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Case report

Anesthetic implications of Jacobsen syndrome

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Summary

Jacobsen syndrome (JS), also known as 11q-syndrome, is a congenital disorder associated with a deletion of the long arm of chromosome 11. Patients with JS characteristically exhibit multiple dysmorphic features, developmental delay, cardiac anomalies, and platelet abnormalities. Anesthetic issues related to the care of patients with JS concern airway management secondary to short neck, abnormal mouth shape and micrognathia/retrognathia, a high incidence of cardiac anomalies, and platelet dysfunction. Importantly, platelet abnormalities affect 95% of reported JS patients and involve platelet number, size and function. Two children with JS who required open heart surgery are presented and anesthetic management issues discussed. These patients represent the first reports regarding the perioperative issues in caring for patients with JS.

Keywords: anesthesia; Jacobsen syndrome; 11q-syndrome; Paris-Trousseau thrombocytopenia syndrome; 11q terminal deletion disorder; cardiac surgery

Introduction

Jacobsen syndrome (JS) is a rare autosomal dominant congenital syndrome associated with a deletion of the long arm of chromosome 11. Other names for the syndrome are '11q terminal deletion disorder' and '11q-syndrome' (1,2). Petrea Jacobsen first described this syndrome in 1973 (3). Since that description, multiple case reports and case series have documented the genetic and clinical features of this disorder. The most prominent clinical features of JS typically include Paris–Trousseau thrombocytopenia (94%), craniofacial anomalies (92%), developmental delay (85%), and cardiac malformations (56%). Other anomalies of the gastrointestinal, endocrine, and genitourinary systems have been described but are much less frequent. Despite JS being a rare genetic disorder, those affected are at a much higher risk to require surgical correction of cranial and cardiac anomalies. In addition, the platelet abnormalities and platelet dysfunction create an increased bleeding risk which is a life long issue for patients with JS. The anesthetic implications of JS regarding initial evaluation, intraoperative management and postoperative care are well illustrated in the two patients presented in this case report. The discussion will focus on the issue of preoperative evaluation, airway management, and homeostasis.

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Case reviews

Patient 1

A 10 kg, 22-month-old, ASA IV male with a diagnosis of JS presented for surgical repair of a double outlet right ventricle. His cardiac disease consisted of 'Tetrology of Fallot' physiology resulting in periodic cyanotic 'Tet-spells'. Additional review of systems was significant for several episodes of epistaxis, easy bruising, and poor feeding. His past medical history was significant for developmental delay, failure to thrive, and resolved renal insufficiency from an episode of hemolytic uremic syndrome (HUS). He was noted to have chronic mild thrombocytopenia. Laboratory studies were remarkable for normal renal function studies, and normal thyroid profile. Preoperative laboratory data were: white blood cell count of $4.4 \times 10^9\ l^{-1}$ (6.0–$18.0 \times 10^9\ l^{-1}$) and a hematocrit of 37.8% (33–39%). The platelet count at this time was undeterminable since the blood sample had clumped on a smear. The coagulation studies were prothrombin time (PT) of 12.5 s (9.6–12.5 s) and partial thromboplastin time (PTT) of 31.0 s (27.1–38.9 s). No bleeding time was done preoperatively. Interestingly, blood specimens had to be redrawn multiple times secondary to clotting. A repeat platelet count was $130 \times 10^9\ l^{-1}$ ($150–350 \times 10^9\ l^{-1}$) and peripheral blood smear demonstrated a low number of large immature platelets consistent with Paris–Trousseau syndrome. A hematology opinion was obtained to assess surgical bleeding risks and obtain perioperative recommendations. The recommendation of the consultant was to consider early platelet transfusion with evidence of bleeding.

On the day of surgery, vital signs were normal. The patient's physical examination was that of an alert and active nonambulatory child, smaller than the stated age. He had obvious facial dysmorphism with trigonocephaly, exopthalmosis, low set ears, and micrognathia. Cardiac examination was significant for a grade IV/VI systolic ejection murmur that obscured S2, yet S1 was normal on cardiac examination. Fasting status was verified and operative consent was obtained.

