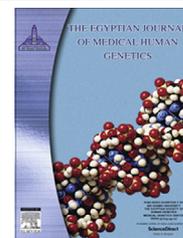




Ain Shams University

The Egyptian Journal of Medical Human Genetics

www.ejmhg.eg.net
www.sciencedirect.com



CASE REPORT

Kabuki make-up syndrome with genitourinary anomalies, ophthalmologic features and hyperpigmentation in an Egyptian child



Rabah M. Shawky*, Radwa Gamal, Nayera Mostafa

Pediatric Department, Genetics Unit, Ain Shams University, Egypt

Received 16 November 2015; accepted 2 December 2015

Available online 21 January 2016

KEYWORDS

Kabuki make-up syndrome;
Genitourinary anomalies;
Hyperpigmentation;
Mental retardation

Abstract We report a 3.5 year old male child, first in order of birth of healthy consanguineous Egyptian parents with typical characteristics of Kabuki make-up syndrome. The patient had microcephaly, high arched sparse eyebrows, hypertelorism, long palpebral fissures with eversion of the lateral third of the lower eyelids, bilateral ptosis, long eyelashes, blue sclera, depressed nasal bridge, broad nose with everted nares, and low set small deformed ears, thin lips, low post hair line, short neck, persistent fingertip pads, dysplastic nails, hypermobile joints, pigmented nevus on the back, lateral side of right foot and right leg and mild hypertrichosis over the lower back. Our patient had also a non-functioning left kidney, multiple chalazions in upper eyelids, enlargement of the glans penis, which were not reported previously, and moderate mental retardation.

© 2016 The Authors. Production and hosting by Elsevier B.V. on behalf of Ain Shams University. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Kabuki make-up syndrome (KMS) is a congenital mental retardation syndrome characterized by typical facial features including: long palpebral fissures with eversion of the lateral third of the lower eyelids, arched eyebrows with sparse outer half, prominent eye lashes, broad and depressed nasal tip, large prominent earlobes, a cleft high-arched palate, micrognathia, low posterior hair line, scoliosis, short fifth finger, persistence of fingerpads, radiographic abnormalities of the vertebrae, hands, and hip joints, and recurrent otitis media in infancy [1].

Additional features include short stature, internal malformations (involving the heart, genitourinary and gastrointestinal systems) and immunological defects [2].

Kabuki make-up syndrome was first described in Japanese children in 1981 [3,4]. The estimated prevalence of KMS in Japan was 1/32,000 people with almost equal sex distribution. Although it was initially considered as a disease affecting exclusively the Japanese population, several reports support a widespread ethnic distribution of KMS [5].

We report a case with the typical features of Kabuki make-up syndrome who has in addition some unreported features after taking consent of the parents.

* Corresponding author.

E-mail address: shawkyrabah@yahoo.com (R.M. Shawky).

Peer review under responsibility of Ain Shams University.

<http://dx.doi.org/10.1016/j.ejmhg.2015.12.001>

1110-8630 © 2016 The Authors. Production and hosting by Elsevier B.V. on behalf of Ain Shams University.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).



Figure 1 Photo of the patient.

2. Case report

A 3.5 year old male child, first in order of birth of healthy consanguineous Egyptian parents. The patient was delivered at full term by cesarean section. His birth weight was 3 kg. No problems were noted during pregnancy. The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams

University complaining of developmental delay and abnormal features.

The patient was born with undescended testes and had repair surgery at the age of 1 year. At the age of 1.5 year, he had multiple chalazions in upper lids of both eyes which resolved spontaneously leaving small scars. Family history was unremarkable. Both parents were normal.

On examination, the patient had mental retardation, his weight was 13.5 kg (5th percentile), his height was 90 cm (5th percentile), and his skull circumference was 47 cm (3rd percentile).

The patient had microcephaly, high arched eyebrows with sparse outer half, hypertelorism, long palpebral fissures with eversion of the lateral third of the lower eyelids, bilateral ptosis, long and prominent eyelashes, blue sclera, depressed nasal bridge, broad nose with everted nares, low set small deformed ears, thin lips, high-arched palate, micrognathia, low post hair line and short neck (Figs. 1 and 2).

