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Original article

Carnitine in severely disabled patients: Relation to anthropometric, biochemical variables, and nutritional intake

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Abstract

Background: Carnitine plays a pivotal role in a variety of cellular functions. Carnitine deficiency often occurs in severely disabled patients, especially under valproic acid administration. However, the possible causative factors underlying carnitine deficiency have not been fully identified. The present study aimed at clarifying the association of various anthropometric and biochemical variables, including dietary intake of carnitine, with carnitine levels in severely disabled patients. *Methods:* Twenty-six severely disabled patients (mean age: 14.1 years; s.d. 7.8) were enrolled. Plasma carnitine levels were evaluated by an enzyme cycling assay. Estimation of the dietary intake of carnitine was made based on dietary records over a 3-day period. *Results:* Plasma total and free carnitine levels in patients were significantly lower than those in controls obtained from the previous report. However, the ratios of free carnitine to total carnitine did not change significantly. Free carnitine levels were well correlated with a nutritional intake of carnitine. Administration of not only valproic acid but also other anti-epileptic drugs was found to cause a significant decrease of free carnitine levels after adjusting the nutritional intake of carnitine. Among various anthropometric or biochemical variables, albumin and uric acid showed a significant correlation with free carnitine levels. *Conclusions:* Physicians should be aware of the fact that severely disabled patients are at risk for carnitine deficiency even in the absence of valproic acid administration, and pay more attention to the nutritional intake of carnitine.

Keywords: Carnitine; Disabled patients; Valproic acid; Dietary intake; Anthropometric measures; Biochemical variables

1. Introduction

Undernutrition or malnutrition is one of the serious problems in severely disabled patients [1,2]. Since these conditions may increase the risk of nutrition-related morbidity and mortality, it is necessary to carefully observe and, if necessary, intervene in the diets of patients [3]. With respect to the causative mechanisms underlying undernutrition or malnutrition, several factors including inappropriate dietary intake, oral motor dysfunction, increased nutrient losses and abnormal energy expenditure have been postulated [1]. Although oral feeding is preferable to tube or parenteral feeding at every clinical setting, oral intake is sometimes hampered in these patients because of their difficulty in chewing and swallowing or expressing their hunger or food preferences [1]. Consequently, tube feedings of

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enteral formula through different routes must sometimes be used [2,3]. During chronic tube feedings, especially in children, patients tend to suffer from selected nutrient deficiencies [4,5].

Carnitine (β-hydroxy-γ-N-trimethylaminobutyric acid) is one of the micronutrients that plays an important role in a variety of intracellular functions [6,7]. In humans, 75% of carnitine is thought to be obtained from the diet. The remaining 25% is synthesized endogenously from lysine and methionine mainly in the liver and kidney [7]. Secondary carnitine deficiency can be observed in various clinical situations, including inherited metabolic disorders, insufficient dietary intake, liver cirrhosis, hemo- or peritoneal dialysis and pharmacological therapy [7,8]. Among drug-induced causes, carnitine deficiency caused by valproic acid (VPA) is relatively common. Therefore, the prevalence and the mechanism of carnitine deficiency by VPA have been particularly well investigated [8–10]. Several hypotheses, i.e., increase of excretion in the form of valproylcarnitine, inhibition of tubular reabsorption, reduction of endogenous synthesis, and inhibition of the membrane carnitine transporter by valproylcarnitine, have been presented to explain the underlying mechanisms [8]. However, studies specifically targeting the association of clinical factors, including those considering the dietary intake of carnitine, are limited [11]. This fact led us to examine the relation of anthropometric, biochemical and nutritional factors to carnitine deficiency in severely disabled patients.

Table 1
Patient characteristics.

Total number	26
Gender	
Male	15
Female	11
Age (years)	
Mean [s.d.]	14.1 [7.8]
0–5	3
6–10	4
11–15	5
16–20	6
21–25	5
26∼	3
Diagnosis	
Perinatal abnormalities	10
Malformation syndromes	7
Epilepsy	2
Post-head trauma	2
Hypoxia	2
Others	3
Nutritional method	
Food only	15
Formula only	9
Both	2
Anti-convulsants	
VPA+*	10
VPA-AED+**	8
None	8

* Use of valproic acid (VPA) as a single drug or with other antiepileptic drugs (AED).
** Use of AED (carbamazepine, clobazam, or lamotrigine) without use of VPA.

