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Effects of L-carnitine supplementation in patients with childhood-onset epilepsy prescribed valproate

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ABSTRACT

Background: The benefits of carnitine supplementation in patients treated with valproate (VPA) are not clear. Therefore, we retrospectively explored the benefits of carnitine supplementation by analyzing laboratory data.
Methods: We measured the serum-free carnitine (FC), VPA, aspartate aminotransferase, alanine aminotransferase, amylase, and ammonia levels, and the platelet count, in 69 patients with childhood-onset epilepsy treated with VPA. Eight patients had received carnitine supplementation. The serum FC and acylcarnitine levels were measured using an enzyme cycling method. We compared laboratory values between patients with and without carnitine supplementation and analyzed the correlations between serum FC levels and laboratory values.
Results: The serum FC levels were normal (median, 48.8 μmol/L; range: 41.9–68.3 μmol/L) in all eight patients with carnitine supplementation, but below normal in 32 of 61 patients without supplementation. The median serum amylase levels were lower in the patients with carnitine supplementation (median, 48 U/L; range: 27–149 U/L) than in those without (median, 7 U/L; range: 14–234 U/L). The platelet count and serum ammonia levels did not differ significantly between patients with and without supplementation. There was no significant correlation between the serum FC level and the platelet count, serum amylase level, or ammonia level.
Conclusions: Carnitine supplementation helps maintain serum FC levels in patients treated with VPA. The lower serum amylase levels in patients with carnitine supplementation may reflect protective effects of carnitine against latent pancreatic injury.

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1. Introduction

Carnitine plays an important role in the mitochondrial oxidation of fatty acids; a deficiency in carnitine can cause several disorders by impairing fatty acid oxidation. Secondary carnitine deficiency has been reported following treatment with valproate (VPA), a widely used, broad-spectrum antiepileptic. Valproate depletes carnitine stores via various mechanisms [1–3]. Valproate combines with carnitine to form valproylcarnitine, which is excreted in urine. Valproylcarnitine also inhibits the membrane carnitine transporter, resulting in decreased transport of extracellular carnitine into the cell and mitochondria. Valproate reduces the tubular reabsorption of free carnitine (FC) and acylcarnitine, and the endogenous synthesis of carnitine, by blocking butyrobetaine hydroxylase.

Carnitine levels are low in patients with epilepsy treated with VPA [4–10]. Some authors have recommended monitoring carnitine levels in patients taking VPA. Carnitine supplementation may be considered in patients at risk of carnitine deficiency, such as those with epilepsy taking VPA. However, the effects of carnitine supplementation are unclear. Most patients with secondary carnitine deficiency are asymptomatic, although it can cause cardiac, hepatic, and muscle dysfunction. Thus, the benefits of carnitine supplementation may be underestimated. We retrospectively analyzed the serum carnitine levels of patients with childhood-onset epilepsy treated with VPA, and assessed the benefits of carnitine supplementation by analyzing laboratory values potentially correlated with the adverse effects of VPA.

2. Patients and methods

We retrospectively identified 87 patients with childhood-onset epilepsy treated with VPA, with or without other antiepileptics,

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who were followed up regularly at the Department of Pediatrics of Aichi Medical University Hospital in 2020. Carnitine levels were measured in 69 of the patients, and L-carnitine supplementation had been prescribed in 8 cases. Some of these patients have been reported elsewhere [11]. The diagnosis and treatment of epilepsy were determined by consensus among three pediatric neurologists (AO, SN, and HK). The epilepsy syndromes were categorized according to the International League Against Epilepsy classification [12]. Nineteen patients were classified into developmental and epileptic encephalopathy, 15 into genetic focal epilepsy, 3 into structural focal epilepsy, 30 into genetic generalized epilepsy, and 2 into structural generalized epilepsy. This study was approved by the ethics committee of Aichi Medical University Hospital. The need for informed consent was waived because we retrospectively analyzed existing data with no identifiable patient information. Furthermore, the ability to opt out was emphasized in the hospital advertisements.

