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CASE REPORT

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Early identification of SOX17 deficiency in infants to guide management of heritable pulmonary arterial hypertension using PDA stent to create reverse Potts shunt physiology

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Abstract

Heritable pulmonary arterial hypertension (HPAH) is a rare progressive condition that includes patients with an identified genetic cause of pulmonary arterial hypertension (PAH). HPAH and idiopathic PAH (IPAH) have an estimated combined incidence of 0.5–0.9 cases per million children-years. Several pathogenic variants have been associated with HPAH in children and adults, including genes *BMPR2*, *TBX4*, and *ACVRL1*, and more rarely with variants in genes such as *SOX17*. HPAH is often difficult to manage and has poor prognosis despite advances in medical therapy with many patients progressing to lung transplantation, right heart failure and death. Surgical and transcatheter Potts shunt creation can reduce systolic burden and has shown reduction in morbidity and mortality in children. Early genetic testing can provide both diagnostic and prognostic value in managing and counseling children with severe PAH and it can guide transcatheter or surgical management in refractory cases despite maximal medical therapies. We describe a patient with HPAH (SOX17 mutation) who underwent percutaneous patent ductus arteriosus stent for right ventricle decompression at 2 months of age with clinical management guidance by genetic testing results.

KEYWORDS
genetics, patent ductus arteriosus, pediatrics, pediatric cardiovascular disease, pulmonary arterial hypertension

CASE DESCRIPTION

A full-term female neonate developed cyanosis shortly after birth and was found to have severe pulmonary hypertension on echocardiography with no other evidence of structural congenital heart disease. She was cannulated onto venovenous extracorporeal membrane oxygenation (ECMO) for severe hypoxemia and presumed severe persistent pulmonary hypertension of the newborn. She was weaned off ECMO within 4 days but continued to have severe pulmonary hypertension and mild right ventricular systolic dysfunction based

on echocardiography with clinical signs of right heart failure. Whole-genome sequencing (WGS) was sent at 2 days of life and revealed a pathogenic de novo missense variant c.208C>G p.Arg70Gly in SOX17 consistent with a diagnosis of heritable PAH (HPAH). No other causes of PAH were identified during her workup. Initial hemodynamic cardiac catheterization at 1 month of life showed suprasystemic right ventricle (RV) pressures and pulmonary vascular resistance index 28 U m^2 and pulmonary capillary wedge pressure 11–14 mmHg consistent with severe pulmonary arterial hypertension (PAH). Her ductus arteriosus had closed by 1 week of life but based on catheterization findings, prostaglandin E (PGE) was immediately started to reestablish ductal patency to offload the right ventricle. While the infant was quickly extubated after cardiac catheterization and weaned to continuous positive airway pressure, she had persistent suprasystemic RV pressures by echocardiography despite multidrug therapy for her PAH (inhaled NO, sildenafil, treprostinil, bosentan). Given the severity of her disease and known poor prognosis of SOX17 variant, at 2 months of age she underwent transcatheter percutaneous PDA stent placement to create reverse Potts shunt physiology (Figure 1). After stent placement, she was weaned off noninvasive positive pressure ventilation and discharged home at 6 months of life on 1 L/min (1.0 FiO_2) nasal cannula and triple-drug therapy with bosentan, tadalafil and subcutaneous trepostinil (60 ng/kg/min). She is now 2 years of age and undergoing lung transplant evaluation due to persistent severe PAH.[1–6]

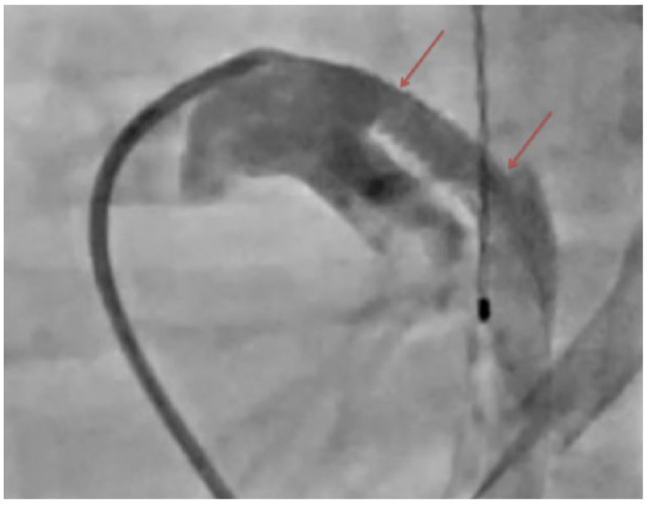

FIGURE 1 Angiogram in a lateral view with contrast injected into the pulmonary artery shows a large stented patent ductus arteriosus with filling of the descending aorta and pulmonary artery. Arrows indicate the two ends of the stent.

DISCUSSION

SOX17 is a member of the SRY-box (SOX) transcription factor family and plays a prominent role in the prenatal formation of the definitive endoderm and pulmonary vascular development and is a transcriptional target of the Wnt/β-catenin pathway.[7,8] Action through several other pathways has also been suggested, including through endothelin, transforming growth factor-β and bone morphogenic protein signaling. In vivo knockout mice studies have shown biventricular hypertrophy, decreased pulmonary blood flow, cardiac enlargement, and increased neonatal lethality. In humans, SOX17 pathogenic variants have been described in children and adults with HPAH. Wu et al.[9] and Hiraide et al.[10] described four patients with SOX17 mutations, including a woman diagnosed with PAH at 33 years old and died 2 years later, a mother (age 51 at diagnosis) and son (age 25 years at diagnosis) who were both managed with combination medical therapy. The fourth case describes a woman diagnosed with IPAH at 2 years of age with severe refractory disease and whole-exome sequencing at 24 years old revealed a heterozygous missense mutation in SOX17. Interestingly, her mother also had a heterozygous missense mutation in SOX17 but was an asymptomatic carrier. SOX17 variants have been linked to lower mean age of presentation for PAH as compared to other commonly described pathogenic variants such as KCNA5.

HPAH is clinically indistinguishable from idiopathic PAH and there may be patients with a diagnosis of IPAH who have an unidentified underlying genetic cause. Epidemiologic studies often do not distinguish between IPAH and HPAH and therefore the incidence and prevalence of HPAH is likely underestimated.[1] Early genetic testing should therefore be considered in neonates with severe PPHN who do not respond to standard medical therapy. By continuing to identify SOX17 and other pathogenic variants through WGS, we can use this data to improve clinical risk stratification and to guide medical and interventional management of these rare neonatal HPAH cases. Further identifying and characterizing SOX17 variants and other genetic mutations associated with PAH through WGS will allow clinical risk stratification and guide the medical and interventional management of these rare neonatal cases.

Surgical and transcatheter Potts shunt creation has been described in all ages, with transcatheter intervention performed as young as 3 weeks of age.[4] Given the poor prognosis of patients with HPAH and low likelihood of reversibility, PDA stent placement can be used as a less invasive alternative to surgical Potts shunt creation for young infants despite maximal medical therapy, in cases where a pathogenic variant is identified.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

N/A.

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