2020

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JACC: CASE REPORTS VOL. 2, NO. 11, 2020

MINI-FOCUS ISSUE: CONGENITAL HEART DISEASE

ADVANCED

CASE REPORT: CLINICAL CASE

Williams Syndrome and Neonatal Cardiac Surgery for Congenital Single Ventricle

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ABSTRACT

Williams syndrome (WS) is an arteriopathic derangement associated with supravalvular aortic stenosis and branch pulmonary stenosis. We describe double-outlet right ventricle with mitral atresia and aortic arch hypoplasia in an infant with WS. This case demonstrates the difficulty in managing patients with WS with complex cardiac defects. To our knowledge, this is the first reported single-ventricle physiology in a patient with WS. (**Level of Difficulty: Advanced.**)

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A female infant was born at 37 weeks of gestation. Apgar scores were 8 and 9 at 1 and 5 min, respectively. Prostaglandin E1 infusion was started at delivery due to a fetal echocardiogram demonstrating congenital heart disease and concern for inadequate systemic blood flow with aortic arch hypoplasia. The infant was transferred to the neonatal intensive care unit from the outside hospital immediately after delivery.

LEARNING OBJECTIVES

- To identify cardiovascular complications associated with WS and recommended components of screening.
- To recognize challenges associated with single-ventricle physiology in conjunction with WS.

Birth weight and length were 2.68 kg (25th percentile) and 45 cm (<3rd percentile), respectively. Heart rate was 168 beats/min with respiratory rate 45/min. Oxygen saturation was 90% and 86% in the right arm and right leg, respectively. Blood pressure was 60/28 and 46/33 mm Hg in the right arm and leg, respectively. Physical examination demonstrated typical findings of Williams syndrome (WS), including a short upturned nose, epicanthal folds, periorbital edema, right ear lower than left, and long philtrum. Cardiac examination revealed a quiet precordium with prominent S2, systolic ejection click, and grade II/VI systolic ejection and II/VI diastolic murmurs.

There was moderate cardiomegaly on chest x-ray with an upturned apex, abdominal situs solitus, and normal thymic shadow. Electrocardiogram showed low atrial rhythm with narrow QRS duration and right

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the *JACC: Case Reports* author instructions page.

Manuscript received March 20, 2020; revised manuscript received May 6, 2020, accepted May 20, 2020.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2020.05.098

ventricular hypertrophy. In the first 24 h of hospitalization, the patient developed respiratory acidosis and required endotracheal intubation.

PRENATAL HISTORY

Pregnancy was complicated by intrauterine growth restriction. Initial prenatal echocardiogram at 29 weeks of gestation was diagnostic for double-outlet right ventricle (DORV), malposition of the great arteries, large subpulmonary ventricular septal defect, confluent branch pulmonary arteries, and severe coarctation (**Figure 1**, Videos 1 and 2). Prenatal chromosomal microarray revealed a 1.48 megabase interstitial deletion at chromosome 7q11.23, consistent with WS. Family history was unremarkable for cardiovascular disease and congenital anomalies.

DIFFERENTIAL DIAGNOSIS

Congenital heart defects occur in approximately 80% of patients with WS, with supravalvular aortic stenosis and peripheral pulmonary artery stenosis occurring most frequently, although Tetralogy of Fallot, complete atrioventricular septal defect, total anomalous pulmonary venous return, double-chambered right ventricle, and Ebstein anomaly of the tricuspid valve also have been reported (1). Based on this patient's prenatal echocardiogram, differential diagnosis included severe unbalanced atrioventricular septal defect with atresia of the left atrioventricular valve and DORV with mitral valve atresia.

INVESTIGATIONS

Transthoracic echocardiogram on the first day of life (DOL) confirmed atrial situs solitus, atrioventricular concordance with mitral atresia, a single ventricle of right ventricular morphology, DORV, and malposition of the great arteries (pulmonary artery anterior and to the left) with large subpulmonary ventricular septal defect. The inferior vena cava connected to the right atrium; there were bilateral superior vena cavae, without bridging vein. The main pulmonary artery (MPA) was of normal diameter, but the right branch pulmonary artery (RPA) and left branch pulmonary artery (LPA) were relatively hypoplastic (RPA 3.2 mm [*z*-score, −1.8]; LPA 3.0 mm [*z*-score, −2.3]). The semilunar valves were normal with a tri-leaflet

