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Successful Management of a Patient With Jacobsen Syndrome and Hypoplastic Left Heart Syndrome

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Abstract

Jacobsen syndrome (JS) is a rare genetic condition characterized by intellectual disability, hematologic abnormalities, and congenital heart defects. A male infant presented at birth with phenotypic findings of JS and echocardiographic findings of hypoplastic left heart syndrome (HLHS). Array comparative genomic hybridization was performed at age three days and revealed an 8.1 Mb terminal deletion on the long arm of chromosome 11, consistent with JS. At five days of age, a hybrid stage 1 procedure was performed. At age 46 days, he underwent a Norwood operation followed by bidirectional Glenn at age six months. He is presently 23 months old and doing well. With careful consideration of the individual patient and comorbidities associated with JS, we propose that at least a subset of patients with JS and HLHS can do well with staged surgical palliation.

Introduction

Jacobsen syndrome (JS; OMIM #147791) is a rare condition characterized by terminal deletions of the long arm of chromosome 11, which affects ~1 in 100,000 newborns.[1,2] The deletion size ranges from 7 to 16 megabases (Mb), with larger deletions associated with more severe clinical phenotypes.[1,3] Variable intellectual disability, growth delay, hematologic abnormalities, immunodeficiency, congenital heart defects, and dysmorphic facies are the most common findings.[1,3] Other characteristic findings include airway obstruction, gastrointestinal, and genitourinary defects.[1,3,4]

Congenital heart defects, most commonly ventricular septal defects and left-sided obstructive lesions, occur in 56% of patients with JS and are the single most common cause of mortality.[1,2] Hypoplastic left heart syndrome (HLHS), one of the most severe congenital heart malformations, occurs in 5% to 10% of patients with JS (compared to 0.02% in the general population[1]). Consequently, JS has one of the highest frequencies of HLHS of any of the known genetic syndromes associated with HLHS.[5]

Human and mouse studies have implicated the avian erythroblastosis virus E26 (V-Ets) Oncogene Homolog-1 (ETS-1) gene, located in the "cardiac critical region" of the terminal portion of chromosome 11, as the cause of congenital heart defects in JS.[6] Historically, there has been hesitation pursuing single ventricle palliation for infants with genetic syndromes, given the overall poor prognosis and often severe accompanying intellectual disability. There is limited data on outcomes for HLHS surgical palliation in patients with associated genetic syndromes. For example, single ventricle

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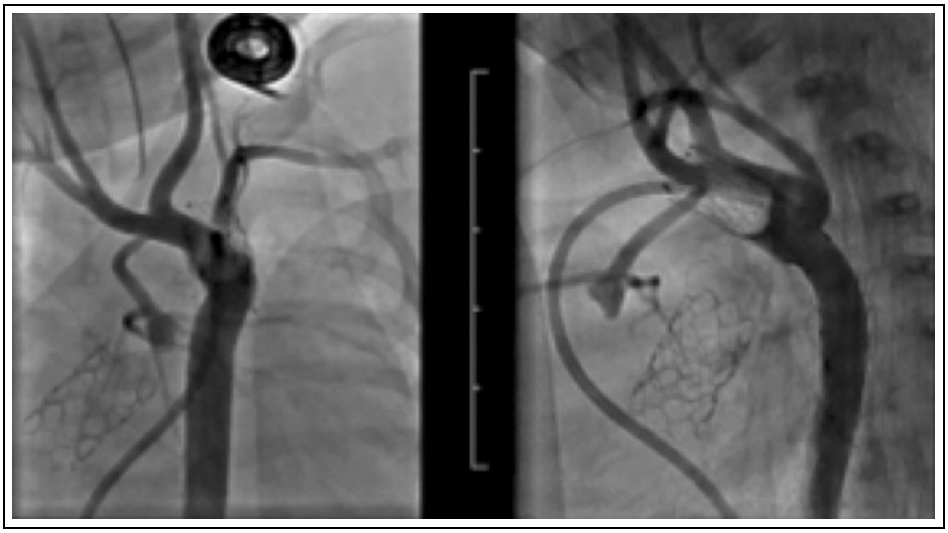