The serum FC and acylcarnitine levels were measured using an enzyme-cycling method [13]. The 2018 Japanese guidelines for diagnosing and treating carnitine deficiency (http://www.jpeds.or.jp/uploads/files/20181207_shishin.pdf) define a normal serum FC level as >36 but ≤74 μmol/L. For patients in whom FC levels were measured twice or more, we analyzed the latest value. We excluded the values from the analysis when a patient had taken pivalate-conjugated antibiotics within 1 month, because FC levels are strongly influenced by pivalate-conjugated antibiotics [11,14]. Instead, we analyzed the most recent values before the use of pivalate-conjugated antibiotics in these patients.

Demographic data were obtained from medical records. We collected data on the VPA dose, serum level, and duration of VPA treatment, platelet count, and serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), amylase, and ammonia levels. In our hospital, the reference values for the platelet count, AST, ALT, amylase, and ammonia are 180–350 × 10^3/μL, 13–33 U/L, 6–30 U/L, 37–125 U/L, and 14–43 μg/dL, respectively. In this study, cognitive disorder was defined as an intelligence or development quotient below 50. The standard deviation score (SDS) for body mass index (BMI) was calculated using the Tools for Growth Evaluation of Children of the Japanese Society for Pediatric Endocrinology (http://jspe.umin.jp/medical/chart_dl.html). No standard data were obtained for patients older than 17.5 years. For these patients, the BMI-SDS was calculated using the standard data for those aged 17.5 years, because standard values are presumed to change slightly until 20 years of age. Feeding problems were defined as the need for a nasogastric tube or gastrostomy for feeding. Patients on a ketogenic diet were included together with those with feeding problems, because a skewed diet is essential in these patients.

We compared age, sex, BMI-SDS, cognitive disorder, feeding problems, VPA dose, serum VPA level, and the use of other antiepileptics between patients with and without L-carnitine supplementation using Fisher's exact probability test for categorical variables and the Mann–Whitney *U* test for numerical variables. We compared the platelet count, and serum AST, ALT, amylase, and ammonia levels using the Mann–Whitney *U* test. As mentioned later, demographic factors were significantly different between patients with and without carnitine supplementation. Thus, we also performed a matched-pair analysis by matching the age of the patients. The associations of the serum FC level with the platelet count and serum ammonia and amylase levels were analyzed using Pearson's correlation, as was the association between the serum VPA and amylase levels. A p-value <0.05 was considered statistically significant. The statistical analyses were performed using EZR ver. 1.33 (available at http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html) [15].

3. Results

Table 1 summarizes the patient characteristics. Eight of the sixty-nine patients were prescribed carnitine supplementation: six because they had carnitine deficiency (<36 μmol/L) and two who were placed on the ketogenic diet and prescribed carnitine supplementation. The L-carnitine dose was 250–1000 mg/day. The patients with carnitine supplementation were younger than those without carnitine supplementation. Cognitive disorder, feeding problems, and the use of other antiepileptics were more frequent in the patients with carnitine supplementation. The VPA dose and serum level were higher in patients with than without carnitine supplementation, whereas the duration of VPA treatment was not significantly different.

The median serum FC level was 48.8 μmol/L (range: 41.9–68.3 μmol/L) in patients with carnitine supplementation and 35.5 μmol/L (range: 14.2–60.7 μmol/L) in those without (Fig. 1).

Table 1
Patients' characteristics and serum aspartate aminotransferase and alanine aminotransferase levels.

	With carnitine supplementation (N = 8)	No carnitine supplementation (N = 61)	P value
Age (months)*	41.5 (12–88)	109 (2–240)	0.0016
Sex (M:F)	5:3	39:22	>0.99
BMI-SDS*	−0.40 (−2.61 to 1.54)	−0.24 (−5.56 to 2.36)	0.619
Epilepsy syndrome			
DEE	5	14	NA
Genetic focal epilepsy	1	14	
Structural focal epilepsy	0	3	
Genetic generalized epilepsy	1	29	
Structural generalized epilepsy	1	1	
Cognitive disorder	7 (88%)	17 (28%)	0.0020
Feeding problem	5 (63%)	4 (6.6%)	<0.001
Serum FC levels (μmol/L)*	48.8 (41.9–68.3)	35.5 (14.2–60.7)	<0.001
Dose of VPA (kg/mg/d)*	35.9 (15.4–44.4)	18.5 (7.5–51.9)	0.0026
Serum VPA levels (μg/mL)*	123 (28–178)	77 (11–147)	0.044
Duration of VPA treatment (months)*	28 (1–80)	13 (1–96)	0.177
Use of other AEDs	6 (75%)	20 (33%)	0.046
AST (U/L)*	32.5 (18–40)	22 (9–72)	0.069
ALT (U/L)*	13.5 (7–20)	12 (5–39)	0.71

