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Anesthesia and pain management of a patient with Kleefstra Syndrome for robotic ureteral reimplantation

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Keypoints

- Kleefstra Syndrome is a rare congenital disorder with multiple end organ effects.
- Perioperative Challenges: airway management, cardiac and urologic issues, and pharmacogenomic variations in analgesic metabolism.
- Hydromorphone Ineffectiveness: avoid using hydromorphone due to lack of efficacy.

Abstract

Kleefstra syndrome (KS) is a genetic disorder caused by a microdeletion in the 9q34.3 chromosome with related clinical conditions requiring surgical intervention and careful consideration for anesthetic management including potential difficult airway, cardiac and neurological considerations, pulmonary infections, reflux and delayed gastric emptying, genitourinary abnormalities, hypotonia, and seizure disorders. In addition, we observed unique perioperative pain control considerations. We present a clinical case involving a 2-year-old female who received anesthesia for robotic ureteral reimplantation surgery. Perioperative implications are discussed and considerations for anesthetic care provided.

Keywords

Airway Management, Anesthesia and Analgesia, Congenital Heart Defects, Kleefstra Syndrome, Pain Management, Pediatrics

Introduction

Kleefstra syndrome (KS) is a congenital disorder resulting from an autosomal dominant chromosome 9q34.3 microdeletion, also known as 9q subtelomeric deletion syndrome (9qSTDS).(1, 2) The prevalence is estimated to be 1:25,000 births, with a female to male ratio of 1:1. The majority of the clinical characteristics are attributed to a dysfunctional euchromatin histone methyltransferase 1 (EHMT1), which encodes the histone methyltransferase enzyme essential for typical development. Clinical features include dysmorphic facial qualities (brachy[-micro]cephaly, midface retrusion, protruding tongue, prognathism); congenital cardiac anomalies (conotruncal heart defects, atrial and ventricular septal defects, pulmonary stenosis, bicuspid aortic valve); mild to moderate cognitive and gross motor delay with autism-like qualities; seizures, hearing and vision impairments, and genitourinary anomalies with hydronephrosis and vesico-ureteral reflux (VUR) well described.(3) Over 500 cases have been diagnosed, with many fold more suspected and the oldest patient reported in current literature was aged 59 years in 2010.(4) To date, this is the second case report regarding the anesthetic management of patients with KS.(5) With written Health Insurance Portability and Accountability Act (HIPAA) authorization from a parent, we present a 2-year-old patient with KS who received anesthesia care for a robotic ureteral reimplantation for VUR. We review perioperative management and

anesthetic implications in KS and update the current considerations for post-operative pain management based on clinical response to systemic opioid analgesics not previously described.

Case report

The patient was a 2-year-old, 12.9-kilogram female who presented for a robotic bilateral ureteral reimplantation for the treatment of VUR. KS was diagnosed at one month of life secondary to failure to thrive, difficulty swallowing, abnormality of the pulmonic valve, and concern for possible Noonan syndrome. The patient's medical history included gastroesophageal reflux disease, seizures, dysphagia, sleep apnea, pulmonary stenosis, aspiration, hypotonia, gastrotomy tube, and VUR. Past surgical history included a laparoscopic Nissen fundoplication with gastrostomy, flexible laryngoscopy, micro-direct laryngoscopy and bronchoscopy, adenoidectomy, tympanostomy tube placement, and esophagogastroduodenoscopy with biopsy. Review of previous anesthetic records showed no history of anesthetic difficulties or complications. Preoperative examination was remarkable for recent upper respiratory infection treated with antibiotics and the physical exam demonstrated transmitted upper airway sounds, but the patient was afebrile and appeared non-toxic. In the operating room, standard American Society of Anesthesiologists' monitors were placed followed by inhalation induction with 40% oxygen and 60% nitrous with sevoflurane. After peripheral intravenous (IV) access was achieved and rocuronium (8 mg) was administered, direct laryngoscopy with a Philips 1 blade was performed revealing a grade 1 view and a 4.0-mm cuffed endotracheal tube was placed and secured at 12cm at the lips. Intraoperative medications during the case included vancomycin (130 mg), gentamicin (40 mg), ondansetron (2 mg), neostigmine (0.9 mg), glycopyrrolate (0.3 mg), albuterol (180 mcg/puff for 15 puffs), propofol (50 mg), and lidocaine (10 mg) along with 20mL/kg of crystalloid solution. Prior to emergence, hydromorphone was titrated IV in 10mcg increments while the patient was spontaneously ventilating for a total of 1.1 mg with no observed impact on respiratory drive or rate, which remained at 28 per minute with 5mL/kg of tidal volume while spontaneous. Upon emergence and awake extubation, she demonstrated some stridor which initially improved with continuous positive airway pressure (CPAP) and gentle jaw thrust, without which oxygen saturations declined to 80-89%. A nasal trumpet was lubricated and gently placed in right nare which alleviated some of the obstruction during CPAP. After careful observation, desaturation occurred again and after gentle suctioning, a laryngeal mask airway (LMA) was placed relieving the obstruction and reducing the stridor to notable with acceptable ventilation with gentle CPAP. The patient was transported on monitors to the post-anesthesia care unit (PACU) where the LMA was removed shortly after arrival. In the PACU the patient was awake and active but exhibited signs of being anxious and uncomfortable. Acetaminophen (194 mg) and ibuprofen (130 mg) were administered followed by 0.25 mg of hydromorphone with a repeat dose of 0.25mg hydromorphone given 15 minutes later. Pain assessment during the PACU stay showed inadequate pain relief with generalized pain and consistent crying resulting in the patient being taken to the floor with a pain score of eight. The PACU stay lasted 1 hour. On the medical/surgical floor she exhibited signs of inadequate analgesia and another 0.19 mg of hydromorphone was given with no relief following this dose. In response, a nurse-controlled titratable continuous morphine infusion was ordered a few hours after arrival to the unit resulting in excellent pain control at 15mcg/kg/hr. She was discharged on post operative day 2 on alternating ibuprofen and acetaminophen analgesics.

