Growth and Metabolic Disturbances in a Patient with Total Parenteral Nutrition: A Case of Hypercalciuric Hypercalcemia

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Abstract. Hypercalciuria is a common side effect during total parenteral nutrition (TPN). We report a patient with long-term TPN, who demonstrated hypercalciuria, hypercalcemia and growth retardation. The patient is a six-year-old Japanese girl with Hirschsprung disease (jejunal agangliosis). Jejunostomy was performed at one-month old and since then her nutrition has depended mostly on TPN. When she was 3 years old, continuous TPN was switched to cyclic TPN (on TPN for 11 hrs and off TPN for 13 hrs). The urinary calcium level has been elevated (Ca/Cr ratio, 1.0) since 3 months of age, whereas serum calcium levels stayed within normal range for a while. The serum calcium levels started to elevate to 12–13 mg/dl when she was 3 years and 8 months old. She showed growth retardation (height SD score was $-4.2SD$ when she was 5 years and 8 months old) and deteriorated renal tubular function with renal glycosuria, elevated beta 2-microglobulin (β_2 -MG) and N-acetyl-beta-D-glucosaminidase. She was referred to our division for the investigation and treatment of growth disturbance and Ca metabolism. Her bone age was delayed (BA/CA 0.62) and serum IGF-I level was decreased but her GH response to provocation test was normal. Bilateral nephrocalcinosis was revealed by renal echogram and CT scan. By reducing calcium content in TPN solution, the serum and urinary calcium levels could be maintained within normal range and her renal function and growth velocity was improved.

Key words: Hypercalciuric hypercalcemia, Cyclic TPN, Growth retardation, PTHrP

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TOTAL parenteral nutrition (TPN) is routinely used for nutritional supplementation of children with severe digestive diseases. Hypercalciuria is a well known complication during TPN treatment. Some hypotheses as to the supposed cause of hypercalciuria are an excessive calcium or vitamin D intake and aluminum loading.

In this paper, we report a patient with long-term TPN, who demonstrated hypercalciuric hypercalcemia, nephrocalcinosis and growth retardation, which

is thought to have been the result of renal dysfunction.

Case

A 5-year-old Japanese girl was referred to our division for short stature. She was an only child of unrelated healthy parents of normal stature (father's height 178 cm, $+1.4SD$, and mother's 154 cm, $-0.8SD$). She was born at term by normal delivery (birth weight 3034 g, birth length 49.0 cm). She was diagnosed as having jejunal agangliosis on the 5th day of life and jejunostomy was performed at one-

month old. Since then her nutrition has depended mostly on total parenteral nutrition (TPN). When she was 3 years old, continuous TPN was switched to cyclic TPN to permit maximum daily activity (on TPN for 11 hrs and off TPN for 13 hrs). Total calcium intake was 1~1.5 mEq/kg/day and total calorie intake was 1000 kcal/day. Her growth retardation has been obvious since she was 4 years old, and she was referred to our division for her short stature. On admission, her height was 91.5 cm ($-4.2SD$), her weight was 13.8 kg ($-1.8SD$), and her bone age was 3 years and 4 months (J-RUS, BA/CA=62%). At that time, she was diagnosed as having hypercalcemia, hypercalciuria, mild metabolic acidosis, and renal dysfunction. Her laboratory data are shown in the Table. Peak growth hormone (GH) response to arginine test was 50.1 ng/ml, to GRF test 72.0 ng/ml, and to glucagon-propranolol test 29.0 ng/ml. Mean and peak GH levels during nocturnal sleep test were 8.0 ng/ml and 18.3 ng/ml, respectively. Urinary GH levels were extremely high. The serum level of parathyroid hormone (PTH) was not increased (c-terminal PTH was 0.3 ng/ml, intact PTH <3 pg/ml, and high sensitivity PTH 440 pg/ml). PTH related-peptide (c-terminal) was slightly increased (160 pmol/l), compared to the age-matched control level. Serum level of $1,25(OH)_2VitD$ was

significantly decreased whereas $25(OH)VitD$ and $24,25(OH)_2VitD$ were slightly increased. Abdominal echogram and CT scan revealed bilateral nephrocalcinosis. Wrist X-P showed epiphyseal calcification. The urinary calcium levels had been elevated ($Ca/Cre >0.3$) since she was 3 months old, while serum calcium levels stayed within normal range until 3 years and 8 months of age. We tried elcitonin administration (20 IU, once daily, subcutaneous injection for 3 days), but could decrease neither serum calcium levels nor urinary calcium excretion. After the reduction of calcium content in the TPN solution, the renal dysfunction and growth disturbance were improved (Figure). Her urinary Ca/Cre ratio, urinary β_2 -MG level, urinary GH excretion were decreased and serum IGF-I level was elevated to 200 ng/dl. On wrist X-ray, excessive epiphyseal calcification seemed to have decreased.