BMI-SDS: standard deviation score of the body mass index, DEE: developmental and epileptic encephalopathy, FC: free carnitine, VPA: valproate, AED: antiepileptic drug, AST: aspartate aminotransferase, ALT: alanine aminotransferase, NA: not assessed.
* Values are shown as median (range).

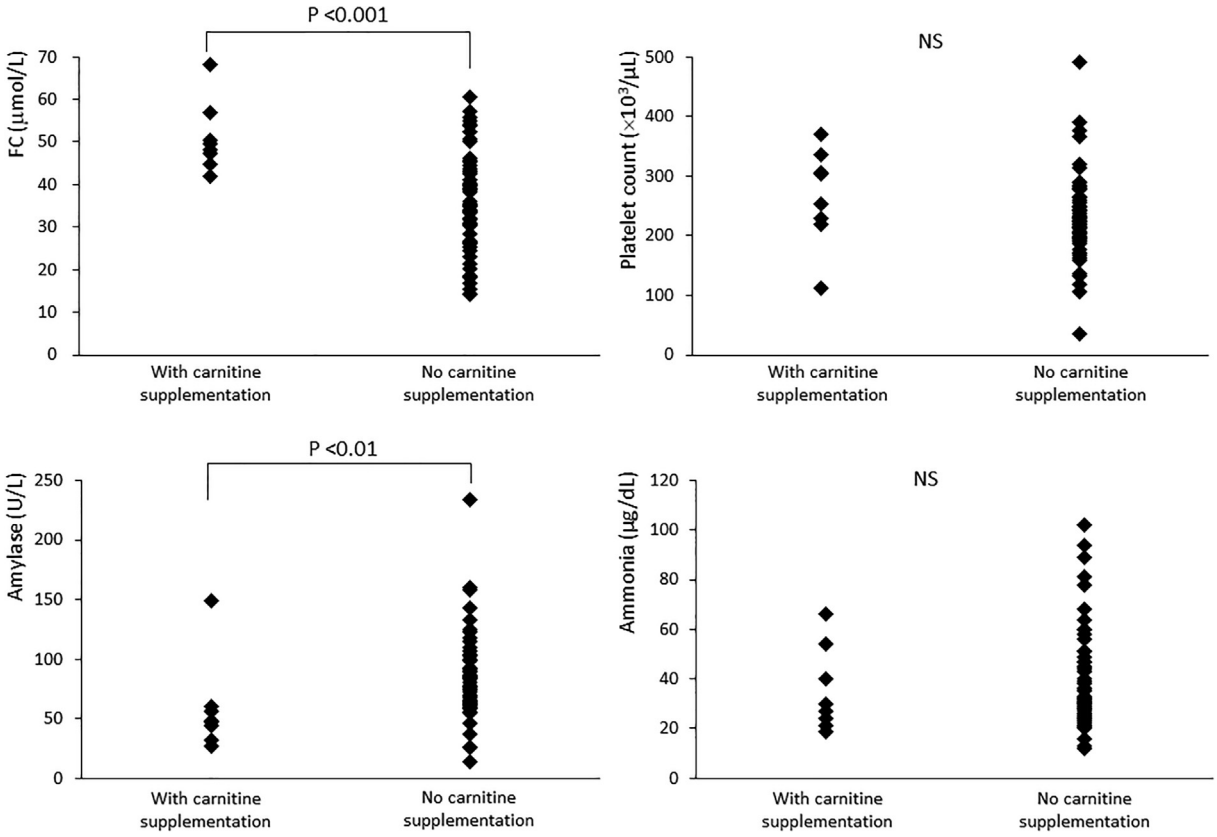

Fig. 1. Comparison of the free carnitine, amylase, and ammonia levels, and platelet count, between patients with and without carnitine supplementation. FC, free carnitine; NS, not significant.

