CASE REPORT

Genetics dictating therapeutic decisions in pediatric pulmonary hypertension? A case report suggesting we are getting closer

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Abstract
Despite therapeutic advances over the past decades, pulmonary arterial hypertension (PAH) and related pulmonary vascular diseases continue to cause significant morbidity and mortality in neonates, infants, and children. Unfortunately, an adequate understanding of underlying biology is lacking. There has been a growing interest in the role that genetic factors influence pulmonary vascular disease, with the hope that genetic information may aid in identifying disease etiologies, guide therapeutic decisions, and ultimately identify novel therapeutic targets. In fact, current data suggest that genetic factors contribute to ~42% of pediatric-onset PH compared to ~12.5% of adult-onset PAH. We report a case in which the knowledge that biallelic ATP13A3 mutations are associated with malignant progression of PAH in young childhood, led us to alter our traditional treatment plan for a 21-month-old PAH patient. In this case, we elected to perform a historically high-risk Potts shunt before expected rapid deterioration. Short-term follow-up is encouraging, and the patient remains the only known surviving pediatric PAH patient with an associated biallelic ATP13A3 mutation in the literature. We speculate that an increased use of comprehensive genetic testing can aid in identifying the underlying pathobiology and the expected natural history, and guide treatment plans among PAH patients.

KEYWORDS
ATP13A3, Potts shunt, pulmonary vascular disease

INTRODUCTION

Despite advances over the past decades, pulmonary arterial hypertension (PAH) and related pulmonary vascular diseases continue to cause significant morbidity and mortality in diverse neonatal, pulmonary, cardiac, and other systemic disorders of childhood.¹ Unfortunately, current therapeutic strategies are based solely on disease severity rather than incorporating underlying biology.

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Among the pediatric PAH patient population, there has been a growing interest in the role that genetic factors influence pulmonary vascular disease, with the hope that genetic information may aid in identifying disease etiologies, guide therapeutic decisions, and ultimately identify novel therapeutic targets. In fact, current data suggest that genetic factors contribute to ~42% of pediatric-onset PH compared to ~12.5% of adult-onset PAH. The molecular genetic basis of PAH is heterogeneous, with at least 26 genes displaying varying levels of evidence for disease causality. In this case report, we present a case in which knowing the patient’s genetic mutation, ATP13A3, helped guide our treatment plan. ATP13A3, which encodes a transmembrane cation polyamine transporter, is widely expressed in a variety of tissues including pulmonary arterial smooth muscle cells. Interestingly, polyamines, which are small metabolites required for normal cell growth and proliferation, were recently reported to be increased in pulmonary hypertension.

**CASE DESCRIPTION**

A 21-month-old female presented with a prolonged history of dyspnea at rest that worsened with activity, and an episode of “fainting” 4 months prior. More recently she was found to be listless and cyanotic while visiting at high altitude that improved upon return to sea level. Echocardiography demonstrated right ventricle (RV) dilatation and hypertrophy, right atrial enlargement, and septal bowing suggestive of suprasystemic pulmonary arterial pressures. Complete adjunct testing was consistent with idiopathic PAH, with no secondary etiologies identified. Cardiac catheterization confirmed severe pulmonary hypertension (pulmonary artery pressure [PAP] 93/49 m69, systemic arterial pressure SAP 132/89 m66), and preserved CI and RV function, 

with preserved RV function,7 despite her young age, the rapidly progressive course of refractory PAH. Because the Potts procedure is most successful when performed with preserved RV function,7 despite her young age, the only mild worsening in her clinical status, and the normal CI, RAP, and BNP, our PH team saw this as a “window of opportunity” and recommended a Potts shunt to the family.