Discussion

It is reported that hypercalciuria is frequently observed during long-term TPN. The possible causes of TPN-related hypercalciuria are 1) an excessive calcium intake, especially in the case of cyclic perfusion, 2) an excessive intake of vitamin D, and 3)

Table Laboratory data

WBC 3190/ml, RBC 367×104 /ml, Hgb 10.3 mg/dl, Plt 20.0×104 ml
Ca12.0 mg/dl, Ca^{++} 1.20 mmol/l, IP 3.8 mg/dl, BUN 20.3 mg/dl, Cre 0.64 mg/dl,
TP 6.4 g/dl, Na 143 mEq/l, K 4.3 mEq/l, Cl 103 mEq/l,
GOT 36 IU/l, GPT 28 IU/l, LDH 633 IU/l, ALP 510 IU/l,
serum aluminium <10 mg/l
venous blood gas analysis: pH 7.441, PCO_2 25.8 mmHg, HCO_3 17.5 mmol/l, BE -4.7
urinary analysis:
S.G. 1.006, pH 7.0, sugar (+) protein (-), ketone body (-), OB (-)
protein 229.3 mg/day alb 27.6 mg/day, glu 482 mg/day Ccr 43.3 ml/min/1.73 m ²
Ca 156 mg/day (11.3 mg/kg/day) Ca/Cre 1.46 NAG 14.6 IU/l β_2 -MG 25520 mg/l
TSH 5.38 mIU/ml, T3 165 ng/dl, T4 9.9 μ g/dl, IGF-I 86 ng/ml (91~344)
urinary GH excretion 79700~110794 pg/mg.Cre
basal and peak GH levels in provocation tests:
Arginine test, from 9.4 to 50.1 ng/ml, GRF test, 9.3 and 72.0 ng/ml,
glucagon-propranolol test, 4.6 and 29.0 ng/ml
mean and peak GH levels during nocturnal sleep test: 8.0 and 18.3 ng/ml
c-PTH 0.3 ng/ml, intact-PTH <3 pg/ml High sensitivity-PTH 440 pg/ml,
c-PTHrP 160 pmol/l calcitonin 96 pg/ml osteocalcin 22 ng/ml
$1,25(OH)_2VitD$ <5.0 pg/ml (20~70) $24,25(OH)_2VitD$ 3.1 ng/ml (1.18 ± 0.56)
$25(OH)VitD$ 25 ng/ml (12.02 ± 6.69), vitamin A 174 IU/dl (65~276)

Fig. 1. Changes in Ca metabolism and growth

aluminum overloading [1]. In our case, the serum level of aluminum was not increased and serum levels of $1,25(\text{OH})_2\text{VitD}$ and PTH were suppressed to low levels. A number of factors in the TPN infusate, such as amino acids, calcium or glucose, may contribute to increase urinary calcium excretion, especially during cyclic TPN, because of the increased rate of nutrient infusion [2]. Many patients receiving long-term TPN have been reported to have had marked hypercalciuria and a negative calcium balance. In this case, it is possible that cyclic infusion of TPN may have caused the development of hypercalciuric hypercalcemia.

The patient's basal status, Hirschsprung disease, may participate in hypercalcemia, since it was reported that hypercalciuria with hyperoxaluria are common in children with a variety of intestinal disorders [3]. But, there was no evidence of oxaluria in this case throughout the clinical course.

The serum c-terminal PTHrP levels in our case

were increased compared to normocalcemic age-matched short children. PTHrP was originally identified in tumors associated with the syndrome of humoral hypercalcemia of malignancy. It is reported that PTHrP is synthesized in many normal tissues, such as skin, hair, smooth muscles of blood vessels and the gastrointestinal tract [4]. Recently, PTHrP has been reported to induce a relaxation of the intestinal smooth muscle, in addition to its classical calcium metabolic effects [5]. Therefore, PTHrP of intestinal origin may play a role in intestinal mobility and serum Ca levels. Though there is no report on the relation of PTHrP expression and intestinal agangliosis, the residual immobile aganglionic intestine, which is stretched by accumulated stool might be related to increases of serum PTHrP and hypercalciuric hypercalcemia.

With improvement of Ca metabolism by regulation of Ca intake in the TPN solution, the patient's serum levels of IGF-I increased to normal range and exces-

sive urinary excretion of GH were decreased significantly.

We concluded that the improvement of growth

might have been attributable to the improvement in abnormal Ca metabolism and consequent improvement in renal tubular dysfunction.

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