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Anesthetic care of a child with Kabuki syndrome

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Keypoints

1. Kabuki syndrome is a rare genetic disorder with unique facial features and multiple organ involvement, caused by de-novo mutation of the KMT2D (MLL2) and KDM6A genes.
2. Of primary concern during anesthetic care is the potential for airway involvement and difficulty with airway management and endotracheal intubation.
3. Additional comorbid conditions may include central nervous system involvement (seizures and hypotonia), congenital heart disease, endocrine involvement, and renal abnormalities. Associated developmental delay and hypotonia in association with obstructive sleep apnea may lead to an increased risk of perioperative respiratory insufficiency.
4. Congenital heart disease may be present in up to 70% of patients, most commonly left-sided obstructive lesions including aortic coarctation or multiple left-sided obstructions similar to those observed in the spectrum of the Shone complex.
5. Cardiac rhythm disturbances may occur in association with structural cardiac abnormalities or as a result of primary conduction system abnormalities.

Abstract

Kabuki syndrome (KS) is a rare genetic disorder associated with unique facial features, developmental delay, and multiple end-organ abnormalities. Specific phenotypic findings include long palpebral fissures, eversion of the lateral third of the lower eyelid, arched eyebrows with sparseness of the lateral one-third, a short columella with a depressed nasal tip, and prominent ears. Patients with KS frequently have associated skeletal deformities, short stature, cleft lip and palate, dental anomalies, joint laxity, cardiovascular abnormalities, renal malformations, recurrent pneumonia, recurrent otitis media, and hearing loss. Given the potential for end-organ involvement and congenital malformations, surgical intervention may be required to address these concerns. We present a patient with Kabuki syndrome who required anesthetic care during two operative interventions: laryngoscopy and supraglottoplasty at 5 months of age and open reduction for hip dislocation at 9 months of age. Previous reports of anesthetic care for patients with Kabuki syndrome are reviewed with discussion of perioperative concerns and options for anesthesia.

Keywords

Kabuki syndrome, pediatric anesthesiology, perioperative care, congenital heart disease, hypotonia

Introduction

Kabuki syndrome (KS) is a rare genetic disorder with unique facial features and multiple organ involvement,

caused by de-novo mutations of the KMT2D gene (KMT2D; formerly MLL2) located on chromosome 12 and the KDM6A gene located on the X-chromosome.[1,2] These genes regulate enzymatic processes of histone methyltransferases, which modify specific DNA proteins, known as histones. Histones are structural proteins that bind to DNA, giving chromosomes their shape and regulating gene function in various tissues throughout the body.[1-3] The name (Kabuki syndrome) is derived from the unique facial features resulting in an appearance similar to the make-up worn by actors in traditional Japanese dance-drama known as Kabuki.[4,5] The term "Kabuki Make-Up Syndrome" was originally coined based on this unique phenotypic presentation. However, given concerns that such a designation may cause parental confusion or consternation, the name was changed to Kabuki syndrome. Following its first description in 1981 by two independent groups of investigators in Japan, sporadic cases of KS have been reported from a diverse geographic and ethnic distribution.[5,6] KS has an estimated incidence of 1/30,000-35,000 in the Japanese population with no gender predilection.

The phenotypic facial features of KS include long palpebral fissures, eversion of the lateral third of the lower eyelid, arched eyebrows with sparseness of the lateral one-third, a short columella with a depressed nasal tip, and prominent ears. Associated end-organ abnormalities may include congenital heart disease (CHD), airway and dental concerns (cleft lip/palate, dental anomalies, microdontia), orthopedic involvement (joint laxity, hip dislocation, scoliosis), genito-urinary malformations, immune dysfunction, recurrent pneumonia, recurrent otitis media, hearing loss, and neurologic involvement (seizures and hypotonia).[7-10] Given the multiple end-organ involvement, anesthetic care is frequently required for surgical investigations and interventions. We present a child with KS who required anesthetic care during two separate surgical interventions; direct laryngoscopy and supraglottoplasty at 5 months of age and open reduction for hip dislocation at 9 months of age. Previous reports of anesthetic care for patients with Kabuki syndrome are reviewed with discussion of perioperative concerns and options for anesthesia.