2. Materials and methods

2.1. Study population

Twenty-six severely disabled patients admitted to Todaiji Medical and Education Center during April and September 2012 were enrolled. This facility specializes in the care and treatment of neurologically disabled patients mainly at age of less than 20 years old. The severity of disability in each patient was defined by using the Gross Motor Function Classification System [12]. Most patients had a disability level of 4 or 5. The patients had not received carnitine supplementation previously. The profiles of these patients are described in Table 1. This study was approved by both the ethical committee for epidemiological study at Nara Women's University and the ethical committee at Todaiji Medical and Education Center. Informed consent was obtained from the guardians of all patients.

2.2. Sample collection

Fasting blood samples were drawn from patients, and were immediately sent to a laboratory (Bio Medical Laboratories, Tokyo, Japan) for the measurement of plasma total carnitine, free carnitine, and acylcarnitine levels. These assays were done by an enzyme cycling assay [13]. Since it is difficult to get substantial numbers of samples from healthy children from ethical reasons at present in Japan, we used the data obtained from the previous report that measured carnitine levels by the same method, an enzyme cycling assay [14]. At the same time, the resting blood samples of the patients were used for evaluating the following biochemical variables: C reactive protein (CRP), creatinine, uric acid, glucose, HbA_1C, albumin, transthyretin, retinol-binding protein, and N-terminal pro-B-type natriuretic peptide (pro-BNP). At the time of blood sampling, patients had been free from any symptoms over the previous week, and their CRP values were less than 1.0 mg/dL in order to minimize the effect of inflammation.

2.3. Anthropometric measurement

Body height and weight were routinely measured by well-trained nurses at this facility. Spine height was measured to the nearest 0.1 cm, and weight was measured to the nearest 0.1 kg. Since most patients had severe spinal curvatures, their height was measured by the two split method, in which the whole body is divided into two

parts, i.e., from the top of the head to the greater trochanter, and from the greater trochanter to the planta [15]. The body mass index (BMI) was calculated by dividing the weight (kg) by the square of the height (m). BMI *z*-scores were estimated by the WHO standards [16,17]. The measurements of arm circumference (AC) and triceps skin folds (TSF) were done by a single well trained dietitian (YH) using a caliber method. Based on these values, arm muscle circumference (AMC) and arm muscle area (AMA) were calculated by the equation of Heymsfield et al. [18]. The mean of measures by both arms was recorded.

2.4. Total carnitine intake

Either the nurses at the ward or patients' guardians kept dietary records for a 3-day period over the previous two weeks of the blood sampling. The intake of carnitine was calculated based on the report of carnitine contents by Lee [19]. This report was utilized because the 149 Korean food items described in the report are quite common in the Japanese diet. Since several foods taken by the patients were not listed, we roughly estimated the carnitine content of these foods by extrapolation from similar foods in this report. The enteral formula used at this facility did not contain any carnitine.

2.5. Statistics

The comparisons of carnitine values among different groups were done by Student *t*-test. The difference in gender distribution of the patients and previously reported controls [14] was evaluated by Chi-square test. The comparison of free carnitine levels in relation to use of anti-epileptic drugs was done by the regression analysis after adjusting the nutritional intake of carnitine. The correlation of free carnitine and various anthropometric or biochemical variables was evaluated by Spearman's rank correlation test. All statistical analyses were carried out using the SPSS version 19.0 (IBM, Tokyo, Japan). *p* Values less than 0.05 were considered to be statistically significant.

3. Results

3.1. Comparison of carnitine levels between patients and controls

As indicated in Table 2, the levels of plasma total and free carnitine were significantly lower in patients than those reported in controls of the previous study [14]. However, the ratios of free carnitine to total carnitine were maintained. Since the total and free carnitine levels were well correlated by Spearman's rank correlation test [coefficient = 0.98, $p < 0.001$], a further analysis was made using only free carnitine levels.

Table 2
Comparison of total, free, and free/total carnitine levels between the patient and control groups.

	Patients	Controls[#]	*p* Values
Total number	26	45	
Age (year)	14.1 [7.8][†]	11.8 [2.6]	0.073[*]
Gender (male:female)	15:11	19:26	0.21[**]
Total carnitine (μM/L)	33.1 [14.7]	57.7 [12.1]	<0.001[*]
Free carnitine (μM/L)	26.9 [12.1]	44.4 [9.9]	<0.001[*]
Free/total carnitine	0.80 [0.06]	0.78 [0.07]	0.21[*]

[#] Control values were obtained from the Ref. [14].
[†] Mean values and s.d. (square bracket) are shown.
[*] Student *t*-test.
[**] Chi-square test.

