

# Endocrinological Features of Hartsfield Syndrome in an Adult Patient With a Novel Mutation of *FGFR1*

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Hartsfield syndrome (HS; OMIM 615465) is a rare congenital disease associated with a mutation of the *fibroblast growth factor receptor 1* gene (*FGFR1*) with the main features of holoprosencephaly and ectrodactyly. Patients with HS also present with endocrinological deficits, such as isolated hypogonadotropic hypogonadism and central diabetes insipidus. Although there are several studies on infancy/childhood history, there is no study of infant/childhood/adolescent/young adult HS natural history and endocrinological findings. Here, we report a male patient with HS associated with a novel de novo *FGFR1* mutation (c. 1868A > C). The endocrinological profile was evaluated at ages 1 and 31 years. This long-term follow-up study highlights functional changes in the posterior pituitary gland and features of bone metabolism disorder. We also describe the anterior pituitary function. To our knowledge this is the first description of the natural history of an HS patient through birth to young adult age. Although the HS infants reported in the literature develop central diabetes insipidus, little is known about the serial changes in pituitary gland function during growth in HS patients. In this study we describe an adult patient with HS who showed improvement of hypernatremia during early adulthood. In addition, we emphasize the importance of prevention and treatment of osteoporosis in HS.

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**Key Words:** *FGFR1* mutation, hypernatremia, hypogonadotropic hypogonadism

Hartsfield syndrome (HS) is a rare congenital disease associated with a mutation of the *fibroblast growth factor receptor 1* gene (*FGFR1*) [1-9]. Little is known about adult HS patients and there is no study on natural history and endocrinological function in adult patients. In the present study, we report a case of a male HS patient with a novel *FGFR1* mutation. We evaluated his endocrinological function both in childhood and adulthood and found interesting changes in the posterior pituitary gland and features of bone metabolism disorder.

Abbreviations: *FGFR1*, fibroblast growth factor receptor 1; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; HS, Hartsfield syndrome; LH, luteinizing hormone.

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## 1. Case Presentation

### A. Infancy and Childhood

The male proband was born at 41 weeks of gestation through vacuum extraction. There was no unusual exposure during pregnancy and the parents were nonconsanguineous. At birth, he was noted to have several congenital abnormalities including cleft lip and bilateral ectrodactyly of the hands and feet. Birth weight was 2724 g and height was 49.2 cm. He had a micropenis. At age 6 months, he was hospitalized to undergo surgery for repair of the cleft lip, and the preoperative laboratory tests results showed a marked hypernatremia with a serum sodium level as high as 158 mmol/L. During a water deprivation test, urine osmolality was partially elevated with a decrease of urine volumes and unchanged serum osmolality (Table 1). Administration of desmopressin increased urinary osmolality, suggesting normal renal sensitivity to desmopressin. Interestingly, serum sodium levels remained as high as 160 mmol/L even after administration of desmopressin (Table 1). At age 9 months, dehydration led to severe hypernatremia (190 mmol/L). He showed refusal to feed despite hypernatremia, suggesting existence of adipsia. At that stage, he was diagnosed with essential hypernatremia by his pediatricians. The term *essential hypernatremia* has previously been used to describe adipsic/hypodipsic patients [10, 11]. Blood test showed a low response of vasopressin to plasma osmolality (Fig. 1A) [12]. Owing to the lack of sense of thirst and low secretion of vasopressin, nasal feeding and carbamazepine in infancy and desmopressin during childhood were used for water balance control. Throughout childhood, the patient suffered intermittent dehydration and poor growth (Table 2). At age 6 years, he had a supracondylar fracture of the left humerus following an accidental fall. Beyond age 10, the long-term use of desmopressin provided adequate water balance. As shown in Table 3, basal serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels were rather high at age 1 year. Gonadotropin-releasing hormone (GnRH) deficiency was suspected because of prolonged and low peaks of LH and FSH in response to GnRH stimulation (Table 3, middle panel). The volume of the testes was 0.5 mL at age 1 year. The volume of the testes remained as small as 0.5 to approximately 1.0 mL at age 11 years. Basal serum gonadotropin levels were low for his age at 12 years (Table 3, upper panel).

