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*Clinical Report*

# Atypical Findings in Kabuki Syndrome:
## Report of 8 Patients in a Series of 20 and Review of the Literature

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**Kabuki syndrome (KS) is a rare multiple congenital anomaly/mental retardation syndrome with an estimated frequency of 1/32,000 in Japan. Five major criteria delineate KS namely postnatal short stature, skeletal anomalies, moderate mental retardation, dermatoglyphic anomalies, and a characteristic facial dysmorphism. Here we report on a series of 20 sporadic KS patients and we focus on some rare and atypical features that we have observed: chronic and/or severe diarrhea (4/20) including celiac disease, diaphragmatic defects (3/20), pseudarthrosis of the clavicles (2/20), vitiligo (2/20), and persistent hypoglycemia (2/20). Other occasional findings were severe autoimmune thrombopenia, cerebellar vermis atrophy, and myopathic features. Interestingly, one of our KS patients presented with a clinical overlap with CHARGE syndrome (right eye microphtalmia with optic nerve coloboma, VSD, bilateral cryptorchidism, and severe deafness). Because these features are more frequent in our series than previously described, we propose to carefully investigate these manifestations during KS patient survey in an attempt to determine their real frequency and in order to improve clinical management.** 

**KEY WORDS: Kabuki syndrome; atypical features; clinical management**

## INTRODUCTION

Kabuki syndrome (KS, Niikawa–Kuroki syndrome, MIM: 147920) is a rare multiple congenital anomaly/mental retardation syndrome described simultaneously by Niikawa et al. [1981] and Kuroki et al. [1981]. The estimated frequency of this syndrome is about in 1/32,000 in Japan and probably less in Caucasians [Niikawa et al., 1988; Philip et al., 1992; Schrander-Stumpel et al., 1994]. Thus far, more than 300 patients have been described in the literature [Wessels et al., 2002]. Five cardinal criteria are required for KS diagnosis, namely postnatal short stature, mental retardation, skeletal anomalies, dermatoglyphic anomalies, and characteristic facial dysmorphism. However, numerous other clinical manifestations have been described in KS patients including cardiac and renal malformations, deafness, ophthalmologic anomalies, hyperlaxity including hip dislocation, missing teeth, frequent infection, feeding difficulties, intestinal malrotation, anorectal anomalies, seizures, and endocrine anomalies [Niikawa et al., 1988; Kluijt et al., 2000]. Here, we report on a series of KS patients focusing on rarely described clinical manifestations observed in 8/20 patients such as hypoglycemic episodes, severe diarrhea, celiac disease, diaphragmatic defect, pseudarthrosis of the clavicles, cerebral white matter hypersignal, and vitiligo.

## PATIENTS AND METHODS

All patients were ascertained in clinical genetics units and fit the clinical criteria for KS: postnatal short stature, mental retardation, skeletal anomalies, dermatoglyphic anomalies, and characteristic facial dysmorphism (Fig. 1). All KS patients had cardiac, renal, ophthalmologic, audiometric, standard, and high resolution blood chromosomes studies and metabolic investigations including plasma amino acids as well as urine organic acids chromatography, and a carbohydrate deficiency screening test. We found that 8 KS patients of our series of 20 patients had atypical features. Table I summarizes the clinical criteria for diagnosis of KS in our eight patients as compared to the literature while Table II summarizes the atypical features observed in that cohort.

### Patient 1

Patient 1 was the second child born to unrelated healthy parents originally from France. Her twin died in utero with hypoplasia of the heart left ventricle. She had severe feeding difficulties requiring tube feeding, ungueal dysplasia, and severe mental retardation (IQ 50). Renal ultrasound revealed double collecting system of the left kidney. She also had a diaphragmatic defect and bilateral pseudarthrosis of clavicles. Unfortunately, necropsy was not performed for the twin of patient 1 presenting with hypoplastic left heart. No molecular study aiming to determine whether patient 1 and her sib were concordant or discordant twins was available.