Discussion

Kleefstra syndrome was first described by Dr. Tjitske Kleefstra in 2007.(6) This is the second case report discussing anesthetic care of a patient with KS and first describing a negligible therapeutic response of

hydromorphone analgesia. Given the co-morbidities associated with KS, there are multiple perioperative implications that influence anesthesia and analgesia. KS can affect individuals with congenital cardiac lesions, musculoskeletal abnormalities, deglutition challenges, urological defects, and craniofacial characteristics with anesthetic management implications. [Table 1]. For those who survive infancy, procedural interventions under anesthesia are common and this patient is no exception. In the only other report regarding the perioperative anesthetic management of a patient with KS, airway assessment and management for diagnostic laryngoscopy and rigid bronchoscopy is described with similar perioperative challenges as that young patient also presented with laryngomalacia.(5) Perioperative pain control for that procedure was not described.

From our case and review of the literature, we would suggest that the top three concerns when preparing for anesthetic management of a KS patient include airway management, associated congenital heart disease, and neurological disorders. Regarding the airway, a major concern in perioperative management is the potential for challenging ventilation and endotracheal intubation given the possibility of craniofacial characteristics such as prognathism of the jaw, midface retrusion, and macroglossia. Tracheo- or bronchomalacia may predispose the patient to respiratory complications. Although we were able to accomplish endotracheal intubation using direct laryngoscopy without complication, we also recommend preparations for laryngomalacia and, in this case, reactive airway. The pertinent equipment for a difficult airway such as indirect laryngoscopy tools and supraglottic airway devices should be readily accessible.(5)

The second major perioperative consideration in the care of a patient with KS is the potential for associated congenital heart defects which is reported in about 50% of patients.(7) Congenital heart defects include tetralogy of Fallot, hypoplastic left heart syndrome, coarctation of the aorta, pulmonic stenosis and bicuspid aorta.(8) Due to concern about defects, preoperative review of cardiac echo- and electrocardiographic studies and assessment of functional status are recommended.

Characteristic	Typical KS phenotype %
Microcephaly	30-80%
Broad forehead	55%
Widely spaced eyes	55-70%
Ocular anomalies	45%
Midface hypoplasia	55-100%
Depressed nasal bridge and short nose	45-100%
Anteverted nares	40-80%
Protruding tongue	40-60%
Ear anomalies	45-80%
Hypoacusia	20-30%
Dental anomalies	10-15%
Psychomotor delay/intellectual disability	100%
Autism spectrum disorder	30-75%
Behavioral problems	65-70%
Cardiovascular anomalies	40-45%
Genital anomalies	45-50% (males)
Renal defects	15-30%
Skeletal anomalies	30-50%
Hypotonia	60-80%
Obesity	30-79%
Seizures	5-30%
Constipation	30-79%
Vomiting/Reflux	5-30%
Recurrent respiratory infections	5-30%
Sleep disturbances	30-79%
Tracheomalacia	5-30%