The patient had also persistent fingertip pads, dysplastic nails (Fig. 3), hypermobile joints (Fig. 4), overlapping of the second toes over third toes, short second toe of the left foot, pigmented nevus on the back, lateral side of the right foot and front of the right leg (Fig. 5). He also had mild hypertrichosis over the lower back.

Abdominal, cardiac and neurologic examinations were normal. The genitals demonstrated enlargement of the glans penis (Fig. 6). IQ was 48.

Extended metabolic screen, serum lactate and serum ammonium were normal.

Karyotype was also normal. Fundus examination, audiometry and EEG were normal.

ECHO cardiography was normal. Abdomino-pelvic ultrasonography revealed non-visualized left kidney. Renal isotope



Figure 2 Microcephaly, high arched sparse eyebrows, hypertelorism, long palpebral fissures, bilateral ptosis, long eyelashes, blue sclera, depressed nasal bridge, broad nose with everted nares, low set small deformed ears, thin lips, low post hair line and short neck.



Figure 3 Persistent fingertip pads and dysplastic nails.

scan revealed normal function of the right kidney and no function of the left kidney. Urinalysis and kidney function tests were normal.

Skeletal survey and MRI brain were normal.

3. Discussion

Kabuki syndrome is characterized by five fundamental features, dysmorphic facies, skeletal anomalies, dermatoglyphic abnormalities, mild to moderate mental retardation as well as postnatal growth deficiency [6].

We report a 3.5 year old male child with the typical facial features of Kabuki make up syndrome including microcephaly, high arched sparse eyebrows, hypertelorism, long palpebral fissures with eversion of the lateral third of the lower eyelids, bilateral ptosis, long eyelashes, blue sclera, depressed nasal bridge, broad nose with everted nares, and low set small

deformed ears, thin lips, low post hair line, short neck, persistent fingertip pads, dysplastic nails, hypermobile joints, overlapping of the second toes over third toes, short second toe of left foot, pigmented nevus on the back, lateral side of the right foot and right leg and mild hypertrichosis over the lower back.

The skeletal anomalies first described in Kabuki syndrome were spinal abnormalities (butterfly vertebrae, sagittal cleft vertebrae and scoliosis), hand anomalies (cone-shaped epiphyses, brachydactyly and clinodactyly) and hip dislocation [7,8]. More recently, pseudarthrosis of the clavicles [9], recurrent dislocation of the patella [10,11], cleft hand, syndactyly [12,13], tarsal coalition and congenital talipes equinovarus have also been reported [11]. Skeletal survey of our patient was normal.

The dermatoglyphic abnormalities which were not detected in our patient comprise excess of ulnar loop patterns on the fingertips, hypothenar loop patterns, ulnar loops in the 4th



Figure 4 Hypermobile joints.

or 5th inter-digital space, single flexion creases of the 4th or 5th finger and excessive minor flexion creases of the palms [14]. Our patient had whorl digit pattern.

Additional phenotypic malformations were prominent fingertip pads and joint hyperlaxity as detected in our patient [15]. Persistent fetal pads are a key feature for the diagnosis (82%) of patients with Kabuki syndrome. Ligamentous laxity and muscle hypotrophy are the major pathologic factors in dislocations with Kabuki syndrome [16].

Pigmented nevi have been occasionally observed in Kabuki syndrome [14]. Our patient had pigmented nevi on the back, lateral side of the right foot and front of the right leg with mild hypertrichosis over the lower back.

The most common ophthalmic abnormalities in Kabuki syndrome are strabismus and ptosis, with reported incidence rates of 20.5% and 14.4% respectively [17]. Other rare abnormalities, such as coloboma, nystagmus, microphthalmos, microcornea, corneal opacities, blue sclera, cataracts, nasolacrimal duct obstruction, caruncle lipoma, corneal pannus, retinal telangiectasia, and retinal pigmentation, have been reported in Kabuki syndrome [17–19]. Our patient had bilateral ptosis and blue sclera. He also had chalazions in both eyes which were not reported before.

