Case Report

20p11.23-p11.21 deletion in a child with hyperinsulinemic hypoglycemia and GH deficiency: A case report

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Abstract. Some neonatal hypoglycemias have genetic origins. For instance, mutation in forkhead box protein A2 (*FOXA2*), located on chromosome 20p11.21, has recently been reported to cause hyperinsulinemic hypoglycemia and hypopituitarism. Here, we report a case of hyperinsulinemic hypoglycemia and GH deficiency (GHD) with 20p11.23-p11.21 deletion, which included *FOXA2*. The boy was diagnosed with hyperinsulinemic hypoglycemia during the neonatal period and subsequently administered diazoxide for treatment. His blood glucose levels gradually stabilized, and the diazoxide dosage was slowly reduced and ultimately fully weaned. The patient was discharged at the age of 29 d. Unfortunately, the patient experienced recurrent hypoglycemia at 3 mo, and diazoxide administration was re-initiated. Further examination, including chromosomal microarray analysis, revealed a 2.48-Mb 20p11.23-p11.21 deletion that encompassed *FOXA2*. In addition, severe GHD was detected, and magnetic resonance imaging of the brain revealed pituitary stalk interruption. Accordingly, GH replacement therapy was started at 0.175 mg/kg/wk, and blood glucose levels were stabilized. Our report suggests that there are pathological conditions that can cause both hyperinsulinemic hypoglycemia and hypopituitarism and reaffirms the importance of evaluating not only insulin and congenital metabolic disorders but also pituitary function in patients with hypoglycemia.

Key words: *FOXA2*, hyperinsulinemic hypoglycemia, GH deficiency, 20p deletion

Introduction

There is a wide variety of diseases in the neonatal period that may cause hypoglycemia. Congenital causes of hypoglycemia include hyperinsulinemia and hypopituitarism (1). Although there are several reports of hypopituitarism with deletions of chromosome 20p, the cause of hyperinsulinemic hypoglycemia and hypopituitarism remains unknown (2). In recent years, mutations in forkhead box protein A2 (*FOXA2*) have been reported in cases of hyperinsulinemic hypoglycemia and hypopituitarism (3). In the present report, we describe a case of hyperinsulinemic hypoglycemia and GH deficiency (GHD) with deletion of 20p11.23-p11.21, which included *FOXA2*.

Case Report

A Japanese boy with healthy non-consanguineous parents was delivered at 39 wk of gestation by emergency cesarean section due to arrest of labor. No fetal distress was observed. The birth height and weight of the newborn were 53.5 cm [+ 2.59 standard deviation (SD)] and 4762 g (+ 4.25 SD) with an Apgar score of 9/10. At 1 h of life, hypoglycemia (11 mg/dL) was detected without symptoms. Despite the initiation of intravenous dextrose, the neonate had persistent hypoglycemia.

The boy was transferred to our neonatal intensive care unit on the first day of life and managed with intravenous dextrose at a glucose infusion ratio (GIR) of 4–6 mg/kg/min. After initial treatment, he experienced recurrent hypoglycemia and required higher GIR (maximum 12.5 mg/kg/min) to maintain euglycemia. A diagnosis of hyperinsulinemic hypoglycemia was made based on critical samples at the time of hypoglycemia on the first day of life (**Table 1**) in accordance with the clinical practice guidelines for congenital hyperinsulinism of The Japanese Society for Pediatric Endocrinology (4). Diazoxide treatment was initiated at 8 mg/kg/d on the first day of life. His blood glucose levels gradually stabilized; therefore, glucose infusion and diazoxide dosage were gradually decreased on day 10 and then

Table 1. Laboratory findings at the time of hypoglycemia on the first day of life