### Patient 2

Patient 2 was the third child out of three born to unrelated healthy parents originally from Portugal. She had severe feeding difficulties requiring gastrostomy, cow's milk protein allergy, frequent and erratic hypoglycemic episodes (ranging from 2.5 to 2 mmol/L) that persisted after 2 years of age, seizures, microcephaly, chronic diarrhea, eczema, premature thelarche, and severe postnatal short stature. IQ was 62. Skeletal survey showed partial hemiagenesis of the sacrum, brachydactyly, small femoral and knee epiphysis, and delayed

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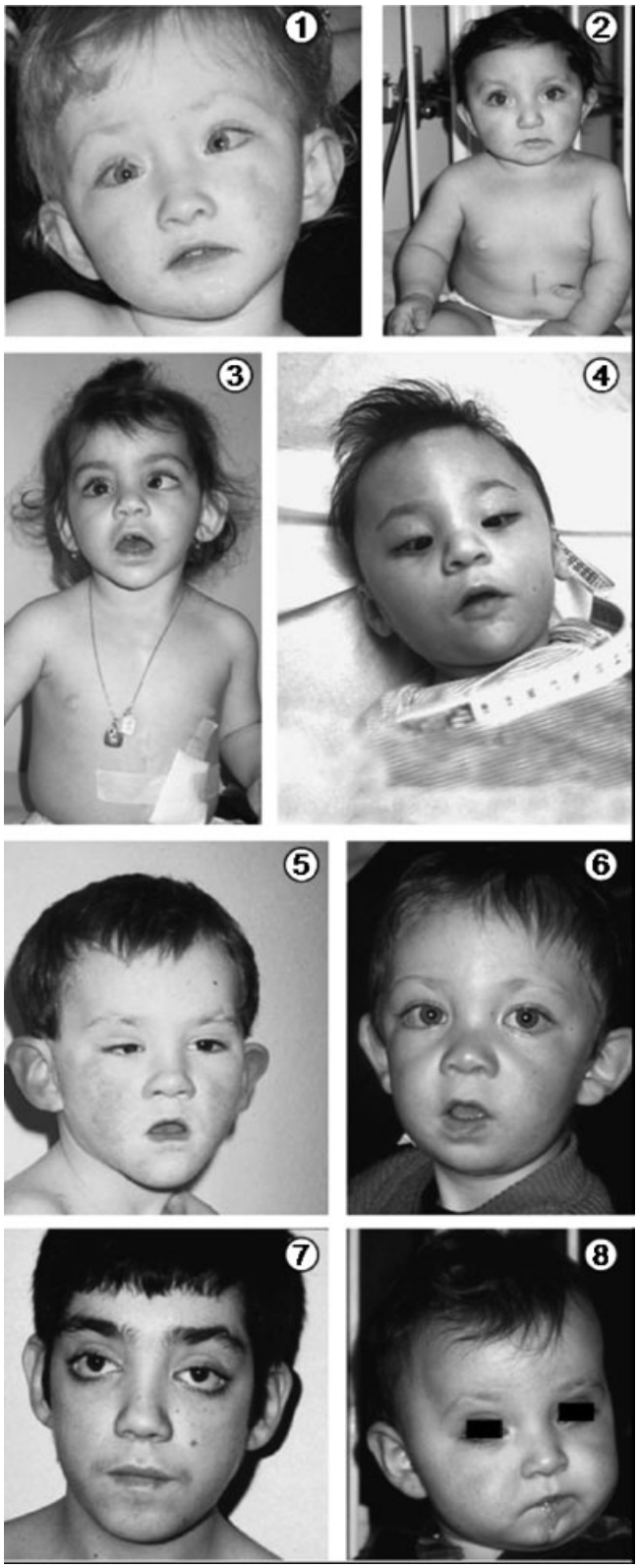


Fig. 1. Front view of Kabuki syndrome (KS) patients 1–8 with atypical features (left to right, and top to the bottom). Note gastrostomy in patient 2 and 3 and right microphtalmia in patient 5.

bone age. Renal ultrasound showed hypoplasia of the left kidney as well as pyelic duplication in the ectopic right kidney. Audiometric studies revealed bilateral mixed deafness (−90 dB).

### Patient 3

Patient 3 was the first child born to unrelated healthy parents originally from France. She needed gastrostomy for severe feeding difficulties. She also had severe persistent erratic hypoglycemic episodes (1.4 and 2.8 mmol/L at 2 and 4 years of age, respectively), chronic diarrhea since the age of 1 year (3–8 foul-smelling and greasy stools daily), and autoimmune features including neutropenia (200/mm$^3$), thrombopenia (5,000/mm$^3$), hypogammaglobulinemia with IgA deficiency (0.18 g/L), and vitiligo. Recurrent immunoglobulin infusions were required to normalize thrombopenia. Superior and inferior lateral incisors as well as premolar teeth were missing. Cardiac ultrasound showed a large VSD.

