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Japanese theatre and neonatology: where is the link?

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Title figure:
The September 1824 production of *Heike Nyōgo-ga-shima* at Osaka Sumi-za theater (Source: Wikipedia)

This male infant was born at 29 0/7 weeks of gestation to a 34-year-old G1/P1. At 28 3/7 weeks of gestation, polyhydramnion had been diagnosed and a fetal ultrasound examination had revealed an atrioventricular septal defect. Three days later, preterm contractions started and increased despite the administration of tocolytic agents. Due to a non-reassuring CTG tracing an emergency Caesarean section was performed. Apgar scores were 6, 9 and 9 at 1, 5 and 10 minutes, respectively, and the arterial umbilical cord pH was 7.26. Due to severe respiratory distress, the infant was intubated and surfactant was administered before admission to our neonatal intensive care unit. His birth weight was 1100 g (P 25 – 50), his length 39 cm (P 50 – 75) and his head circumference 27 cm (P 25 – 50).

Clinical examination revealed a number of anomalies: a singular umbilical artery, hypertelorism, lateral turning up of the lower eyelids, blue sclerae, depressed nasal tip, a long and flat philtrum, a submucosal cleft palate, prominent ears with bilateral preauricular fistulae, a bipartite clavicle on the right side (Fig. 1), short fingers and clinodactyly. Furthermore, mild muscular hypotonia was present on neurological examination.

During the first few weeks of life, repeated episodes of invasive (14 days) and non-invasive (51 days) respiratory support were necessary and consequently, severe bronchopulmonary dysplasia was diagnosed at

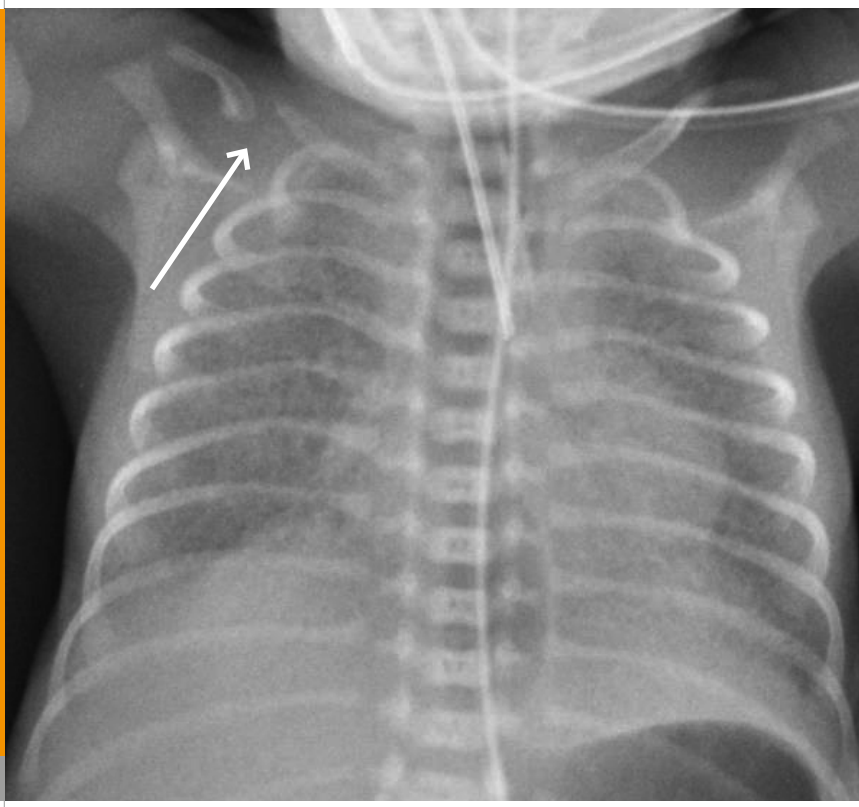

Fig. 1

Chest X-ray on the first day of life with evidence of hyaline membrane disease and a right-sided bipartite clavicle (arrow).