Complete blood count		Blood chemistry test		Blood chemistry test	
WBC	14,600/μL	TP	6.2 g/dlL	IRI	3.3 μIU/mL
Hb	13.4 g/dL	Alb	3.8 g/dL	TKB	10 μmol/L
Hct	42.1%	AST	23 IU/L	AcAc	7 μmol/L
Plt	18.5×10^4/μL	ALT	9 IU/L	3-OHBA	3 μmol/L
		BUN	5 mg/dL	FFA	0.04 mmol/L
		Cre	0.7 mg/dL	IGF-1	8 ng/ml
		Na	142 mEq/L	TSH	1.60 μIU/mL
		K	4.7 mEq/L	FT_3	3.46 pg/mL
		Cl	108 mEq/L	FT_4	1.21 ng/dL
		Ca	10.3 mg/dL	ACTH	27.5 pg/mL
		P	4.8 mg/dL	Cortisol	16.3 μg/dL
		Glu	39 mg/dL		
		NH_3	35 mg/dL		

WBC, white blood cell; Hb, hemoglobin; Hct, hematocrit; Plt, platelets; TP, total protein; Alb, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; Na, sodium; K, potassium; Cl, chloride; Ca, calcium; P, phosphorus; Glu, glucose; NH_3, ammonia; IRI, immune reactive insulin; TKB, total ketone body; AcAc, acetoacetic acid; 3-OHBA, 3-Hydroxybutyric acid; FFA, free fatty acid; FT_3, free triiodothyronine; FT_4, free thyroxine.

weaned off on the 20th day of life. Blood glucose levels remained at 60–70 mg/dL without diazoxide, and he was discharged on the 20th day of life. During hospitalization, there were no findings suggestive of cholestasis. He was treated with phototherapy for jaundice on day 7, which was subsequently resolved. There were no special findings on the physical examination. Genetic testing for congenital hyperinsulinism was performed after obtaining informed consent, wherein all coding exons of *ABCC8* and *KCNJ11* were amplified by polymerase chain reaction and directly sequenced. The results revealed no pathogenic sequences.

The child experienced recurrent hypoglycemia at 3 mo of age. Blood test results were as follows: blood glucose, 47 mg/dL; insulin, 2.1 μIU/mL; IGF-1, 16 ng/mL; TSH, 0.743 μIU/mL; free T_3, 3.39 pg/mL; and free T_4, 1.36 ng/dL. Diazoxide treatment was initiated. The patient was not hypoglycemic, especially during the morning fasting. Convulsion and disturbance of consciousness were not observed. However, hypoglycemia occurred particularly when the patient remained fasting in the morning. Even after restarting diazoxide, the patient was inactive in the morning and blood glucose levels were unstable. Therefore, diazoxide was increased to 15 mg/kg/d. Cornstarch and frequent meals were started as a medical nutrition therapy. Despite the introduction of these treatments, hyperinsulinemic hypoglycemia persisted. We suspected the possibility of syndromic persistent hyperinsulinemic hypoglycemia and consulted a medical geneticist for additional genetic analysis. Peripheral blood samples were collected, and DNA was extracted. Array comparative genome hybridization (CGH) was performed after obtaining informed consent using the SurePrint G3 Human CGH 4 × 180 K Microarray kit (Agilent Technologies, Santa Clara, CA, USA) according to the manufacturer's instructions.

The data were analyzed using the Agilent Cytogenomics software (ver 2.9) and the UCSC genome browser (http://genome.ucsc.edu). Chromosomal microarray analysis revealed a 2.48-Mb deletion of chromosome 20p11.23-p11.21, which encompassed *FOXA2* (**Fig. 1**).

A combined pituitary stimulation test was performed to evaluate pituitary function at 1 yr 8 mo because his growth rate declined after 11 mo of age, and hypopituitarism with deletion of chromosome 20p11 has been reported (2). GH stimulation tests revealed severe GHD (**Table 2**). Magnetic resonance imaging of the brain revealed an ectopic posterior pituitary and pituitary stalk interruption (**Fig. 2**). Based on these results, GH replacement therapy was initiated at 0.175 mg/kg/wk. At this time, his physical appearance was characterized by a broad forehead and saddle nose that were not clear at birth. After GH replacement therapy, blood glucose levels were approximately 70 mg/dL in the morning fasting period, and his previously noted inactivity resolved.

