



CASE REPORTS

TWO NEW KABUKI CASES OF KABUKI MAKE-UP SYNDROME

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ABSTRACT

Kabuki syndrome (Kabuki make-up syndrome, Niikawa–Kuroki syndrome) is a multiple congenital anomaly/mental retardation syndrome. We report on an 11-month-old girl with Kabuki make-up syndrome who has premature telarche, premature pubarche and epilepsy, and a 4-month-old boy with Kabuki make-up syndrome who had been operated due to diaphragmatic hernia and had mesocardia confirmed by echocardiography. In the study, we emphasize that careful phenotypic examination of children should be performed in every patient presenting with mental retardation and epilepsy to diagnose Kabuki syndrome and the patients diagnosed as Kabuki syndrome should be followed for precocious puberty. We suggest that mesocardia, which has not been reported in the literature yet, may be considered as one of the cardiological findings of Kabuki syndrome and all Kabuki patients should be evaluated for life-threatening complications of congenital diaphragmatic hernia.

Keywords: Diaphragmatic hernia, epilepsy, Kabuki syndrome, premature telarche

KABUKİ MAKE-UP SENDROMUNUN İKİ YENİ VAKASI

ÖZET

Kabuki sendromu (Kabuki make-up sendromu, Niikawa-Kuroki sendromu) çoklu doğumsal anomali/mental gerilik sendromudur. Epilepsi, prematür telarş ve prematür pubarş olan Kabuki make-up sendromlu 11 aylık kız ve ekokardiyografi ile mezokardisi doğrulanmış ve diyafragma hernisi nedeniyle opere edilen Kabuki make-up sendromlu 4 aylık erkek çocuğu sunuyoruz. Mental gerilik ve epilepsi ile prezente olan her hastada dikkatli fenotipik inceleme yapılması gerektiğini ve Kabuki sendromu teşhisi konulan hastaların erken puberte için takip edilmesi gerektiğini vurguluyoruz. Bunun yanında, henüz literatürde bildirilmeyen mezokardinin Kabuki sendromunun kardiyolojik bulgularından birisi olarak dikkate alınabileceğini ve Kabuki sendromlu bütün hastaların doğumsal diyafragma hernisinin yaşamı tehdit eden komplikasyonları için değerlendirilmesi gerektiğini öneriyoruz.

Anahtar Kelimeler: Diafragma hernisi, epilepsi, Kabuki sendromu, prematür telarş

INTRODUCTION

Kabuki syndrome (Kabuki make-up syndrome, Niikawa–Kuroki syndrome) is a multiple congenital anomaly/mental retardation syndrome that was first described simultaneously by two groups in Japan, Niikawa et al.¹ and Kuroki et al.². The prevalence of Kabuki syndrome in the Japanese population has been estimated to be 1/32,000³. The designation Kabuki make-up refers to the resemblance of the facial features with the characteristic make-up used by actors of Kabuki, a traditional Japanese theatrical form¹. Premature telarche, premature pubarche and epilepsy

association with Kabuki make up syndrome have been rarely reported in the literature⁴. Diaphragmatic defect is an uncommon finding in Kabuki syndrome, reported in only two female patients with a diaphragmatic eventration⁵ and in an aborted fetus with a diaphragmatic hernia⁶. Mesocardia accompanied by Kabuki syndrome in the literature has not been reported yet. We report on an 11-month-old girl with Kabuki make up syndrome who has premature telarche, premature pubarche and epilepsy, and a 4-month-old boy with Kabuki make up syndrome who has mesocardia and diaphragmatic hernia.