ABBREVIATIONS AND ACRONYMS

DOL = day of life

DORV = double-outlet right ventricle

LPA = left pulmonary artery

MPA = main pulmonary artery

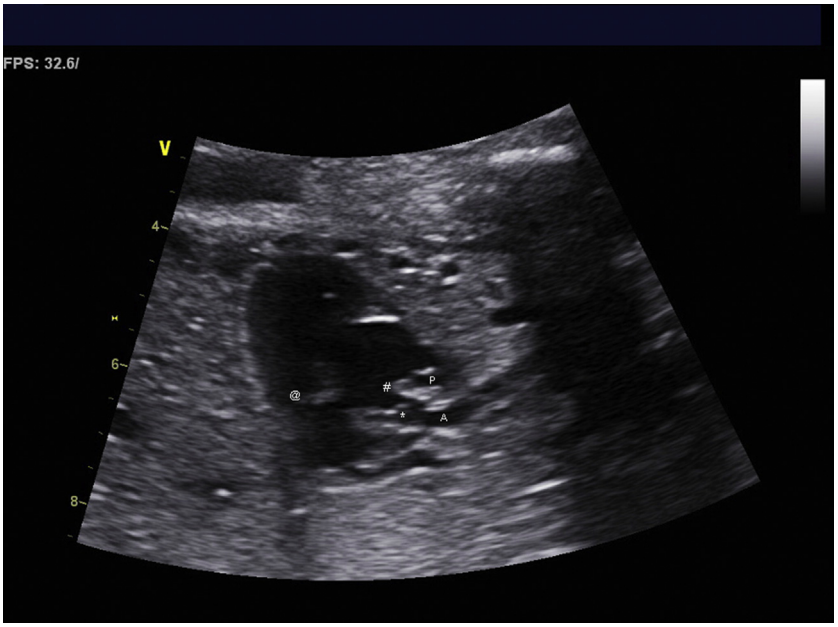
POD = post-operative day

RPA = right pulmonary artery

RV = right ventricle

WS = Williams syndrome

FIGURE 1 Single-Ventricle Anatomy on Fetal Echocardiogram



Still frame in 2-dimension using fetal echocardiogram at 29 weeks estimated gestation. Inflow-outflow view demonstrating single-ventricle anatomy with normal atrioventricular valve (@), prominent subaortic conus (#), normal aortic root (*), diffuse hypoplasia of the ascending aorta (A), and normal pulmonary root (P).

aortic valve; however, there was significant narrowing beginning at the sinotubular junction with diffuse aortic arch hypoplasia and severe coarctation at the aortic isthmus. Unrestrictive left-to-right flow was present across multiple fenestrations at the atrial septum. The left atrium was mildly hypoplastic, but with normal pulmonary venous return. There was normal ventricular function with dysplastic tricuspid valve and mild-to-moderate tricuspid valve regurgitation. Coronary arteries were of normal origin. A large ductus arteriosus was present with right-to-left flow. Renal ultrasound demonstrated no evidence of renal artery stenosis. Head ultrasound demonstrated normal structures.

MANAGEMENT

On DOL 4, the patient underwent surgical aortic arch reconstruction with patch augmentation of the ascending aorta, atrial septectomy, tricuspid valve commissuroplasty, banding of the MPA, and ligation/division of the ductus arteriosus on cardiopulmonary bypass.

Postoperatively, desaturation episodes required increased supplemental oxygen and intermittent intervention with manual ventilation (post-operative day [POD 9]). Frequent echocardiogram assessments demonstrated effective MPA band gradients, but on POD 10 there was an increase in velocity in the RPA (maximum 4.6 m/s). On DOL 15 (POD 11), the patient returned to the operating room where ductal tissue impinging the branch pulmonary arteries was excised, the MPA band was revised, and bilateral proximal patch pulmonary arterioplasty was performed. During subsequent hospital course, effective MPA band gradient was documented using echocardiogram (3.5 m/s).