The patient underwent an uneventful mask induction with sevoflurane. Peripheral intravenous access was secured and rocuronium 1 $mg \cdot kg^{-1}$ administered. A direct laryngoscopy using a Macintosh 2 blade was performed with cricoid pressure. Only the arytenoids and the posterior portion of the vocal cords were visible (grade II view). A 4.5 tracheal tube was passed orally into the trachea. Arterial access was in the right radial artery and central venous access in the right internal jugular vein with a four French guage, 8 cm double lumen catheter. The maintenance anesthetic consisted of isoflurane 1–2%, fentanyl 16 $\mu g \cdot kg^{-1}$, and pancuronium 0.1 $mg \cdot kg^{-1}$. Baseline activated clotting time (ACT) was 118 s (normal, ≤120 s, preheparinization). Aminocaproic acid, an antifibrinolytic agent, was administered by 150 $mg \cdot kg^{-1}$ intravenous loading dose over 1 h followed by a maintenance infusion of 17 $mg \cdot kg^{-1} \cdot h^{-1}$. Through a median sternotomy, cardiopulmonary bypass (CPB) was achieved without complication following anticoagulation with 200 $\mu g \cdot kg^{-1}$ of intravenous heparin. The cardiac repair went smoothly with a CPB time of 207 min and aortic cross clamp time of 165 min.

Separation from CPB was uneventful and the patient was maintained on aminocaproic acid, epinephrine (0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$), and milrinone (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusions. Heparin reversal was achieved with the appropriate dose of protamine 1.5 $mg \cdot kg^{-1}$. Subsequent ACT was 101 s (normal, ≤150 s, after protamine). However, bleeding was still problematic and one weight-equivalent dose of platelets (10 $ml \cdot kg^{-1}$) was given. As the platelets were transfusing, oozing from the wound became noticeably less. The median sternotomy was closed and the patient taken to the pediatric intensive care unit (PICU) sedated with the tracheal tube in place.

Postoperative coagulation studies were normal – PT of 11.1 s, a PTT of 34.3 s, and an INR of 1.0. No significant postoperative bleeding events were noted in the PICU. A single postoperative transfusion of 10 $ml \cdot kg^{-1}$ packed red blood cells was given for hemoglobin of 9.4 $g \cdot dl^{-1}$. The aminocaproic acid infusion was allowed to continue for approximately 4 h. Daily postoperative platelet counts were greater than $150 \times 10^9\ l^{-1}$ and the hemoglobin remained stable. Chest tube drainage the PICU stay was 22 ml for the first 6 h, followed by 178 ml on the first postoperative day and 20 ml for the second day. He was extubated on the first postoperative day. The patient was discharged on the fifth hospital day.

Patient 2

A 4.8 kg, 6 month-old, ASA IV female infant with JS presented for repair of a ventricular septal defect (VSD). Her past medical history was significant for congestive heart failure and failure to thrive. Her JS consisted of abnormal facies and cardiac defects. No abnormalities of platelet function were noted. She had no evidence of central nervous system, gastrointestinal or genitourinary involvement. Her vital signs were normal. Her physical examination was notable for a triangular shaped face with prominent frontal bones, small mouth opening and mild retrognathia. She had a harsh, III/VI systolic ejection murmur with a prominent second heart sound. Her lungs were clear and liver was 2 cm below the right costal margin. She was warm and well perfused. Preoperative laboratory data included hemoglobin 11 $g \cdot dl^{-1}$, platelets 193×10^9 l^{-1}, PT 10.3 s, and PTT 27.5 s. Her renal function was normal.

The patient underwent mask induction of anesthesia using sevoflurane. After several unsuccessful attempts at peripheral intravenous access, she was intubated with deep inhalational anesthesia. Under direct laryngoscopy with a Miller 1 blade and cricoid pressure, the larynx was very anterior and only the posterior arytenoid cartilage and epiglottis could be visualized (grade III view). The trachea was orally intubated with a styletted, 3.5 tracheal without visualizing the vocal cords.

The right internal jugular vein was cannulated with a four French gauge, 5 cm double lumen central venous catheter and a right radial arterial line was placed. Maintenance anesthesia consisted of desflurane 3–6%, fentanyl 15 $\mu g \cdot kg^{-1}$ and pancuronium 0.1 $mg \cdot kg^{-1}$. Low dose aprotinin was followed starting with a 1 ml test dose of aprotinin (10 000 $kiu \cdot ml^{-1}$, 1.4 $mg \cdot ml^{-1}$), and followed by a loading dose of 15 ml given over 1 h and a 9.6 $ml \cdot h^{-1}$ maintenance infusion established prior to the initiation of CPB. Baseline ACT was 120 s. The VSD was repaired by pericardial patch without event. CPB time was 80 min. The patient separated from bypass on infusions of aprotinin, epinephrine (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and milrinone (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$).

