Pituitary (2013) 16:133–138
DOI 10.1007/s11102-012-0386-8

Hypothalamic pituitary complications in Kabuki syndrome

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Published online: 21 March 2012

Abstract Kabuki syndrome is characterized by distinctive facial features, multiple anomalies and mental retardation. In this syndrome, structural CNS abnormalities are commonly observed, but congenital abnormalities in the pituitary gland or hypothalamus have rarely been reported. We searched the published medical literature on the complications in hypothalamic pituitary axis in this syndrome. As a result, only nine patients with Kabuki syndrome had been reported to have complications in hypothalamic pituitary axis in previous papers. Among the nine reported patients and one presented case in this report, GH deficiency was the most frequent complication and found in six patients. Precocious puberty and central diabetes insipidus (DI) was identified in two cases, respectively, and ACTH deficiency was found in one. One case had combination of GH deficiency and central DI. Three of the 10 patients demonstrated abnormal pituitary findings in MRI study. Two of the six patients with GH deficiency were accompanied with premature thelarche. This review highlights that patients with Kabuki syndrome could present various clinical manifestations due to abnormalities in hypothalamic pituitary axis.

Keywords Kabuki syndrome · Central diabetes insipidus · Hypothalamic pituitary axis · *MLL2* gene

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Abbreviations

AVP	Arginine-vasopressin
CNS	Central nervous system
DDAVP	1-deamino-8-D-arginine vasopressin
DI	Diabetes insipidus
eGFR	Estimated glomerular filtration rate
GH	Growth hormone
MLL	Mixed lineage leukemia
MRI	Magnetic resonance imaging

Introduction

Kabuki syndrome is a rare, multiple malformation disorder characterized by a distinctive facial appearance, cardiac anomalies, skeletal abnormalities, immunological defects and mental retardation [1, 2]. Besides these typical manifestations, clinical symptoms and congenital abnormalities are considerably variable. Malformation in central nervous system are frequently observed in this syndrome with great differences [3], whereas, congenital abnormalities in the pituitary gland or hypothalamus have rarely been reported. In particular, central diabetes insipidus (DI) in a patient with Kabuki syndrome has only been reported in one previous paper [4]. We herein briefly report a case of Kabuki syndrome with central DI who presented with polydipsia and polyuria. Then, we searched the published medical literature on the complications in hypothalamic pituitary axis in Kabuki syndrome.

Case report

The patient was born at term from non-consanguineous parents with no family history of congenital malformations.

Table 1 Clinical features for Kabuki syndrome in the patient at 8 years of age

Craniofacial abnormality	
Characteristic face	+
Microcephaly	−
Long palpebral fissures	+
Epicanthus	+
Lower palpebral eversion	+
Ptosis	+
Strabismus	−
Blue sclera	−
Short nasal septum	−
Prominent forhead	−
Arched eyebrows	+
Prominent ear	+
Depressed nasal tip	+
Auticualr deformity	−
Preauricular pits/tags	−
Abnormal dentition	−
Hypodontia	+
High-arched palate	+
Micrognathia	+
Cleft lip/cleft palate	+
Lower lip pits	+
Lower posterior hairline	+
Bone abnormality	
Skeletal abnormality	−
Short 5th finger	+
Clinodactyly (V)	+
Spine/rib abnormality	+
Scoliosis	−
Hip joint dislocation	−
Dermatoglyphic findings	
Abnormal dermatoglyphic findings	+
Prominent finger tip pads	+
Neurological abnormality	
Developmental delay	+
Intellectual disability	+
Hypotonia	−
Hypotonia in infancy	+
Seizure	+[a]
Brain atrophy	−
CNS malformation	−
Stature	
Short stature	+[b]
Prenatal growth retardation	−
Postnatal growth retardation	+
Visceral abnormality	
Generalized hirsutism	−
Cardiovascular abnormality	+
Umbilical hernia	−
Kidney/uterther malformation	+[c]
Kidney dysfunction	+[d]
Cryptorchism	−
Anogenital anomaly	−
Liver abnormality	−
Spleen abnormality	−
Hormonal abnormality	+[e]
Others	
Joint laxity	+
Recurrent otitis media	+
Deafness	−
Premature thelarche	+
Neonatal hyperbilirubinemia	+
Obesity	−
Anemia	−

