Journal of Pediatric Neurology 10 (2012) 275–281
DOI 10.3233/JPN-120582
IOS Press

Plasma carnitine levels in children with idiopathic epilepsy treated with old and new antiepileptic drugs

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Received 19 March 2012
Revised 14 July 2012
Accepted 19 July 2012

Abstract. Prolonged antiepileptic drugs (AEDs) treatment can result in secondary carnitine deficiency. Clinical studies indicate a decrease in free and total carnitine levels in children treated with old-generation AEDs (especially valproate). A number of studies on the effect of valproic acid and/or other AEDs on carnitine concentrations yielded contradictory results. The effect of new AEDs as oxcarbazepine and lamotrigine on carnitine metabolism has not been reported previously. The aim of this study was to evaluate the plasma carnitine level in children with idiopathic epilepsy treated with old AEDs (valproic acid and carbamazepine) and new AEDs (lamotrigine and oxcarbazepine). Fifty children with newly diagnosed idiopathic epilepsy were selected from those attending the pediatric neurology out-patient clinic at Tanta University Hosptial. Thirty-four males and 16 females were enrolled in the study with the mean age was (6.8 ±3.1 yr). Patients were grouped according to their antiepileptic treatment into: group 1, 20 patients received valproic acid as monotherapy with no prior AEDs use. Group 2, 10 patients received valproic acid as polytherapy after 3 mo treatment with carbamazepine. Group 3, 10 patients received lamotrigine as monotherapy, and group 4, 10 patients received oxcarbazepine as monotherapy. Twenty healthy children served as control group with mean age was (8.5 ±2.3 yr). Estimation of the plasma carnitine levels were done for all the studied groups. Group 1 and group 2 epileptic children, treated with valproic acid monotherapy and polytherapy respectively had significantly lower plasma carnitine levels than that of the control group ($P < 0.05$). There was significant correlation between the age and the plasma carnitine in group 1 and group 2 epileptic children, the younger the age the greater the reduction in the plasma carnitine levels. Patients treated with valproic acid polytherapy had significantly lower plasma carnitine levels than those of the patients treated with valproic acid monotherapy ($P < 0.05$). There was no significant difference in the plasma carnitine levels between the controls and children with epilepsy treated with oxcarbazepine and lamotrigine ($P > 0.05$). In conclusion**,** carnitine deficiency is not uncommon among children with epilepsy and is mainly linked to valproate therapy. In contrast, new-generation AEDs probably do not cause carnitine deficiency. These findings suggest a need to monitor serum carnitine levels in children treated with valproic acid therapy.

Keywords: Carnitine, children, epilepsy, antiepileptic drug

1. Introduction

Prolonged antiepileptic drugs (AEDs) treatment can result in secondary carnitine deficiency [1]. Clinical studies indicate a decrease in free and total carnitine levels in children treated with old-generation AEDs (especially valproate) [2]. Some studies on valproic acid (VPA)-induced hepatotoxicity showed decreased free serum carnitine in patients treated with VPA, but some did not [3]. A number of studies on the effect of VPA and/or other antiepileptic agents on carnitine concentrations yielded contradictory results.

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The majority of studies involved adult patients [4]. In pediatric practice, the effect of VPA on carnitine metabolism was age-dependent with more pronounced effects in children younger than 10 yr. This may be in line with the observation that young children are especially at risk of developing VPA-associated hepatotoxicity [5].

An alteration in carnitine concentration could be due to an abnormality in inherited errors in metabolism [6]. A reduction in serum carnitine levels have been reported in patients with AEDs use, while VPA used as monotheraphy or in combination with other AEDs. VPA inhibits the biosynthesis of carnitine and may contribute in this way to the carnitine deficiency [7]. Some contradictory studies demonstrated that other AEDs specifically carbamazepine, phenytoin and phenobarbital, also cause carnitine deficiency in about 21% of the patients to whom they are administered [8]. The effect of new AEDs as lamotrigine and oxcarbazepine on carnitine metabolism has not been reported previously [9].