At 6 yr and 4 mo of age, diazoxide was decreased to 5 mg/kg/d (previously, the maximum dosage was 15 mg/kg/d). The patient exhibited no side effects owing to the treatment. A combined pituitary stimulation test has been performed each year, and no central hypothyroidism or central adrenal dysfunction has been revealed. His developmental stage was age-equivalent and normal. Informed consent for publication of this case was obtained from the patient's mother because the patient was underaged.

Discussion

The present case exhibited hypoglycemia due to congenital hyperinsulinism and GHD. Most previous reports of deletions involving the proximal 20p are
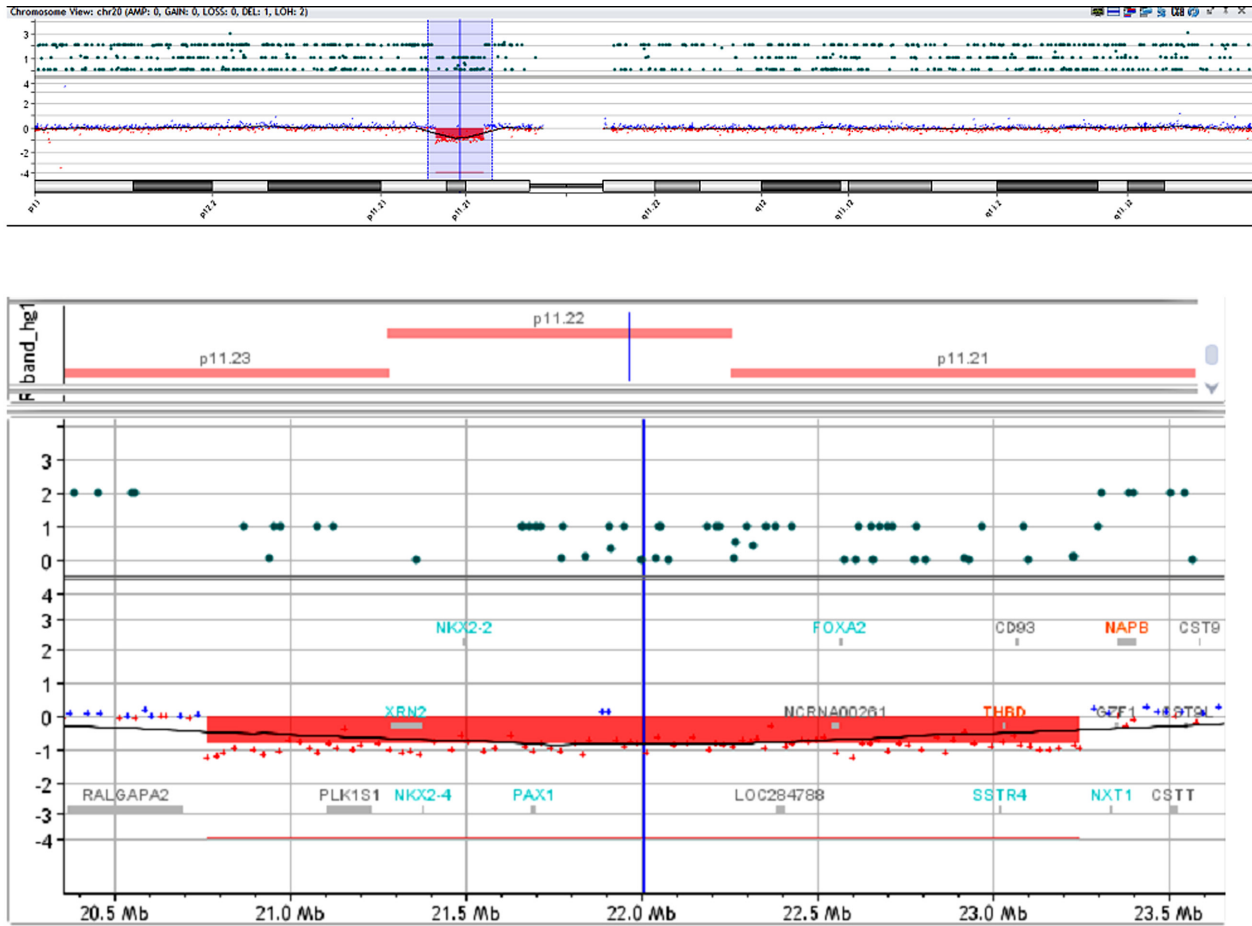
Fig. 1. Chromosomal microarray analysis of the patient in the current case report.