The serum FC level was subnormal (<36 μmol/L) in 32 of the 61 (52%) patients without carnitine supplementation. The FC levels were higher in patients with carnitine supplementation than in those without ($P < 0.001$). The median platelet count did not differ significantly between the two groups (Fig. 1), at $279 \times 10^3/\mu L$ (range: $112–370 \times 10^3/\mu L$) in patients with carnitine supplementation and $223 \times 10^3/\mu L$ (range: $35–491 \times 10^3/\mu L$) in those without ($P = 0.095$). The median serum amylase level was 48 U/L (range: 27–149 U/L) in patients with carnitine supplementation and 77 U/L (range: 14–234 U/L) in those without (Fig. 1). The amylase levels were lower in patients with carnitine supplementation ($P = 0.0066$). The median ammonia level did not differ significantly between the two groups (Fig. 1), at 29 μg/dL (range: 19–66 μg/dL) and 32 μg/dL (range: 12–102 μg/dL) in patients with and without supplementation, respectively ($P = 0.47$). Any AST or ALT elevation tended to be mild. The serum AST and ALT levels did not differ significantly between the two groups (Table 1).

Fig. 2 shows the correlations of the serum FC levels with the platelet count, amylase levels, and ammonia levels. None of the correlations were significant. The serum VPA levels were not correlated with the serum amylase levels (Fig. 2). There were no symptoms suggesting pancreatitis in any patient.

Table 2 shows the results of a matched-pair analysis. By matching the age of the patients, the differences in demographic factors were resolved except for the rate of feeding problems and the duration of VPA treatment. Serum FC levels were higher in patients with carnitine supplementation than in those without. Serum amylase levels were significantly lower in patients with carnitine supplementation than in those without, whereas platelet count, ammonia, AST or ALT levels were not different between the two groups.

4. Discussion

Valproate has been long used as one of the most efficient antiepileptic drugs. Valproate has a broad spectrum of actions, including the regulation of ionic currents and the facilitation of GABAergic over glutamatergic transmission at pre and postsynaptic levels, resulting in modulation of neurotransmitter release and strengthened threshold for seizure activity [16]. Moreover, recent studies showed potential epigenetic and neuroprotective effects [16]. Thus, VPA is still an essential drug in epilepsy.

We investigated the effects of carnitine supplementation in patients with epilepsy treated with VPA. Serum FC levels were maintained within the normal range in patients with carnitine supplementation, while low FC levels were seen in about half of the patients without carnitine supplementation. The lower amylase levels in patients with carnitine supplementation suggest that it protects against the latent pancreatic toxicity of VPA.

In our series, carnitine supplementation was given to patients at high risk of carnitine deficiency. Therefore, the patient background differed markedly between those with and without carnitine supplementation. Cognitive disorder, feeding problems, and the use of other antiepileptic drugs were more frequent, and the VPA dose and serum level were higher in patients with carnitine supplementation. We additionally performed a matched-pair analysis. After matching the age of the patients, the results of statistical analysis were not altered, although the bias of demographic factors was resolved except for the rate of feeding problems and the duration of VPA treatment. Previously, we revealed that a low BMI and cognitive disorders were related to a low FC in patients with epilepsy [4], even if they were not treated with VPA. In this study, the serum FC levels were normal in the patients with carnitine supplementa-