Carnitine is a protein that is essential to the metabolism of long chain fatty acids that are metabolized by the mitochondria within the cell. Carnitine is essential to this process, because fatty acids by themselve cannot penetrate the membrane of the mitochondria [10]. Each molecule of fatty acid has to be transported across the mitochondrial membrane by binding with a molecule of carnitine. After fatty acid is metabolized in the mitochondria, and generated the energy rich adenosine-5-triphosphate (ATP), carnitine is again required to transport the waste product out of the mitochondria [11]. Carnitine comes in two forms, L-carnitine and D-carnitine, both have exactly the same chemical formula and structure. It is only L-carnitine which is the active chemical in the metabolic process, whereas D-carnitine has no effect [12]. Carnitine is rapidly excreted from the body, its half life is estimated at 17 h. This means that carnitine must be replaced continuously [13]. In the normal human, approximately 75% of the carnitine is obtained directly as a protein in food and the remaining 25% is synthesized by the body from other proteins in food. Carnitine is typically available in L-carnitine form, and acetyl-L-carnitine. L-carnitine is typically recognized for its contributions to a healthy heart while, acetyl-L-carnitine is used for brain health [14]. Carnitine deficiency may manifest as encephalopathy, such as limp, unresponsive and comatose. Pyramidal movements or minimal athetoid movements, myopathy such as hypotonia or progressive proximal weakness may be found. Cardiomyopathy, onset may occur with rapidly progressive heart failure, cardiomegaly may be found on the physical examination, associated with a heart murmur. A gallop rhythm can be found, associated with a dilated cardiomyopathy [15].

This study was performed to evaluate plasma carnitine levels in children with idiopathic epilepsy treated with old AEDs (VPA and carbamazepine) and new AEDs (lamotrigine and oxcarbazepine) in order to asses whether AEDs cause carnitine deficiency.

2. Materials and methods

2.1. Patient selection

This study was carried out in Tanta University Hospital Pediatric Department, Neurology Unit. Fifty children with newly diagnosed idiopathic epilepsy were selected from those attending the pediatric neurology outpatient clinic. Thirty-four males and 16 females were enrolled in the study with the age range of 1−12 yr with the mean age of 6.8 ± 3.1 yr. Thirty patients had generalized seizures and 20 patients had partial seizures. Patients were grouped according to their AEDs treatment into: group 1, 20 patients received VPA as monotherapy without any AEDs treatment before. Group 2, 10 patients received VPA as polytherapy after 3 mo treatment with carbamazepine. Group 3, 10 patients received lamotrigine as monotherapy, and group 4, 10 patients received oxcarbazepine as monotherapy, duration of treatment was 6−12 mo. Twenty healthy children served as control group with the age range was 2−12 yr, with the mean age of 8.5 ±2.3 yr. All the epileptic children had no history of liver, renal diseases, metabolic diseases, or history of AEDs intake or carnitine intake before the study. The group characteristics are described in Table 1. All children were included in the study after written informed parental consent had been obtained. The study was approved by the local ethics committee of the Faculty of Medicine Tanta University.

Full history about the initial presentation and frequency of seizures, age of onset, drug intake before, developmental history and family history were recorded. These children with idiopathic epilepsy had no apparent underlying cause of idiopathic epilepsy, such as a structural problem in the brain or metabolic disorder. Most of these children had positive family

Table 1
Demographic, clinical and therapeutic characteristic of the studied groups and the controls

	Group 1	Group 2	Group 3	Group 4	Controls
Number	20	10	10	10	20
Males/females	18/2	7/3	4/6	5/5	12/8
Age (yr), range	1−11	5−12	4−12	7−10	2−12
Duration of treatment (mo)	6−12	6−12	6−12	6−12	−
Types of epilepsy generalized/partial	18/2	1/9	6/4	5/5	−
Therapy	Valproic acid Monothrapy	Valproic acid + carbamazepine polytherapy	Lamotrigine Monotherapy	Oxcarbazepine Monotherapy	−

history of epilepsy. Complete clinical examination for exclusion of hepatomegaly, cardiomegaly, renal diseases, hypotonia or progressive proximal weakness were performed. Other routine laboratory test including complete blood picture, liver function, kidney function and fasting blood sugar were obtained. The estimation of the plasma carnitine was performed before the start of treatment, after 6 mo and after 1 yr of the AEDs treatment. Electroencephalography for the epileptic children and brain magnetic resonance imaging for the epileptic children for exclusion of any structural brain lesions were reviewed.