Table 2. TRH/CRH/LHRH/GH provocation tests

Test		0 min	30 min	60 min	90 min	120 min
TRH test	TSH (µIU/mL)	1.027	9.778	6.931	4.438	2.95
	PRL (ng/mL)	5.8	11.52	9.5	7.59	6.76
CRH test	ACTH (pg/mL)	17.1	47.2	28	20.2	19.1
	Cortisol (µg/dL)	13.6	22.7	20.3	14.7	13.8
LHRH test	LH (mIU/mL)	< 0.1	1.96	2.03	1.95	1.75
	FSH (mIU/mL)	1.5	4.14	6.47	7.14	7.45
L-dopa test	GH (ng/ml)	0.63	0.59	0.73	N/A	N/A
Clonidine test	GH (ng/ml)	0.68	0.57	0.73	N/A	N/A

LHRH, luteinizing hormone-releasing hormone; L-dopa, L-dioxyphenylalanine. L-dopa and clonidine tests were discontinued because of severe hypoglycemia.

associated with Alagille syndrome, which causes hereditary intrahepatic cholestasis due to the *JAG1* mutation. Recently, several cases of proximal 20p11 deletions have been reported, and most cases have been associated with pituitary hormone deficiencies (2, 5–7). Giri *et al.* have indicated that *FOXA2*, located at 20p11.21, is implicated in the pathogenesis of both hyperinsulinism and hypopituitarism (8). Foxa2 is a transcription factor that regulates the expression of genes involved in the regulation of insulin secretion,

such as *ABCC8* and *KCNJ11*, which encode the SUR1 and Kir6.2 subunits of the adenosine triphosphate-sensitive potassium channel in pancreatic β-cells (9). Loss-of-function mutations in these genes result in congenital hyperinsulinism (10). Although only proven in mice, Foxa2 controls the expression of several genes related to the morphogenesis of the central nervous system, including *Gli2*, *SHH*, and Nkx2-2. Therefore, the hyperinsulinemic hypoglycemia and hypopituitarism observed in this case were hypothesized to be due to the
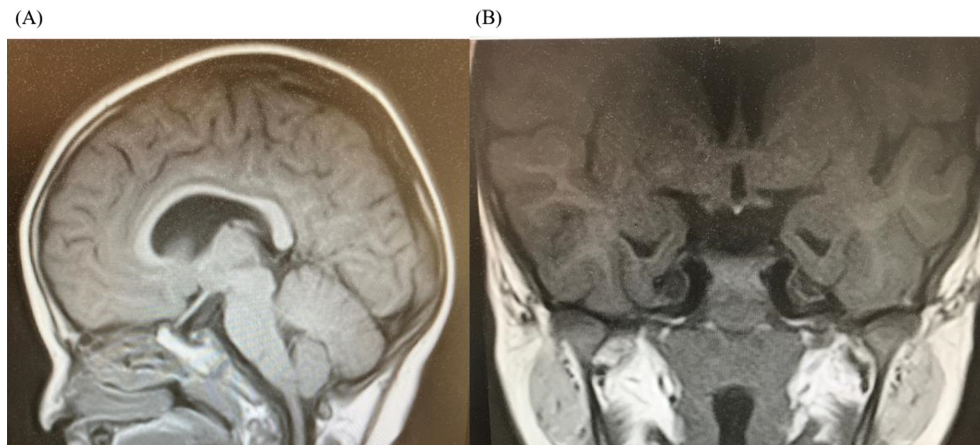
(A)   (B)