Otologic problems, particularly recurrent otitis media, were common in KMS which were not detected in our patient [20].



Figure 5 Dysplastic nails, overlapping of the second toes over third toes, short second toe of the left foot, pigmented nevus on the back, lateral side of the right foot and front of the right leg.



Figure 6 Enlargement of the glans penis.

Hearing is normal in our patient. However, a wide spectrum of ear anomalies can be detected in KMS. Hearing loss reported in KMS has usually been attributed to sensorineural or mixed hearing loss [21]. So it is recommended that children with KMS have their hearing monitored regularly [14].

Dental abnormalities have been reported in over 60% of patients with KMS and were not detected in our patient including most commonly hypodontia (particularly of central/lateral incisors and premolars) associated with interdental spacing and microdontia [16] as well as absence of both permanent mandibular lateral incisors, malocclusion, small dental arches, severe maxillary recession and midfacial hypoplasia [15,17]. Also supernumerary taurodontism teeth in the maxillary arch were reported [18].

Endocrinologic abnormalities such as premature thelarche in females were detected in patients with KMS [15].

Variable cardiac anomalies which were also described in KMS and were not detected in our patient include atrial and ventricular septal defects, coarctation of the aorta, bicuspid aortic valve, mitral valve prolapse and hypertrophic cardiomyopathy [19].

Genitourinary and gastrointestinal anomalies in KS include anal atresia and diaphragmatic hernia [19]. Renal problems and frequent urinary tract infections are not uncommon in KS [20,21]. Ewart-Toland et al. described patients with renal and hepatic anomalies, ileal perforation, hydronephrosis, hydronephrosis and dysplastic kidneys [22]. Abdomino-pelvic ultrasonography of our patient revealed non-visualized left kidney and renal isotope scan detected no function of the left kidney. He also had undescended testes which have been reported in KMS [14].

KMS patients have increased susceptibility to infection due to immune defects, particularly hypogammaglobulinemia [23]. This syndrome is sometimes associated with autoimmune abnormalities, such as idiopathic thrombocytopenic purpura (ITP) [20], autoimmune hemolytic anemia, leukoplakia, vitiligo and thyroiditis which were not detected in our patient. Since the autoimmune disease does not occur until later childhood, the real frequency of autoimmune conditions in this syndrome might be underestimated [20].

Patients with KMS exhibit mild to moderate mental retardation. Our patient had moderate mental retardation. A significant delay in expressive language as revealed in our child is a commonly reported feature of Kabuki Syndrome [24].

Seizures, which were not detected in our patient, were seen in less than half of the patients with KMS [20]. Corpus callosum hypoplasia and Dandy-Walker malformation might

occur concomitantly with Kabuki syndrome [25]. Our patient had normal MRI brain.

Anesthetic concerns specific to this syndrome relate to possible airway difficulties, congenital heart disease, pulmonary function, joint laxity and a latex allergy [19].

Our patient had normal karyotype. However, many cytogenetic abnormalities have been reported, and the most common change is related to chromosome X [4]. Genetic studies reveal submicroscopic duplication on the 8th chromosome at 8p22-23.1 to be the cause behind this disorder [4]. Lo et al., found an interstitial duplication of the short arm of chromosome 1 with breakpoints involving 1p13.1 and 1p22.1 in a patient with some features suggesting Kabuki syndrome [26]. Using comparative genomic hybridization (CGH), Milunsky and Huang found an 8p23.1-p22 duplication in 6 unrelated patients with Kabuki syndrome [27].

Although the parents of our patient are consanguineous, (consanguinity rate is high in Egypt [28]), we believe that our patient is a sporadic case in his family. Kabuki syndrome is mostly sporadic, although some familial cases have been reported. Inheritance is thought to be autosomal dominant or X-linked recessive. Dominant inheritance with variable expressivity was supported by the mother and child reported by Courtens et al. [29].