Figure 1. Pre-Norwood cardiac catheterization. AP and lateral views showing a small (2 mm) ascending aorta. The interatrial and ductal stents are visualized in good position.

surgical palliation in patients with Down syndrome is frequently ill advised, due to confounding comorbidities that increase pulmonary vascular resistance.[7] Turner syndrome also appears to be associated with high mortality in patients with HLHS undergoing single ventricle palliation.[8] The other genetic defects/syndromes that are encountered with single ventricles are DiGeorge, heterotaxy, Klinefelters, cat eye, cri-du-chat and Dandy-Walker syndromes, CHARGE, CHILD, and VACTERAL associations.[9] Nonetheless, there is a growing body of experience suggesting that patients with JS with HLHS can undergo successful three-stage surgical palliation.[4,10] Here, we report a male infant with JS and HLHS who has successfully undergone the first two stages of single ventricle palliation. With careful consideration, a subset of patients with JS with single ventricle physiology can do well with surgical palliation.

Case Presentation

A full-term male infant born via emergent caesarean section was noted to have an oxygen saturation of 70% and a grade IV/VI systolic murmur. Prenatal course was complicated by limited care and maternal tobacco and marijuana use. He had down slanting palpebral fissures and plagiocephaly. Echocardiography revealed HLHS with mitral and aortic valve atresia, a severely hypoplastic left ventricle, a severely hypoplastic aorta, and an intact ventricular septum. He also had a solitary right kidney and thrombocytopenia. Array comparative genomic hybridization (see Note 1) revealed an 8.1 megabase terminal deletion on the long arm of chromosome 11 (11q24.2-ter), consistent with a diagnosis of JS. Due to the numerous comorbidities and after discussion with the patient's mother, on day of life 5 (prior to the genetic diagnosis) at an outside facility, he underwent a hybrid stage 1 procedure with branch pulmonary artery banding, followed by ductal stenting, balloon atrial septostomy, and atrial septal stenting (Figure 1). The procedure was complicated by postoperative acute kidney injury and oliguria, requiring temporary peritoneal dialysis. Following the hybrid procedure, the patient was started empirically on baby aspirin. On day of life 40, he was transferred to our institution for further management. His renal function normalized and on day of life 46 he underwent a Norwood/Sano (RV-PA shunt) procedure with the placement of a 5-mm Gor-Tex shunt and removal of the interatrial and ductal stents. The decision to proceed with a Norwood procedure was related to increasing arch gradients at the level of the ductal stents in the presence of aortic atresia. Additionally, in our experience, long-term banding has resulted in needing more pulmonary artery interventions, both intraoperatively and in the cardiac catheterization lab, and we felt we could decrease this associated morbidity by intervening with the Norwood operation earlier.

The coarctation was resected, a posterior interdigitating anastomosis was performed to reconstruct the aorta, along with homograft patch reconstruction of the arch. (Cross-clamp time 65 minutes, pump time 150 minutes, circulatory arrest 52 minutes.) Postoperatively, he remained thrombocytopenic (80,000/microliter), with platelet function testing significant for collagen/epinephrine >300 seconds (normal 80-184 seconds) and collagen/adenosine diphosphate 220 seconds (normal 57-115 seconds). He received milrinone postoperatively for two weeks and then transitioned to oral captopril and baby aspirin. He developed necrotizing enterocolitis three weeks postoperatively requiring cessation of the aspirin. He was able to restart aspirin one month later and has had no further bleeding complications. His course was further complicated by poor weight gain, requiring laparoscopic Nissen fundoplication and gastrostomy tube at two months of age. He was discovered to have a left collecting system kidney stone after an episode of hematuria at 2.5 months, necessitating transition from Lasix to hydrochlorothiazide. The patient was discharged home in stable condition on day of life 100. A follow-up catheterization, performed at age 3.5 months in preparation for his Glenn procedure, demonstrated moderate obstruction at the distal arch reconstruction site that was relieved with an 8-mm balloon dilation.