Despite acceptable echocardiogram findings, the patient developed hypotension and anasarca, which was refractory to medical management. Cardiac catheterization was performed on DOL 26. Direct pulmonary venous saturations were 93% to 95%. Index cardiac output was decreased at 2.2 l/min/m^2, with Qp:Qs of 1.5:1. Mean right atrial pressure was 15 mm Hg, without significant gradient across the atrial septum. Peak right ventricular (RV) systolic pressure was 100 mm Hg, with an increased RV end-diastolic pressure of 17 mm Hg. There was a peak gradient of 45 mm Hg across the pulmonary artery band, with a distal MPA pressure of 55/15 mm Hg. Additional pressure gradient was seen into the bilateral branch pulmonary arteries, with distal LPA pressure of 29/12 (mean, 22) mm Hg and distal RPA pressure of 17/13 (mean, 15) mm Hg. Ascending aortic pressure was 80/32 mm Hg, demonstrating a RV to aortic peak instantaneous gradient of 20 mm Hg. There was no additional gradient by pullback through the aortic arch. Indexed pulmonary vascular resistance on room air was 2.1 WU/m^2.

Angiography demonstrated mild dilation of the transverse aorta that was consistent with the surgical patch augmentation (Videos 3 and 4); however, brachiocephalic branching demonstrated generally hypoplastic vessels with a distally displaced left subclavian artery. The descending aorta was diffusely hypoplastic, but without discrete stenosis. The RV demonstrated vigorous RV systolic function, without significant tricuspid valve insufficiency. On levophase, pulmonary veins returned normally to the left atrium. Pulmonary arteriography demonstrated good band position with hypoplastic branch pulmonary arteries without discrete branch pulmonary artery stenosis; however, RPA and LPA remained hypoplastic (RPA 3.1 mm [z-score, −2.3]; LPA 3.1 mm [z-score, −2.5]).

Despite the cardiac surgical repair, the patient required escalating intensive care for worsening renal function and abdominal ascites. An intracranial hemorrhage occurred, necessitating an Ommaya reservoir to relieve intracranial pressure. The patient developed metabolic acidosis, systemic hypotension, and refractory hypoxemia.

DISCUSSION

WS results from a sporadic deletion encompassing the elastin gene, resulting in diffuse arterial stiffness from hypertrophy of arterial walls with consequent luminal narrowing (2–4). Elastin creates recoil potential within blood vessels. The resulting deficiency of elastin leads to increased stiffness within vascular structures (2). In general, patients with WS with outflow tract obstruction, ventricular hypertrophy, or coronary ostial stenosis are at highest risk of cardiovascular complications and death (5). Current guidelines recommend that all patients with WS undergo cardiovascular screening with examination by a pediatric cardiologist, including 4-extremity blood pressure and transthoracic echocardiogram. Renal ultrasound with Doppler is routinely obtained to screen for renal artery stenosis. Progressive arterial narrowing is well recognized (1).

In the case presented, postoperative renal and intracranial complications presented significant postoperative comorbidity. Balanced pulmonary and systemic arterial blood flows were demonstrated using hemodynamic catheterization. A mild obstruction was present between the ventricle and the ascending aorta,

although further intervention typically is reserved for more severe obstruction in patients with WS (6).

Distal arterial changes are difficult to quantify, particularly in the neonate with WS. Despite adequate surgical palliation of single ventricle anatomy, diffuse arteriopathy likely contributed to post-operative complications in this neonatal case. Imaging of renal, coronary, mesenteric, and intracranial arteries might be performed at preoperative baseline using various modalities, including ultrasound with Doppler, computed tomography, and/or magnetic resonance imaging angiography; however, specific risk stratification is not yet available for patients with WS in relation to the size of extracardiac vascular structures and interrogation of peripheral arterial/venous flow (5).

FOLLOW-UP

Despite aggressive inotropic and metabolic support, the patient showed minimal improvement and the decision was made to withdraw life-sustaining treatment.

CONCLUSIONS

This case illustrates potential difficulties that may be encountered in neonates with complex cardiac anatomy and known diffuse arteriopathy. Arteriopathy associated with WS may increase postoperative risk after palliative cardiac surgery, where balanced, unobstructed systemic and pulmonary arterial blood flow are critical. This risk must be considered when discussing surgical intervention with families of patients with WS.

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KEY WORDS aortic arch hypoplasia, congenital heart disease, genetic syndrome, pulmonary artery stenosis

APPENDIX For supplemental videos, please see the online version of this paper.