Carnitinuria in rickets due to vitamin D deficiency

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In this study, we measured the serum-urine total carnitine levels and PTH levels before and after treatment in 18 patients with nutritional rickets. The urine and blood samples were taken on the first (pretreatment) and the 15th day of the study (post-treatment). The total carnitine levels of serum and urine somples, serum PTH and serum-urine creatinine concentrations were determined. We found that the levels of carnitine excreted in the urine on the first (pre-treatment) and on the 15th day (post-treatment) were higher than the reference levels. Decrease in carnitine excretion on the 15th day seemed to be correlated with decrease in aminoaciduria at that time. The study showed a significant correlation between urinary carnitine excretion and serum PTH levels. In our study we did not find any significant difference between the serum total carnitine levels on the first (pre-treatment) and the 15th day (post-treatment), and both values were lower than the reference values for the same age group. We observed that the total serum carnitine levels did not change on the 15th day of the post-treatment period in spite of a decrease in urinary carnitine excretion. The results of the present study indicated that carnitine metabolism is disturbed in nutritional rickets. Further evaluation of rickets cases and new studies will probably lead to a better understanding of carnitine metabolism in nutritional rickets.

Key words: carnitine, nutritional rickets, carnitinuria, hypocarnitinemia, cardiomyopathy.

Rickets due to vitamin D deficiency is often encountered during the period of rapid growth between three months and two years of age. In recent years rickets cases due to vitamin D deficiency with accompanying cardiomyopathy have been reported[1-3]. The exact mechanism of cardiomyopathy in these cases has not been completely understood although it has been observed that cardiomyopathy resolves completely after vitamin D and calcium replacement therapy. Carnitine, the deficiency of which causes cardiomyopathy, has an essential role in the oxidation of long chain fatty acids. It has been shown that Fanconi's syndrome is one of the causes of secondary carnitine deficiency in which the amount of carnitine excreted correlates with the severity of aminoaciduria[4,5].

The fact that aminoaciduria is also one of the main laboratory findings in rickets due to vitamin D deficiency led us to postulate that cardiomyopathy in rickets is related to increased carnitine excretion, with accompanying aminoaciduria. In this study, we aimed to clarify the carnitine status in rickets cases caused by vitamin D deficiency. For this reason, serum and urine total carnitine levels before and after treatment with vitamin D and calcium were measured.

Material and Methods

A total of 18 patients aged between four and 10 months diagnosed as having nutritional rickets according to clinical, biochemical and radiological findings were included in this study. Reasons for secondary carnitine deficiency such as renal dysfunction, hepatic problems and metabolic disorders which could cause primary carnitine deficiency were excluded. Nutritional status of the patients was evaluated according to the Gomez classification[6]. All the patients were given calcium lactate (75 mg/kg/day as elementary calcium for 10 days) and vitamin D

(300,000 units i.m. as a single dose) for treatment. Urine and blood samples were taken on the first (pre-treatment) and 15th day of the study (post-treatment). The samples were stored at -20 °C until they were assayed. Total carnitine levels in serum and urine were measured using a modified radio-enzymatic assay[7]. The serum PTH level was measured with the chemiluminescence method. Serum and urine creatinine concentrations were determined using an automated Jaffe method. The presence of aminoaciduria was evaluated by paper chromatography. Cardiomyopathy was investigated in only eight of the 16 patients before treatment by echocardiography. Informed consent was obtained from the parents before the study. Mean pre-treatment and post-treatment serum and urine carnitine levels were compared with reference values by the unpaired t-test; the relation of these values with serum PTH levels and other biochemical parameters was evaluated by linear regression analysis.

Results

The study showed that there was no significant difference between serum total carnitine levels measured on the first (pre-treatment) and the 15th day of the study (post-treatment). Both values were lower than the reference values for the same age group. The levels of carnitine excreted in the urine on the first (pre-treatment) and on the 15th day (post-treatment) were higher than the reference levels (Table I)[8]. A significant correlation between the amount of urinary carnitine excreted and serum PTH levels was found ($p = 0.003$). No findings of cardiomyopathy were detected in the eight patients who were examined by echocardiography. We detected a decrease in aminoaciduria on the 15th day of the treatment in all patients. Eight of the 16 patients were suffering from first-degree malnutrition with a body weight ranging from 76 to 90 percent of the standard; the remaining patients were of normal weight.

