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A Four-year-old Girl with Pit-1 Gene Mutation, Extremely Short Stature and Hypoglycemia

Takahiro Mochizuki[1], Chika Tanaka[1], Keinosuke Fujita[1], Takashi Shimizu[2] and Eiichi Kinoshita[2]

[1]*Department of Pediatrics, Osaka City General Hospital, Osaka, Japan*

[2]*Department of Pediatrics, Nagasaki University, Nagasaki, Japan*

Abstract We report a case of a 4-yr-old girl with extremely short stature 65 cm (–9.6 SD), low body weight 7.3 kg (–4.6 SD), a characteristic face and hypoglycemia. She did not have her condition diagnosed until she was 4 yr old. She visited our hospital at 4 yr of age when her family moved from Aichi Prefecture. We suspected that she has had complete GH deficiency (CGHD), because her GH value was 0.08 ng/ml at the time of hypoglycemia (BS 35 mg/dl). GRF challenge test showed a peak of GH of 0.2 ng/ml. TRH challenge test showed a peak of TSH of 1.56 IU/ml and a peak of PRL less than 0.5 ng/ml. LH-RH challenge test showed a peak of LH of 3.0 mIU/ml and a peak of FSH of 20.8 mIU/ml. CRH challenge test showed a peak of ACTH of 218 pg/ml and a peak of cortisol of 27.0 μg/dl. The pituitary gland on the brain MRI was normal in size and position. Her bone age was below 1-yr-old by TW-2 RUS. She was diagnosed as having combined pituitary hormone deficiency of GH, TSH and PRL. A common mutation of the Pit-1 gene was detected at R271W in the heterozygous state. A previous paper reported that hypoglycemia was rare in patients with PIT-1 gene mutation but this case experienced hypoglycemia, which was improved after GH and thyroid replacement therapies were started.

Key words: GH, TSH, PRL, Pit-1 gene mutation, hypoglycemia

Pituitary transcription factor-1 (Pit-1) is a prototypic member of the POU transcription factor family and plays a critical role in the pituitary-specific action of GH, PRL, and thyroid-stimulating hormone (TSH) (1). Pit-1 gene mutation shows combined pituitary hormone deficiency of GH, TSH and PRL. Common symptoms are short stature, jaundice and frontal bossing. Hypoglycemia is rare in patients with PIT-1 gene mutation.

We report the case of a 4-yr-old girl with extremly short stature, 65 cm (–9.6 SD), body weight, 7.3 kg (–4.6 SD), a characteristic face and hypoglycemia.

Correspondence: Dr. Takahiro Mochizuki, Department of Pediatrics, Osaka City General Hospital, 2-13-22 Miyakojima-hondoori, Miyakojima-ku, Osaka 534-0021, Japan
E-mail: m4601256@msic.med.osaka-cu.ac.jp

Case Report

The patient was a 4-yr-old girl whose chief complaint was short stature and hypoglycemia. She was not diagnosed until she was 4 yr old. She visited our hospital at 4 yr old when her family moved from Aichi prefecture. We suspected that she has had complete GH deficiency (CGHD), because her GH value was 0.08 ng/ml at the time of hypoglycemia (BS 35 mg/dl). The height of her father was 175 cm and that of her mother was 167 cm (Fig. 1).

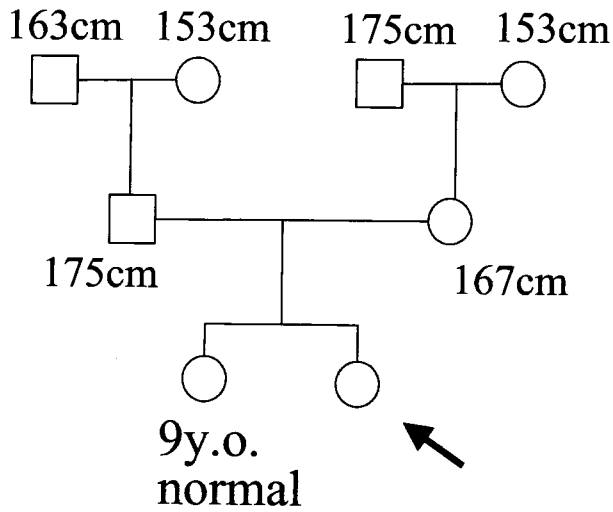

Fig. 1 Family tree.