### B. Adolescence and Adulthood

The patient remained relatively healthy and showed an almost normal growth curve (Table 2). However, he was diagnosed with type 2 diabetes mellitus at age 17 years. Oral glucose-lowering agents, including alogliptin (25 mg/day), an inhibitor of dipeptidyl peptidase 4, and voglibose (0.6 mg/day), an  $\alpha$ -glucosidase inhibitor, were used to control blood glucose levels. During adulthood, he was encouraged to drink more than 1.5 L water per day to cope with adipsia, and used desmopressin nasal drops by sliding-scale, though serum sodium levels remained slightly high, ranging from 147 to 154 mmol/L. With normal activities of daily living, he graduated from the school for handicapped children and worked at a welfare workshop.

At age 31 years, he was hospitalized at NTT West Osaka Hospital (Daini Osaka Police Hospital at present) following a fracture of the left proximal femur. His orthopedic surgeon asked us to manage the patient's water-electrolyte balance. His body height and weight were 161 cm and 58 kg, respectively. Secondary sexual features, including voice changes at puberty, beard, and pubic hair, were lacking. He had a micropenis and small testes. The patient showed distinctive facial dysmorphism, including hypertelorism and a low nasal bridge (Fig. 2A) with bilateral ectrodactyly of the hands and feet (Fig. 2B-E). Epiphyseal fusion was noted and neurological examination showed mild hyperreflexia of bilateral upper and lower extremities with mild mental developmental delay. Brain magnetic resonance imaging (MRI) showed holoprosencephaly and olfactory bulb hypoplasia (Fig. 2F and 2G). Perception of smell of flowers and food was intact, although a brain MRI showed a reduced

**Table 1. Results of Water Deprivation Test and Desmopressin Challenge Tests for Evaluation of Posterior Pituitary Function. Serum Levels of Sodium and Vasopressin, Serum Osmolarity, and Urine Osmolarity After Cessation of Desmopressin Treatment**

<b>Water deprivation test</b>									
	Time, h								
	0	2	6						
Posm, mOsm/kg	344	339	338						
Na, mmol/L	165	164	167						
Uosm, mOsm/kg	235	239	337						
Urine volume, mL/min	–	0.47	0.2						
Body weight, g	6320	6220	6000						
<b>Desmopressin challenge test</b>									
	Age 6 mo			Age 3 y			Age 31 y		
	Time, h			Time, h			Time, h		
	0	3	5.5	0	1	7	0	4	6
Uosm, mOsm/kg	475	548	703	503	496	838	677	782	871
Urine volume, mL/min	–	0.19	0.06	0.67	0.29	0.12	–	0.47	0.3
<b>Desmopressin deprivation test</b>									
	Time, d								
	1	2	5 <sup>a</sup>						
Na, mmol/L	155	152	153						
Vasopressin, pg/mL	0.9	0.5	0.8						
Posm, mOsm/kg	315	311	310						
Uosm, mOsm/kg	504	677	294						
Urine volume, L/d	1.2	1.1	1.5						