3.2. Comparison of free carnitine levels in relation to nutritional methods

Fig. 1 demonstrates the good correlation between free carnitine levels and the nutritional intake of carnitine in all patients [coefficient = 0.63, $p < 0.01$]. The patients were divided into three groups based on the nutritional methods, i.e., food intake only, formula intake only, and both. The patients with food intake only exhibited significantly higher free carnitine levels than those with formula intake only (Fig. 2).

3.3. Comparison of free carnitine levels in relation to use of anti-epileptic drugs (AEDs)

The patients were divided into three groups based on their use of AEDs, i.e., (i) a VPA+ group, in which VPA was used alone or with other AEDs; (ii) a VPA-AED+ group, in which either carbamazepine, clobazam, or lamotrigine was used as mono-therapy or multi-therapy without VPA; and (iii) an AED- group, in which AEDs,

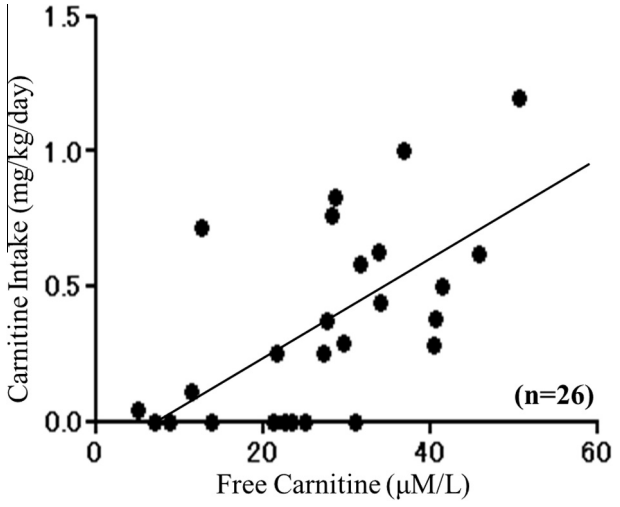

Fig. 1. Correlation of plasma free carnitine levels and nutritional carnitine intake.

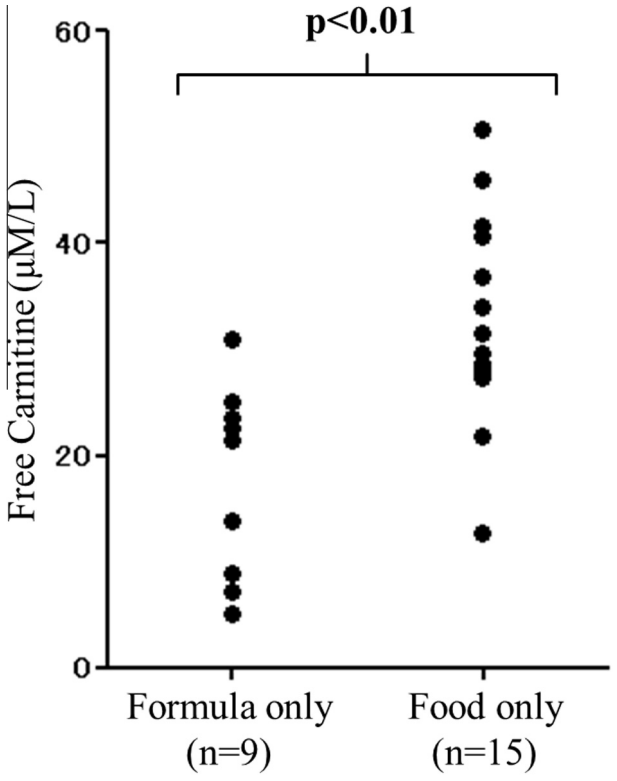

Fig. 2. Comparison of plasma free carnitine levels between formula only and food only patients.

including VPA, were not used. After adjusting the nutritional intake carnitine, the VPA+ and VPA-AED+ groups showed significantly lower free carnitine levels than the AED- group. However, the difference in the free carnitine level between the VPA+ and VPA-AED+ groups was not significant (Table 3).