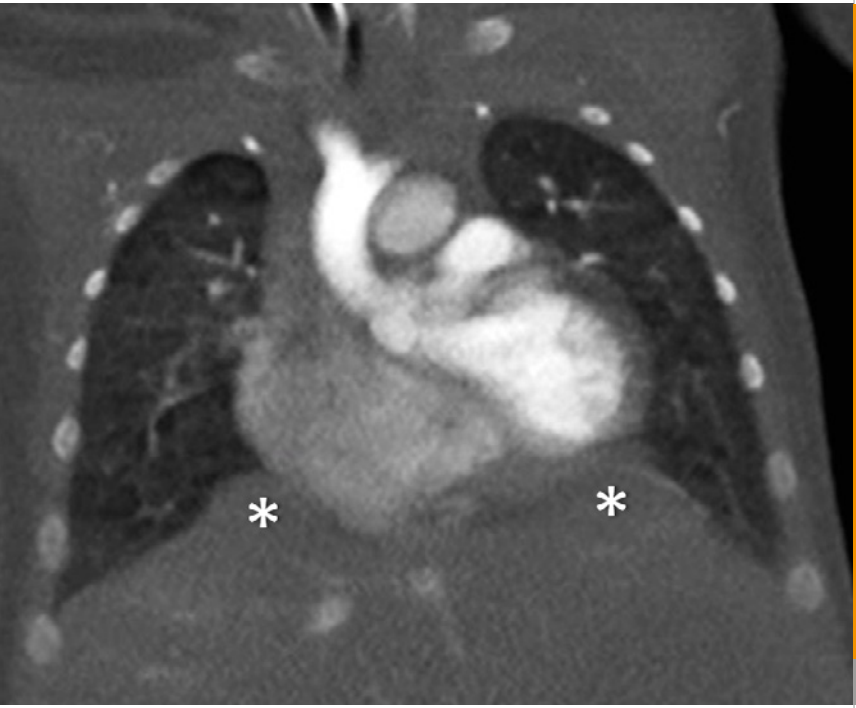

Fig. 2

CT of the chest: bilateral eventration of the diaphragm (asterisks).

36 weeks' postmenstrual age. The respiratory course was further complicated by the presence of bilateral eventration of the diaphragm (Fig. 2) and compression of the left main bronchus (most likely caused by the descending aorta) causing intermittent symptoms of airway obstruction.

Echocardiography demonstrated a dysplastic and moderately stenotic mitral valve and mild coarctation of the aorta. Due to an increasing pressure gradient across the coarctation, surgical resection was performed at 39 0/7 postmenstrual weeks. Abdominal ultrasound showed right-sided renal agenesis, but duplex kidneys with normal function on the left side (Fig. 3).

Cerebral imaging by repeated cerebral ultrasound examinations and cerebral MRI at term revealed no malformations. However, delayed myelination consistent with preterm birth and a small subependymal hemorrhage in the right caudothalamic groove were noted.

Feeding problems secondary to the above-mentioned respiratory difficulties, muscular hypotonia and the submucosal cleft led to a prolonged hospital stay. Nasogastric tube feedings were necessary until a corrected age of 3 months. He developed postnatal growth deficiency (weight at discharge 4.8 kg (P <3, down from P 25 – 50 at birth), length 59 cm (P 3 – 10, down from P 50 – 75 at birth), head circumference