2.2. Estimation of the plasma level of carnitine

Venous blood samples were collected in heparinized tubes in the morning after an overnight fasting and blood samples were allowed to centrifuged and the plasma were collected into dry tubes and stored at −70 ℃. Carnitine plasma levels (provided by Roch Diagnostics-Germany, Cat.No.11 242 008 001) were determined by enzymatic ultraviolet method. L-carnitine is acetylated to acetyl carnitine by acetyl coenzyme a in the presence of the enzyme carnitine acetyl transferase. The resulting coenzyme a is acetylated back to acetyl coenzyme a in the presence of ATP and acetate, catalyzed by the enzyme acetyl coenzyme a synthetase. This results in the formation of adenosine-5-monophosphate and inorganic pyrophosphate. In the presence of ATP, adenosine-5-monophosphate forms twice the amount of adenosine-5-diphosphate supported by myokinase. This is converted in the following reaction with phosphoenol pyruvate in the presence of pyruvate kinase. The pyruvate formed is reduced to L-lactate by reduced nicotinamide adenine dinucleotide in the presence of lactate dehydrogenase. The amount of nicotinamide adenine dinucleotide consumed during the reaction is equivalent to half the amount of L-carnitine. It is determined on the basis of the absorption with spectrophotometer [16,17]. The estimation of the plasma carnitine was performed before the start of treatment, after 6 mo and after 1 yr, of the AEDs treatment.

2.3. Statistical analysis

Collected data were coded, analyzed and computed using the Statistical Package for Social Sciences version 10. Results were expressed as mean ± SD, and differences between the means of different variables were tested using the Student *t*-test. Pearson's correlation coefficient was used to study the correlation between different variables. Differences were considered significant statistically when $P < 0.05$.

3. Results

The results of this study are shown in the Tables 2−4. Table 2 shows comparison of the mean plasma levels of carnitine in children with idiopathic epilepsy and the controls before the start of treatment. The mean plasma carnitine levels of group 1, group 2, group 3, and group 4, epileptic children were 77.45 ± 16.23 μmol/L, 74.13 ± 14.26 μmol/L, 78.35 ± 15.24 μmol/L and 81.45 ± 9.36 μmol/L respectively, these values show no significant difference than the mean plasma carnitine levels of the control group which was 80.44 ± 3.25 μmol/L ($P_1 > 0.05$).

Table 3 shows comparison of the mean plasma levels of carnitine in children with idiopathic epilepsy and the controls after 6 mo of treatment with the antiepileptic drugs. The mean plasma carnitine level of group 1 epileptic children was 57.33 ± 4.25 μmol/L

Table 2
Plasma carnitine levels in children with epilepsy and the controls before the start of treatment

Plasma carnitine (μmol/L)	Group 1	Group 2	Group 3	Group 4	Controls
Range	40−100	50−100	55−99	67−100	60−110
Mean ± SD	(77.45 ± 16.23) *	(74.13 ± 14.26) *	(78.35 ± 15.24) *	(81.45 ± 9.36) *	(80.44 ± 13.25) *

* (Significant: $P < 0.05$)

Table 3
Plasma carnitine levels in children with epilepsy and the controls after 6 m of treatment

Plasma carnite (μmol/L)	Group 1	Group 2	Group 3	Group 4	Controls
Range	45−75	44−53	55−110	69−100	60−110
Mean ± SD	(57.33 ± 4.25) *	(48.46 ± 3.45) *	(73.27 ± 18.40)	(85.44 ± 12.65)	(80.44 ± 13.25)

* (Significant: $P < 0.05$)

Table 4
Plasma carnitine levels in children with epilepsy and the controls after 1 yr of treatment