[a] Afebrile seizures

[b] −4.03 SD at 8 years of age

[c] Hypoplastic and malpositioned right kidney

[d] eGFR = 48–122 ml/min/1.73 m^2 at 8 years of age

[e] Central diabetes insipidus

She was doing well at birth, and her birth weight was 2,915 g. A physical examination detected a cleft in the soft palate, which caused feeding difficulties requiring tube feeding until the cleft closure operation was performed at 2 years of age. She also had a ventricular septal defect, which closed spontaneously by 1 year of age. At the age of 1 year, she was diagnosed to have Kabuki syndrome on the basis of her characteristic facial appearance, including long palpebral fissures, lower palpebral eversion, arched eyebrows, lower lip pits, a depressed nasal tip and prominent ears, with distinctive symptoms of short 5th fingers and prominent finger tip pads (Table 1). At 5 years of age, a routine examination by abdominal ultrasound imaging detected a hypoplastic and malpositioned right kidney. This renal malformation was asymptomatic, but careful check-ups for her renal function were started then. At 6 years of age, polydipsia and polyuria gradually emerged, and the patient was referred to our hospital at the age of 8 years for evaluation of her renal function, because her serum creatinine levels were transiently elevated to 0.52–0.91 mg/dL (eGFR = 48–84 ml/min/1.73 m^2) during the time.

At the admission, the patient's height and weight were 105.7 cm (−4.03 standard deviation) and 16.6 kg. Her serum BUN and creatinine levels were 14 and 0.36 mg/dL, respectively (eGFR = 122 ml/min/1.73 m^2), therefore, her polydipsia and polyuria might not be explained by secondary nephrogenic diabetes insipidus due to the hypoplastic kidney, and the transient increase of serum creatinine levels had been probably derived from mild

Water deprivation starting ⬇ AVP administration ⬇

	0 hr	1 hr	2 hr	3 hr	4 hr	1 hr	2 hr
ADH (pg/ml)	1.4	1.5	1.7	1.4	1.5	N/A	N/A
Serum osmotic pressure (mOsm)	287	286	287	290	291	N/A	N/A
Urine osmotic pressure (mOsm)	86	115	270	395	451	550	560
Urine volume /hr (mL/hr)	N/A	60	30	20	20	N/A	N/A

Fig. 1 The results of the water deprivation test and the subsequent administration of AVP. The time course of the serum ADH levels or serum and urine osmotic pressures after starting water deprivation are shown. AVP administration at 4 h after water deprivation decreased the urine output and increased the urine osmotic pressure appropriately. N/A, not assessed

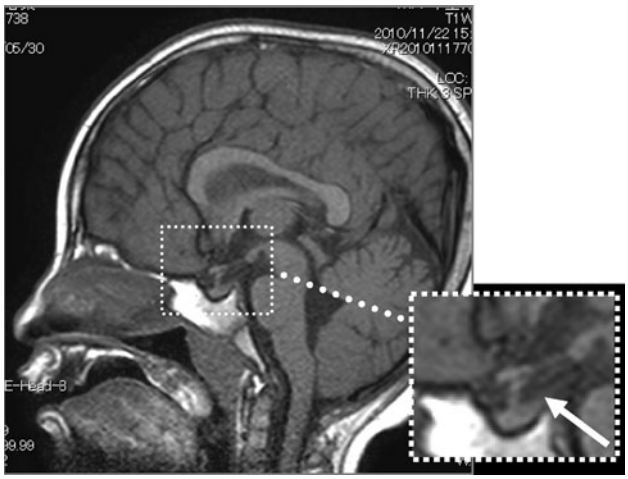

Fig. 2 The sagittal section of T1-weighted brain MRI. A *rectangle area* bounded by *dotted lines* is enlarged to show the details of the pituitary gland and its surrounding region. The *arrow* indicates the absence of a high intensity signal of the posterior lobe in pituitary gland

dehydration by polyuria. The following data about the serum arginine-vasopressin (AVP) level and serum/urine osmolarity ratio indicated the existence of impaired AVP secretion. A water deprivation test and the subsequent administration of AVP showed that endogenous vasopressin was not appropriately secreted (Fig. 1). T1-weighted magnetic resonance imaging (MRI) of the brain demonstrated the absence of a high intensity signal of the posterior lobe in the pituitary gland, without cell infiltration or inflammation in the hypothalamus or pituitary gland (Fig. 2). There were no other anatomical abnormalities in the brain. The laboratory data that would suggest the co-existence of autoimmune disease, such as anti-nuclear antibodies, rheumatoid factor or anti-pituitary gland antibodies, were all negative, and the serum immunoglobulin and complementary factor levels were within the normal range.