Table 1. Kleefstra Syndrome Phenotypic Prevalence

Neurological comorbidities have been described in patients with KS, seizures being common for 30% of individuals. Our patient had a history of what the parents

believed was seizure activity; however, magnetic resonance imaging and ambulatory electroencephalogram were both normal and no anticonvulsive medication was prescribed. Other neurological manifestations include hearing loss, brain anomalies, and psychiatric disorders with the majority of patients exhibiting intellectual disabilities, autism spectrum disorder, motor and developmental milestones delays, childhood hypotonia, and irregularities of gross and fine motor skills.(9)

Urological abnormalities are common, as demonstrated in our patient who underwent robotic ureteral reimplantation for VUR and hydronephrosis. Reviewing renal function and considerations for renally cleared medications would be the primary anesthetic considerations and, for this procedure, pain management is equally important.(7)

Pain management in patients with KS has largely been unreported. In our case, the patient did not demonstrate a therapeutic response to repeat hydromorphone administration at substantial doses for a pediatric patient of this size. As hydromorphone provided inadequate anesthesia, the analgesic was changed and morphine resulted in excellent pain control. In one study, a pharmacogenomic sequence was done on a 23-year-old male with KS and found reduced metabolic activity of the cytochrome P450 2D6 enzyme (CYP2D6).(10) CYP2D6 is a major liver enzyme responsible for metabolizing a variety of drugs, including hydrocodone and codeine. There has been no research done on the enzyme UDP-glucuronosyltransferase 2B7 (UGT2B7), the enzyme known for the metabolism of morphine and hydromorphone, although per correspondence with Dr. Tjitske Kleefstra and her team there are ongoing metabolic investigations on pharmacogenomics affecting interventions to improve sleep and psychiatric disorders; so, we do expect more information to be forthcoming (email correspondence).

To summarize, KS is a unique genetic disorder associated with multiple co-morbidities affecting various organ systems. Airway, congenital heart defects, renal abnormalities and neurological disorders are pathognomonic and preoperative evaluation of airway status, cardiac standing, and other co-morbidities guide the anesthetic method. As pharmacogenomic studies continue, we recommend against the use of hydromorphone for analgesia due to poor pharmacokinetics in this population known for a high pain tolerance and support continued research into the pharmacogenetics of individual KS patients.

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References

1. Kleefstra T, Smidt M, Banning MJ, Oudakker AR, Van Esch H, de Brouwer AP, et al. Disruption of the gene Euchromatin Histone Methyl Transferase1 (Eu-HMTase1) is associated with the 9q34 subtelomeric deletion syndrome. J Med Genet. 2005;42(4):299-306.

2. Kleefstra T, de Leeuw N. Kleefstra Syndrome. In: Adam MP, Everman DB, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, et al., editors. GeneReviews((R)). Seattle (WA)1993.

3. Kohli U. Shone's complex in a patient with chromosome 9q34.3 deletion (Kleefstra syndrome). Cardiol Young. 2019;29(2):249-51.

4. Verhoeven WM, Egger JI, Vermeulen K, van de Warrenburg BP, Kleefstra T. Kleefstra syndrome in three adult patients: further delineation of the behavioral and neurological phenotype shows aspects of a neurodegenerative course. Am J Med Genet A. 2011;155A(10):2409-15.

5. Yamaguchi Y, D'Mello A, Willer BL, Argote-Romero G, Tobias JD. Anesthetic Management of an Infant With

Kleefstra Syndrome During Direct Laryngoscopy and Rigid Bronchoscopy: A Case Report. A A Pract. 2020;14(7):e01222.

6. Stewart DR, Kleefstra T. The chromosome 9q subtelomere deletion syndrome. Am J Med Genet C Semin Med Genet. 2007;145C(4):383-92.

7. Campbell CL, Collins RT, 2nd, Zarate YA. Severe neonatal presentation of Kleefstra syndrome in a patient with hypoplastic left heart syndrome and 9q34.3 microdeletion. Birth Defects Res A Clin Mol Teratol. 2014;100(12):985-90.

8. Okur V, Nees S, Chung WK, Krishnan U. Pulmonary hypertension in patients with 9q34.3 microdeletion-associated Kleefstra syndrome. Am J Med Genet A. 2018;176(8):1773-7.

9. Bock I, Nemeth K, Pentelenyi K, Balicza P, Balazs A, Molnar MJ, et al. Targeted next generation sequencing of a panel of autism-related genes identifies an EHMT1 mutation in a Kleefstra syndrome patient with autism and normal intellectual performance. Gene. 2016;595(2):131-41.

10. Mitra AK, Dodge J, Van Ness J, Sokeye I, Van Ness B. A de novo splice site mutation in EHMT1 resulting in Kleefstra syndrome with pharmacogenomics screening and behavior therapy for regressive behaviors. Mol Genet Genomic Med. 2017;5(2):130-40.