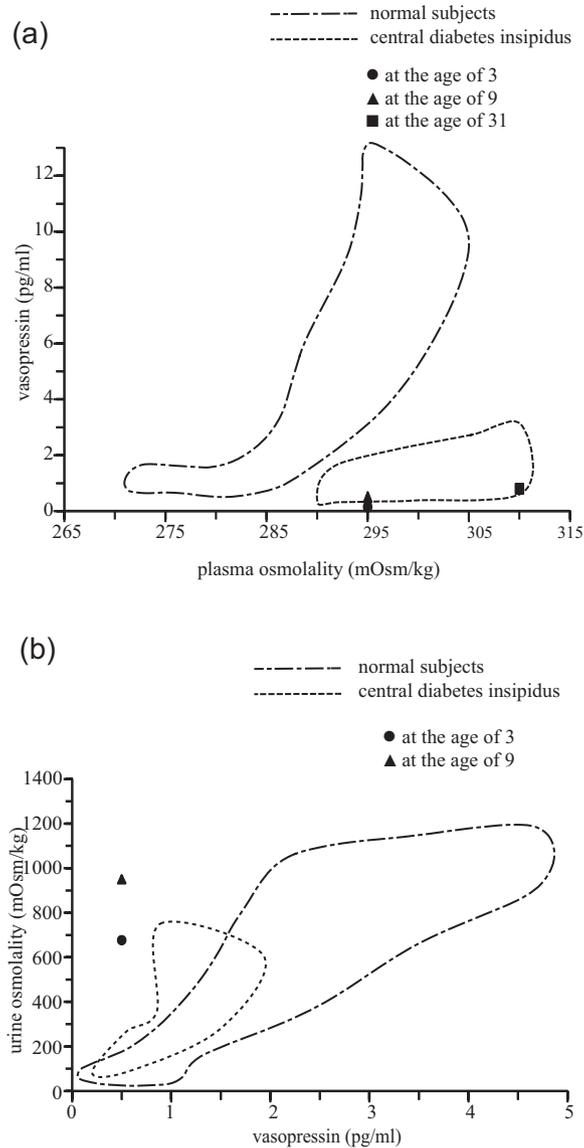
–, not measured; upper panel: water deprivation test; middle panel: desmopressin challenge test; lower panel: serum levels of sodium and vasopressin, serum osmolarity, and urine osmolarity after cessation of desmopressin treatment. Parameters also measured on the fifth day after drinking 1 L of water just before sleep on the fourth day.

<sup>a</sup>On the fourth day, the patient drank 1 L of water before sleep.

olfactory bulb. The pituitary gland was small with absence of the posterior pituitary bright spot (Fig. 2H). Based on the listed features and history, the provisional diagnosis was HS. Hormonal assays at age 31 years indicated hypogonadotropic hypogonadism (Table 3). Neither basal serum LH, basal serum FSH, nor basal serum testosterone levels were measurable. Insulin–thyrotropin-releasing hormone–GnRH challenge test showed low secretion of LH and FSH in response to GnRH, indicating hypogonadotropic hypogonadism. Other endocrinological dysfunctions such as hypothyroidism, adrenal insufficiency, and growth hormone deficiency were ruled out by evaluating multiple series of measurements of serum basal levels of hormones and clinical manifestation.

During hospitalization at age 31 years, the patient was diagnosed with severe osteoporosis based on extremely low bone mineral density (BMD, 42% of average for young adult males). Other secondary osteoporosis due to endocrine disorders, gastrointestinal disorders, and autoimmune diseases was excluded by evaluating his general condition and blood examinations [13]. Then, we decided to start testosterone replacement therapy for treatment of osteoporosis. Testosterone replacement therapy gradually increased his BMD, with concomitant improvement in bone turnover markers as shown in Table 4.

Blood tests showed a low response of vasopressin to plasma osmolality (Fig. 1A), and this finding was comparable for the response of central diabetes insipidus, at age 3 and confirmed at 31 years. Interestingly, urine osmolality was higher than plasma osmolality regardless of the poor serum vasopressin secretion (Fig. 1B). It is noteworthy that he had never observed polyuria during his lifetime. Daily urine volume never exceeded 3 liters. While the blood tests showed hyponatremia, urine osmolality was higher than 300 mOsm/kg. The clinical



**Figure 1.** Relationships of vasopressin with plasma osmolality and one with urine osmolality, using data obtained during years growing up. A, Correlations of urine osmolality with plasma vasopressin in normal individuals (dashed lines) and of patients with central diabetes insipidus (dotted lines). B, Correlations of urine osmolality with plasma vasopressin in normal individuals (dashed lines) and of patients with central diabetes insipidus (dotted lines). The data obtained in this work are inserted on the correlation curve made by using previous data provided by Robertson et al [12].