### Patient 4

Patient 4 was the first child born to unrelated healthy Caucasian parents. He had severe feeding difficulties needing nasogastric tube feeding, trigonocephaly, hypotonia, scoliosis, and nystagmus. After having presenting with chronic diarrhea during the first month of life, severe constipation and failure to thrive occurred. Intestinal biopsy and positive anti-endomysium and anti-gliadin antibodies demonstrated coeliac disease as the cause of diarrhea and constipation. A gluten free diet was then undertaken.

### Patient 5

Patient 5 was the third child out of three born to unrelated healthy Caucasian parents. He had severe congenital malformations including Pierre Robin sequence, right hip dislocation, bilateral cryptorchidism, bilateral hearing loss with Mondini dysplasia, optic nerve coloboma and right microphtalmia, severe scoliosis, right diaphragmatic hernia, ASD, and pseudarthrosis of the right clavicles. He also had vitiligo. He was referred to our genetic department with the diagnosis of CHARGE association. We proposed that this patient had KS because we believed that his facial dysmorphism is consistent with this diagnosis. Telomeric FISH analysis was normal.

### Patient 6

Patient 6 was the second child out of three born to unrelated healthy Caucasian parents. He had hearing loss and severe chronic diarrhea (5–7 liquid stools per day) with malabsorption starting from birth, despite low lactose and fibers diet, and requiring naso-gastric tube feeding. Decreased carbohydrate absorption was noted but growth was normal. Skeletal survey showed a butterfly vertebrae (11th thoracic vertebrae), and cardiac ultrasound showed ASD. Cerebral MRI showed cortical and periventricular hyper signal of the white matter. Electroencephalogram was normal.

### Patient 7

Patient 7 was the first child out of three born to unrelated healthy Caucasian parents. He had muscular biopsy for severe muscular involvement. Histological results argue for mitochondrial defect (peripheral and intermyofibrillar mitochondrial accumulation) but respiratory chain studies and molecular analysis of mitochondrial DNA were normal.

### Patient 8

Patient 8 was the third child born to unrelated healthy Caucasian parents. She had cleft palate, bifid tongue,

TABLE I. Clinical Features in Eight KS Patients Compared to the Literature (n = 313)

| | Case | | | | | | | | All KS | |
|---|---|---|---|---|---|---|---|---|---|---|
| Clinical features in KS | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | N = 313[a] | % |
| General | | | | | | | | | | |
| Gender | F | F | F | F | M | M | M | F | F = 164 | 52 |
| Post natal growth retardation | + | + | − | − | + | − | + | + | 212/312 | 68 |
| Feeding difficulties | + | + | + | + | + | + | ? | + | 59/206 | 29 |
| Frequent infections | − | + | + | + | + | + | ? | + | 120/195 | 61 |
| Facial dysmorphism | | | | | | | | | | |
| High/sparse eyebrows | + | + | − | + | + | + | + | + | 245/287 | 85 |
| Large palpebral fissures | + | + | + | + | + | + | + | + | 297/300 | 99 |
| Eversion of lower palpebral fissure | + | + | + | + | − | + | + | + | 281/299 | 94 |
| Depressed nasal tip | + | + | + | + | + | + | + | + | 176/221 | 79 |
| Large/malformed ears | + | + | + | + | + | + | + | + | 234/293 | 80 |
| Cleft (C) or high palate (H) | H | − | − | H | C | H | ? | C | 139/248 | 56 |
| Micrognathia | + | + | + | − | + | + | + | + | 42/132 | 32 |
| Blue sclerae | − | + | − | − | − | − | − | + | 46/179 | 25 |
| Strabismus | + | − | + | + | − | − | − | + | 65/233 | 28 |
| Ptosis | + | − | − | + | + | + | + | − | 33/98 | 33 |
| Abnormal dentition | ? | ? | + | + | ? | ? | ? | − | 141/249 | 56 |
| Cerebral anomalies | | | | | | | | | | |
| Mental retardation | + | + | + | + | + | + | + | + | 275/311 | 88 |
| Hypotonia | + | + | + | + | + | + | + | + | 77/178 | 43 |
| Seizures | − | + | − | − | − | − | − | − | 27/198 | 13 |
| Microcephaly | − | − | + | + | − | − | − | + | 74/269 | 27 |
| Skeletal anomalies | | | | | | | | | | |
| Fetal pads | + | + | + | + | + | + | + | + | 234/297 | 79 |
| Brachy/clinodactyly 5th finger | + | + | + | + | + | + | + | + | 192/243 | 79 |
| Hip dislocation | − | − | − | + | + | − | + | − | 42/274 | 15 |
| Hyperlaxity | + | + | + | + | + | + | + | + | 126/188 | 67 |
| Scoliosis/vertebral malformation | − | + | − | + | + | + | + | + | 79/276 | 29 |
| Visceral anomalies | | | | | | | | | | |
| Cardiac | − | − | + | − | + | + | ? | + | 119/293 | 40 |
| Genital | − | − | − | − | + | + | ? | − | 40/300 | 13 |
| Renal | + | + | − | − | − | − | ? | + | 52/261 | 20 |
| Endocrine features | | | | | | | | | | |
| Premature thelarche | − | − | − | + | I | I | I | − | 39/159 | 25 |
| Deafness | ? | + | − | − | + | + | ? | + | 55/308 | 18 |

