Pediatric Anesthesia and Critical Care Journal 2015; 3(1):26-31
doi:10.14587/paccj.2015.5

PACCJ

Perioperative management of a patient with Jacobsen syndrome

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Key points

Jacobsen Syndrome is a rare congenital disorder associated with multiple end organ effects. Perioperative anesthetic challenges include potential difficulties with airway management, bleeding concerns related to platelet dysfunction, and the high incidence of associated congenital cardiac disease. Preoperative airway assessment, hematology consultation, and cardiac assessment are compulsory in preparation for safe anesthetic management of a patient with Jacobsen Syndrome.

Abstract

Jacobsen syndrome is a genetic disorder caused by partial deletion of the long arm of chromosome 11. Less than 300 cases have been reported, with some being diagnosed as late as the 4th decade of life. Clinical features include growth and psychomotor delay, characteristic facial anomalies involving the eyes, nose, mouth and ears, skull deformities, abnormal platelet function, congenital heart defects, malformations of the renal, gastrointestinal tract, genitalia, central nervous system, and skeleton. Pathognomonic traits of most concern to the anesthesia provider are those effecting the airway, cardiovascular system, and platelet dysfunction. Given the invariable association of this chromosomal disorder with cardiac, craniofacial, ear, otorhinolaryngologic, and genitourinary malformations, patients with Jacobsen syndrome may present for anesthetic care during various surgical procedures. Primary concerns during such care including potential difficulties with airway management (due to micrognathia/retrognathia, short neck, abnormal mouth size and shape, skull shape), bleeding concerns related to platelet dysfunction, and the high incidence of associated congenital cardiac disease, makes the anesthetic care of such patients challenging. We present a 5-year-old boy with Jacobsen syndrome who required anesthetic care for urologic surgery. The perioperative implications are discussed and suggestions for anesthetic care provided.

Keywords: Jacobsen syndrome, difficult airway, coagulation disorder

Introduction

Jacobsen syndrome (JS) is a congenital disorder resulting from a deletion of the long arm (q) of chromosome 11, which is why it is also known as 11q terminal deletion disorder. It was first described by Dr. Petrea Jacobsen in 1973 in Denmark.[1,2] The prevalence is estimated to at 1:100,000 births, with a female to male ratio of 2:1. There have been a wide range of phenotypes of varying

severity reported, with a literature review showing that the severity of clinical abnormalities is not correlated with the extent of the 11q deletion.[3] The deletion is *de novo* in ~85% of reported cases, with the remainder following autosomal dominant inheritance. Diagnosis is often made clinically in infancy when a patient exhibiting the classic dysmorphic facial features, global developmental delay, and thrombocytopenia, with confirmation on karyotyping.[4] Common clinical features include dysmorphic facial characteristics including trigonocephaly and hypertelorism, retrognathia, down-slanting palpebral fissures, low set ears; congenital cardiac anomalies (ventricular septal defect, atrial septal defect, tetralogy of Fallot, hypoplastic left heart syndrome, and aortic coarctation); dysmegakaryopoiesis leading to platelet abnormalities such as thrombocytopenia, abnormal platelet function (platelet pool storage deficiency) or pancytopenia (collectively Paris-Trousseau syndrome); mild to moderate cognitive and gross motor delay; short stature; and, genitourinary anomalies.[5-7] Endocrine, ophthalmologic, immunologic, hearing, gastrointestinal, renal, central nervous system and skeletal malformations may also be present. Twenty percent of children with JS perish before they reach age two secondary to complications of congenital heart disease, rather than bleeding.[8] Patients surviving past this age have an unknown life expectancy, but it conceivably correlates with the severity of the comorbid conditions. The oldest patient reported in current literature was 45 ages of age in 2009, while the oldest diagnosis was at age 40 years in a patient from Japan.[2,3]

Given the invariable association of this chromosomal disorder with cardiac, craniofacial, and other congenital malformations, it can be estimated that greater than 90% of patients with Jacobsen syndrome who survive infancy may present for anesthetic care for various surgical procedures. Potential difficulties with airway management (due to micrognathia/retrognathia, short neck, abnormal mouth size and shape, skull shape), coupled with platelet dysfunction, and the high incidence of congenital cardiac disease, may have significant impacts on the anesthetic care of these patients. To date, there is only one other publication regarding the anesthetic management of patients with Jacobsen syndrome.[9] We present a 5-year-old male with Jacobsen syndrome who required anesthetic care for urologic surgery. The perioperative implications are discussed and suggestions for anesthetic care provided.