After starting the administration of 1-deamino-8-D-arginine vasopressin (DDAVP), the polydipsia and polyuria drastically disappeared. The basal levels of the anterior pituitary hormones and related factors were within normal ranges as follows: plasma ACTH, 12.9 pg/ml; serum cortisol, 16.4 μg/dl; LH, <0.2 U/L; FSH, 3.5 U/L; prolactin, 5.2 ng/ml; TSH, 3.80 microU/mL; free T4, 1.74 ng/dL. A growth hormone (GH) provocative test by intravenous arginine administration showed normal GH secretion (peak value 8.5 ng/ml at 60 min). The IGF-1 level was low (42 ng/ml; normal range, 95–437), but was recovered to the normal level (118 ng/ml) 5 months after starting AVP treatment. She was then annually performed the MRI follow-up evaluation. The sequence analysis of the *MLL2* gene did not detect any mutations in the coding regions. Besides the previously reported SNPs, a novel non-synonymous SNP; c.8813C > T, p.Pro2938Leu, was identified in the *MLL* gene of the patient, and was transmitted from her asymptomatic father. This SNP was found in 4 in 363 normal individuals (allele frequency, 0.55 %).

Review of complications in hypothalamic pituitary axis in Kabuki syndrome

To the best of our knowledge, only nine patients with Kabuki syndrome had been reported to have complications in hypothalamic pituitary axis in previous papers [4–12]. Among the 10 patients including the present case, GH deficiency was the most frequent complication and found in six patients [4, 5, 8, 9, 11, 12]. Next, precocious puberty and central DI was identified in two cases [4], respectively, and ACTH deficiency was found in one [6]. One case had combination of GH deficiency and central DI [4]. Three of the 10 patients demonstrated abnormal pituitary findings in MRI study [4, 12]. Two of the six patients with GH deficiency were accompanied with premature thelarche [8, 11].

Table 2 Endocrine complications in hypothalamic pituitary axis in Kabuki syndrome

References	Age at endocrine evaluation	Sex	Complications in HP axis	Endocrine data in HP axis Serum hormone levels	Stimulation	Provocative tests Peak levels	Other endocrine data or complications	MRI findings in HP
Kuroki et al. [7]	11 months	F	Precocious puberty	PRL, 38.8 ng/ml (NR: 5–10)	LH-RH	LH, 66.7 ng/dL (NR: 4–63) FSH, 1,141.7 ng/ml (NR: 0–150)	E2, 43.0 pg/mL (NR: 2–10) Advanced bone age	N/D[a]
Niikawa et al. [5]	5 years	M	GH deficiency	N/D	N/D			N/D
Handa et al. [8]	1 year	F	GH deficiency	N/D	Arginine	GH, 8.6 ng/ml (NR: >10)	Premature thelarche	N/D
Franceschini et al. [10]	7 years 6 months	F	Precocious puberty	Increase in gonadotropin secretion	N/D		Advanced bone age	N/D
Satoh et al. [12]	2 years 11 months	M	GH deficiency	IGF-1, 0.32 U/ml	Arginine	GH, 0.8 ng/ml		Abnormal[b]
					Glucagon	GH, 2.5 ng/ml		
Tawa et al. [4]	4 years	M	Diabetes insipidus		Water deprivation	Urine osmolarity, <260 mOsm/kg H_2O[e];		Abnormal[c]
			GH deficiency	IGF-1, 0.40 U/ml	Sleep	GH, 3.6 ng/ml		
Devriendt et al. [11]	1 year 6 months–3 years 6 months	F	Hypothalamic GH deficiency	IGF-1, <10 ng/ml (at 3.5 years of age)	Glucagon	GH, 9.8 ng/ml (at 23 months of age) GH, 8.1 ng/ml (3.5 years of age)	Premature thelarche	Normal
					GRF	GH, 40 ng/ml (18 months of age)		
Gabrielli et al. [9]	9 years	M	GH deficiency	IGF-1, 1.0 U/ml (NR: 0.87–2.06)	Clonidine	GH, 5.2 ng/ml		N/D
					Arginine	GH, 5.0 ng/mL		
					Sleep	GH, 2.7 ng/ml (NR: >3.2)		
Ma et al. [6]	6 years	M	ACTH deficiency		CRH	Cortisol, <6 nmol/L ACTH, 18 pg/ml (NR: 9–52)		Normal
The present case	6 years	F	Diabetes insipidus		Water deprivation	Fig. 1[e]		Abnormal[d]

ACTH adrenocorticotropin hormone, *CT* computed tomography, *E2* estradiol, *FSH* follicle-stimulating hormone, *F* female, *GH* growth hormone, *HP* hypothalamic pituitary, *IGF-I* insulin-like growth factor-I, *LH* luteinizing hormone, *LH-RH* luteinizing hormone releasing hormone, *M* male, *MRI* magnetic resonance imaging, *N/D* not described, *NR* normal range, *PRL* prolactin

