolism and functions in humans. Annu Rev Nutr 1996;6:41–66.

[4] Stanley CA. New genetic defects in mitochondrial fatty acid oxidation and carnitine deficiency. Adv Pediatr 1987;34:59–88.

[5] Rebouche CJ. Carnitine function and requirements during the life cycle. Fed Am Soc Exp Biol J 1992;6:3379–86.

[6] Pons R, Carrozzo R, Tein I, Walker WF, Addonizio LJ, Rhead W, et al. Deficient muscle carnitine transport in primary carnitine deficiency. Pediatr Res 1997;42:583–7.

[7] De Vivo DC, Tein I. Primary and secondary disorders of carnitine metabolism. Int Pediatr 1990;5:134–41.

[8] 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.

[9] Coulter DL. Carnitine deficiency in epilepsy: risk factors and treatment. J Child Neurol 1995;10(Suppl. 2):S32–S9.

[10] Igarashi N, Sato T, Kyouya S. Secondary carnitine deficiency in handicapped patients receiving valproic acid and/or elemental diet. Acta Paediatr Jpn 1990;32:139–45.

[11] 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.

[12] Van Wouwe JP. Carnitine deficiency during valproic acid treatment. Int J Vitam Nutr Res 1995;65:211–4.

[13] Chung S, Choi J, Hyun T, Rha Y, Bae C. Alterations in the carnitine metabolism in epileptic children treated with valproic acid. J Korean Med Sci 1997;12:553–8.

[14] Hiraoka A, Arato T, Tominaga I. Reduction in blood free carnitine levels in association with changes in sodium valproate (VPA) disposition in epileptic patients treated with VPA and other anti-epileptic drugs. Biol Pharm Bull 1997;20:91–3.

[15] Castro-Gago M, Eiris-Punal J, Novo-Rodriguez MI, Couceiro J, Camina F, Rodriguez-Segade S. Serum carnitine levels in epileptic children before and during treatment with valproic acid, carbamazepine, and phenobarbital. J Child Neurol 1998;13:546–9.

[16] Verrotti A, Greco R, Morgese G, Chiarelli F. Carnitine deficiency and hyperammonemia in children receiving valproic acid with and without other anticonvulsant drugs. Int J Clin Lab Res 1999;29:36–40.

[17] Beghi E, Bizzi A, Codegoni AM, Trevisan D, Torri W. Valproate, carnitine metabolism, and biochemical indicators of liver function. Collaborative group for the study of epilepsy. Epilepsia 1990;31:346–52.

[18] Hug G, Mc Graw CA, Bates SR, Landrigan EA. Reductions of serum carnitine concentrations during anticonvulsant therapy with phenobarbital, valproic acid, phenytoin and carbamazepine in children. J Pediatr 1991;119:799–802.

[19] Zelnik N, Fridkis I, Gruener N. Reduced carnitine and antiepileptic drugs: cause relationship or co-existence? Acta Paediatr 1995;84:93–5.

[20] De Vivo DC, Bohan TP, Coulter DL, Dreifuss FE, Greenwood RS, Nordli Jr DR, et al. L-carnitine supplementation in childhood epilepsy: current perspectives. Epilepsia 1998;39:1216–25.

[21] Thom H, Carter PE, Cole GF, Stevenson KL. Ammonia and carnitine concentrations in children treated with sodium valproate compared with other anticonvulsant drugs. Dev Med Child Neurol 1991;33:795–802.

[22] Riva R, Albani F, Gobbi G, Santucci M, Baruzzi A. Carnitine disposition before and during valproate therapy in patients with epilepsy. Epilepsia 1993;34:184–7.

[23] Hirose S, Mitsudome A, Yasumoto S, Ogawa A, Muta Y, Tomoda Y. Valproate therapy does not deplete carnitine levels in otherwise healthy children. Pediatrics 1998;101:E9.

[24] Berry-Kravis E, Booth G, Sanchez AC, Woodbury-Kolb J. Carnitine levels and the ketogenic diet. Epilepsia 2001;42:1445–51.

[25] Fung EL, Tang NL, Ho CS, Lam CW, Fok TF. Carnitine level in Chinese epileptic patients taking sodium valproate. Pediatr Neurol 2003;28:24–7.

[26] Ohtani Y, Endo F, Matsuda I. Carnitine deficiency and hyperammonemia associated with valproic acid therapy. J Pediatr 1982;101:782–5.

[27] Murphy JV, Groover RV, Hodge C. Hepatotoxic effects in a child receiving valproate and carnitine. J Pediatr 1993;123:318–20.