I, inappropriate.
[a]The numbers of patients assessed for each of the features described in this table are based on the data available in the literature (see Matsumoto and Niikawa [2003] for review).

diaphragmatic defect, and chronic diarrhea until the age of 3 years. X-rays showed a butterfly vertebrae (11th thoracic), and scoliosis. Cardiac and renal ultrasound showed ASD and right kidney duplication, respectively. Cerebral MRI showed vermis atrophy.

## DISCUSSION

KS is a rare syndrome and to date no biological proof is available to confirm this disease. Therefore, the diagnosis of KS is based on a series of clinical arguments including five major criteria proposed by Niikawa and Kuroki [Kuroki et al., 1981; Niikawa et al., 1981, 1988]. However, a series of less frequent features are very helpful for the clinician when performing KS diagnosis. Atypical features seem to be more commonly observed in our series than previously described in the literature, according to the report of Ming et al. [2001a] on 14 KS patients with rare manifestations, namely, persistent hypoglycemia in 2/14 patients with hyperinsulinism in 1, chronic diarrhea (2/14) requiring enteral nutrition in 1, autoimmune thrombopenia (1/14), and autoimmune anemia (1/14). Here, we report on atypical features in eight patients with KS with, to our knowledge, four hitherto unreported anomalies including myopathic features with mitochondrial changes in muscle histology, sacral hemiagenesis, hypersignal of the white matter, and celiac disease (Table II).

Muscle weakness has been observed several times in KS but histological studies were rarely performed and were found to be normal in such reported patients [Philip et al., 1992]. Otherwise, metabolic screening including blood lactate performed in some KS patients, was normal except in one patient [Wilson, 1998; patient 1]. Here, we describe a patient (patient 7) with myopathic and histological features suggestive of a mitochondrial defect. The discrepancy between abnormal histological studies and normal respiratory chain function has been also observed in non-KS patients, suggesting a secondary anomaly resulting from a non specific mitochondrial dysfunction.

Skeletal features were one of the five major criteria for KS diagnosis. Although vertebral malformations were frequently observed in patients with KS, sacral hemiagenesis has not been described in the literature. Pseudarthrosis of the clavicles resulting from obstetric trauma could be excluded in our patients. Fryns and Devriendt [1998] reported hypoplastic clavicles in a KS patient with hypermobility of both shoulders and bone X-rays showing bilateral bipartite clavicles compatible with pseudarthrosis of the clavicles. Since then, two other KS patients have been reported with defective clavicles [Hinrichs et al., 2002]. One of them had a right hypoplasia

TABLE II. Atypical Features in our Series as Compared to the Literature

| Clinical features | Case 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | Total | Literature (n = 313) | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chronic diarrhea | − | + | + | − | + | − | + | + | 5 | 7/313 (2.2%) | Philip et al. [1992]; Bay et al. [1993]; Li et al. [1996]; Kawame et al. [1999]; Ming et al. [2001a] |
| Diaphragmatic defect (eventration or hernia) | + | − | − | + | − | − | + | − | 3 | 12/313 (3.8%) | Braun and Schmid [1984]; Halal et al. [1989]; Philip et al. [1992]; Bay et al. [1993]; Lynch et al. [1995]; Silengo et al. [1996]; Tsukahara et al. [1997]; Donadio et al. [2000]; McGaughran et al. [2000]; Van Haelst et al. [2000] |
| Abnormal claviculae | − | − | − | + | − | + | − | − | 2 | 3/313 (1%) | Fryns and Devriendt [1998]; Hinrichs et al. [2002] |
| Sacral hemiagenesis | − | + | − | − | − | − | − | − | 1 | 0 | |
| Vitiligo | − | − | + | + | − | − | − | − | 2 | 3/313 (1%) | Schrander-Stumpel et al. [1993]; Ewart-Toland et al. [1998]; McGaughran et al. [2000] |
| Neonatal hypoglycemia | − | + | + | − | − | − | − | − | 2 | 21/313 (6.7%) | Niikawa et al. [1988]; Philip et al. [1992]; Bay et al. [1993]; Burke and Jones [1995]; Ewart-Toland et al. [1998]; Kluijt et al. [2000]; Bereket et al. [2001]; Ming et al. [2001a]; Wilson [1998] |
| Persistent hypoglycemia | − | + | + | − | − | − | − | − | 2 | 4/313 (1%) | Bay et al. [1993]; Bereket et al. [2001]; Ming et al. [2001a]; Niikawa et al. [1988] |
| Auto-immune thrombopenia | − | − | + | − | − | − | − | − | 1 | 7/313 (2.2%) | Niikawa et al. [1988]; Bay et al. [1993]; Watanabe et al. [1994]; Hostoffer et al. [1996]; McGaughran et al. [2000]; Ming et al. [2001a] |
| White matter hypersignal | − | − | − | − | + | − | − | − | 1 | 0 | |
| Vermis atrophy | − | − | − | − | − | − | + | − | 1 | 1 | Yano et al. [1997] |
| Myopathic features | − | − | − | − | − | + | − | − | 1 | 0 | |