3.4. Correlations of free carnitine levels with various anthropometric or biochemical variables

In our investigation of the correlation between free carnitine levels and various anthropometric or biochemical variables, albumin and uric acid were significantly associated with the free carnitine level (Table 4). In addition, AMA levels were found to be weakly correlated with the free carnitine levels, but the correlation was not statistically significant ($0.05 < p < 0.1$).

Table 4
Correlation between serum free carnitine levels and anthropometric or biochemical variables.

Variables	Coefficient (r)*	p Values
Anthropometric variables		
Body weight (z-scores)	0.041	0.85
BMI (z-scores)	−0.017	0.91
Arm circumference	0.17	0.41
Triceps skinfolds	−0.043	0.84
Arm muscle circumference	0.27	0.17
Arm muscle area	0.38	0.075
Biochemical variables		
NH3	−0.27	0.39
Albumin	0.42	0.043
Transthyretin	−0.059	0.76
Retinol-binding protein	−0.20	0.31
Uric acid	0.42	0.035
Creatinine	0.24	0.33
Glucose	−0.059	0.75
HbA_1C	0.19	0.36
Pro-BNP**	−0.23	0.25

* Spearman's rank correlation test.
** N-terminal pro-B-type natriuretic peptide.

Table 5
Comparison of total, free, and free/total carnitine levels between before and after L-carnitine administration in patients with initial low carnitine levels ($n = 7$).

	Before	After	p Values*
Total carnitine (μM/L)	14.1 [6.1]**	60.9 [12.8]	<0.001
Free carnitine (μM/L)	11.4 [5.3]	49.8 [10.8]	<0.001
Free/total carnitine	0.81 [0.07]	0.82 [0.04]	0.84

* Paired Student t-test.
** Mean values and s.d. (square bracket) are shown.

3.5. Effects of L-carnitine on free carnitine levels in patients with low carnitine levels

For 7 patients whose total carnitine levels were less than 20 μM/L, L-carnitine (30 mg/day) was administered for 2 weeks. As indicated in Table 5, total and free

Table 3
Comparison of free carnitine levels in relation to use of anti-epileptic drugs.

Anti-convulsants*	Partial regression coefficient**	95% CI	p Values*
VPA+ (10)*** vs none (8)	−10.6	−18.1 to −3.0	0.019
VPA-AED+ (8) vs none (8)	−13.9	−23.4 to −4.3	0.0096
VPA+ and AED+ (18) vs none (8)	−10.9	−18.2 to −3.5	0.0076
VPA+ (10) vs VPA-AED+ (8)	−0.28	−9.2 to 8.6	0.47

* VPA; valproic acid, AED; anti-convulsants other than VPA.
** Regression analysis was performed after adjusting the nutritional intake of carnitine. In the analysis, the groups with use of anti-convulsants were given score 1 and the group without use of anti-convulsants was given score 0.
*** Number in parentheses indicate the number of patients.

carnitine levels were significantly restored without changing the ratio of free to total carnitine levels.

4. Discussion

Carnitine is highly associated with the production of energy in mitochondria. Carnitine in the form of acyl-derivatives, especially long chain acylcarnitine, facilitates the passage of fatty acids across the mitochondrial membrane. Transported fatty acids produce ATP through β-oxidation in the mitochondrial matrix. Short and medium-chain acetylcarnitine esters, on the other hand, play a role in removing organic acids [6,7]. Since carnitine is mainly distributed in muscles, carnitine deficiency causes cardiac manifestations (i.e., hypotension or cardiac failure) and muscle manifestations (i.e., lethargy and easy fatigability) [7]. For effective cellular functions, the maintenance of both total carnitine levels and the ratio of acylcarnitine to free carnitine is necessary.