Kabuki syndrome-1 (KABUK1) is caused by heterozygous mutation in the MLL2 gene on chromosome 12q12-q14. Kabuki syndrome-2 is caused by mutation in the KDM6A gene on chromosome Xp11.3 [30]. MLL2 mutations were identified in 50 (61.7%) of 81 patients with Kabuki syndrome. Although Kabuki syndrome can be phenotypically variable, facial morphology study of this syndrome suggested that nearly all patients with typical Kabuki syndrome facial features have pathogenic MLL2 mutations. In addition, Banka et al. showed that KABUK1 patients were more likely to have feeding problems, kidney anomalies, early breast bud development, joint dislocations, and palatal malformations in comparison with MLL2 mutation-negative patients. High-arched eyebrows, short fifth fingers, and infantile hypotonia were more commonly seen in patients with MLL2 mutations than in those with KDM6A mutations [31]. Our patient most probably belongs to Kabuki syndrome type 1.

To conclude: Kabuki syndrome is a multiple congenital anomalies syndrome characterized by characteristic facial features and varying degrees of mental retardation. We report a patient with the typical features of KS who has in addition unreported features including non-functioning left kidney, chalazions and enlargement of the glans penis. Highlighting the signs and symptoms of KMS will help in better understanding of this unique syndrome.

Conflict of interest

No conflict of interest.

References

- [1] Niikawa N, Kuroki Y, Kajii T, Matsuura N, Ishikiriyama S, Tonoki H, et al. Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 62 patients. *Am J Med Genet* 1988;31(3):565-89.
- [2] Armstrong L, Abd El Moneim A, Aleck K, Baumann C, Braddock SR, Gillessen-Kaesbach G, et al. Further delineation