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CASE PRESENTATION

Case 1

An 11-month-old girl was referred to emergency clinics for diarrhea and vomiting. She was born by cesarean section due to breech presentation after a term gestation to a primigravida mother. The parents were healthy first-degree cousins. She had psychomotor developmental delay and seizures at ten months of age. However, the breast development was tanner stage 2 at 4 months of age. The pubic hair was tanner stage 2 at 9 months of age. Her height was 69 cm (50-75 p), weight 7.3 kg (3-10 p) and head circumference 40 cm (< 3 percentile). She had facial dysmorphism with high arched eyebrows sparse laterally, long palpebral fissures with everted lower eyelids, long eyelashes accompanying microcephaly. Her nose was broad with depressed tip, and ears were prominent and protruding (Fig. 1). On oral examination she had high arched palate. She had a generalized hypotonia. She had both premature telarche and premature pubarche. The other system findings were normal. During one hour follow up, generalized afebrile tonic-clonic seizures, lasting longer than 30 min were observed. The status epilepticus was well controlled by an appropriate treatment. On admission biochemical investigations, including serum electrolytes, liver function tests, lipid profiles, and coagulation tests were all within normal limits except for presence of leukocytosis ($28.1 \times 10^9/L$) in the complete blood count. The electroencephalography and magnetic resonance imaging of the brain and pituitary region were normal as well as abdomen and pelvic ultrasonography, and echocardiographic examination. Ophthalmologic examination revealed normal findings. Bone age was at six months girl. Gonadotrophin releasing hormone test was performed to rule out the presence of precocious puberty revealed an exaggerated follicle stimulating hormone response and prepubertal level of luteinizing hormone response. She was diagnosed as Kabuki syndrome due to her clinical findings. Testing of three consecutive stool specimens showed *Entamoeba histolytica* as the causative agent for the diarrhea and vomiting. Stool cultures were negative for other enteropathogens. The patient was treated successfully by metronidazole. She improved clinically during her stay at the hospital, and was discharged in 10 days.



Figure 1: An 11 months old girl showing facial dysmorphism typical for Kabuki syndrome with long palpebral fissures, arched eyebrows sparse laterally, epicanthic folds, and premature telarche.

Case 2

A 4-month-old boy was referred to pediatric endocrinology division to be evaluated for facial dysmorphism. He was born to a normal pregnancy by vaginal delivery. His birth weight was 2700 g. His parents were healthy and non-consanguineous. There was no family history for mentally retarded persons nor individuals with congenital anomalies. Immediately after birth, he had been diagnosed as having diaphragmatic hernia and was intubated by endotracheal tube. At 3 days of age, a surgical operation for an anterior diaphragmatic hernia through the foramen of Morgagni was performed. He had been followed by mechanic ventilation for 25 days in the newborn intensive care unite, and antibiotic therapy was administered for sepsis during follow-up. At 4 months of age, physical examination revealed his height as 64.5 cm (50 p), weight 4500 g (3 p) and head circumference 37.6 cm (< 3 p). He was noted to have facial dysmorphic features—long palpebral fissures with eversion of the lower lateral eyelids, arched eyebrows with lateral sparseness, depressed nasal tip, large, prominent and cupped ears (Fig. 2).



In addition to the distinct facial features, he also had high arched palate, persistent fetal finger pads, arachnodactyly, bilateral simian line and umbilical hernia. Cardiac examination revealed no significant murmurs. The other system findings were normal. Laboratory examinations were within normal limits. Chest radiography showed no cardiac enlargement. Echocardiography demonstrated mesocardia with no other associated cardiac anomalies. He was diagnosed as Kabuki make up syndrome due to clinical findings.



Figure 2: Male patient showing facial dysmorphic features suggestive for Kabuki make-up syndrome.