Our present study clearly indicated that plasma total and free carnitine levels in severely disabled patients were significantly lower than those of controls in the previous literature [14], whereas the free- to total-carnitine ratio was restored. Although the studies of reference levels of plasma carnitine in healthy children were quite limited [20,21], Cavedon et al. showed by tandem mass spectrometry that mean free carnitine levels were fairly stable (around 35–37 μM/L; 95% confidence intervals, 32–40 μM/L) after 1.5 years old until adulthood [20]. In comparison with these levels, the free carnitine levels in our patients group were considered to be lower. In addition, seven patients (26.9%) fulfilled the definition of carnitine deficiency of free plasma creatinine $\leqq$20 μM/L in children [9,10]. After adjusting the nutritional intake of carnitine, we found that administration of AEDs caused significant reduction of free carnitine irrespective of VPA. The effects of AEDs other than VPA on carnitine levels are not fully understood. Coppola et al. demonstrated that 3 out of 21 patients being treated with carbamazepine suffered from carnitine deficiency [10]. On the other hand, none of the 20 patients who received oxcarbazepine or carbamazepine were reported to have carnitine deficiency [22]. Therefore, a further study on the role of AEDs other than VPA in carnitine metabolism using a larger cohort is necessary. We also showed that free carnitine levels were a function of the nutritional intake by evaluating the dietary records of subjects taken over a period of 3 days. To our knowledge, this is the first report to calculate the carnitine intake precisely from food in disabled patients, although Lennon et al. conducted an evaluation in healthy individuals [11]. Since enteral formula does not contain any or only negligible amounts of carnitine [23], the dietary intake of carnitine warrants more attention.

Nutritional assessment in children is important in clinical practice. This is particularly true in disabled patients, since inadequate nutrition may have a more profound effect, such as growth retardation or an increase of severe infections, in such cases [1,24]. There are several tools that can be used for nutritional assessment, i.e., anthropometry, blood chemistry, food/nutrition history and body composition analyses such as those by dual energy X-ray absorptiometry [25,26]. Among them, anthropometric measures such as body weight and height, including BMI, BMI *z*-scores, BMI centile, and Waterlow scores, have been the most commonly used [25–27]. Since each measure has its own advantages and disadvantages, which measure is most feasible is an issue of discussion. In the present study, we used the following anthropometric measures, i.e., weight *z*-scores, BMI *z*-scores, AC, TSF, AMC, and AMA, for evaluating the relation with plasma carnitine levels. However, we failed to detect any significant correlation with these variables. Of interest is that AMA was weakly correlated with the plasma carnitine, but not significant ($0.05 < p < 0.1$). This result may suggest the possibility that carnitine levels are associated with body muscle mass, given the report that AMA is a good indicator of body muscle mass in patients with sarcopenia [28]. This issue should be ascertained by using more patients.

Among several biochemical variables, albumin levels were found to be correlated weakly with carnitine levels. However, rapid turnover proteins (retinol-binding protein and transthyretin) did not show any correlation. Lark et al. demonstrated that serum prealbumin (transthyretin) and albumin were not effective markers for nutritional status in children with cerebral palsy [29]. Considering the half-life of these proteins, the association between albumin and carnitine in the present study may indicate the possibility that chronic undernutrition status affects the carnitine metabolism. The significant association of uric acid and carnitine found in the present study is intriguing. One possible explanation for the association is the impairment of proximal tubular function, partly due to the use of VPA [8,30]. The proximal tubule is known to play a role of re-absorption of carnitine and uric acid [31]. Second possibility is the influence of the nutritional method. In fact, Yoshikawa et al. demonstrated that significantly lower serum uric acid levels in patients with elemental enteral nutrition compared with those with non-elemental nutrition [32]. For clarifying these hypotheses, measurement of urinary excretion of carnitine and uric acid, and evaluation of purine body intake are necessary. Finally, although previous reports presented an association between carnitine deficiency and hypoglycemia [33,34], we failed to detect this phenomena as judged by blood glucose and HbA_1C.

There are several limitations in the present study. First, the number of patients enrolled in the present

study was small. In addition, since the study cohort consisted of patients with diverse disorders, their metabolic background was thought to be quite heterogeneous. Second, we did not have our own control data, thereby applying the reference values in the previous reports established by the enzyme cycling assay for comparison [14]. However, when we used other historical data obtained from a LC–MS/MS method [20,21], the fact that the carnitine levels of our patients were lower remained true. Finally, because the present study was a cross-sectional study, we only measured carnitine and the other variables once. A longitudinal study in which the variables are measured twice or more will be needed to confirm our present findings.

Despite the above, our present study provides important information. Carnitine deficiency in severely disabled patients may occur not only with administration of VPA but with administration of other AEDs and low nutritional intake of carnitine. In addition, the association of carnitine levels with biochemical variables (albumin and uric acid) provides us insight into the mechanisms of occurrence of carnitine deficiency. Therefore, when physicians care for these patients, they should be aware of these facts in order to prevent carnitine deficiency. The further knowledge of how to supplement carnitine in carnitine-deficient patients by enteral or parenteral nutrition is thought to be essential.

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