Case report

Institutional Review Board approval is not required at Nationwide Children's Hospital (Columbus, Ohio) for the presentation of single case reports. The patient was a 5-year-old, 17.8 kilogram boy who presented for cystoscopy, urodynamic monitoring and evaluation, and bilateral Deflux® injection for the treatment of vesicoureteral reflux (VUR). His past history was significant for Jacobsen syndrome with mosaic trisomy 16q, gastroesophageal reflux disease, ventriculoseptal defect (VSD), hypospadia, ankyloglossia, bronchopulmonary dysplasia with severe nasoseptal deviation leading to neonatal oxygen dependence, cryptorchidism, micrognathia with deviation of mandible to the left, thrombocytopenia with platelet storage pool deficiency, seizures, hypertelorism secondary to trigonocephaly, global developmental delay, blepharoptosis and VUR. The genetics consultant stated "seizures and brain abnormalities are not commonly reported with Jacobsen, but given the platelet dysfunction these could be related to ischemic events in the brain parenchyma". The patient had been delivered at 39 weeks via spontaneous vaginal delivery with a birth weight of 3390 grams. Respiratory difficulties required the administration of supplemental oxygen and a two week admission to the Neonatal Intensive Care Unit (NICU) admission with discharge home on 1/8th liter per minute of oxygen via nasal cannula. The maternal history was positive for four miscarriages and one typical child by the same father, with the father's genetic history including many aunts with multiple miscarriages and neonatal deaths of unknown cause. The father was found to be a balanced 11q translocation carrier

prior to the birth of the patient. Jacobsen syndrome was diagnosed during his initial NICU stay via cytogenic analysis after noting the association of thrombocytopenia and dysmorphic facial features. The patient's past surgical history included nasal septoplasty with lingual frenulotomy for treatment of oxygen dependence and poor feeding after birth, hypospadias and urethrocutaneous fistula repair, left orchidopexy for cryptorchidism, left brow lift for eye deformity and cystoscopy with urethral dilation. Review of previous anesthetic records showed the utility of a laryngeal mask airway during an anesthetic 8 months earlier for magnetic resonance imaging under general anesthesia. At that time, mask ventilation was not problematic. The most recent record of direct laryngoscopy was 13 months prior where three attempts at direct laryngoscopy were required with cricoid pressure providing a grade two Cormack and Lehane view with a CMAC® video laryngoscope after only grade three views were possible with appropriate sized Miller and Macintosh laryngoscope blades. Current home medications included oxybutynin, topiramate (seizure prophylaxis after seizure at 4 months of age with none since then), cetirizine, a multivitamin, hydrocodone-acetaminophen as needed, and lansoprazole for GERD. Preoperative physical examination revealed a small-statured boy with deep set eyes, trigonocephaly with acquired plagiocephaly on his right posterolateral occiput, and frontal bossing. There was no excessive bruising or petechiae on skin exam. Airway revealed a small mouth with limited opening (two centimeters), moderate retrognathia (thyromental distance of one centimeter), generalized microdontia in good repair, and limited range of motion (flexion and extension) of his relatively short neck. A previous echocardiogram showed that his membranous VSD was mild with near total occlusion by aneurysmal tissue formation resulting in mild left-to-right flow, and normal biventricular function. The most recent platelet count was 155,000/mm^3. Hematology consultation was obtained and they recommended a preoperative 10mL/Kg platelet transfusion for his platelet pool storage deficiency and thrombocytopenia (Paris-Trousseau Syndrome). Lack of intravenous access and the likelihood of difficult placement, led to the decision to administer the product in the operating room after intravenous access had been established. On the day of surgery, the patient was held *nil per os* for 6 hours. He was transported to the operating room and routine American Society of Anesthesiologists' monitors were applied. General anesthesia included inhalation induction with 50% nitrous and oxygen, and incremental sevoflurane given his previous history of non-problematic bag-valve-mask ventilation. Peripheral intravenous access was obtained and supplemental propofol was administered intravenously (2 mg/kg) prior to airway instrumentation. In light of his past medical history of gastroesophageal reflux disease and the possibility of an open abdominal procedure, airway management included endotracheal intubation. Direct laryngoscopy was performed with a Wisconsin 1.5 blade, which revealed a grade IV view (posterior pharynx only) despite positioning adjustments and cricoid pressure. His neck extension was minimal. A GlideScope® video laryngoscope with a size 2 blade enabled a grade I Cormack and Lehane view, and a 4.5 mm cuffed endotracheal tube was placed on the first attempt using a stylet to direct the ETT toward the vocal cords. Abnormalities noted during endotracheal intubation included redundant periarytenoid tissue creating a tunnel-like passageway in the subglottic space. This anatomy created narrowing and more difficulty than traditional laryngoscopic methods of vocal cord visualization. Following endotracheal tube securement, a platelet transfusion was administered. Maintenance anesthesia included sevoflurane (end-tidal concentration 2-3%) titrated to maintain hemodynamic stability and fentanyl (3 µg/kg). Given the underlying platelet disorder, neuraxial analgesia (caudal blockade) was not performed. Additional medications included dexamethasone (4 mg), intravenous acetaminophen (15 mg/kg) and ondansetron (0.1 mg/kg). Intraoperative fluids included 230 mL of isotonic crystal-

