Title

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

Journal

Pulmonary circulation, 12(1)

ISSN

2045-8932

Authors

Stevens, Leah
Colglazier, Elizabeth
Parker, Claire
et al.

Publication Date

2022

DOI

10.1002/pul2.12033

Peer reviewed

DOI: 10.1002/pul2.12033

CASE REPORT

Pulmonary Circulation Open Access | PVRI Pulmonary Vascular Research Institute | WILEY

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

Leah Stevens[1] | **Elizabeth Colglazier**[2] | **Claire Parker**[2] | **Elena K. Amin**[1] | **Hythem Nawaytou**[1] | **David Teitel**[1,3] | **Vadiyala M. Reddy**[4] | **Carrie L. Welch**[5] | **Wendy K. Chung**[5] | **Jeffrey R. Fineman**[1,3]

[1]Department of Pediatrics, University of California San Francisco, San Francisco, California, USA

[2]Department of Nursing, University of California San Francisco, San Francisco, California, USA

[3]Cardiovascular Research Institute, University of California San Francisco, San Francisco, California, USA

[4]Department of Surgery, University of California San Francisco, San Francisco, California, USA

[5]Department of Pediatrics and Medicine, Columbia University Irving Medical Center, New York, New York, USA

Correspondence
Jeffrey R. Fineman, Department of Pediatrics, University of California San Francisco, 550 16th St, 5th Floor, San Francisco, CA 94143, USA.
Email: jeff.fineman@ucsf.edu

Funding information
None

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.

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.[2] The molecular genetic basis of PAH is heterogeneous, with at least 26 genes displaying varying levels of evidence for disease causality.[3] 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.[4] Interestingly, polyamines, which are small metabolites required for normal cell growth and proliferation, were recently reported to be increased in pulmonary hypertension.[5]

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 m105), an indexed pulmonary vascular resistance (PVRi) of 34.3 WU and a low cardiac index (CI 1.7 L/min/m^2) that was mildly responsive to oxygen and inhaled nitric oxide (PVRi decreased to 25.5 WU). See table below for other data obtained at this time. Given her clinical history and pulmonary hemodynamics, balloon dilatation of her patent foramen ovale (PFO) was performed, and aggressive therapy that included subcutaneous treprostinil (titrated up to a dose of 95 ng/kg/min), bosentan, sildenafil, digoxin, aspirin, and oxygen was initiated. Following balloon dilatation of the PFO, saturations remained 100% on oxygen, but desaturation into the mid 80s was noted with agitation.

Subsequent genetic testing revealed heterozygous *ATP13A3* c.3595G>T and *ATP13A3* c. 3079dup mutations in trans. Review of the literature at the time confirmed monoallelic *ATP13A3* variants were associated with adult-onset PAH, but neither monoallelic nor biallelic *ATP13A3* had been reported in childhood PAH.[6] 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.[2] This cohort has been subsequently published, and now includes our patient, her family's genotypes, and a portion of her clinical course.[3]

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.

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.

TABLE 1 Functional class and hemodynamics before and after medical and surgical treatments

	WHO functional class	PVRi(WU)	CI(L/kg/m^2)	RVEF MRI(%)	RVFAC ECHO(%)	TAPSE ECHO(cm)	RAP(mmHg)	BNP (pg/ml)
At presentation	IV	34.3	1.7		23	0.75	11	3120
12 months of triple therapy	II	12.2	3.6		39	1.75	7	13
Pre Potts shunt (18 months of triple therapy)	III	22	3.3	49%	35	1.75	4	19
One year post Potts shunt	II	26	3.4	47%	34	1.8	3	15

Abbreviations: BNP, B-type natriuretic peptide; CI, cardiac index; ECHO, echocardiography; PVRi, indexed pulmonary vascular resistance; RAP, right atrial pressure; RVEF, right ventricular ejection; RVFAC, right ventricular fractional area change; fraction; TAPSE, tricuspid annular plane systolic excursion.

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.[2] 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.[8] 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.[9,10] 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[6] 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.

ACKNOWLEDGMENT

No funding supported this report.

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.

