CLINICAL VIGNETTE

Anesthetic Considerations for Pediatric Patients with Kabuki Syndrome

Diana T. Phan, MD and Michelle H. Zhang

Introduction

Kabuki Syndrome (KS) or Niikawa-Kuroki syndrome is a rare congenital disorder affecting approximately 1:30,000 births in Japan and 1:80,000 in other countries.[1] KS is named so because of its unique facies that resemble traditional makeup used in Japanese stage theatre *kabuki*. Other commonly seen clinical presentations include intellectual and developmental delays, heart abnormalities, feeding difficulties with failure to thrive, skeletal abnormalities, and hypotonia.[1,2] We report siblings with KS and discuss the anesthetic considerations in managing patients with this syndrome.

Case Report

Two sisters, both diagnosed with KS with similar medical histories, presented to our hospital for MRI studies for evaluation of central precocious puberty (CPP). Patient 1 (P1) is a 10-year-old female with global and speech delays requiring therapy, mild asthma, severe anxiety and behavioral disorder requiring medication, asymptomatic ventricular septal defect without interventions, scoliosis, and gastrostomy tube-dependence since age 2 for failure to thrive (FTT). She is followed by Endocrinology for growth of pubic hair, breast development, and menarche by age 9. Her latest bone scan shows bone age of 13 when chronological age was 9 years. Her sister Patient 2 (P2) is an 8-year-old female with a similar history of developmental and speech delays since 6 months of age, severe anxiety requiring medications, and gastrostomy tube-dependence since age 2 for FTT. P2 also had signs of CPP including pubic hair and early breast development by age 8. Unlike P1, P2 had a normal echocardiogram and normal bone age. Of note, both patients were started on leuprolide injections 1 year prior with improvement in their CPP symptoms. Both sisters had one prior surgery under general anesthesia without complications, and neither had any drug allergies.

On the day of their MRI scans, P1 and P2 arrived together with their guardian. Both patients displayed the characteristic KS facial appearance including arched eyebrows, elongated eyelids, wide and flattened nose, downturned mouths, and large prominent ears. Both had normal airway exams but mouth exam showed small, sharp teeth with several missing teeth. Initially, the sisters were playful and interacting comfortably with staff and both midazolam 0.5 mg/kg was easily given. After 30 minutes, peripheral IV placement was attempted in P2 and she quickly grew anxious and began shrieking. Her sister P1 also became hysterical and uncooperative prior to her own IV placement. It took several staff members to hold, soothe, and eventually place IV's. After that, both patients returned to their cheerful states and were cooperative the rest of the day. The MRI scans for P1 and P2 were performed under monitored anesthesia care with IV propofol infusions (100-200 mcg/kg/min). Throughout the procedure, P1 and P2 were continuously monitored according to ASA standards while on 4 L of oxygen via facemask. Both MRI scans lasted approximately 40 minutes without any events, after which sedation was turned off and both patients were awake and alert upon arrival in the recovery area. After uneventful recovery lasting approximately 2 hours, both patients were sent home with stable vital signs on room air and return to their preoperative baselines.

Discussion

KS includes two genetic variants that may be inherited in an autosomal dominant or X-linked manner.[1] In 1988, Niikawa et al. reported five cardinal manifestations seen in 62 patients with KS: unique facial features (100%), skeletal anomalies (92%), dermatoglyphic abnormalities (93%), intellectual disability (92%), and postnatal growth deficiency (83%).[1,2] However, KS may affect many systems to varying degrees including structural anomalies and functional differences that anesthesiologists need to be aware of.

Craniofacial - Most characteristic of KS is the unique facial features which include long palpebral fissures with eversion of the lower lateral eyelids, arched eyebrows with the lateral one-third sparse, depressed nasal tip, and prominent cupped ears.[1,2] Nearly one third of KS patients have cleft lip and/or palate and three quarters have high-arched palates which may cause feeding and speech difficulties, as well as difficult intubations for the anesthesiologist.[1,3-5] Several dental anomalies have also been reported in KS including hypodontia, malocclusion, and abnormal dentition (including flathead- or screwdriver-shaped, small, and widely spaced teeth).[1] Anesthesiologists should perform a thorough preoperative exam and prepare for a possible difficult airway.

Cardiovascular - It is estimated that 30-70% of individuals with KS can have congenital heart defects which most commonly include coarctation of the aorta, septal defects, bicuspid aortic valve, mitral valve anomalies, conotruncal heart defects, and hypoplastic left heart syndrome.[1-4] Individuals with KS should be assessed preoperatively with an echocardiogram with

visualization of the aortic arch and possibly an EKG. Careful selection of anesthetics should be taken into account based on cardiac symptoms and functional limitations, especially in those with poor ventricular function.[4]

Gastrointestinal - Feeding difficulties are reported in up to 70% of KS patients and may be related to hypotonia, poor oromotor coordination, or cleft lip/palate. Many KS patients may also have gastroesophageal reflux or delayed gastric emptying. Some will require gastrostomy tube placement early in life for FTT as seen in our patients.[1,4-5]