Following reversal of heparin with protamine (1.5 $mg \cdot kg^{-1}$), the ACT was 135 s. However, the patient was noted to have an unusual amount of oozing from surgical sites, and two units of platelets (20 $ml \cdot kg^{-1}$) were given. Hemoglobin was 7.3 $g \cdot dl^{-1}$, and 10 $ml \cdot kg^{-1}$ of packed red blood cells were transfused. The patient was transported to the PICU with the tracheal tube in place.

Postoperatively, the PT and PTT were prolonged at 13.6 and 110.5 s respectively. Cryoprecipitate (2 $ml \cdot kg^{-1}$) was given. Postoperative hemoglobin was 11 $g \cdot dl^{-1}$ and platelets 260×10^9 l^{-1}. Brisk mediastinal drainage at time of PICU admission slowed after cryoprecipitate administration. The aprotinin infusion was continued until 2 h after PICU admission. Mediastinal drain output was 20 ml for the first 7 h and 12 ml on the first postoperative day. The hemoglobin was 9.9 $g \cdot dl^{-1}$ and an additional 10 $ml \cdot kg^{-1}$ of packed red cells was given. The patient's extubation was delayed until the first postoperative day secondary to the bleeding. Once extubated, the patient was transferred from the PICU. The remainder of the hospital stay was uncomplicated and the patient was discharged on the third postoperative day.

Discussion

Jacobsen syndrome is the name given to an autosomal dominant inheritable disorder characterized by dysmorphic facial features, cardiac malformations and thrombocytopenia. The incidence is reported to be 1 per 100 000 live births (1). Diagnosis is often suspected on clinical features but is confirmed by genetic karyotype. The chromosomal abnormality involves deletions of the long arm of Chromosome 11, thus the alternative name of '11q deletion disorder'. There is increasing evidence that these deletions may originate from breakage and/or loss during cellular division at the folate-sensitive regions in the DNA (2,4). The result is a unique phenotype characterized by trigonocephaly, endocardial cushion defects, and platelet defects. The exact biochemical or metabolic relationship of the genetic defect to these systemic organ dysfunctions and malformations has not been found (5). Both of the patients described had diagnosis made by karyotyping at birth, because of their dysmorphic features and cardiac abnormalities.

Cardiac malformations are present in over half of patients diagnosed with JS (3,6,7). Many of the reports describe the abnormalities as endocardial

cushion defects. Grossfield *et al*. (1) in their prospective review of 110 JS patients found two-thirds of the patients with cardiac lesions to have hemodynamically significant VSD, or left sided obstructive lesions involving abnormalities of the mitral and aortic valves. They also noted a much higher incidence of hypoplastic left heart syndrome and coarctation of the aorta. Of those patients with cardiac lesions, almost all required surgical intervention. In patients presenting with failure to thrive and JS, it may be difficult to know, as in our cases, whether the growth failure was due to JS, underlying endocrinologic dysfunction or cardiac disease. In both patients, preoperative testing had been done to exclude these comorbidities and the cardiac lesions were felt to be responsible for the growth failure. Anesthesiologists and other physicians caring for patients with JS should be aware of the multifactorial nature of poor growth in these patients and their risk for cardiac abnormalities. Careful evaluation of their cardiac anatomy by a pediatric cardiologist should be undertaken; this may include electrocardiogram, echocardiography, and cardiac catheterization.

The spectrum of dysmorphic features in patients with JS is quite diverse. Abnormalities of the face, hands and feet are most common. The most often described facial dysmorphisms are abnormal shapes of the eyes and lips, and low set ears (1,6). The most common abnormalities of the hands and feet involve digital anomalies (3,7). Our patients demonstrated all of the above except abnormalities of the digits. In addition our patients had wide spaced eyes and ptosis, both of which have been described in patients with JS (7).

The neurological manifestations of JS are common and quite variable effecting vision, hearing, and learning. Retinal abnormalities and colobomas of the eye and eyelid are reported (7). Hearing deficits have also been reported and are potentially multifactorial in etiology (1). Many patients with JS have developmental delay, neonatal hypotonia, and abnormalities of gross and fine motor skills. However, the severity is quite variable and there are rare reports of patients with JS having normal intelligence (1). Almost all case reports and studies describe older children with JS as ambulatory (1,6,7). Structural problems with skull growth include metopic craniosynostosis, or trigonocephaly, which results in a triangularly shaped forehead and narrow temples (6). Both of our patients have trigonocephaly, developmental delay, and hypotonia. No other neurologic manifestations were noted in our patients at the time of our evaluation.