DISCUSSION

Kabuki make-up syndrome was established with clinical findings in both patients. Currently, there is no consensus on the diagnostic criteria for Kabuki syndrome and there is no clinically available genetic test to confirm the diagnosis. In 1988, Niikawa et al. reported on the clinical findings in 62 patients diagnosed with Kabuki syndrome. Based on the findings in these patients, five cardinal manifestations were defined. These included a 'peculiar face' (eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip, and prominent ears) in 100% of their patients, skeletal anomalies (deformed spinal column with or without sagittal cleft vertebrae, and brachydactyly V) in 92% of their patients, dermatoglyphic abnormalities (fingertip pads, absence of digital triradius c and/or d, and increased digital ulnar loop and hypothenar loop

patterns) in 93% of their patients, mild to moderate mental retardation in 92% of their patients, and postnatal growth deficiency in 83% of their patients. There have also been a number of less frequent findings reported in Kabuki syndrome, including visceral abnormalities, premature breast development in females, and susceptibility to frequent infections^{3,7}. Tutar et al. reported the first non-Japanese Asian case with Kabuki make up syndrome who had premature thelarche from Turkey⁸. In our study, the female patient had premature telarche and serious infection was established in the boy. The dysmorphic features of our patients are in accordance with detailed clinical findings observed in Kabuki patients.

Although diagnosis relies on dysmorphic features, neurological symptoms are the most invalidating manifestations in the Kabuki syndrome clinical spectrum, often presenting as the first complaint; nevertheless, Kabuki syndrome is still a rare diagnoses at neurology clinics⁴. Neurological and endocrinological anomalies that are reported to include neonatal hypotonia, feeding problems, seizures, West syndrome, microcephaly, brain atrophy, growth hormone deficiency, precocious puberty, hypoglycemia, delayed sexual development, and diabetes insipidus. Other neurological abnormalities observed are subatrophy of the optic nerves, subarachnoid cyst, cerebellar and brainstem atrophy, and epilepsy^{2,9,10}. In accordance with the literature, the female patient presented with developmental delay and seizures. On the other hand she also had microcephaly. Schrandt-Stumpel et al. reported 29 Caucasian patients and reviewed 60 Japanese and 29 non-Japanese patients, noting that non-Japanese patients with this syndrome had more marked neurological symptoms. In over 80% of non-Japanese patients, neurological symptoms were a major clinical problem¹¹. Precocious puberty is an occasional finding in the syndrome. Early breast development was noted in 7 of 31 female Japanese patients. Endocrine studies in 5 cases demonstrated markedly elevated plasma follicle-stimulating hormone and moderately high prolactin levels³. Bereket et al. reported that the diagnosis of Kabuki syndrome should be considered in patients with hypoglycemia or premature thelarche when associated with developmental delay and a peculiar facies¹⁰. The girl patient did not have precocious puberty but had markedly elevated plasma follicle-stimulating hormone levels which is consistent with literature data.



Diaphragmatic defects have been reported previously in only five patients with Kabuki syndrome. Bilateral eventration of the diaphragm was reported in two Kabuki syndrome patients⁵. Diaphragmatic defects were prenatally diagnosed in a fetus of a mother with minor facial anomalies of Kabuki syndrome and a previous child with Kabuki syndrome⁶. A partial defect of the right diaphragm with herniation of the liver into the thorax was present in a fourth patient¹². Recently, a fifth patient with diaphragmatic hernia was reported¹³. The male patient supports the previous suggestion that Kabuki syndrome should be added to the list of syndromes rarely associated with diaphragm defects.

In recent studies, it has been reported that congenital heart defect is present in 58% of patients with Kabuki syndrome¹⁴. The most common finding appears to be juxtaductal coarctation of the aorta, a relatively rare heart defect, followed by VSD and ASD¹⁵. To the best of our knowledge, a patient with mesocardia in Kabuki make up syndrome hasn't been reported yet and our patient will be the first ever reported.

In conclusion, careful dysmorphological examination should be performed in all patients presenting with mental retardation and epilepsy to diagnose Kabuki syndrome. The patients diagnosed as Kabuki syndrome should be followed for premature telarche and precocious puberty. Furthermore, we suggest that mesocardia should be kept in mind as a cardiological finding of Kabuki syndrome, and all cases should be evaluated for life-threatening anomalies such as congenital diaphragmatic hernia and its complications.

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