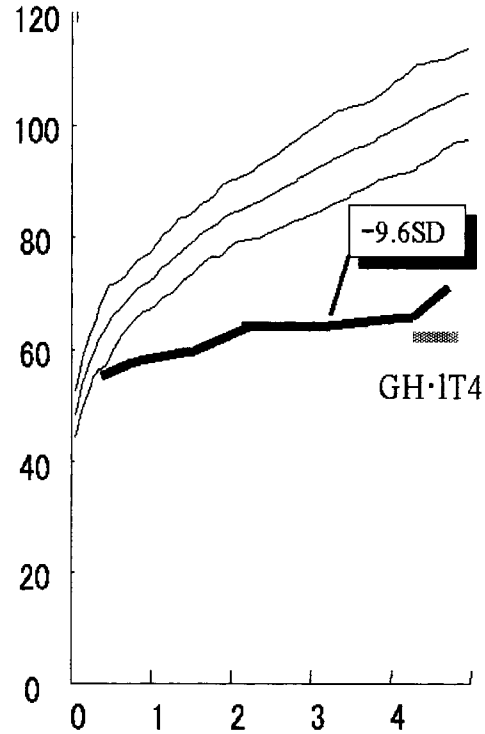

Fig. 2 Growth curve.

This patient was born at 41 wk 3 days gestation. Her Apgar score was 8/1 min. Birth weight was 3,425 g and birth height was 51 cm. She was treated by phototherapy for neonatal jaundice, but her physical development was very slow (Fig. 2). On admission the physical examination revealed that height was 65 cm (–9.6 SD), weight 7.3 kg (–4.6 SD), and there were frontal bossing and heart murmur due to pulmonic stenosis (Fig. 3). The mental test was DQ57. Laboratory studies (Table 1) revealed that the blood glucose level was 35 mg/dl, fT3 2.1 pg/ml, fT4 less than 0.4 ng/dl and TSH 1.31 IU/ml. She was examined by a quadruple loading test (GH-RH, TRH, LH-RH, CRH), had 20% glucose injected at 30 min due to hypoglycemia (Table 2). GH-RH challenge test showed a peak value of GH 0.2 ng/ml. TRH challenge test showed a peak value of TSH 1.56 IU/ml and a peak of PRL less than 0.5 ng/ml. LH-RH challenge test showed the peak values of LH and FSH of 3.0 mIU/ml and 20.8 mIU/ml, respectively. On CRH challenge test, a peak of ACTH was 218 pg/ml and a peak of cortisol 27.0 μg/dl. The anterior pituitary gland on the brain MRI was rather small in size (Fig. 4). Her bone age was below 1 year old by the TW-2 RUS method. She was diagnosed as having combined pituitary hormone deficiency of GH, TSH and PRL. Common mutation of the Pit-1 gene was detected at R271W in a heterozygous state by the PCR-RFLP analysis with a modified primer (Fig. 5, Fig. 6).

Discussion

She was diagnosed as having combined pituitary hormone deficiency of GH, TSH and PRL. Common mutation of Pit-1 gene was detected at R271W in a heterozygous state.

A previous paper reported that the hypoglycemia was rare in patients with PIT-1 gene mutation. A case of panhypopituitarism had hypoglycemia commonly due to GH and ACTH deficiency. The reason why the hypoglycemia is rare in these cases may be due to normal secretion of ACTH and cortisol. But this case had hypoglycemia. The hyopoglycemia improved after GH and thyroid replacement therapies were start.