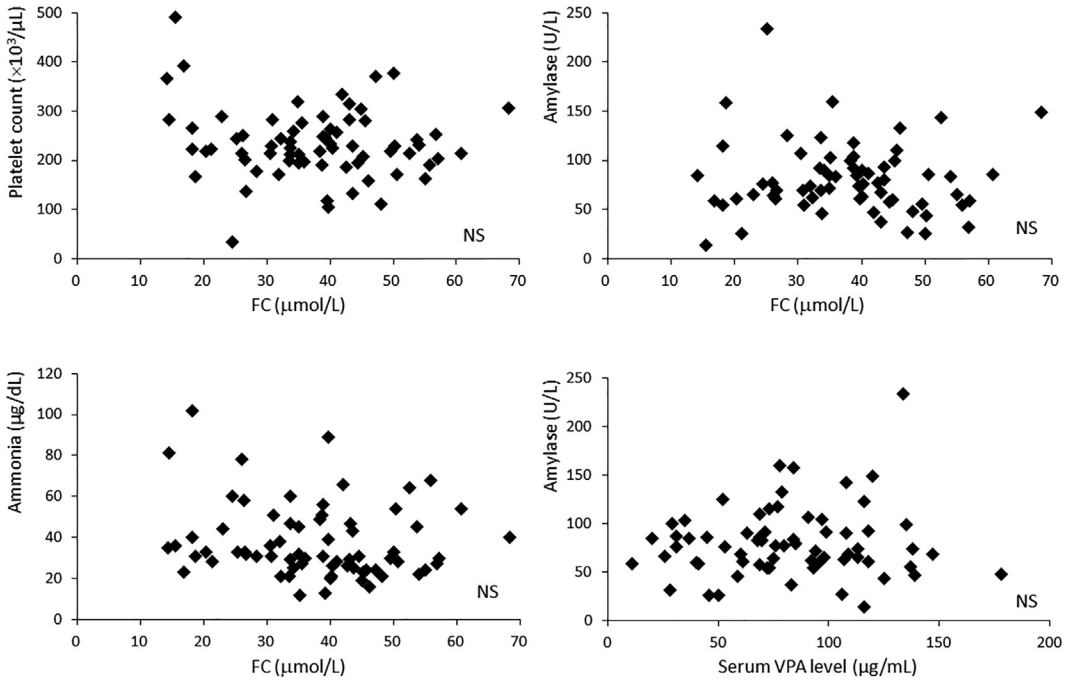

Fig. 2. Correlations between laboratory values. FC, free carnitine; NS, not significant; VPA, valproate.

Table 2
Matched pair analysis.

	With carnitine supplementation ($N = 8$)	No carnitine supplementation ($N = 8$)	*P* value
Age (months)*	41.5 (12–88)	40.5 (15–90)	0.958
Sex (M:F)	5:3	7:1	0.569
BMI-SDS*	−0.40 (−2.61 to 1.54)	0.13 (−1.30 to 2.36)	0.279
Epilepsy syndrome			
DEE	5	5	NA
Genetic focal epilepsy	1	1	
Structural focal epilepsy	0	0	
Genetic generalized epilepsy	1	2	
Structural generalized epilepsy	1	0	
Cognitive disorder	7 (88%)	3 (38%)	0.119
Feeding problem	5 (63%)	0	0.026
Serum FC levels (μmol/L)*	48.8 (41.9–68.3)	36.6 (14.2–43.5)	<0.001
Dose of VPA (kg/mg/d)*	35.9 (15.4–44.4)	30.9 (25.0–41.7)	0.462
Serum VPA levels (μg/mL)*	123 (28–178)	90.5 (37–135)	0.234
Duration of VPA treatment (months)*	28 (1–80)	5.5 (2–16)	0.027
Use of other AEDs	6 (75%)	3 (38%)	0.315
Platelet count (×10³/μL)*	278.5 (112–313)	269 (133–367)	0.916
Amylase (U/L)*	47.5 (27–149)	84.5 (37–104)	0.049
Ammonia (μg/dL)*	28.5 (19–66)	43.5 (32–56)	0.161
AST (U/L)*	32.5 (18–40)	28.5 (20–56)	0.958
ALT (U/L)*	13.5 (7–20)	12 (9–35)	0.833

BMI-SDS: standard deviation score of the body mass index, DEE: developmental and epileptic encephalopathy, FC: free carnitine, VPA: valproate, AED: antiepileptic drug, AST: aspartate aminotransferase, ALT: alanine aminotransferase, NA: not assessed.
* Values are shown as median (range).

tion, but below normal in about half of those without carnitine supplementation. Although a low serum FC level is not always associated with adverse events, carnitine deficiency may cause serious disorders, such as hyperammonemic encephalopathy [17,18] and hypoglycemia [19,20]. Monitoring serum FC levels should be considered in patients with epilepsy treated with VPA.