The patient underwent a Potts shunt via a left thoracotomy, utilizing an 8 mm Gore-tex vascular graft. Her trachea was extubated in the operating room, and she was discharged home on post-op Day 6. Her recovery was unremarkable, with a pre and post Potts shunt saturation difference of 10%–15%. Recent evaluation 12 months post the Potts shunt demonstrates preserved cardiac output and RV function, with clinical improvement (WHO FC II) and no increase in diuretic needs, despite continued suprasystemic PAP (98/55 m75, SAP 89/54 m65) and marked elevation of her PVRI. Given her known mutation and continued rise in PVRI, she remains on triple therapy, and will likely undergo lung transplant evaluation in 6–12 months.

confirmed monoallelic ATP13A3 variants were associated with adult-onset PAH, but neither monoallelic nor biallelic ATP13A3 had been reported in childhood PAH. However, data unpublished at the time from two other families with four affected children who presented at a young age (<2.5 years) demonstrated an aggressive course that was refractory to aggressive PH therapies, resulting in death. For example, three of the four patients were treated with triple therapy that included sildenafil, bosentan, and prostacyclins. Two of these patients died 6 and 17 months following presentation and initiation of therapy, while the third went on to lung transplantation within 2 years and died 4 years thereafter. This cohort has been subsequently published, and now includes our patient, her family’s genotypes, and a portion of her clinical course.

Initiation of therapy resulted in dramatic improvement in the patient’s dyspnea, activity, and weight gain (From WHO FC IV to II). This correlated with marked improvement in hemodynamics demonstrated at cardiac catheterization 1 year posttherapy initiation (PAP 77/37 m56, SAP 93/50 m66, PVRI 12.2; CI 3.6, right atrial pressure [RAP] 7, B-type natriuretic peptide [BNP] 13 pg/ml). However, over the ensuing 6 months, the patient’s clinical progress stalled, and mild signs of decreased activity and dyspnea upon exertion returned (WHO FC III). Repeat cardiac catheterization demonstrated an increase in PVRI to 22, suprasystemic PAP (104/59 m74, SAP 96/51 m66), and preserved CI and right ventricular function (Table 1 below).

Given her genetic mutation, our multidisciplinary PH team was concerned that this was the start of a rapidly progressive course of refractory PAH. Because the Potts procedure is most successful when performed with preserved RV function,7 despite her young age, the only mild worsening in her clinical status, and the normal CI, RAP, and BNP, our PH team saw this as a “window of opportunity” and recommended a Potts shunt to the family.
DISCUSSION

The emerging importance of genetic testing for PAH cannot be overstated, particularly in pediatric-onset PAH, which appear to have a greater genetic burden that adult-onset disease. Knowledge of a causal gene for pulmonary vascular disease may aid in the diagnosis, the underlying pathobiology, and the expected natural history and response to treatment. For example, identifying a mutation in FOXF1 in a neonate with refractory PAH strongly suggests a diagnosis of alveolar capillary dysplasia without the need for lung biopsy, resulting in either redirection of care or immediate lung transplant evaluation, given its expected lethal course. Importantly, biologic investigation of BMPR2 mutation-induced disease, the most common form of heritable disease, has resulted in the development of potential novel therapies targeting the resulting perturbed cascades. In this report, we present a case in which the recently appreciated knowledge that biallelic ATP13A3 mutations are associated with malignant progression of PAH in young childhood, led us to alter our traditional treatment plan. Despite modest symptomatology (WHO FC III, normal CI, RAP, and BNP), we elected to perform a historically high-risk Potts shunt before expected rapid deterioration. Short-term follow-up (2.5 years postdiagnosis and 1 year post Potts) is very encouraging; she remains the only known surviving pediatric PAH with an associated biallelic ATP13A3 mutation in the literature. Ultimately, the increased use of extensive genetic testing will aid in the identification of molecular subtypes of pediatric PAH that will likely aid in risk stratification, the development of novel, more precise treatment plans, and improved outcomes.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

This study was performed under an Institutional IRB approval. Consent for this case report was obtained by the family and a UCSF IRB approval.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to the conception of the work; revising the work critically for important intellectual content; have approved the final version to be published; and agree to be accountable for all aspects of the work in ensuring that questions related
to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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