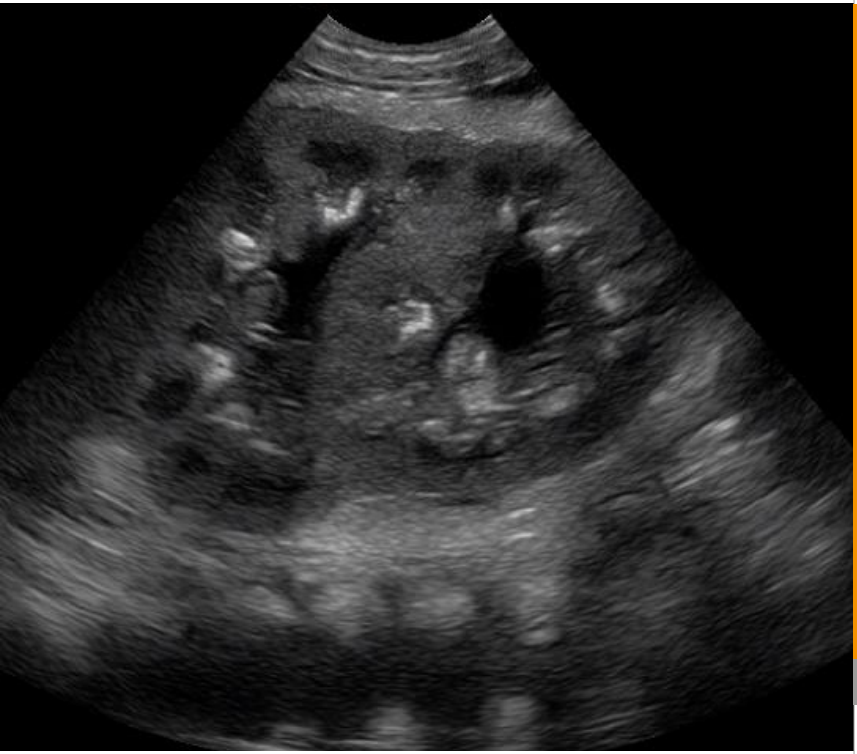

Fig. 3

Abdominal ultrasound revealing duplex kidneys on the left side.

38.5 cm (P 3 – 10, down from P 25 – 50 at birth)). The infant was discharged home almost 6 months after birth at a corrected age of 3 months.

Developmental follow-up examinations showed cognitive and gross motor developmental delay. At the most recent examination at 9 months corrected age, the infant presented with significant developmental delay with a developmental age of approximately 5 to 6 months (developmental quotient 50 – 60). On neurological examination, generalized muscular hypotonia was noted. Subsequently, he developed severe sleep apnea syndrome, which, in combination with chronic lung disease, led to a requirement for nocturnal supplemental oxygen. Early intervention therapy was initiated at the age of 9 months.

Because of multiple congenital anomalies affecting various organ systems, a dysmorphic syndrome was suspected. Differential diagnosis included Ritscher-Schinzel syndrome and Kabuki syndrome. High-resolution microarray was normal, but exome sequencing identified a heterozygous mutation in KMT2D, which is a known cause of Kabuki syndrome. Since his parents tested negative, the syndrome was due to a *de novo* mutation in our infant.

Kabuki syndrome (also known as Niikawa-Kuroki syndrome) was first described in Japan in 1981 (1). It was named after a traditional Japanese dance-drama because the typical facial features of patients with Kabuki syndrome are reminiscent of the characteristic make-up used in Kabuki theatre (Fig. 4 and 5) (2).

The incidence of the disorder is estimated at 1:32'000 in Japan (2). There is no data on the incidence outside of Japan, but as Kabuki syndrome has been reported in almost all ethnic groups, the incidence may be similar across the world (3). Niikawa et al. listed five cardinal manifestations of Kabuki syndrome (table 1) (2), which were all present in our case. Other typical malformations associated with Kabuki syndrome are summarized in table 2.

Table 1. Cardinal signs of Kabuki syndrome (1 – 4)

Organ system	Incidence	Specific features
Typical facial features	Up to 100%	Elongated palpebral fissures, eversion of the lateral third of the lower eyelid, arched eyebrows with sparse lateral third, depressed nasal tip, prominent ear lobes
Skeletal anomalies	50 – 75%	Spinal column abnormalities, brachydactyly, clinodactyly of fifth digits, joint laxity, patella dislocation, hip dislocation
Dermatoglyphic anomalies	50 – 80%	Persistence of fetal fingertip pads