In addition to abnormalities of the head shape, malformations of the jaw and palate are common and may be a source of difficult airway. The literature reports many syndromes and conditions with features of micrognathia and retrognathia resulting in difficult airways (for example, Pierre Robin Sequence, Treacher Collins, Cohen Syndrome, etc.) (8–10). However, evaluation of the airway by examination in these disorders can be difficult (8). Thus, the anesthesiologist must anticipate difficulties and have a plan to maintain the airway while the assessment and management occurs. Both of our patients had high arched palates and small, receding jaws. Also, both had very anterior laryngeal openings and gave grade II–III views on direct laryngoscopy. A clear airway examination was difficult prior to induction of anesthesia, as it is with most children this age. However, because of the micrognathia difficult airways were anticipated. A short acting relaxant (rocuronium) was intended for intubation in both patients with conversion to a longer acting paralytic (pancuronium) after the airway was secure for CPB. When unable to obtain secure intravenous access but still able to mask ventilate a difficult airway, we opt for a deep volatile intubation attempt as performed in the second patient. There is no information in the literature to suggest that over time children with JS will experience worsening or improvement of these airway issues. Our experience reinforces the need for careful assessment and preparation for a potentially difficult airway secondary to oropharyngeal abnormalities that are prevalent in JS.

Platelet abnormalities are a consistent feature of JS. The most common abnormality is Paris–Trousseau platelet syndrome (1). This platelet syndrome affects 95% of patients with JS. The platelet abnormality may manifest in infancy as thrombocytopenia and/or pancytopenia. As patients age, they may have normalization of their platelet numbers, however, peripheral blood smears will often demonstrate large stippled platelets (5). The 'stippling' results from arresting in the platelets development and premature release from the marrow. These

abnormal platelets have been demonstrated to be dysfunctional, resulting in bleeding problems. Patients may have normal coagulation studies but prolonged bleeding times. Platelet abnormalities and the resultant clotting problems require careful consideration by the anesthesiologist and surgeon prior to the procedure. Although other case reports have referred to the potential for bleeding problems and increased bruising in patients with JS, there are no prior reports of intraoperative management of these patients. Arrangements may need to be made to have platelets available during the procedure as well as other interventions to improve platelet function. Pretreatment with desmopressin acetate (DDAVP) has been proposed as a treatment option in patients with bleeding or for less invasive procedures (1). Consultation with a hematologist prior to the procedure may prove helpful in planning for treatment of perioperative bleeding issues. In addition to routinely used coagulation measures, thromboelastography (TEG) during cardiac surgery, neurosurgery and other high-blood loss procedures has been shown to reduce perioperative blood loss (11). Preoperative and intraoperative usage of TEG could prove useful in directing blood product and/or antifibrinolytic therapy (12). However, the effect of JS platelet abnormalities on TEG results is unknown. Use of antifibrinolytic therapy is our practice in caring for children undergoing cardiac surgery, and may have been beneficial in this setting through promotion of clot formation (13, 14). The usage of aminocaproic acid or aprotinin was based on surgeon's preference. Through a carefully planned approach to our JS patients, bleeding problems were anticipated and treated aggressively with platelet transfusions and perioperative antifibrinolytic agents to help minimized surgical bleeding and postoperative bleeding complications.

Growth failure is a common feature of the disorder and may be multifactorial as with the two patients presented. There are multiple case reports and evidence from the prospective study by Grossfield *et al*. that these children are at high risk for abnormalities of growth hormone levels, adrenal insufficiency and hypothyroidism (15). IGF-1 levels are often low in patients with JS, and may require hormone therapy (1). Other abnormalities of pituitary function should be investigated during routine evaluation and adequate treatment of abnormalities prompt referral and treatment by a pediatric endocrinologist.