presentation and results of laboratory tests do not meet the criteria of classical form of central diabetes insipidus in this patient. Administration of desmopressin increased urinary osmolality, suggesting normal renal sensitivity to desmopressin (Table 1). While in the hospital, the patient was deprived of dosing of desmopressin under careful observation. As shown in Table 1 (lower panel), water intake ( $> 1.5$  L/day) and restriction of daily sodium intake ( $< 7$  g/day) were sufficient to keep serum sodium levels and urine volumes at normal levels. Although drinking another 1 L of water before sleep at night lowered urine osmolality, it did not affect serum sodium level (which remained normal) the following morning. Based on these findings, it was concluded that desmopressin nasal drops were no longer needed. However, to fulfill the patient's desire to reduce night urination, he was discharged on oral intake of one-quarter tablet (15  $\mu$ g) of desmopressin just before falling asleep. At age

**Table 2. Growth Chart for Patient's Height and Weight in Childhood**

Age	Height		Weight	
	Centimeters	SD	Kilograms	SD
6 mo	64	−0.5	6.4	−1.5
9 mo	72	NA	6.59	NA
23 mo	85	−0.5	11.4	−0.5
39 mo	94.5	Mean	14	Mean
6.5 y	116	Mean	20	Mean
7.5 y	122	Mean	24	Mean
8 y	126.2	Mean	28.7	+1.0
9 y	129.5	Mean	30.75	+1.0
10 y	135	Mean	36	+1.0
11.2 y	142	Mean	42	+1.0
12 y	142	Mean	47	+1.0

Abbreviation: NA, not assessed.

32 years, cessation of oral intake of desmopressin was sometimes but not always associated with the appearance of nocturnal polyuria (900 mL/night). At the last clinical examination at our hospital at age 33 years, he was not on desmopressin with surprisingly normal serum sodium levels (138–142 mmol/L) and normal concentrated urine and free from nocturnal polyuria.

### C. Genetic Analysis

Genomic DNA was obtained from blood cells subjected to direct Sanger sequencing of all exons in the *FGFR1* gene. A novel heterozygous missense variant, NM\_023110.2: c. 1868A > C (p. Asp623Ala) was detected in the *FGFR1* gene. DNA samples were also obtained from the asymptomatic parents and found to lack the variant (Fig. 2I). Three different amino-acid changes in the residue had previously been reported to be associated with the syndrome: Asp623Glu, Asp623Gly, and Asp623Tyr [1, 3, 9] (Table 5). In addition, the p. Asp623Ala variant was predicted to be disease causing by several major algorithms (PolyPhen2, SIFT, PROVEAN, PANTHER, and Mutation Taster).

Written informed consent was obtained from the patient and his parents. The institutional review board of Osaka University approved this study.

## 2. Discussion

Although there are several observational studies on infant and childhood HS cases, little is known about adult HS patients (Table 5). This is the first report that describes the developmental outcome and endocrinological abnormalities of an adult HS patient.

The patient was found to have a novel heterozygous missense variant c. 1868A > C in *FGFR1*. The residue Asp623 is located in the intracellular tyrosine kinase domain, and variants in this residue have been predicted to behave as dominant negative in HS [1, 3, 9]. We reported here a novel heterozygous *FGFR1* variant—p. Asp623Ala—and in silico analysis supported the pathogenicity of this missense variant.

FGFR1 is expressed in cranial neural crest-derived mesenchyme and involved in embryogenesis [14, 15]. The FGF signaling pathway is essential for ventral telencephalon development and digit formation. FGF signals are required for the development of the olfactory bulbs [16] and gonadotropin-secreting neurons [17]. Although basal serum gonadotropin levels were rather high at age 1 year, basal serum gonadotropin and testosterone levels were low for his age at age 12 years (Table 3) [18, 19]. Moreover, neither basal serum LH nor basal serum FSH levels were measurable at age 31 and low response to GnRH stimulation was observed. We diagnosed him as having hypogonadotropic hypogonadism. In patients