loid solution and 110 mL of platelets. The estimated blood loss was 5 mL. Following completion of the surgical procedure, the patient's trachea was extubated awake in the operating room without difficulty. He was transferred to the post anesthesia care unit (PACU) in stable condition. Postoperative pain control was provided with hydrocodone *per os* as needed on the inpatient ward. The remainder of his postoperative course was uncomplicated and he was discharged home on postoperative day 1.

Discussion and conclusions

Given the significant co-morbidities associated with Jacobsen syndrome, there are several specific perioperative implications which may significantly impact the risk for perioperative morbidity and mortality. As with the anesthetic care of all patients, the focus of effective perioperative care begins with the preoperative examination and the identification of end-organ involvement by the primary disease process. To date, there is only one previous report regarding the perioperative management of patients with JS.[9] In that report, the authors review their experience with the perioperative care of two patients during surgery for congenital heart disease. Of note, in both of their patients, they had some challenges with airway management. Although bag-valve-mask ventilation was effectively provided, direct laryngoscopy revealed a grade II view in one patient and a grade III view in the other, both with the application of cricoid pressure. Both patients were successfully intubated using direct laryngoscopy.

From our experience and the review of the literature, we would suggest that the top three concerns when preparing for anesthetic management of a JS patient include airway management, associated congenital heart disease, and platelet dysfunction. Regarding the airway, a major concern in perioperative management is the potential for difficult ventilation and difficult endotracheal intubation in a JS patient given the presence of restricted mouth opening, micrognathia and retrognathia, and limited neck movement as were noted in our patient. Although we were able to successfully accomplish endotracheal intubation using indirect video laryngoscopy, the glottic view was less than optimal given the aforementioned difficulty not only entering the oropharynx, but visualizing the vocal cords through the anomalous redundant periarytenoid tissue. When presented with a patient with a known difficult airway, we would recommend preparing for all pathways on the difficult airway algorithm.[10] Although various options including sedated or awake intubation may be feasible in the adult population, the usual approach in the pediatric patient remains inhalation induction with sevoflurane with maintenance of spontaneous ventilation. The ability to accomplish adequate bag-valve mask ventilation should be demonstrated prior to the use of neuromuscular blocking agents. The appropriate equipment for dealing with the difficult airway should be readily available including indirect laryngoscopy tools.[11] Reassessment of a growing difficult airway with direct laryngoscopy in subsequent encounters may be successful and may decrease the preparation time when compared to other means of airway management such as fiberoptic airway management. In addition to these concerns, our approach was somewhat modified by the associated platelet dysfunction thereby making nasal approaches to the airway relatively contraindicated due to the bleeding risk. Judicious intraoperative opioid administration as well as strict adherence to tracheal extubation criteria can lead to an uneventful emergence and postoperative course, as was demonstrated in our case.