Life expectancy for patients with JS is unknown (1,6,7). However, the morbidity and mortality of this rare syndrome is suspected to result from the high occurrence of congenital heart lesions and/or bleeding complications (1). In the perioperative setting, interest should also be given to airway management as anomalies of the skull shape and oropharynx are prevalent. Though other published reviews of syndromes have mentioned this syndrome, our case report emphasizes the potential bleeding and airway difficulties that JS patients may represent (16). Therefore, anesthesiologists, surgeons and intensivists must be aware of the possible risks that patients with JS bring to the operative and perioperative period. Issues of platelet function and bleeding risk should be addressed prior to the procedure and a plan of action in place if bleeding problems arise. For most operative procedures DDAVP and platelet transfusions should be sufficient. However, for cardiac surgery and other high blood loss procedures, a more aggressive approach with the addition of antithrombolytic therapy may prove beneficial as illustrated in our cases. Consideration should be given to a preoperative anesthesiology evaluation for assessment of hematologic parameters, cardiac status and airway issues.

References

1 Grossfield PD, Mattina T, Lai Z *et al*. The 11q terminal deletion disorder: a prospective study of 110 cases. *Am J Med Genet* 2004; **129A:** 51–61.
2 Penny LA, Dell'Aquila M, Jones MC *et al*. Clinical and molecular characterization of patients with distal 11q deletions. *Am J Med Genet* 1995; **56:** 676–683.
3 Jacobsen P, Hauge M, Henningsen K *et al*. An (11;21) translocation in four generations with chromosome 11 abnormalities in offspring. *Hum Hered* 1973; **23:** 568–585.
4 Jones C, Mullenbach R, Grossfeld P *et al*. Co-localization of CCG repeats and chromosome deletion breakpoints in Jacobsen syndrome: evidence for a common mechanism of chromosome breakage. *Hum Mol Genet* 2000; **9**(8)**:** 1201–1208.
5 Raslova H, Komura E, Le Couedic JP *et al*. FLI1 monoallelic expression combined with its hemizygous loss underlies Paris–Trousseau/Jacobsen thrombopenia. *J Clin Invest* 2004; **114**(1)**:** 77–84.
6 Lewanda AF, Morsey S, Reid CS *et al*. Two craniosynostosis patients with 11q deletions, and review of 48 cases. *Am J Med Genet* 1995; **59**(2)**:** 193–198.
7 Pivnick EK, Velagaleti GV, Wilroy RS *et al*. Jacobsen syndrome: report of a patient with severe eye anomalies, growth hormone deficiency, and hypothyroidism associated with

deletion 11 (q23q25) and review of 52 cases. *J Med Genet* 1996; **33**(9)**:** 772–778.
8 Nargozian C. The airway in patients with craniofacial abnormalities. *Pediatr Anesth* 2004; **14**(1)**:** 53–59.
9 Takita K, Kobayashi S, Kozu M *et al.* Successes and failures with the laryngeal mask airway (LMA) in patients with Treacher Collins syndrome – a case series. *Can J Anaesth* 2003; **50**(9)**:** 969–970.
10 Meng L, Quinlan JJ, Sullivan E. The anesthetic management of a patient with Cohen syndrome. *Anesth Analg* 2004; **99**(3)**:** 697–698.
11 Williams GD, Bratton SL, Riley EC *et al.* Coagulation tests during cardiopulmonary bypass correlate with blood loss in children undergoing cardiac surgery. *J Cardiothorac Vasc Anesth* 1999; **13**(4)**:** 398–404.
12 Shore-Lesserson L, Manspeizer HE, DePerio M *et al.* Thromboelastography-guided transfusion algorithm reduces transfusions in complex cardiac surgery. *Anesth Analg* 1999; **88**(2)**:** 312–319.
13 Chauhan S, Kumar BA, Rao BH *et al.* Efficacy of aprotinin, epsilon aminocaproic acid, or combination in cyanotic heart disease. *Ann Thorac Surg* 2000; **70**(4)**:** 1308–1312.
14 Rao BH, Saxena N, Chauhan S *et al.* Epsilon aminocaproic acid in paediatric cardiac surgery to reduce postoperative blood loss. *Indian J Med Res* 2000; **111:** 57–61.
15 Haghi M, Dewan A, Jones KL *et al.* Endocrine abnormalities in patients with Jacobsen (11q-) syndrome. *Am J Med Genet* 2004; **129A:** 62–63.
16 Butler MG, Hayes BG, Hathaway MM *et al.* Specific genetic diseases at risk for sedation/anesthesia complications. *Anesth Analg* 2000; **91**(4)**:** 837–855.

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