**Table 3. Results of Basal Hormone Levels at Ages 1, 3, 6, 12, 31, and 32 Years and Hormone Challenge Tests for Evaluation of Anterior Pituitary Function at Ages 1 and 31 Years**

Assessment of basal hormones							
	1 y	3 y	6 y	12 y	31 y	32 y	Reference <sup>d</sup>
Blood glucose, mg/dL	–	88	–	–	84	88	
TSH, $\mu$ IL/mL	2.0	1.5	–	–	1.14	1.74	0.27-4.2
FT3, pg/mL	–	4.8	–	–	3.77	–	2.3-4.0
FT4, ng/dL	–	1.3	–	–	0.826	1.2	1.0-1.8
FSH, mIU/mL	9.1	–	0.7	1 (2.9-8.2) <sup>a</sup>	< 0.3	< 0.3	1.5-12.4
LH, mIU/mL	17.3	–	< 0.5	< 0.5 (1.8-5.2) <sup>b</sup>	< 0.3	< 0.3	1.7-8.6
Testosterone, ng/mL	0.28	–	0.1	–	0.23	3.4 <sup>c</sup>	1.31-8.71
PRL, ng/mL	35.6	–	3.5	–	54.5	11.8	4.3-13.7
ACTH, pg/mL	–	–	–	–	58.8	30.9	7.2-63.3
Cortisol, $\mu$ g/dL	–	–	–	–	8.2	5.6	2.9-19.6

Hormone challenge test at age 1 y							
	Stimulus	Time, min					
		0	30	45	60	90	120
GH, ng/mL	Insulin	1.7	–	–	12.6	–	–
TSH, mIU/mL	TRH	2.0	–	11.2	–	–	–
LH, mIU/mL	GnRH	17.3	–	18.6	–	28.8	19.7
FSH, mIU/mL	GnRH	9.1	–	11.5	–	13.7	8.0
PRL, ng/mL	TRH	35.6	35.6	–	–	26.4	24.0

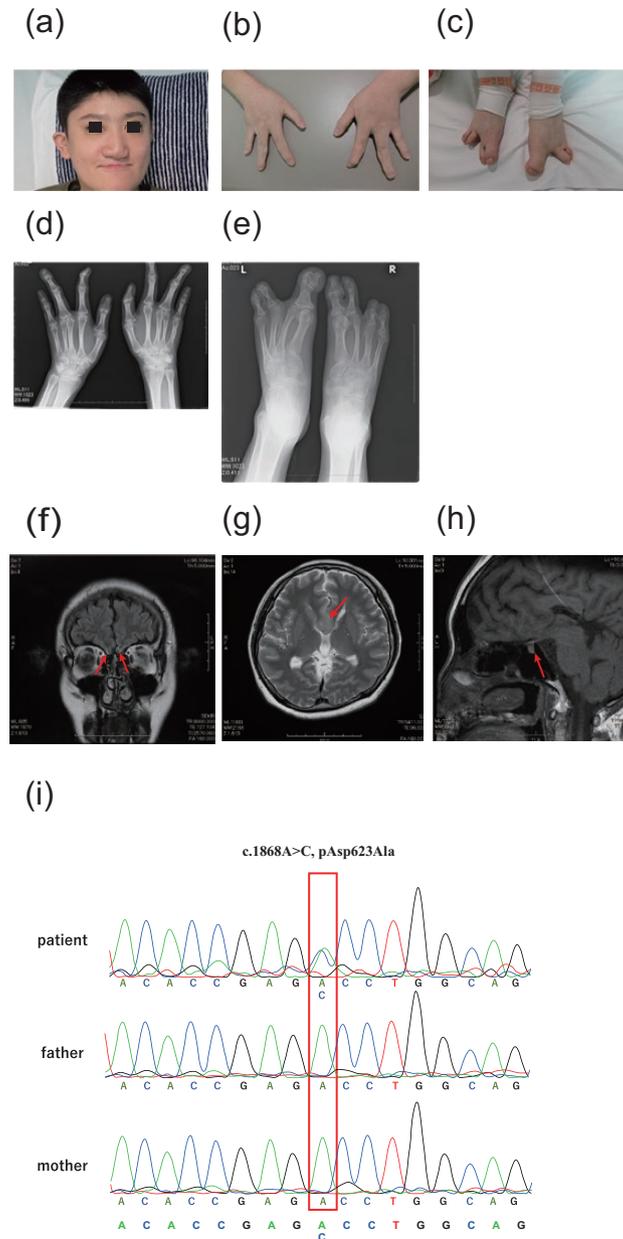
Hormone challenge test at age 31 y							
	Stimulus	Time, min					
		0	15	30	60	90	120
Blood glucose, mg/dL	Insulin, TRH, GnRH	84	65	46	64	73	74
TSH, $\mu$ IL/mL		1.14	5.18	6.68	4.77	3.21	2.3
FT3, pg/mL		3.77	–	–	–	–	4.41
FT4, ng/dL		0.826	–	–	–	–	1.03
GH, ng/mL		0.25	0.23	0.85	9.68	7.6	7.13
FSH, mIU/mL		ND	ND	ND	ND	ND	ND
LH, mIU/mL		ND	0.4	0.8	1.4	1.7	2.4
PRL, ng/mL		54.5	119.1	96.2	56.8	56.6	75
ACTH, pg/mL		58.8	–	56.7	147.8	92.2	64.4
Cortisol, $\mu$ g/dL		8.2	–	7.1	12.6	10.3	8.6