Organ system	Incidence	Specific features
Postnatal growth deficiency	35 – 80%	Including feeding and drinking difficulties
Mild to moderate intellectual disability	70 – 90%	

Table 2. Malformations commonly associated with Kabuki syndrome (2 – 8)

Organ system	Specific features	Incidence
Head region	**Eyes**	
	• blue sclerae, strabismus, coloboma	33%
	Ears	
	• external malformations	nearly all
	• chronic otitis media	frequent
	• hearing loss	up to 40%
	• preauricular pits	
	Lips and palate	
	• cleft lip and/or palate	33%
	• high-arched palate	75%
	• submucosal cleft palate	under-diagnosed
	Dental anomalies including hypodontia	50 – 80%
Cardiovascular system	**Congenital heart disease**	40 – 60%
	• coarctation of the aorta	
	• septal defects	
Urogenital system	**Kidneys**	> 25%
	• hydronephrosis	
	• ectopic kidneys	
	• renal dysplasia	
Gastrointestinal system	**Intestines**	uncommon
	• imperforate anus	
	• malrotation of the colon	
	Other	
	• diaphragmatic hernia	
	• biliary atresia	

Organ system	Specific features	Incidence
Neuromuscular system	• muscular hypotonia	25 – 90%
	• seizures	10 – 40%
	• structural brain anomalies	rare
Endocrine system	• premature thelarche	7 – 50%

Apart from the above-mentioned malformations, patients with Kabuki Syndrome can present with a variety of rare findings and complications. Respiratory problems due to bilateral eventration of the diaphragm have previously been described in patients with Kabuki syndrome (9, 10). This may be an important cause of respiratory distress and increased respiratory morbidity in affected newborns. In addition, stenosis of the central airways has been described as a rare complication of Kabuki syndrome in a case review (10), and should be considered in patients with acute respiratory symptoms. In 40 – 60% of individuals with Kabuki syndrome, congenital heart defects are present, with coarctation of the aorta most commonly observed (6). Bipartite clavicles are also associated with the syndrome and have been reported previously (11).

Two gene mutations have been identified as causes of Kabuki syndrome. In around 75% of individuals with Kabuki syndrome, a mutation in the KMT2D gene on chromosome 12 has been reported (12, 13). The second gene mutation causing Kabuki syndrome is in the KDM6A gene, however, this mutation is only responsible for about 6% of all cases (14).

Fig. 4

Traditional Japanese Kabuki theatre make-up (source: Google). Note the elongation of palpebral fissures and the prominent eyebrows, both typical facial features of Kabuki syndrome.

Fig. 5

Typical facial features of children with Kabuki syndrome: note the elongated palpebral fissures and the arched eyebrows, reminiscent of Kabuki theatre make-up. Other typical facial features are eversion of the lateral lower eyelid, depressed nasal tip and prominent ears (source: Google).

In the remaining 20% of patients, the genetic etiology of Kabuki syndrome has remained unclear. KMT2D-related Kabuki syndrome is inherited in an autosomal dominant manner. Hence, each child of an individual with KMT2D-related Kabuki syndrome has a 50% risk to inherit the syndrome. However, the vast majority of cases are caused by *de novo* mutations (3). The gene product of KMT2D is MLL2, a histone-lysine-methyltransferase, which regulates gene transcription and chromatin structure in early development (15). A recent study demonstrated abnormalities in craniofacial structures, heart and brain in KMT2D and KDM6A knockout zebrafish, providing further evidence of the important role of these genes in organogenesis (16).

To our knowledge, there is no data regarding long-term mortality and morbidity risks in patients with Kabuki syndrome. However, they are likely to be related to the highly prevalent and often severe cardiac anomalies, respiratory problems and compromised neuromuscular function (10). Developmental delay and intellectual disability, usually ranging from mild to moderate, are present in nearly all individuals with Kabuki syndrome (2). Vaux et al. reported that children with Kabuki syndrome are able to walk unassisted at 20 months on average (range 15 to 30 months) and are able to speak single words at 21 months of age (range 10 to 30 months) (17).