Case Report

Review of this case and presentation in this format followed the guidelines of the Institutional Review Board of Nationwide Children's Hospital (Columbus, Ohio). The patient presented initially for direct laryngoscopy and bronchoscopy at 6 months of age and then for open reduction of bilateral spontaneous hip dislocations at 9 months of age. The patient's history was significant for a term birth; however, there was a prolonged Neonatal ICU course for treatment of respiratory concerns related to potential sepsis and meconium aspiration requiring mechanical ventilation. During the immediate neonatal period, the patient continued to have respiratory concerns with upper airway obstruction. Evaluations by pediatric pulmonary and otolaryngology consultants led to the recommendation for supraglottoplasty to treat upper airway obstruction. Additional end-organ involvement included congenital heart disease (parachute mitral valve), a right pelvic kidney, hypothyroidism, ectopic neurohypophysis, preauricular sinuses, hearing loss, facial palsy with ptosis, and atypical facies. During the evaluation for the multiple congenital anomalies, developmental delay, and abnormal facies, whole exome sequencing revealed KMT2D gene variant confirming the diagnosis of Kabuki syndrome. At 5 months of age (weight 6.9 kilograms), the patient presented for direct laryngoscopy and supraglottoplasty. Preoperative airway, cardiovascular, and respiratory examinations were unremarkable. Medications included oral levothyroxine (hypothyroidism diagnosed on the newborn screen), inhaled fluticasone (2 puffs twice a day), and as needed albuterol. Based on a sleep study, the patient was on supplemental oxygen via nasal cannula at 0.1 liters/minute due to oxygen desaturation while sleeping. The patient was held *nil per os* for 6 hours and transported to the operating room where routine American Society of Anesthesiologists' monitors

were placed. Anesthesia was induced by the inhalation of incremental concentrations of sevoflurane in 100% oxygen, supplemented by ketamine (0.5-1 mg/kg), propofol (0.5-1 mg/kg), and dexmedetomidine (0.5 µg/kg). Topical airway anesthesia was provided by the aerosolized administration of lidocaine (2 mg/kg). A grade 1 view was obtained via direct laryngoscopy by the pediatric otolaryngology team. After direct laryngoscopy, bronchoscopy, and airway examination, the trachea was intubated with a 4.0 mm uncuffed ETT with a leak at 18 cmH2O. Maintenance anesthesia included sevoflurane (2.5-3%) in air/oxygen supplemented by incremental bolus doses of ketamine (total dose of 3 mg/kg) and propofol (total dose of 3 mg/kg). To prevent postoperative airway edema, dexamethasone was administered. The surgical procedure lasted approximately 90 minutes. The patient's trachea was extubated and he was transported to the post-anesthesia care unit (PACU). His postoperative course was unremarkable. A single postoperative respiratory treatment with inhaled racemic epinephrine 2.25% (0.25 mL) was administered as well as two postoperative doses of dexamethasone. He was discharged home on the second postoperative day.

At 9 months of age (weight 9.8 kilograms), he presented for open reduction of bilateral spontaneous hip dislocations. Despite the preceding airway intervention at 5 months of age, the patient continued to have significant OSA with an ongoing oxygen requirement. There were no new acute or chronic concerns reported by the parents. The patient was held *nil per os* for 6 hours and transported to the operating room where routine American Society of Anesthesiologists' monitors were placed. Anesthesia was induced by the inhalation of sevoflurane in oxygen and nitrous oxide supplemented by propofol (1 mg/kg) after peripheral intravenous access was achieved. Bag-valve-mask ventilation was unremarkable. A grade 1 view was obtained by direct laryngoscopy with a Wis-Hipple 1.5 blade with minimal cricoid pressure and the airway was intubated with a 3.5 mm cuffed ETT. Maintenance anesthesia included sevoflurane in air/oxygen supplemented by morphine (total dose 0.06 mg/kg). The surgical procedure lasted approximately 180 minutes. After completion of the surgical procedure, residual neuromuscular blockade was reversed with intravenous sugammadex (3 mg/kg). The patient's trachea was extubated and he was transported to the post-anesthesia care unit (PACU). Given the history of significant OSA, the patient was admitted to the Pediatric ICU for close monitoring of his respiratory status. He was discharged home on the second postoperative day.