–; not measured.

Abbreviations: ACTH, adrenocorticotropin; FSH, follicle-stimulating hormone; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; ND, not detected; PRL, prolactin; TRH, thyrotropin-releasing hormone; TSH, thyroid-stimulating hormone.

<sup>a,b</sup>Reference data of the Japanese adult male when our patient was age 12 years.<sup>c</sup>Data under testosterone replacement therapy.<sup>d</sup>Reference data of the Japanese adult male: reference data for peak values of hormone challenge test at age 31 as follows: TSH is more than 6.0  $\mu$ IU/ml, FSH increases 2 times, LH increases 5 times, PRL increases 2 times; ACTH increases 2 times, and cortisol more than 18  $\mu$ g/dL.

with hypogonadotropic hypogonadism, the response to the GnRH test is highly variable and depends on the severity of gonadotropin deficiency [20]. Congenital hypogonadotropic hypogonadism is often accompanied by the absence of minipuberty. One-third of congenital hypogonadotropic hypogonadism cases have partial GnRH deficiency with normal penile development and testicular descent at birth and some degree of spontaneous testicular development during adolescence. Thirteen percent of patients with Kallmann syndrome, which presents with isolated hypogonadotropic hypogonadism with anosmia, had evidence of partial puberty [21]. High basal serum levels of LH and FSH at age 1 year might suggest prolonged minipuberty with unrevealed mechanisms [22]. We speculated that gonadotropin-producing cells were alive at age 1 year, but suppression of stimulation by hypothalamic



**Figure 2.** A, Photograph of the 31-year-old patient with Hartsfield syndrome. Note the midface hypoplasia and repaired cleft lip; B, syndactyly of fingers; and C, split feet. D and E, Radiographs of the hands show absence of the proximal phalanges in both hands and feet. Brain magnetic resonance imaging shows F, hypoplasia of the olfactory bulb, G, partial fusion of the frontal lobes on axial image, and H, partial absence of the anterior part of the corpus callosum on the sagittal scan. Arrows indicate lesion sites. I, Sanger sequencing showing the c. 1868A > C nucleotide change in *FGFR1*.

GnRH gradually attenuated the actions of gonadotrophs, with a decrease of numbers of gonadotrophs at age 31 years.