Plasma carnite (μmol/L)	Group 1	Group 2	Group 3	Group 4	Controls
Range	30−60	30−45	55−110	69−100	60−110
Mean ± SD	(50.46 ± 8.64) *	(37.67 ± 5.48) *	(73.27 ± 18.40)	(85.44 ± 12.65)	(80.44 ± 13.25)

* (Significant: $P < 0.05$)

this value was significantly lower than the mean plasma carnitine level of the control group which was 80.44 ± 13.25 μmol/L ($P_1 < 0.05$). The mean plasma carnitine level of group 2 epileptic children was 48.46 ± 3.45 μmol/L, this value was significantly lower than the mean plasma carnitine level of the control group which was 80.44 ± 13.25 μmol/L ($P_2 < 0.05$). The mean plasma carnitine level of group 3 epileptic children was 73.27 ± 18.48 μmol/L, this value show no significant difference than the mean plasma carnitine level of the control group which was 80.44 ± 13.25 μmol/L ($P_3 > 0.05$). The mean plasma carnitine level of group 4 epileptic children was 85.44 ± 12.65 μmol/L, this value show no significant difference than the mean plasma carnitine level of the control group which was 80.44 ± 13.25 μmol/L ($P_4 > 0.05$).

Table 4 shows comparison of the mean plasma levels of carnitine in children with idiopathic epilepsy and the controls after 1 yr of treatment with antiepileptic drugs. The mean plasma carnitine level of group 1 epileptic children was 50.46 ± 8.64 μmol/L, this value was significantly lower than the mean plasma carnitine level of the control group which was 80.44 ± 13.25 μmol/L ($P_1 < 0.05$). The mean plasma carnitine level of group 2 epileptic children was 37.67 ± 5.48 μmol/L, this value was significantly lower than the mean plasma carnitine level of the control group which was 80.44 ± 13.25 μmol/L ($P_2 < 0.05$). The mean plasma carnitine level of group 3 epileptic children was 73.27 ± 18.40 μmol/L, this value show no significant difference than the mean plasma carnitine level of the control group which was 80.44 ± 13.25 ($P_3 > 0.05$). The mean plasma carnitine level of group 4 epileptic children was 85.44 ± 12.65 μmol/L, this value show no significant difference than the mean plasma carnitine level of the control group which was 80.44 ± 13.25 μmol/L ($P_4 > 0.05$).

4. Discussion

This study was performed to evaluate carnitine deficiency in children with epilepsy. Prolonged antiepileptic drug treatment can result in secondary carnitine deficiency and clinical studies indicate a decrease in free and total carnitine in children treated with old-generation AEDs (especially valproate) [18].

Carnitine is essential for the brain and heart health, with proven benefits for many of the symptoms tied to heart disease. It is also considered a potent addition to popular brain nutrients, such as coenzyme Q10 [11]. Carnitine is involved with energy production in the cell. More specifically, it helps transport of fatty acids into the powerhouse of the cell, the mitochondria. From there, the fatty acids can be used in the energy production cycle [13]. Carnitine is necessary for mitochondrial metabolism of valproate and a carnitine deficit has been proposed in the pathogenesis of

valproate-induced hepatotoxicity [19,20]. In the present work, the plasma concentrations of total carnitine, was measured in 50 epileptic patients treated with VPA, carbamazepine plus VPA, oxcarbazepine and lamotrigine. Patients medicated only with VPA either monotherapy or polytherapy tended to have a lower plasma carnitine level than the controls, and patients treated with VPA-antiepileptic drug polytherapy had lower carnitine plasma levels than patients receiving VPA monotherapy. On the other hand, patients treated with lamotrigine and oxcarbazepine had normal plasma carnitine levels. VPA, inhibits the biosynthesis of carnitine, and may contribute in this way to carnitine deficiency associated with VPA therapy either monotherapy or polytherapy also, VPA metabolites causing a secondary disturbance of intermediary metabolism and direct inhibition of fatty acid oxidation enzymes [21]. It has been shown that, in cultured fibroblasts, VPA impairs the plasma membrane carnitine uptake in vitro. This impairment of carnitine uptake may explain serum depletion caused by decreased renal tubular reabsorption of carnitine and muscle depletion caused by decreased muscle uptake [22].