Musculoskeletal - Up to 50-75% of KS patients report joint hypermobility and frequent dislocations occurring most often in the hips, patellae, and shoulders. Other common conditions include scoliosis and kyphosis associated with vertebral anomalies (hemivertebrae, butterfly vertebrae, sagittal clefts). Careful positioning should be maintained during anesthesia, especially during intubation because of joint laxity which can affect the cervical spine. Also noted are dermatoglyphic abnormalities from persistent fetal fingertip pads and other hand findings (such as brachydactyly and clinodactyly).[1,2,4] Muscular hypotonia is common in KS and may cause obstructive sleep apnea and be mistaken for neuromuscular blockade perioperatively. Alternately, because seizures occur in 10-39% of KS patients, a larger dose of nondepolarizing muscle relaxant may be required if there is concomitant anti-convulsant use.[4,5]

Endocrine - KS patients are typically within normal growth parameters at birth. However, postnatal growth deficiencies become evident by 12 months, and lack of a growth spurt during puberty may exacerbate their short stature. With growth hormone therapy, they are able to catch up to their peers but anesthesiologists will have to use case-specific sized airway equipment.[1] Hyperinsulinism may be a presenting sign in neonates though all KS patients should be monitored for hypoglycemia due to combined pituitary and growth hormone deficiencies.[1,6] Premature thelarche in girls is the most common endocrine finding in KS (16-41%) while true precocious puberty is less commonly reported in small subsets.[1]

Immune - In a study of 177 KS patients, 44% had increased susceptibility to infections and 13% had an autoimmune disease such as vitiligo, immune thrombocytopenia, diabetes mellitus, and hemolytic anemia.[1] Pediatric anesthesiologists should obtain thorough histories in KS patients because of their frequent and recurrent infections such as upper respiratory infections and otitis media.[1,4]

Psychiatric/Behavioral - The majority of KS patients will display mild to moderate intellectual disability with deficits in comprehension and speech, though this may be related to hearing, neurologic, and cognitive defects. It is reported that KS patients have more difficulties with daily living than with communication, often being described as "pleasant and outgoing." A subset of KS patients may also have attention-deficit/hyperactivity disorder.[1] And although anxiety disorders are rarely reported in KS,[1] both our patients had severe, medicated anxiety that made the cases challenging.

Kabuki Syndrome is not commonly seen by anesthesiologists, but it is important to be aware of this syndrome and its implications. Notably, KS patients may have significant cardiac lesions, craniofacial anomalies that can affect airway management, musculoskeletal disorders that can affect positioning, and behavioral challenges.

REFERENCES

1. **Adam MP, Hudgins L, Hannibal M**. Kabuki Syndrome. 2011 Sep 1 [updated 2022 Sep 15]. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, editors. *GeneReviews®* [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023. PMID: 21882399.
2. **Niikawa N, Kuroki Y, Kajii T, Matsuura N, Ishikiriyama S, Tonoki H, Ishikawa N, Yamada Y, Fujita M, Umemoto H, et al**. Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 62 patients. *Am J Med Genet*. 1988 Nov;31(3):565-89. doi: 10.1002/ajmg.1320310312. PMID: 3067577.
3. **Paik JM, Lim SY**. Kabuki Syndrome with Cleft Palate. *Arch Plast Surg*. 2016 Sep;43(5):474-6. doi: 10.5999/aps.2016.43.5.474. Epub 2016 Sep 21. PMID: 27689058; PMCID: PMC5040853.
4. **Atalay YO, Kaya C, Ustun YB, Sahinoglu AH**. Anesthesia management in a patient with kabuki syndrome. *Med Arch*. 2014 Oct;68(5):359-60. doi: 10.5455/medarh.2014.68.359-360. Epub 2014 Oct 15. PMID: 25568573; PMCID: PMC4269532.
5. **Johnson G, Mayhew JF**. Anesthesia for a child with Kabuki Syndrome. *Paediatr Anaesth*. 2007 Sep;17(9):900-1. doi: 10.1111/j.1460-9592.2007.02221.x. PMID: 17683412.
6. **Yap KL, Johnson AEK, Fischer D, Kandikatla P, Deml J, Nelakuditi V, Halbach S, Jeha GS, Burrage LC, Bodamer O, Benavides VC, Lewis AM, Ellard S, Shah P, Cody D, Diaz A, Devarajan A, Truong L, Greeley SAW, De Leó-Crutchlow DD, Edmondson AC, Das S, Thornton P, Waggoner D, Del Gaudio D**. Congenital hyperinsulinism as the presenting feature of Kabuki syndrome: clinical and molecular characterization of 9 affected individuals. *Genet Med*. 2019 Jan;21(1):233-242. doi: 10.1038/s41436-018-0013-9. Epub 2018 Jun 15. Erratum in: *Genet Med*. 2018 Aug 11;: PMID: 29907798; PMCID: PMC7597849.