clavicle while the other had a bipartite right clavicle with a missing medial third.

CNS malformations have been described several times in patients with KS, including subarachnoid cyst (2), cerebellar and brainstem atrophy, hydrocephalus with aqueductal stenosis, periventricular neuronal heterotopia with digenesis of the corpus callosum and polymicrogyria with no white matter hyper signal [Chrzanowska et al., 1997; Chu et al., 1997; Yano et al., 1997; Kasuya et al., 1998; Di Gennaro et al., 1999; Mihci et al., 2002].

Chronic diarrhea has been reported 7-times in patients with KS. In our series, four patients suffered from chronic diarrhea and in one patient, celiac disease, a newly reported feature, could be demonstrated. Patient 6 suffered from digestive malabsorption but, no specific cause could be diagnosed.

Autoimmunity has been described several times in KS patients, namely hypothyroidism [Ewart-Toland et al., 1998; Kawame et al., 1999], anemia or thrombopenia [Niikawa et al., 1988; Bay et al., 1993; Watanabe et al., 1994; Hostoffer et al., 1996; McGaughran et al., 2000; Ming et al., 2001a], and vitiligo [Schrander-Stumpel et al., 1993; Ewart-Toland et al., 1998; McGaughran et al., 2000]. In our series, one patient had autoimmune thrombopenia and two patients have vitiligo. Interestingly, patient 4 had celiac disease with anti-endomysium combined with anti-gliadin antibodies, expanding the field of autoimmune features in KS.

Neonatal hypoglycemias were described in 21 KS patients but persistent hypoglycemia was reported in only 4 patients [Niikawa et al., 1988; Bay et al., 1993; Bereket et al., 2001; Ming et al., 2001a]. Hyperinsulinism was suspected in one patient [Ming et al., 2001a]. In our series, two KS patients present with chronic and severe but erratic hypoglycemia. No treatment; other than that to relieve symptoms, was proposed because hypoglycemic episodes were rare and unpredictable. Along these lines, we think that chronic hypoglycemia should be suspected in KS patients with seizures such as those observed in our patient 2.

Some of the rare features observed in our patients are incapacitating (myopathy, chronic diarrhea, diaphragmatic defect, or hernia) or responsible for life-threatening complications (severe thrombopenia). In a series of 18 KS patients, Kawame et al. [1999] emphasizes on the variability of the phenotypic spectrum and management issues comprising chronic diarrhea in 2/18 patients including malabsorption in 1, hypothyroidism (3/18) and autoimmune thrombocytopenia with hypogammaglobulinemia and hemolytic anemia (1/18). Van Haelst et al. [2000] report on unexpected life-threatening complications in two KS patients. One had a diaphragmatic defect and the other had extra hepatic bilary atresia. Ewart-Toland et al. [1998] also report on one patient with sclerosis cholangitidis requiring liver transplantation and another patient with dysplastic kidneys, also requiring transplantation.

Interestingly, clinical overlap between CHARGE association and KS is observed in our patient 5. Recently, Ming et al. [2001b] described two patients with KS and an initial diagnosis of CHARGE association. The similar phenotype observed in our patient suggests that this clinical association is not fortuitous.

In conclusion, we proposed a systematic examination of all patients with KS for rare features in attempt to (i) determine the real frequency of these features, (ii) eventually, use them as useful diagnostic criteria, and (iii) improve clinical management for these patients.

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