- of Kabuki syndrome in 48 well-defined new individuals. *Am J Med Genet A* 2005;132A(3):265–72.
- [3] McMahon J, Reardon W. The spectrum of congenital cardiac malformations encountered in six children with Kabuki syndrome. *Cardiol Young* 2006;16(1):30–3.
- [4] Adam MP, Hudgins L. Kabuki syndrome: a review. *Clin Genet* 2004;67(3):209–19.
- [5] Micale L, Augello B, Fusco C, Selicorni A, Loviglio MN, Silengo MC, et al. Mutation spectrum of MLL2 in a cohort of Kabuki syndrome patients. *Orphanet J Rare Dis* 2011;9:6–38.
- [6] Medina FMC, Rodriguez P, Cabral RTS, Castro MB, Llerena Jr JC, Japiassú RM. Kabuki syndrome: a case report with severe ocular abnormalities. *Rev Bras Oftalmol* 2013;72(5):341–3.
- [7] Kuroki Y, Suzuki Y, Chyo H, Hata A, Matsui I. A new malformation syndrome of long palpebral fissures, large ears, depressed nasal tip, and skeletal anomalies associated with postnatal dwarfism and mental retardation. *J Pediatr* 1981;99:570–3.
- [8] Niikawa N, Matsuura N, Fukushima Y, Ohsawa T, Kajii T. Kabuki make-up syndrome: a syndrome of mental retardation, unusual facies, large and protruding ears, and postnatal growth deficiency. *J Pediatr* 1981;99:565–9.
- [9] Hinrichs B, Gramss B, Meinecke P. Defective clavicles in Kabuki syndrome. *Genet Couns* 2002;13(4):477–9.
- [10] Ikegawa S, Sakaguchi R, Kimizuka M, Yanagisako Y, Tokimura F. Recurrent dislocation of the patella in Kabuki make-up syndrome. *J Pediatr Orthop* 1993;13(2):265–7.
- [11] Kurosawa K, Kawame H, Ochiai Y, Nakashima M, Tohma T, Ohashi H. Patellar dislocation in Kabuki syndrome. *Am J Med Genet* 2002;108(2):160–3.
- [12] Philip N, Meinecke P, David A, Dean J, Ayme S, Clark R, et al. Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 16 non-Japanese cases. *Clin Dysmorphol* 1992;1(2):63–77.
- [13] Phillips S, Hemmady S, Thomas P, O'Doherty D. Kabuki syndrome presenting with congenital talipes equinovarus. *J Pediatr Orthop B* 2005;14(4):285–6.
- [14] Lu Y, Cao K. A case report: hearing disorder in Kabuki make-up (Niikawa-Kuroki) syndrome in China. *J Otol* 2014;9(3):136–40.
- [15] Giordano et al. Autoimmune haematological disorders in two Italian children with Kabuki syndrome. *Italian J Pediatr* 2014;40:10.
- [16] Wada A et al. Surgical treatment of hip dislocation in Kabuki syndrome: use of incomplete periacetabular osteotomy for posterior acetabular wall deficiency. *J Child Orthop* 2012;6(4):261–7.
- [17] Ming JE, Russell KL, Bason L, McDonald-McGinn DM, Zackai EH. Coloboma and other ophthalmologic anomalies in Kabuki syndrome: distinction from charge association. *Am J Med Genet A* 2003;123A(3):249–52.
- [18] Matsumoto N, Niikawa N. Kabuki make-up syndrome: a review. *Am J Med Genet C Semin Med Genet* 2003;117C(1):57–65.
- [19] Evans SL, Kumar N, Rashid MH, Hughes DS. New ocular findings in a case of Kabuki syndrome. *Eye (Lond)* 2004;18(3):322–4.
- [20] Kawame H, Hannibal MC, Hudgins L, Pagon RA. Phenotypic spectrum and management issues in Kabuki syndrome. *J Pediatr* 1999;134(4):480–5.
- [21] Schrandt-Stumpel CT et al. Kabuki syndrome: clinical data in 20 patients, literature review, and further guidelines for preventive management. *Am J Med Genet A* 2005;132A(3):234–43.
- [22] Ewart-Toland A, Enns GM, Cox VA, Mohan GC, Rosenthal P, Golabi M. Severe congenital anomalies requiring transplantation in children with Kabuki syndrome. *Am J Med Genet* 1998;80(4):362–7.
- [23] Hoffman JD, Ciprero KL, Sullivan KE, Kaplan PB, McDonald-McGinn DM, Zackai EH, et al. Immune abnormalities are a frequent manifestation of Kabuki syndrome. *Am J Med Genet A* 2005;135(3):278–81.
- [24] Upton S, Stadter CS, Landis P, Wulfsberg EA. Speech characteristics in the Kabuki syndrome. *Am J Med Genet A* 2003;116A(4):338–41.
- [25] Atalay YO et al. Anesthesia management in a patient with Kabuki syndrome. *Med Arh* 2014;68(5):359–60.
- [26] Lo IF, Cheung LY, Ng AY, Lam ST. Interstitial dup(1p) with findings of Kabuki make-up syndrome. *Am J Med Genet* 1998;78(1):55–7.
- [27] Milunsky JM, Huang XL. Unmasking Kabuki syndrome: chromosome 8p22-8p23.1 duplication revealed by comparative genomic hybridization and BAC-FISH. *Clin Genet* 2003;64(6):509–16.
- [28] Shawky RM, El-Awady YM, Elsayed SM, Hamadan GE. Consanguineous matings among Egyptian population. *Egypt J Med Hum Genet* 2011;12(2):157–63.
- [29] Courtens W, Rassart A, Stene JJ, Vamos E. Further evidence for autosomal dominant inheritance and ectodermal abnormalities in Kabuki syndrome. *Am J Med Genet* 2000;93(3):244–9.
- [30] <<http://www.omim.org/entry/147920>> .
- [31] Miyake N, Koshimizu E, Okamoto N, Mizuno S, Ogata T, Nagai T, Kosho T, Ohashi H, Kato M, Sasaki G, Mabe H, Watanabe Y, et al. MLL2 and KDM6A mutations in patients with Kabuki syndrome. *Am J Med Genet* 2013;161A(9):2234–43.