Discussion

Kabuki syndrome is a rare genetic disorder first identified by its phenotypic appearance and then later linked to specific alterations in the genome. The clinical diagnosis is based on the typical phenotypic features with confirmation by exome sequencing analysis. KS results from a spectrum of de-novo mutations of the KMT2D gene on chromosome 12 or de-novo partial or complete deletions of the KDM6A gene on the X-chromosome. Based on this genetic distinction, KS has been subdivided into KMT2D-associated, autosomal-dominant KS type 1 (KS1); and KDM6A-associated, X-linked-dominant KS type 2 (KS2).[1-3] It has been reported that 56%-75% of patients carry the KMT2D variant, while 3%-8% of cases carry the KDM6A variant. Patients with other distinctive mutations may manifest similar phenotypic findings and may be referred to as Kabuki-like syndrome.[3,11] In the clinical setting, there are limited differences between the subtypes; however, the typical facial appearance, short stature, feeding problems and renal anomalies are more often displayed with KS subtype 1.[11,12]

Planning for anesthetic and perioperative care begins with a thorough preoperative assessment and identification of the end-organ involvement. Of primary importance to the anesthesiologist is the potential for difficulties with airway management. Physical features and associated oral involvement with KS include a high arched palate, abnormal dentition, malocclusion, and cleft lip and/or palate.[13] Our review of the literature noted

3 previous reports of anesthetic care for patients with KS.[14-16] Although all of the authors provide caution regarding the potential for difficulties with airway management and endotracheal intubation, care in these patients was uncomplicated. Only 1 patient had a Lehane-Cormack grade 3 view of the glottis during direct laryngoscopy with the requirement for use of a stylet.

Another factor that may impact airway management is the theoretical potential for ligamentous laxity and cervical vertebral involvement.[17] In our patient, we noted no problems with airway management during either anesthetic including bag-valve-mask ventilation and endotracheal intubation. However, given the limited number of published clinical reports, the appropriate equipment for dealing with the difficult airway including indirect videolaryngoscopy and various sizes of laryngeal mask airways should be readily available prior to anesthetic induction.[18] When there are concerns of airway management, general anesthesia can be induced by the inhalation of sevoflurane in 100% oxygen with the maintenance of spontaneous ventilation. The administration of neuromuscular blocking agents (NMBAs) should be avoided until adequate bag-valve-mask ventilation is demonstrated. Additionally, Van Haelst et al. reported distal airway abnormalities in two patients, one with local stenosis of the right upper lobe bronchus and the other with severe bronchomalacia and an abnormal right bronchial tree.[19]

Central nervous system involvement with KS may include seizures, hypotonia, developmental delay, and microcephaly.[20] Preoperative management should include optimization of anticonvulsant therapy prior to elective surgical procedures. Preoperative administration and continuation of anticonvulsant medications during the perioperative period is suggested.[21] Associated hypotonia can impact the choice of neuromuscular blocking agents (NMBAs). The depolarizing agent, succinylcholine, may be contraindicated due to the risk of rhabdomyolysis. Pre-existing motor weakness and hypotonia may increase sensitivity to the effects of non-depolarizing NMBAs. A prolonged effect can be expected even with intermediate-acting non-depolarizing agents (atracurium, rocuronium or vecuronium).[22] The novel reversal agent, sugammadex, may effectively reverse even profound neuromuscular blockade in patients with neuromyopathic conditions.[23] The limited available literature has not demonstrated an increased sensitivity to the effects of NMBAs in patients with KS, but this adverse effect should be considered due to the associated hypotonia.

The risk of perioperative respiratory failure may be increased by pre-existing respiratory dysfunction, hypotonia, poor cough effort, chronic aspiration, recurrent pneumonia, and sleep disordered breathing. Given these concerns, the use of short acting anesthetic agents should be considered and continuous postoperative monitoring of respiratory function may be indicated for prolonged surgical procedures.