Fig. 3 Patient's photograph at 4 years old.

Table 1

1) Labo data		TSH	1.3 IU/ml
WBC	6240 /μl	F-T4	<0.4 ng/dl
Hb	11.4 g/dl	F-T3	2.1 pg/ml
Plt	38.8×10^4 /μl	LH	<0.2 mIU/ml
Na	135 mEq/l	FSH	5.6 mIU/ml
K	4.2 mEq/l	PRL	0.5 ng/ml
Cl	101 mEq/l	ACTH	592 pg/ml
Ca	9.3 mg/dl	Cortisol	25.5 μg/dl
P	3.7 mg/dl	IGF-1	6.3 ng/ml
Tbil	1.0 mg/dl	IGFBP-3	0.28 μg/ml
AST	56 IU/l	2) Chromosome	
ALT	23 IU/l	46XX	
LDH	322 IU/l	3) Bone age	
BUN	16.0 mg/dl	1.0 yr old (TW2-RUS)	
Cre	0.4 mg/dl	1.0 yr old (Roche)	
Tcho	224 mg/dl	4) Brain MRI	
BS	50 mg/dl	pituitary rather small	
(minimum	35 mg/dl)	5) Mental test (4 yr old)	
		DQ57	

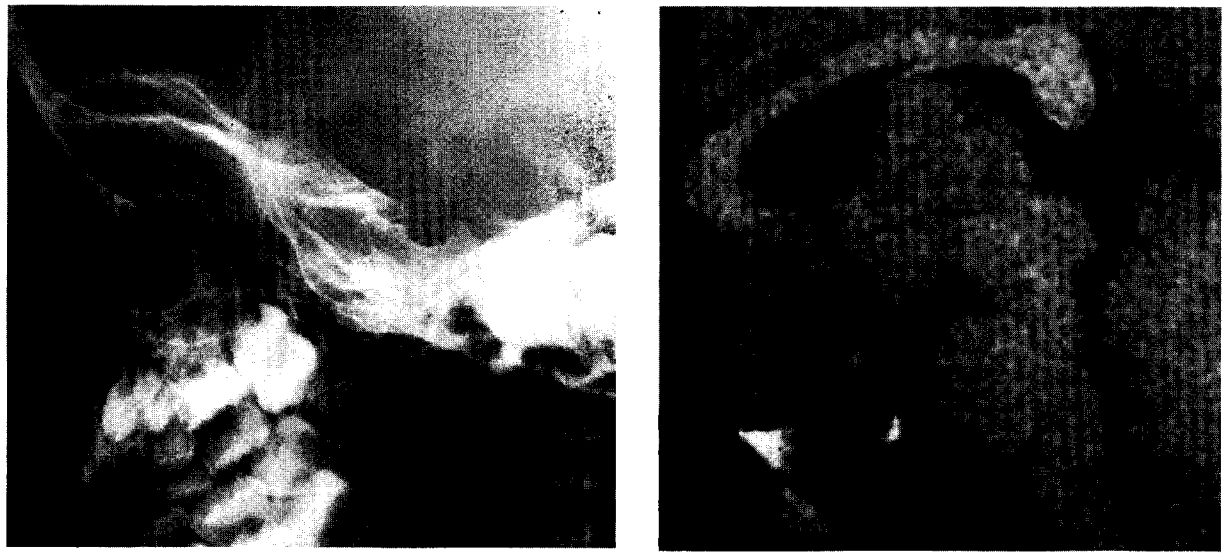

Fig. 4 Brain MRI.