These results were in agreement with Zelnik et al. [23]; who had studied serum carnitine in epileptic children treated with VPA, vigabatrin, lamotrigine, and topiramate. These drugs were given as monotherapy or polytherapy and had found that, new-generation AEDs probably do not cause carnitine deficiency. In contrast, valproate may induce carnitine deficiency, but most cases are asymptomatic. Also these results agree with Castro-Gago et al. [24] who had studied serum carnitine in epileptic children treated with VPA, carbamazepine and phenobarbital before and after treatment and had found that, both free and total carnitine levels showed a significant decline with respect to pretreatment levels. This decline was most marked and most consistent in patients treated with VPA only. Our results also agree with Hiraoka et al. [25] who had found reduction in the blood free carnitine level as a side effect of sodium valproate treatment in epileptic children. The results of this study also agree with Opala et al. [26] who had studied plasma carnitine in epileptic children treated with VPA monotherapy and polytherapy, and had found that, carnitine deficiency occur in both epileptic children treated with VPA monotherapy and polytherapy with significantly lower carnitine level in polytherapy treated group.

In this study, new AEDs such as oxcarbazepine had no effect on the plasma carnitine level, this result agrees with the results obtained by Kurul et al. [27] who had studied serum carnitine in 20 epileptic children treated with oxcarbazepine as monotherapy and found no significant difference was observed in the serum levels of total and free carnitine in the epileptic children and the controls. The results of this study also agree with the results obtained by Coppola et al. [28] who had studied the plasma carnitine in a large series of epilepsy in children and adolescents treated with old and new AEDs with or without ketogenic diet and had found that, carnitine deficiency is not uncommon among epileptic children and adolescents and is mainly linked to valproate therapy. In agreement with this study, the results obtained by Chung et al. [29] who had studied the plasma carnitine in epileptic children treated with VPA monotherapy and polytherapy and had found that, patients treated with VPA polytherapy had lower carnitine levels than those treated with VPA monotherapy. On the other hand, Freeman et al. [30] had studied study the role of carnitine supplementation in VPA therapy using a carefully controlled, double blind, crossover method. They assessed the effect of carnitine supplementation on patients who were receiving VPA and other antiepileptic drugs. They found that, no favorable effect of carnitine supplementation was observed on the well-being or cognitive functions of their subjects compared with the placebo group; they concluded that the benefits of prophylactic carnitine supplementation for patients taking VPA were unproven.

The results of this work show that, carnitine deficiency is more common in children less than 10 yr and there was significant positive correlation between the age and plasma carnitine levels, the younger the age, the more reduction in the plasma carnitine levels, because during infancy and childhood years, cell and tissue growth is usually rapid such that the demand for tissue accretion and energy utilization leads to the depletion of L-carnitine at a rate faster than the ability to synthesize it [31,32].

From this study we can conclude that, VPA was the only antiepileptic drug reported to inhibit carnitine uptake and carnitine supplementation may reduces the adverse reactions caused by VPA. Despite the lack of prospective, randomized clinical trials documenting efficacy of carnitine supplementation in preventing VPA-induced hepatotoxicity, the few limited studies available have recommended, carnitine supplementa-

tion to result in subjective and objective improvements along with increases in carnitine serum concentrations in patients receiving VPA [33]. Thus, carnitine was strongly recommended for children at risk of developing a carnitine deficiency. Although carnitine has been well tolerated, future studies are needed to evaluate the efficacy of prophylactic carnitine supplementation for the prevention of hepatotoxicity in epileptic children.

In conclusions, carnitine deficiency is not uncommon among children with epilepsy and is mainly linked to valproate therapy. Valproate may induce carnitine deficiency, but most cases are asymptomatic. In contrast, new-generation AEDs probably do not cause carnitine deficiency. These findings suggest a need to monitor serum carnitine levels in children treated with VPA either, monotherapy or polytherapy. We recommend that studies are needed to investigate the role of carnitine supplementation in reducing adverse effects in patients receiving valproate.

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