ORCID

Jeffrey R. Fineman http://orcid.org/0000-0001-9740-405X

REFERENCES

1. Rosenzweig EB, Widlitz AC, Barst RJ. Pulmonary arterial hypertension in children. Pediatr Pulmonol. 2004;38:2–22.
2. Welch CL, Chung WK. Genetics and genomics of pediatric pulmonary arterial hypertension. Genes (Basel). 2020;11(10):1213–28.
3. Machado RD, Welch CL, Haimel M, Bleda M, Colglazier E, Coulson JD, Debeljak M, Ekstein J, Fineman JR, Golden WC, Griffin EL, Hadinnapola C, Harris MA, Hirsch Y, Hoover-Fong JE, Nogee L, Romer LH, Vesel S, Gräf S, Morrell NW, Southgate L, Chung WK. Biallelic variants of *ATP13A3* cause dose-dependent childhood-onset pulmonary arterial hypertension characterized by extreme morbidity and mortality. J Med Genet. 2021;17:107831. https://doi.org/10.1136/jmedgenet-2021-107831
4. Hamouda NN, Van den Haute C, Vanhoutte R, Sannerud R, Azfar M, Mayer R, Calabuig AC, Swinnen JV, Agostinis P, Baekelandt V, Annaert W, Impens F, Verhelst SHL, Eggermont J, Martin S, Vangheluwe P. ATP13A3 is a major component of the enigmatic mammalian polyamine transport system. J Biol Chem. 2021;296:1–17.
5. He YY, Yan Y, Jiang X, Zhao JH, Wang Z, Wu T, Wang Y, Guo SS, Ye J, Lian TY, Xu XQ, Zhang JL, Sun K, Peng FH, Zhou YP, Mao YM, Zhang X, Chen JW, Zhang SY, Jing ZC. Spermine promotes pulmonary vascular remodelling and its synthase is a therapeutic target for pulmonary arterial hypertension. Eur Respir J. 2020;56:1–14.
6. Zhu N, Pauciulo MW, Welch CL, Lutz KA, Coleman AW, Gonzaga-Jauregui C, Wang J, Grimes JM, Martin LJ, He H, Shen Y, Chung WK, Nichols WC. Novel risk genes and mechanisms implicated by exome sequencing of 2572 individuals with pulmonary arterial hypertension. Genome Med. 2019;11(69):1–16.
7. Grady RM, Canter MW, Wan F, Shmalts AA, Coleman RD, Beghetti M, Berger RMF, Marin MJDC, Fletcher SE, Hirsch R, Humpl T, Ivy DD, Kirkpatrick EC, Kulik TJ, Levy M, Moledina S, Yung D, Eghtesady P, Bonnet D. Pulmonary-to-systemic arterial shunt to treat children with severe pulmonary hypertension. JACC. 2021;78(5):468–77.
8. Slot E, Edel G, Cutz E, van Heijst A, Post M, Schnater M, Wijnen R, Tibboel D, Rottier R, de Klein A. Alveolar capillary dysplasia with misalignment of the pulmonary veins: clinical, histological, and genetic aspects. Pulm Circ. 2018;8(3):1–8.
9. Dunmore BJ, Jones RJ, Toshner MR, Upton PD, Morrell NW. Approaches to treat pulmonary arterial hypertension by targeting BMPR2: from cell membrane to nucleus. Cardiovasc Res. 2021;117:2309–25.
10. Humbert M, McLaughlin V, Gibbs JSR, Gomberg-Maitland M, Hoeper MM, Preston IR, Souza R, Waxman A, Subias PE, Feldman J, Meyer G, Montani D, Olsson KM, Manimaran S, Barnes J, Linde PG, de Oliveira Pena J, Badesch DB. Sotatercept for the treatment of pulmonary arterial hypertension. N Engl J Med. 2021;384(13):1204–15.

How to cite this article: Stevens L, Colglazier E, Parker C, Amin EK, Nawaytou H, Teitel D, Reddy VM, Welch CL, Chung WK, Fineman JR. Genetics dictating therapeutic decisions in pediatric pulmonary hypertension? A case report suggesting we are getting closer. Pulm Circ. 2022;12:e12033. https://doi.org/10.1002/pul2.12033