Discussion

Carnitine deficiency may develop due to a primary defect (e.g., carnitine transport disorders, carnitine palmitoyltransferase I and II deficiency) or to a secondary cause (e.g., Fanconi's syndrome, organic acidemias, hemodialysis, malnutrition). A relationship between the degree of aminoaciduria and that of carnitinuria in patients with Fanconi's syndrome has been reported, and it was proposed that the similarity between the mass and electrical charge of carnitine and amino acids could explain this relationship[4]. We found that the levels of carnitine excreted in the urine both on the first (pre-treatment) and on the 15th day (post-treatment) were higher than the reference levels; a significant difference between the pre- and post-treatment urine total carnitine level was also found ($p < 0.001$) (Table I). Decrease in carnitine excretion on the 15th day correlated with a decrease in aminoaciduria.

Table I. The Total Serum and Urine Carnitine, Serum Parathyroid Hormone (PTH), Serum Calcium (Ca), Serum Phosphorus (P) and Serum Alkaline Phosphatase (AP) Levels of the Patients on the First (Pre-Treatment) and on the 15th Day (Post-Treatment) of the Treatment

	1st day	15st day	Normal values	P value
Urinary carnitine (µmol/g Cr)	n = 18 370 ± 160.9 (193.9-799.5)	n = 17 207.2 ± 98.9 (86.5-460.8)	146.6 ± 91.3[6]	0.001
Serum carnitine (µmol/L)	n = 18 24.2 ± 13.3 (6.9-55.5)	n = 16 26.9 ± 12.3 (11.3-52.4)	44.5 ± 11.3[6]	NS
PTH (ng/ml)	n = 15 366.7 ± 111.5 0	n = 14 111.9 ± 44.1 0	0.2-0.7	0.04
Ca (mg/dl)	n = 18 6.7 ± 1.1 (4-8.8)	n = 17 8.9 ± 0.5 (8-10.1)	8.8-10.8	0.000
P (mg/dl)	n = 18 4.1 ± 1.4 (2.1-7.0)	n = 17 5.3 ± 0.7 (4.5-7.1)	4-7	0.003
AP (IU/L)	n = 18 987.0 ± 381.3 (618-2191)	n = 16 606.8 ± 166.5 (294-847)	200-420	0.001

* expressed as: mean ± SD, NS: not significant, Cr: creatinine.

We found a significant correlation between urinary carnitine excretion and serum PTH levels ($p = 0.003$). Previous studies have indicated that aminoaciduria in vitamin D deficiency is not related with elevated levels of PTH, but with calcium status and dietary intake of phosphate[9-11]. The obvious correlation between urinary carnitine excretion and the serum PTH level led us to hypothesize that PTH may play a role in renal carnitine loss. However, further studies should be carried out for a detailed understanding of the PTH effect on carnitinuria in nutritional rickets cases.

In this study, no significant difference between the pre- and post-treatment serum total carnitine levels was found. Both values were lower than the reference values for the same age group (Table I). Although carnitine can be synthesized by the human body, most of the daily requirement has to be gained from food. Therefore, an inadequate supply can easily lead to carnitine deficiency. Malnutrition is known to be one of the causes of low serum carnitine levels. However, we believe that carnitinuria might be an important contributing factor for the low serum carnitine level in our patients as well as malnutrition.

Previous studies have indicated that total serum carnitine level is closely related with urinary carnitine excretion and may not accurately reflect the tissue carnitine level[12]. Although the tissue carnitine level was not measured in our study, we would expect low tissue carnitine levels due to malnutrition and carnitinuria in our cases. We observed that the serum total carnitine levels did not change on the 15th day of the post-treatment period, but decreased significantly in urinary carnitine excretion in the same period. Therefore, we postulated that even though more carnitine was supplied to the blood due to decreased carnitine excretion, it was immediately withdrawn from circulation by the carnitine-depleted tissues, thereby resulting in a pre-treatment serum carnitine level similar to that seen in the post-treatment period. In conclusion, it can be expected that the serum total carnitine levels would return to normal as urinary carnitine loss decreased and malnutrition was cured completely.

In recent years, rickets cases accompanied by cardiomyopathy have been published under the heading of "rickets cardiomyopathy" in which the pathogenesis is not known[8-12]. We detected neither clinical nor echocardiographic findings of cardiomyopathy in eight rickets patients studied. The results of the present study indicate that carnitine metabolism is disturbed in nutritional rickets. However, we failed to establish a "cause and result" relationship between cardiomyopathy and disturbed carnitine metabolism in nutritional rickets. Further evaluation of rickets cases and new studies will probably lead to a better understanding of carnitine metabolism in nutritional rickets.

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