A Japanese Girl with Familial Hypocalciuric Hypercalcemia Discovered with Skin Nodules of Calcium Deposition: A Case Report

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Abstract A case of Familial hypocalciuric hypercalcemia (FHH) whose proband was a child and discovered with skin nodules of calcium deposition was reported. The proband was a 4-year and 8-month old Japanese girl in November 1996. A high serum thyroid-stimulating hormone (TSH) level was pointed out in a neonatal mass screening program. She was diagnosed as having congenital hypothyroidism due to an iodine transport defect, and thyroid hormone replacement therapy was started. At 1 year and 1 month old, skin nodules were noticed and diagnosed as metastatic calcinosis cutis on skin biopsy. Skin nodules in her mother were also pointed out. In view of the high serum calcium level, low urinary calcium excretion and normal serum parathyroid hormone (PTH) level, both of them were diagnosed as having FHH.

Key words: familial hypocalciuric hypercalcemia, child, skin nodules, calcium deposition

Introduction

Familial hypocalciuric hypercalcemia (FHH) is usually characterized by a high serum calcium level, relatively low urinary calcium excretion (ratio of calcium clearance to creatinine clearance $[C_{Ca}/C_{Cr}] < 0.01$), and an inappropriately normal serum parathyroid hormone (PTH) level. This disorder is inherited in an autosomal dominant manner and shows almost complete penetrance. Despite life-long hypercalcemia, the affected individuals are usually asymptomatic and do not exhibit kidney stones, renal parenchymal dam-

age, or skeletal complication (1-3). Most of probands were therefore discovered with an accidental serum calcium measurement after growing up. Although a number of FHH cases have been reported, no FHH case whose proband is a child discovered with skin nodules of calcium deposition has been reported. The present study deals with a very rare case of FHH.

Case Report

The proband was a 4-year and 8-month old Japanese girl in November 1996. A high serum thyroid-stimulating hormone (TSH) level was pointed out in a neonatal mass screening program and then the girl was admitted to the department of pediatrics of Himeji Red Cross Hospital at 44 days old. A high serum TSH level, low serum free thyroxine level and high serum

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thyroglobulin level were revealed. A normal sized and sited thyroid gland was observed on both ultrasonography and computed tomography (CT) scan, but the thyroid gland was not detected on Tc-99m scintigraphy. In view of these results, she was diagnosed as having congenital hypothyroidism due to iodine transport defect (4) and thyroid hormone replacement therapy was started. At 1 year and 1 month old, a lot of skin nodules on the abdomen and both thighs were noticed and diagnosed as metastatic calcinosis cutis with skin biopsy. Skin nodules on both hands in her mother were also pointed out. The parathyroid function of the proband and her mother was examined. Table 1 shows the laboratory data for them. A high serum calcium level of 11.3 mg/dl, a low urinary ratio of calcium to creatinine (Ca/Cr) of 0.015-0.054, and a normal serum C-terminal parathyroid hormone (PTH) level of 0.5 ng/ml (normal range: ≤ 0.5 ng/ml) were recognized in the proband. A high serum calcium level of

10.5 mg/dl, low urinary ratio of Ca/Cr of 0.03-0.059, and normal serum C-terminal PTH level of 0.3 ng/ml were recognized in her mother. A brain CT scan revealed no calcium deposition and renal ultrasonography revealed no kidney stone in the proband. These results coincided with the laboratory data for FHH. As shown in Table 2, the serum calcium level gradually normalized and has been maintained within the normal range since the proband was 2 years and 6 months old. A high serum C-terminal PTH level of 0.9-1.0 ng/ml and a high serum intact PTH level of 240-290 pg/ml (normal range: 15-30 pg/ml) have been maintained since the proband was 4 years and 1 month old, and a low urinary ratio of Ca/Cr of 0.038-0.085 and extremely low ratio of calcium clearance to creatinine clearance (C_{Ca}/C_{Cr}) of 0.001-0.003 have been maintained. Also, as shown in Table 2, thyroid function has been controlled to normal with thyroid hormone replacement therapy.

Discussion

FHH is usually characterized by life-long hypercalcemia and a paradoxically normal PTH level. In this case, the serum calcium level decreased to the normal range from 11.3 mg/dl but serum PTH inversely increased to three or four times the normal value. McMurtry *et al.* (5)

Table 1 Laboratory data on parathyroid function

		Proband	Mother
Serum Ca	(mg/dl)	11.3	10.5
Serum P	(mg/dl)	6.0	3.8
C-terminal PTH	(ng/ml)	0.5	0.3
Urinary Ca/Cr		0.054; 0.015	0.003; 0.059

Table 2 Course of laboratory data

		44d	1y3m	1y6m	1y11m	2y6m	3y5m	4y1m	4y3m	4y6m
Serum Ca	(mg/dl)	10.1	11.3	10.7	10.5	9.4	8.7	9.1	9.0	9.7
Serum P	(mg/dl)		6.0	5.8	6.6	5.3	6.4	6.1	6.7	6.4
C-terminal PTH	(ng/ml)		0.5		0.4	0.5		1.0	0.9	1.0
intact PTH	(pg/ml)							290	240	260
Urinary Ca/ Cr			0.054					0.038	0.085	0.069
C_{Ca}/C_{Cr}								0.001	0.003	0.002
%TRP									95.5	94.4
TSH	(μ U/ml)	41.1	3.6	4.3	3.1	5.9	6.1		5.7	8.5
Free-T3	(pg/ml)	3.0	5.3				3.1		3.6	3.0
Free-T4	(ng/dl)	0.89	1.70	1.45	1.38	1.66	1.15		1.18	1.07

surveyed a large kindred of FHH composed of 46 members spanning 5 generations ranging from a 1.5 to a 91-year-old and reported the effect of age on serum PTH levels and serum calcium levels. They reported that serum PTH levels were within the normal range but rapidly increased with age in both children and young adults and serum PTH levels had risen to above the normal range by approximately age 30. They also reported that serum calcium levels showed a statistically significant decline with age. But, in this report, there was no case in which the serum calcium level decreased to the normal range and the serum PTH level increased to above the normal range in childhood such as in our patient. Furthermore, there was no other report which deals with the course of the serum calcium level and serum PTH level in an FHH patient.

The gene defect in FHH is thought to disturb the ability of the parathyroid gland and kidneys to recognize or respond to changes in the extracellular Ca^{2+} concentration (1, 2, 6-8). Recently Brown *et al.* isolated a complementary DNA encoding an extracellular Ca^{2+} -sensing receptor from bovine parathyroid (9), Pollak *et al.* described three mutations in the receptor gene in FHH and neonatal severe hyperparathyroidism (NSHPT) individuals (10). One of the mutations was identified in an FHH/NSHPT family and an NSHPT member was homozygous for the mutation, whereas FHH members were heterozygous. On the other hand, Aida *et al.* (11) identified another mutation of Ca^{2+} -sensing receptor gene from an FHH family, but the proband, who was homozygous for the mutation, had a high serum calcium level with no symptom, whereas her parents, who were heterozygous, had a borderline serum calcium level. In other reports, NSHPT occurred in some families in which only one parent had clinical characteristics of FHH (12-16) or even in which both parents were normocalcemic (17, 18). These results suggest that there is a spectrum of phenotypes in FHH and NSHPT, and that our case is one phe-

notype of FHH.

Ours may be the first case of FHH complicated with congenital hypothyroidism due to iodine transport defect. The authors were not able to clarify the genetical relationship between FHH and congenital hypothyroidism due to an iodine transport defect.

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