[a] CT scans showed normal

[b] Transection of pituitary stalk, atrophic anterior pituitary lobe, ectopic posterior pituitary lobe

[c] Small anterior pituitary lobe, narrow pituitary stalk, absence of high intensity signal of posterior pituitary lobe

[d] Absence of high intensity signal of posterior pituitary lobe

[e] Increase of urine osmolarity with response to vasopressin administration

Discussion

Kabuki syndrome (or Niikawa-Kuroki syndrome; MIM# 147920) was originally described by Niikawa et al. [1] and Kuroki et al. [2] independently in 1981. Both papers reported patients with multiple anomalies and mental retardation syndrome characterized by distinctive facial features. This syndrome was accompanied by various organ anomalies and health-related issues, in particular, structural CNS abnormalities, such as microcephaly, hydrocephalus, Alnord Chiari I malformation and Dandy–Walker malformation are frequently observed in these patients [3]. In contrast, endocrine problems did not seem common in Kabuki syndrome. Premature thelarche, which usually requires no special treatment, was at relatively high frequency (about 20 %) according to the previous review article [5]. Congenital hypothyroidism was found in 3 of 18 children with Kabuki syndrome [13]. In contrast, congenital abnormalities in hypothalamic pituitary axis have rarely been reported. As shown in Table 2, GH deficiency was at the highest complication in the hypothalamic pituitary axis, and most of them were successfully treated with recombinant GH. The second frequent complication was precocious puberty. Pathogenesis of premature thelarche and precocious puberty are, at least in part, overlapped and derived from hypothalamic dysfunction [14]. Two cases showed central DI either with or without a structural abnormality in the pituitary gland. Central DI can be caused by congenital malformation or secondary destruction or degeneration of neurons originating from the supraoptic and paraventricular nuclei of the hypothalamus. The causes of secondary destruction or degeneration include neoplasms, such as a germinoma or craniopharyngioma, Langerhans cell histiocytosis, autoimmune or infectious inflammation, vascular diseases, or trauma [15]. Congenital mid-brain malformation also causes congenital central DI, whereas about half of the cases are classified as the idiopathic type. The present case developed polydipsia and polyuria at 6 years of age, but neither potentially responsible destructive disease nor hypothalamic pituitary dysgenesis was identified, hence the etiology of her central DI would be classified as the idiopathic type. The other case was suggested that central DI might be derived from pituitary dysgenesis, because structural abnormality was observed in MRI. We speculate that the posterior pituitary gland of both cases may have already been partially defective on a congenital basis, and became insufficient to secrete an appropriate level of AVP during the patient's growth and development. Alternatively, it is possible that self destruction or apoptosis of the cells occurred in the posterior lobe of the pituitary gland and finally led to the development of the central DI.

Kabuki syndrome has an estimated incidence of 1 in 32,000 births on the basis of data from "Monitoring for Congenital Anomalies" in Kanagawa Prefecture in Japan [5]. Most of the cases are sporadic, and a few cases were shown to be transmitted from mildly affected parents [16, 17]. Mutations in the *mixed lineage leukemia 2* (*MLL2*) gene were found in 62–75 % of patients with Kabuki syndrome [18–21], thus suggesting that there is a wide range of variable expressivity or the existence of other causal gene(s). Although congenital abnormalities in the pituitary gland or hypothalamus are rare in Kabuki syndrome, the potential for such abnormalities should be taken into account for all Kabuki patients.

The molecular mechanism(s) responsible for the *MLL2* gene mutations on the development of symptoms in Kabuki syndrome remains unknown, and the genotype-phenotype correlation has not been clearly identified. The *MLL2* gene encodes H3-K4 histone methyltransferase which forms a complex assembly with other proteins and regulates the gene transcription [22]. It is possible that variations in interacting proteins or polymorphisms in the *MLL2* gene itself may be responsible for the phenotypic variability of Kabuki syndrome. A biochemical analysis of the MLL2 complex would be useful to better understand the mechanism responsible for the variable expressivity and incomplete penetrance of Kabuki syndrome.

In summary, various potential manifestations of Kabuki syndrome, especially on the hypothalamic pituitary axis should be carefully evaluated. The accumulation of genetic data and clinical symptoms will provide important information to understand the molecular mechanism(s) by which the *MLL2* gene results in the development or clinical variability of Kabuki syndrome.

Conflict of interest The authors declare that they have no conflict of interest.

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