CHD has been reported in two separate reports by Digilio and colleagues.[24,25] The first report, which was published in 2001, reported CHD in 35 of 60 patients (58%). Of the 35 children with CHD, coarctation of the aorta was most common (23%) followed by atrial septal defect (20%) and ventricular septal defect (17%).[24] A subsequent study published in 2017 by the same group of investigators noted CHD in 28 patients with a molecularly proven diagnosis of Kabuki syndrome (KMT2D gene variant in 27 patients and KDM6A gene in one patient).[25] CHD was diagnosed in 19 of 27 patients (70%) patients with KMT2D variant, while the single patient with KDM6A change had an anatomically normal heart. Again, aortic coarctation was most common; present in 4 of 19 patients (21%). The authors also reviewed CHD in patients with KS reported in the literature and noted that CHD is present in 70% of patients with KMT2D pathogenic variants, most commonly left-sided obstructive lesions, including multiple left-sided obstructions similar to those observed in the spectrum of the Shone complex and septal defects. Given these concerns, the preoperative evaluation should include an echocardiogram especially in cases without previous cardiac imaging. Cardiac rhythm disturbances

may occur in association with structural cardiac abnormalities. Additionally, anecdotal reports suggest that arrhythmias may be related to a primary conduction system abnormality in the absence of associated CHD.[26] A preoperative electrocardiogram and electrophysiologic studies may be warranted in patients presenting with arrhythmias.

Additional end-organ involvement in KS may include renal and endocrine involvement. Renal malformations have been reported in up to 25% of patients with KS including malposition of the kidneys, hydronephrosis, renal hypoplasia or dysplasia, fusion defects of the kidneys, duplications of the collecting system, ureteropelvic junction obstruction, and hydroureter.[8,11,27] Depending on the specific anatomic malformation, progressive renal insufficiency or failure may occur. Renal imaging of our patient revealed malposition of the right kidney in the pelvis. Preoperative serum creatinine and blood urea nitrogen were normal. Preoperative urinalysis and renal function evaluation (blood urea nitrogen and creatinine) may be indicated in patients with renal anomalies or history of frequent recurrent urinary tract infections. Patients with abnormal renal function may require further imaging procedures to rule out anatomical causes. Avoidance of potentially nephrotoxic agents and attention to intravascular volume and renal blood flow are required in patients with high risk for renal deterioration.

A wide variety of endocrine disorders have been reported in patients with KS including premature thelarche, short stature with or without growth hormone deficiency, pituitary hormone deficiency, adrenal insufficiency, diabetes insipidus, hypothyroidism, and altered glucose homeostasis (hyperglycemia and hypoglycemia).[7,8,28] Our patient had an ectopic neurohypophysis associated with concerns for possible panhypopituitarism. He was also diagnosed with primary hypothyroidism on his newborn screen and was maintained on oral levothyroxine therapy. Subsequent laboratory analysis demonstrated a normal free T4 and TSH while on oral therapy. An additional consideration during the neonatal period and early infancy is the potential for hypoglycemia, occurring in approximately 8-10% of patients with KS. Contributing factors may include growth hormone deficiency, adrenal insufficiency and hyperinsulinism. Intraoperative monitoring of blood glucose may be indicated for prolonged procedures to provide early detection and management of hypoglycemia.

In summary, we present the anesthetic care of a child with KS during two different surgical procedures. Of primary importance to the anesthesiologist is the potential for difficulty with airway management endotracheal intubation. During the preoperative evaluation, potential end-organ involvement should be identified including associated congenital heart disease, CNS involvement (seizures, hypotonia), renal anomalies, and endocrine involvement. Continuous postoperative respiratory monitoring and the use of short acting anesthetic agents may be indicated given the potential for comorbid respiratory insufficiency, poor cough effort, hypotonia, and OSA which may result in postoperative respiratory failure. Additionally, as noted in our patient and mentioned anecdotally in the literature, patients with KS may present difficulties with vascular access necessitating inhalation induction or the use of ultrasound-guided techniques.

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