The second main concern in perioperative management of a surgical patient with JS is platelet dysfunction. Guidelines have been published regarding perioperative platelet transfusion parameters and previous case reports have outlined the approach to the pediatric patient with qualitative platelet disorders.[12,13] In patients with JS, there is a quantitative and a qualitative platelet abnormality. Paris-Trousseau syndrome is the highly penetrant platelet abnormality affecting greater than 85% of JS cases, with a storage pool deficit.[6,7] Paris-Trousseau

syndrome manifests as neonatal thrombocytopenia (some cases resolve), and persistent platelet dysfunction. Increased bleeding times and blood loss with high-risk procedures in JS patients has been described. Preoperative consultation with a hematologist for perioperative planning is advisable. Preoperative transfusion of platelets for invasive surgical procedures is suggested. In the report of Easley et al, both patients required platelet transfusions following separation from cardiopulmonary bypass. Additionally, as is routine in many centers, an antifibrinolytic agent (epsilon aminocaproic acid) was used as part of the perioperative hemostatic regimen. The administration of desmopressin acetate (DDAVP) may also be helpful to improve platelet function for minor procedures.[5] Although neuraxial anesthesia (caudal blockade) or other types of regional anesthesia are commonplace in the practice of pediatric anesthesia, given the associated platelet dysfunction, such practices are relatively contraindicated even after the administration of platelets.

The third major perioperative consideration in the care of a patient with JS is the potential for associated congenital heart disease with such problems being reported in >50% of patients.[5] Approximately 90% of the early mortality in the overall JS population is secondary to complications of the severe cardiac diagnoses including hypoplastic left heart syndrome, VSD, abnormalities of the aortic/mitral valves, and coarctation of the aorta. Given this concern, preoperative review of current echocardiographic studies along with assessment of functional status and consultation with cardiology as needed are recommended. The only case report to date describing anesthetic implications of Jacobsen syndrome specifically addressed cardiac surgery for repair of congenital anomalies. This report described the need to maintain a secure airway post-operatively until hemodynamic stability, specifically control of bleeding, was being addressed.

Co-morbid neurological conditions have been described in patients with JS. While our patient was on anticonvulsant medication and had a history of epileptiform activity during infancy, neurologic evaluation and genetic review determined that it may have been triggered by respiratory distress or cerebrovascular abnormality related to his Paris-Trousseau syndrome rather than typical etiologies. Seizure disorders are not specific to JS, and our patient had not had a seizure for more than four years on presentation. Other neurological manifestations of JS may affect vision, hearing, and learning.[5,14] Retinal abnormalities and colobomas of the eye and eyelid have been reported.[14] (7). The majority of patients with JS have delays in achieving motor and developmental milestones, hypotonia during the neonatal period, and abnormalities of gross and fine motor skills. There are rare reports of normal intelligence and development in patients with JS.

In summary, Jacobsen syndrome is a genetic disorder caused by partial deletion of the long arm of chromosome 11. It is associated with multiple co-morbidities affecting various organ systems. Airway, cardiac and platelet abnormalities are pathognomonic and may significantly impact perioperative care. The preoperative anesthetic evaluation of airway abnormalities, cardiac status, and platelet number and function (as well as assessment of other end-organ impairments) can be used to guide the anesthetic plan. Close postoperative monitoring is suggested until the residual effects of the anesthetic agents have dissipated.

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