Fig. 2. Magnetic resonance images of the brain of the patient in the current case report. (A) Sagittal image. (B) Coronal image.

deletion of *FOXA2*.

In our present case, hyperinsulinemic hypoglycemia and GHD were associated with a 20p11.23-p11.21 deletion, which encompasses *FOXA2*. Most cases of mutation-based defects in ß-cell ATP-sensitive potassium (KATP) channels are resistant to diazoxide (11). However, our case showed a certain responsiveness to diazoxide in treating hyperinsulinemic hypoglycemia, despite the deletion of 20p11.23-p11.21. According to functional analysis by mutation (c.770G>T, p.R257L) in *FOXA2* (3), transactivation of *ABCC8* and *KCNJ11* was substantially decreased compared with that of wild-type *FOXA2* (*ABCC8*, 30.8% decrease; *KCNJ11*, 27.0% decrease). Although the transactivation of *ABCC8* and *KCNJ11* is decreased by *FOXA2*, it is not completely eliminated. This may explain the level of responsiveness to diazoxide observed in the present case.

In addition to *FOXA2*, the other deletions identified in our case were *NKX2-2*, *CD93*, *THBD*, *XRN2*, *PAX1*, *SSTR4*, and *PLK1S1*. Except for *SSTR4* and *Nkx2-2*, these genes are not involved in pituitary formation or pancreatic development. Our literature search failed to reveal any reports of hyperinsulinemic hypoglycemia and hypopituitarism in humans due to *SSTR4* and *Nkx2-2* deletion.

We compared our case with those reported to have deletions of chromosome 20p11.2, including *FOXA2* (2, 5–7, 12–14). All cases except one reported hypopituitarism. However, only a few reports have described hyperinsulinemic hypoglycemia in detail, whereas several reports have described clinical findings suggestive of hyperinsulinemic hypoglycemia (13, 14). It has been reported that many cases of epilepsy are associated with 20p11.2 deletions, but our patient did not develop epilepsy. In these cases, the deletions also included *CST3*, which has been related to the reorganization of the epileptic dentate gyrus and an intrinsic neuroprotective mechanism (15). Therefore, *CST3* haploinsufficiency may be involved in the development of epilepsy phenotypes. Since *CST3* deletion was not observed in our patient, epilepsy might not be developed.

This case report has several limitations. First, we did not measure GH levels during the neonatal period. Generally, IGF-1 levels in the neonatal period are low and are not useful in the diagnosis of GHD. However, GH level has been considered useful for the diagnosis of GHD in newborns (16). In our patient, hypoglycemia improved once in the neonatal period, but it cannot be denied that GHD may have occurred since the neonatal period. Second, the deletions in our case not only included *FOXA2* but also other genes, such as *NKX2-2*, which has been reported to be involved in pituitary development in an animal model (17). Therefore, we cannot rule out the possibility that this case may not be a phenotype because of *FOXA2* deletion.

In conclusion, we report a case with a deletion of 20p11.23-p11.21, including *FOXA2*, which presented with neonatal hypoglycemia as a result of both hypopituitarism and hyperinsulinism. Our report suggests that several pathological conditions may cause both hyperinsulinemic hypoglycemia and hypopituitarism and reaffirms the importance of evaluating not only insulin and congenital metabolic disorders in patients with hypoglycemia but also pituitary function.

Acknowledgments

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