The observed hypernatremia in our patient could be explained by an inappropriate set point for vasopressin (Fig. 1A). It is noteworthy that the extremely small amount of autonomic and secretory vasopressin was sufficient to regulate serum sodium levels and urine osmolality during adulthood. We speculate that this finding is related to improvement in vasopressin sensitivity. Previous studies reported the common prevalence of diabetes insipidus in patients with HS but little is known about the pathology of posterior pituitary

**Table 4. Results of Changes in Bone Mass and Bone Resorption/Formation Markers During Testosterone Replacement Treatment**

		Treatment duration, mo				Reference
		0	2	11	33	
Femur	BMD, g/cm <sup>2</sup>	0.435	0.483	0.505	0.473	
	T score	-3.4	-3	-2.8	-3.1	
	Z score	-3.3	-2.9	-2.8	-3	
	BMC, g	2.55	2.43	2.98	2.56	
Lumbar	BMD, g/cm <sup>2</sup>	0.47	0.517	0.54	0.657	
	T score	-4.9	-4.5	-4.3	-3.3	
	Z score	-4	-3.7	-3.5	-2.7	
	BMC, g	19.61	21.98	23.27	27.1	
Bone Resorption/ Formation Markers	BAP, U/L	41.3	28.5	-	12.5	3.7-20.9
	sNTx, nmolBCE/L	48.2	34.2	-	-	9.5-17.7
	TRACP-5b, mU/dL	489	357	-	133	170-590

-, not measured.

Abbreviations: BAP, bone-specific alkaline phosphatase; BMC, bone mineral content; BMD, bone mineral density; sNTx, serum N-telopeptide; TRACP-5b, tartrate-resistant acid phosphatase 5b.

glands in HS (Table 5). Our patient showed adipsic hypernatremia, and vasopressin secretion was impaired. Absence of posterior pituitary hyperintensity on brain MRI suggested the existence of partial central diabetes insipidus [23-25]. But he was not diagnosed as having a classical form of central diabetes insipidus because of concentrated urine. Urine volume never exceeds 3 L per day and urine osmolarity has been rather high. The clinical scenario of only one patient resembled that of our patient (identification number 19 in Table 5). Are the endocrinological findings on the posterior pituitary gland observed in our patient commonly seen in HS? Further publications on HS may shed light and provide an answer to this question. Considering that all individuals with holoprosencephaly do not need treatment for diabetes insipidus, as described previously [26], enhanced sensitivity to vasopressin could compensate for the lower secretion of vasopressin in patients with HS.

Unfortunately, we could not determine in this single case the exact pathophysiological mechanisms of hypernatremia and HS clinical manifestations. To date, there is no evidence for the involvement of FGFR1 in sodium reabsorption in the renal tubules, but it is possible that *FGFR1* variants induce dysfunction of renal aquaporin receptors. Recently, a novel dominant-negative *FGFR1* variant was found to be associated with impairment of the autophagic process [8]. FGFR1 deficiency in the renal distal tubules was also reported to be associated with cardiomegaly without affecting serum sodium concentrations [27]. Further studies are needed to determine the effect of the variant identified in *FGFR1* in our patient on renal tubular function. Sodium levels are monitored in the brain and autoimmunity toward the sodium-level sensor induced adipsic (or essential) hypernatremia [28]. It is possible that yet unidentified autoantibodies to the sodium level sensor may be the culprit behind the high plasma sodium levels.

Our patient was diagnosed with diabetes mellitus as early as age 17 years. At age 31 years, his fasting blood glucose levels were as high as 198 mg/dL and the serum levels of C-peptide were 3.7 ng/mL, indicating that insulin secretion ability was still maintained. Until now, neither diabetes mellitus nor hyperlipidemia has been reported in HS patients. FGF19 and FGF21, which are FGFR1 ligands, promote energy expenditure and improve glucose metabolism [29-31]. Agonist of FGFR1 enhances thermogenesis in brown adipose tissue and is involved in weight loss and glucose and lipid metabolism [32]. The early onset diabetes mellitus in our patient might be linked to FGFR signaling in endocrine organs such as adipose tissue and liver.