Valproate is one of the most common causes of drug-induced pancreatitis [21]. Since the first report by Batalden et al. [22], there have been several reports of VPA-associated pancreatitis have been reported [23–26]. In a study of the clinical features of 22 patients with VPA-induced pancreatitis, Werlin and Fish reported that VPA-associated pancreatitis does not depend on serum VPA levels, as seen here, and may occur at any time after starting therapy [27]. Moreover, an elevated serum amylase level without pancreatitis is observed in some patients receiving VPA [28,29]. However, no studies have examined the relationship between the serum FC and amylase levels in patients receiving VPA. In our series, the serum amylase levels were lower in patients with than without carnitine supplementation, suggesting that carnitine supplementation reduces serum amylase levels. However, the pathogenesis of pancreatitis and asymptomatic elevation of serum amylase levels are not understood. Although there have been no experimental or clinical studies of the role of carnitine in VPA-induced pancreatitis, some experimental studies of pancreatitis associated with dif-

ferent agents have shown the beneficial effects of carnitine [30–33]. These studies suggested protective effects of carnitine against tissue degeneration, oxidative stress, and lipid peroxidation. Mantadakis et al. reported a rapid improvement in acute pancreatitis with intravenous administration of L-carnitine in a child with isovaleric acidemia [34]. These reports suggest that carnitine has protective effects against the pancreatic injuries caused by several different drugs and disorders. This hypothesis should be investigated experimentally and clinically.

Hyperammonemia and liver toxicity are well-known adverse effects of VPA that are presumed to be mediated, at least in part, by carnitine deficiency [18]. Carnitine supplementation should prevent, correct, or attenuate these adverse effects. Several authors have found that serum ammonia levels correlate with the VPA dose or serum level, and negatively correlate with the serum FC level [1–3]. In our study, a mild elevation of the serum ammonia level was seen only in patients without carnitine supplementation, although the correlation between serum FC and ammonia levels was not significant. This discrepancy may be explained by the lack of patients with severe hyperammonemia in this study.

Thrombocytopenia is another well-known adverse effect of VPA. Nasreddine et al. found an association between VPA and thrombocytopenia, and a negative correlation between the plasma VPA level and platelet count [35]. However, the relationship between platelet count and serum FC level in patients treated with VPA has not been sufficiently investigated, although several authors have reported that L-carnitine inhibits collagen-induced platelet aggregation and modulate oxidative stress [36,37]. Our previous study found no correlation between the platelet count and serum FC level in children with epilepsy [4]. Similarly, no significant correlation was found between the platelet count and serum FC level in this study. The pathogenesis of thrombocytopenia in patients treated with VPA will not be related to the patient's carnitine status.

This study had some limitations. First, it was a retrospective single-center study including a small number of subjects. To obtain stronger evidence, prospective multicenter studies should be performed. This study analyzed the cross-sectional data of patients treated with VPA. Serial data of patients before and after carnitine supplementation would be useful for determining its effects on clinical and laboratory data. Patients receiving carnitine supplementation were overrepresented in this study. Randomized trials are necessary to clarify the effects of carnitine supplementation in patients treated with VPA.

In summary, carnitine supplementation should help maintain serum FC levels in patients at high risk of carnitine deficiency. The lower serum amylase levels in patients with carnitine supplementation may reflect a protective effect of carnitine against latent pancreatic injury caused by VPA. Further studies are necessary to clarify the beneficial effects of carnitine in patients treated with VPA. The necessity of carnitine supplementation is unclear at present. Adverse effects of carnitine deficiency are not always obvious. Studies of latent beneficial effects of carnitine will help to determine how carnitine supplementation should be done.

5. Disclosure

None of the authors has any conflict of interest to disclose.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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