At six months of age, he underwent a successful right ventricular to pulmonary artery (RV-PA) shunt takedown and bidirectional Glenn with homograft patch repair of the pulmonary arteries (no cross-clamp time, cardiopulmonary bypass time 91 minutes, induced fibrillation time of 6 minutes—to allow complete removal of the Sano shunt and closure of the ventriculotomy). He received platelets intraoperatively but did not require any additional blood products postoperatively. He received intravenous milrinone for four days postoperatively. His postoperative course was unremarkable, with a length of stay of 26 days, the long stay related to social issues. Follow-up echo at age eight months showed stenosis of the Glenn anastomosis, and subsequent catheterization identified no gradient across the aortic arch, a Glenn pressure of 13 mm Hg, moderate stenosis of the Glenn anastomosis, and moderate proximal left pulmonary artery stenosis. He underwent balloon angioplasty of the proximal left pulmonary artery and Glenn anastomosis with a 7-mm balloon and coil occlusion of multiple left innominate venovenous collaterals. The patient is presently 23 months old. He is below the third percentile for weight and

height and is at the 31st percentile for head circumference. His appearance is noteworthy for characteristic phenotypic findings of JS, including ocular hypertelorism, downslanting palpebral fissures, a broad nasal bridge, an upturned nose, and posteriorly rotated ears.

He has severe temper tantrums but is meeting all developmental milestones. He is stable on a baby aspirin, enalapril, and furosemide, and does not have a home oxygen requirement. He has had one subsequent hospitalization for a pseudomonas urinary tract infection and in the last six months has had infections with influenza, respiratory syncytial virus (RSV), and two episodes of croup. He is followed closely by immunology, most recently at 22 months he had a normal T-cell mitogen response, with an interval decline in his absolute T-cell count from normal (mid-700 seconds) to low normal (mid-300 seconds) levels. He has received all immunizations with the exception of the live vaccines. He failed to mount an appropriate antibody response to 22 of 23 pneumococcal antigens but did mount an appropriate response to tetanus antigen. He does not currently require antibiotic prophylaxis.

Discussion

Historically, single ventricle surgical palliation has been contraindicated in some patients with severe genetic syndromes, given the comorbidities that may predispose to poor outcomes. In this report, we describe a child with JS and HLHS that has undergone successful stage I and II surgical palliation. Interestingly, several other patients with JS and HLHS have undergone successful three-stage surgical palliation, with the oldest known living survivor now 14 years old. The patient in this report has severe intellectual disability and continues to have stable hemodynamics with moderate tricuspid regurgitation and normal right ventricular function, currently only on enalapril. In these cases, moderate to severe intellectual disability is not an independent risk factor for a poor surgical outcome (Grossfeld, 2018, unpublished data).

Nonetheless, in JS, other comorbidities may influence the outcome. For example, $\sim 10\%$ of patients have structural kidney defects, as in the present case, and careful attention must be paid to preserving renal function in the operative and perioperative period. In addition, many patients have significant immunodeficiency. One child who had successfully undergone the three-stage surgical palliation for HLHS developed protein losing enteropathy after a series of infections several years after her Fontan operation, likely multifactorial due to multiple gastrointestinal infections combined with Fontan physiology. She died a year after being diagnosed with protein-losing enteropathy. Consequently, aggressive preventive measures including intravenous immunoglobulin infusions and/or prophylactic antibiotics (amoxicillin) should be considered in patients with JS undergoing single ventricle surgical palliation. Furthermore, a subset of patients with JS has scoliosis and airway obstruction, which may significantly impact Fontan physiology.[4] Finally, most patients with JS also have Paris-Trousseau syndrome, characterized by thrombocytopenia and impaired platelet function. Consequently, patients are at increased risk of postoperative bleeding, therefore postsurgical anticoagulation warrants careful consideration. Our specific clinical recommendations are listed in the Table 1.