The supracondylar fracture of the left humerus at age 6 years required 2 years of treatment because of delayed bone adhesion. In contrast, the fracture of the left proximal femur

Table 5. Summary of Previously Reported Hartsfield Syndrome Patients

ID	Sex/Age	Genetic analysis		Brain imaging			Endocrinological deficiency	Follow-up	Reference
		c. Mutation	p. Mutation	Affected domain	HPE	Pituitary			
1	M/5 y	c494T > C	p.Leu165Ser	Ig II	AL	Normal	NR	Died at age 5 y	1
2	M/4 y	c572T > C	p.Leu191Ser	Ig II	L	NR	NR	Died at age 4 y	1
3	M/14 y	c758A > C	p.His253Pro	Ig III	SL	Normal	HH	NR	5
4	M/19 y	c1029G > A	p.Ala343Ala	Ig III	L	NR	HH	Has mild intellectual disability	9
5	F/14 y	c1029G > A	p.Ala343Ala	Ig III	Abnormal corpus callosum	Abnormal corpus callosum	CDI	Has mild developmental delay and intellectual disability	9
6	NR	c1454G < T	p.Gly485Val	TK	NR	NR	NR	NR	6
7	M/33 y	c1459G > T	p.Gly487Asp	TK	Abnormal corpus callosum	Abnormal corpus callosum	CDI, HH, mild hypothyroidism	Resides in home with 24-h community living support staff	7
8	M/7 mo	c1460G < A	p.Gly487Asp	TK	L	NR	NR	NR	3
9	M/12 y	c1468G > C	p.Gly490Arg	TK	SL	NR	NR	Has developmental age of about 7 mo	1
10	F/NR	c1867G > T	p.Asp623Tyr	TK	L	NR	CDI, HH, normal GH secretion, low response to TRH	Mainstream school with support	1
11	M/33 y	c1868A > C	p.Asp623Ala	TK	L	No high intensity in posterior pituitary gland	HH, normal GH secretion, adipsia-hypernatremia	Works at welfare workshop	Patient in present study
12	M/7 y	c1868A > G	p.Asp623Gly	TK	SL	NR	NR	Presented with severe intellectual disability with absent speech	9
13	NR	c1869C > G	p.Asp623Glu	TK	HPE	NR	NR	NR	3
14	M/6 y	c1880G > C	p.Arg627Thr	TK	SL	NR	CDI, GH deficiency	NR	2
15	M/0Y	c1880G > C	p.Arg627Thr	TK	SL	NR	NR	NR	2
16	M/1Y	c1883A < G	p.Asn628Ser	TK	SL	NR	CDI, HH	Has tumoral calcinosis	4
17	M/19Y	c1884 T > G	p.Asn628Lys	TK	SL	Normal	CDI, HH, normal GH secretion, low response to TRH	Lives in an institution	1
18	F/11Y	c1921G > A	p.Asp641Asn	TK	SL	Hypoplasia	GH neurosecretory dysfunction, neurogenic hypernatremia	Has developmental delay	3
19	M/12Y	c1934C > T	p.Ala645Val	TK	L	NR	DI (suspected at 4 mo)→hypodipsia-hypernatremia (diagnosed at age 10 y)	NR	8
20	M/29Y	c2174 G > A	p.Cys725Tyr	TK	L	Normal	CDI, HH, normal GH secretion, low response to TRH	Works in sheltered workshop	1

Abbreviations: AL, alobar; CDI, central diabetes insipidus; DI, diabetes insipidus; F, female; GH, growth hormone; HH, hypogonadotropic hypogonadism; HPE, holoprosencephaly; ID, identification; Ig II, immunoglobulin-like 2 domain, Ig III; immunoglobulin-like 3 domain; L, lobar; M, male; NR, not reported; SL, semilobar; TK, tyrosine kinase domain; TRH, thyrotropin-releasing hormone.

at age 31 healed within 1 year. It is possible that the testosterone replacement therapy during adulthood enhanced fracture healing. The treatment was designed to bring serum testosterone levels to the lower limits of normal levels, and such an approach resulted in a gradual and successful increase in BMD. These findings highlight the importance of careful monitoring of BMD and prevention of osteoporosis in adult HS.

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