Kabuki syndrome is a rare congenital genetic disorder, in most cases caused by heterozygous mutation in the KMT2D gene on chromosome 12. It is characterized by typical facial features, skeletal abnormalities, persistence of fetal finger pads, mild to moderate developmental deficiency, and postnatal growth deficiency. Other findings may include congenital heart defects, genitourinary malformations and cleft palate. Kabuki syndrome is one of those rare congenital disorders that affect a various number of organs. Therefore, routine screening of all major organ systems is of particular importance in all patients with the characteristic dysmorphic features. Additionally, long term care of affected patients is complex and involves many different medical disciplines. Effective case management provided by the general pediatrician is crucial to the quality of life of affected patients and their families.

REFERENCES

1. 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: 565-569 *(Abstract)*

2. Niikawa N, Kuroki Y, Kajii T, et al. Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 62 patients. Am J Med Genet 1988;31:565-589 *(Abstract)*

3. Adam MP, Hudgis L., Hannibal M. Kabuki Syndrome. GeneReviews® [Internet]. University of Washington, Seattle, WA, 2011 Sep 01 (updated 2013 May 16) *(Abstract)*

4. Wessels MW, Brooks AS, Hoogeboom J, Niermeijer MF, Willems PJ. Kabuki syndrome: a review study of three hundred patients. Clin Dysmorphol 2002;11:95-102 *(Abstract)*

5. 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:249-252 *(Abstract)*

6. Hughes HE, Davies SJ. Coarctation of the aorta in Kabuki syndrome. Arch Dis Child 1994;70:512-514 *(Abstract)*

7. Kawame H, Hannibal MC, Hudgins L, Pagon RA. Phenotypic spectrum and management issues in Kabuki syndrome. J Pediatr 1999;134:480-485 *(Abstract)*

8. Matsumoto N, Niikawa N. Kabuki make-up syndrome: a review. Am J Med Genet C Semin Med Genet 2003;117C:57-65 *(Abstract)*

9. McGaughran J, Aftimos S, Jefferies C, Winship I. Clinical phenotypes of nine cases of Kabuki syndrome from New Zealand. Clin Dysmorphol 2001;10:257-262 *(Abstract)*

10. Van Haelst MM, Brooks AS, Hoogeboom J, et al. Unexpected life-threatening complications in Kabuki syndrome. Am J Med Genet 2000;94:170-173 *(Abstract)*

11. Fryns JP Devriendt K. Hypoplastic claviculae in the Kabuki (Niikawa-Kuroki) syndrome. Genet Couns 1998;9:57-58 (no abstract available)

12. Ng SB, Bigham AW, Buckingham KJ, et al. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nat Genet 2010;42:790-793 *(Abstract)*

13. Hannibal MC, Buckingham KJ, Ng SB, et al. Spectrum of MLL2 (ALR) mutations in 110 cases of Kabuki syndrome. Am J Med Genet A 2011;155A:1511-1516 *(Abstract)*

14. Miyake N, Mizuno S, Okamoto N, et al. KDM6A point mutations cause Kabuki syndrome. Hum Mutat 2013;34:108-110 *(Abstract)*

15. Prasad R, Zhadanov AB, Sedkov Y, et al. Structure and expression pattern of human ALR, a novel gene with strong homology to ALL-1 involved in acute leukemia and to Drosophila trithorax. Oncogene 1997;15:549-560 *(Abstract)*

16. Van Laarhoven PM, Neitzel LR, Quintana AM, et al. Kabuki syndrome genes KMT2D and KDM6A: functional analyses demonstrate critical roles in craniofacial, heart and brain development. Hum Mol Genet 2015;24:4443-4453 *(Abstract)*

17. Vaux KK, Jones KL, Jones MC, Schelley S, Hudgins L. Developmental outcome in Kabuki syndrome. Am J Med Genet A 2005;132A:263-264 *(Abstract)*

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