Table 1. Intra and Postoperative Risks Associated With Jacobsen Syndrome.

Risks	Problem	Management Considerations
Bleeding	Thrombocytopenia and platelet dysfunction secondary to Paris Trousseau syndrome	• Preoperative platelet function testing • Postoperative platelet transfusions • Judicious use of anticoagulants; inhibitors of clotting factors may be contraindicated (depending on the severity of platelet dysfunction) • Use medications that inhibit platelet function judiciously
Acute kidney injury	Structural renal anomalies	• Maintain good perfusion pressure during cardiopulmonary bypass to optimize renal blood flow, use Near-Infrared Spectroscopy (NIRS) monitoring • Renal dosing of medications, as indicated
Infection	Variable degree of immunodeficiency	• Recommend complete immune evaluation preoperatively and consider long-term prophylaxis with antibiotics and/or intravenous immunoglobulin (IVIg) • High index of suspicion for infections and low threshold for broad spectrum antibiotics
Airway obstruction	Upper airway obstruction, variable degree of scoliosis	Controlled intubation/airway stabilization

Comment

In summary, there is growing evidence indicating that at least some patients with JS and single ventricle physiology may be able to undergo successful long-term surgical palliation, independent of the degree of intellectual disability. Careful attention should be given to each individual patient in order to address comorbidities that could compromise long-term quality of life and survival before embarking on the three-stage surgical palliation pathway.

Authors' Note

The authors Paul Grossfeld and Raghav Murthy contributed equally to the preparation of the manuscript. The family of this patient provided consent for the publication of case report and photographs. Institutional review board approval was not required for this case report. The authors had full control of the data and production of the manuscript.

Note

1. Microarray genetic analysis was performed by UCSC Genome Browser, DECIPHER database, Database of Genomic Variants, OMIM and published medical literature.

Declaration of Conflicting Interests

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Anomalous Left Subclavian Artery from the Left Pulmonary Artery in Transposition of the Great Arteries with Right Aortic Arch

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Abstract

Anomalous origin of the subclavian artery from the pulmonary artery is a rare but well-described entity. We report a case of anomalous origin of the left subclavian artery from the left pulmonary artery in a patient with transposition of the great arteries. We discuss the safe intraoperative management of this anomaly in a patient in whom the diagnosis was made intraoperatively.

Introduction

Anomalous origin of the subclavian artery from the pulmonary artery is a rare congenital anomaly. Suspicion arises arises only through the subtle signs provided by meticulous four-limb pulse oximetry and blood pressure measurements or by diligent echocardiography done for other associated lesions. We report a case of anomalous origin of left subclavian artery (LSCA) from left pulmonary artery (LPA) in association with transposition of great arteries which was encountered intraoperatively and managed successfully. We also discuss the

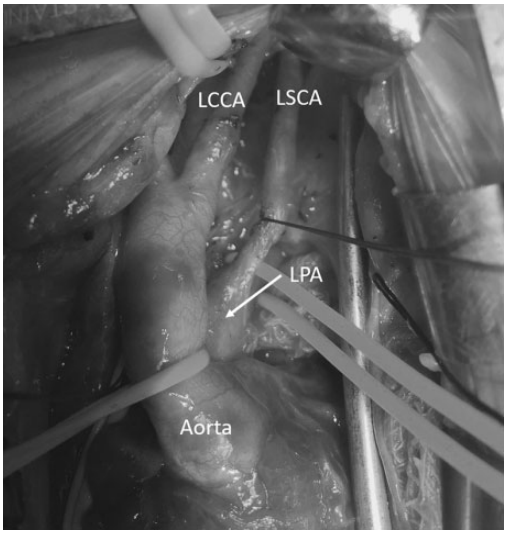

Figure 1. Intraoperative image of anomalous left subclavian artery arising from the left pulmonary artery. LCCA indicates left common carotid artery; LPA, left pulmonary artery; LSCA, left subclavian artery.

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