Table 2 Result of quadruple loading test (GH-RH, TRH, LH-RH, CRH)

	0 min	30 min	60 min	90 min	120 min
BS	50	Low	120	91	71
GH	0.06	0.09	0.15	0.13	0.23
TSH	1.3	1.5	1.3	1.2	0.9
PRL	<0.5	<0.5	<0.5	<0.5	<0.5
LH	<0.2	3.9	3.0	2.6	2.0
FSH	5.6	20.8	20.7	18.8	17.5
ACTH	592	218	183	119	45
Cortisol	25.5	27.0	26.9	26.2	25.4

She was injected 20% glucose at 30 min due to hypogly.

Hypothyroidism is presented in the early stages of infancy. The degree of TSH secretion differs in the case by case. l-T4 substitution therapy was needed even though this was not a clear case of cretinism. Therefore we suspected that her mental retardation was mainly due to hypoglycemia but not hypothyroidism.

As for the final height, this patient is expected to reach normal final height, because she began the GH therapy at four years old.

Puberty is reported to delay a little in cases of Pit-1 gene abnormality, but adrenarche and puberty can be reached (2). Abnormality of function in pregnancy would occur in the future, because ovulation and impregnation abnormalities due to PRL deficiency have been reported (2). It is assumed that it is possible to give birth to a healthy child if the pregnancy is approved. But it is thought that agalactosis will be caused in the puerperal period (2).

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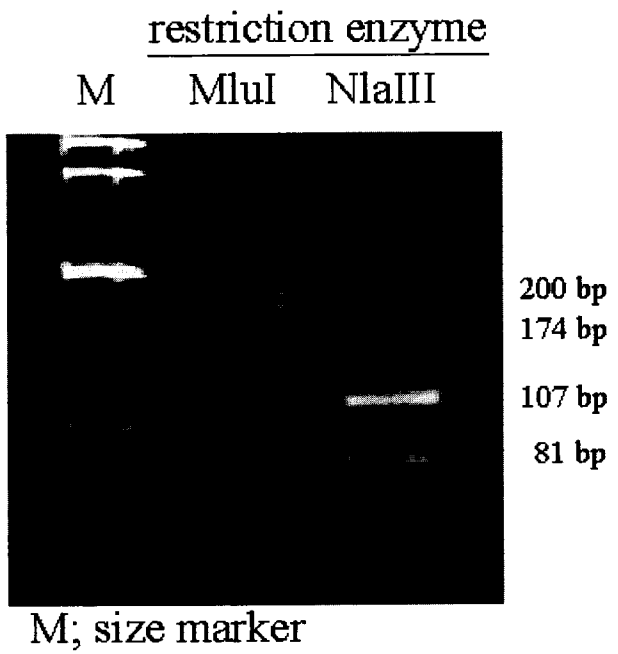

Fig. 5 DNA sequence analysis of PIT-1 gene at R271W in a heterozygous state

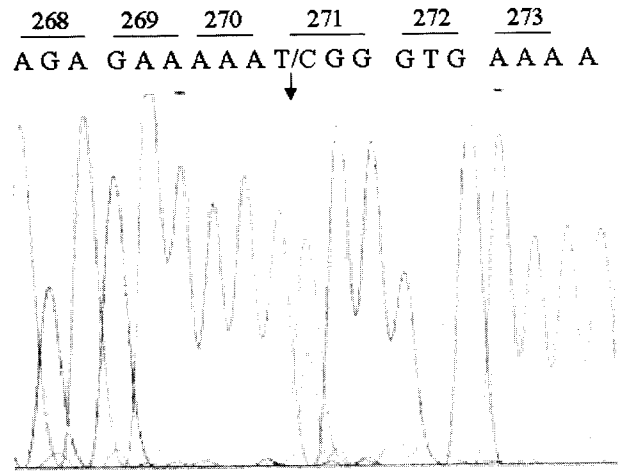

Fig. 6 PCR-RFLP by modified primer analysis of PIT-1 gene at R271W in a heterozygous state. MluI digestion: mutant allele 200 bp, wild allele 174bp and 26 bp. NlaIII digestion: wild allele 107 bp, mutant allele 81bp and cermia 26 bp.

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