

Early-onset and severe pulmonary arterial hypertension due to a novel compound heterozygous association of rare *VHL* mutations: A case report and review of existing data

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Abstract

Very rare cases of pulmonary arterial hypertension (PAH) have been linked to homozygous or compound heterozygous von Hippel–Lindau (*VHL*) tumor suppressor gene mutations, while heterozygous *VHL* mutations lead to *VHL* tumor syndrome. Although those entities are defined, the genotype–phenotype correlation is incompletely understood, and patient management recommendations are lacking. Here, we describe a case of severe early-onset PAH due to a so-far unreported compound heterozygous association of *VHL* mutations and review the existing data.

KEYWORDS

blood cells, genetics, hypoxia inducible factor, pulmonary circulation

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare and severe disease of heterogeneous etiologies, characterized by distal pulmonary artery remodeling leading to elevated pulmonary arterial pressures and pulmonary vascular resistance.¹ It is now well known that a genetic predisposition underlies certain forms of PAH.² Most of the heritable PAH cases are transmitted in an autosomal dominant manner with incomplete penetrance and *BMPR2* mutations are the most frequent.² However, very rare cases of polycythemia and documented PAH due to homozygous or compound heterozygous von Hippel–Lindau (*VHL*) tumor suppressor gene mutations

have been reported.^{3–6} Our aim is to describe a case of early-onset and severe PAH due to a novel combination of previously reported *VHL* mutations and review existing data on *VHL*-associated PAH.

CASE DESCRIPTION

We report the case of a boy diagnosed with severe PAH at 18 months of age. He was born at term following an uneventful pregnancy. He is the third child from the same union and his parents are first cousins of Moroccan Berber ethnicity. His parents (in their forties) and his siblings (11 and 15 years old) are

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TABLE 1 Blood test results and hemodynamics of the patient

Characteristics	Values	Normal range
Biological		
Hb (g/dl)	16.1	11.5–14
RBC ($\times 10^6/\mu\text{l}$)	8.91	3.9–5.3
Ht (%)	57.7	33–39
MCV (fL)	65	70–86
MCH (pg)	18.1	23–31
MCHC (g/dl)	27.9	30–35
Reticulocytes ($\times 10^3/\mu\text{l}$)	222.8	22.5–147.0
Leukocytes ($\times 10^3/\mu\text{l}$)	15.05	6.00–17.50
Platelets ($\times 10^3/\mu\text{l}$)	233	150–440
Ferritin ($\mu\text{g/L}$)	12	30–350
Iron ($\mu\text{g/dl}$)	30	50–150
Transferrin (mg/dl)	240	200–360
NTproBNP (pg/ml)	18,780	<125
Hemodynamics		
mPAP (mmHg)	70	
RAP (mmHg)	8	
PAWP (mmHg)	7	
PVRi (WU m^2)	21	
Qp/Qs	1:1	

Abbreviations: Hb, hemoglobin; Ht, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; mPAP, mean pulmonary artery pressure; NTproBNP, N-terminal pro-B-type natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVRi, pulmonary vascular resistance index; Qp/Qs, pulmonary to systemic blood flow ratio; RAP, right atrial pressure; RBC, red blood cells.

healthy. His mother noted learning and walking difficulties early on, followed by feeding difficulties. He was admitted to the hospital at 18 months because of clinical worsening due to an infection. An echocardiography was performed revealing an estimated systolic pulmonary artery pressure (PAP) of 70 mmHg with marked right ventricular hypertrophy and dilatation, and a small interatrial communication (1 mm) with right-to-left shunting. A pericardial effusion was visible posteriorly to the right ventricle. An abdominal ultrasound demonstrated a congestive hepatopathy and a homogeneous splenomegaly (9 cm). Neither vascular malformations nor signs of pulmonary emboli were observed on his chest CT. The notable results of his blood work and the hemodynamic parameters obtained during his diagnostic right heart catheterization (RHC) are listed in Table 1. The patient did not respond to pulmonary vasodilator

testing using inhaled nitric oxide. He presented with polycythemia, initially thought to be linked to his lung disease.

The patient was diagnosed with pre-capillary pulmonary hypertension (PH). PAH due to congenital heart disease was excluded because the severity of the patient's hemodynamics could not be explained by the very small interatrial communication initially observed on trans-thoracic echocardiogram, which could also be a patent foramen ovale. In line with this, the communication was not visible on a control echocardiogram performed 1 month after treatment was started, nor was it visualized on any subsequent echocardiogram. Although no trans-esophageal echocardiogram was performed, both imaging and hemodynamic assessments reasonably rule out that PAH may be explained by a congenital heart defect. Also, abnormal pulmonary venous return was excluded by chest CT angiography. The clinical workup excluded all other possible causes of pre-capillary PH. He was first treated with sildenafil, a phosphodiesterase type 5 (PDE5) inhibitor, quickly followed by dual oral therapy with the addition of bosentan, an endothelin receptor antagonist (ERA). The use of intravenous prostacyclin was deferred after the patient's condition stabilized. Due to low iron and ferritin levels, oral iron supplementation was also prescribed.

After obtaining the parents' written consent, targeted next-generation sequencing using an in-house designed panel of 11 PAH-associated genes (*BMPR2*, *ENG*, *ALK1*, *KCNK3*, *CAV1*, *BMPR1B*, *SMAD4*, *SMAD9*, *GDF2*, *TBX4*, *EIF2AK4*) was performed. Copy number variants (CNVs) were excluded for *BMPR2*, *ENG*, and *ALK1* using multiplex ligation-dependent probe amplification (MLPA). Neither point mutations nor CNVs were found. The analysis was completed by clinical exome sequencing (also called mendeliome sequencing) of parent-child trio revealing compound heterozygous mutations in the *VHL* gene: c.162G>C (p.Met54Ile) and c.376G>A (p.Asp126Asn). The c.162G>C (p.Met54Ile) mutation was inherited from the mother and the c.376G>A (p.Asp126Asn) mutation was inherited from the father. We found the c.162G>C (p.Met54Ile) variant in the heterozygous state in four out of 2350 cases sequenced for various diseases and in two out of 5850 controls in our home database. The c.376G>A (p.Asp126Asn) variant was found in the heterozygous state in one control in our home database. The patient's circulating erythropoietin (EPO) level was exceedingly elevated (9895 U/L, n.v. 4.3–29) and he did not carry other mutations in the oxygen-sensing pathway (*EGLN1/PHD2*, *EPAS1/HIF2A*). Both *VHL* mutations have been separately linked to polycythemia with an elevated EPO level and PAH.^{3–7} However, our patient's combination of *VHL* mutations

has never been reported so far, we classified these variants as pathogenic based on the increased EPO level in our patient, the previously reported cases as well as the available functional data.⁸

CLINICAL EVOLUTION

The patient has been maintained on the same regimen of dual oral therapy (PDE5 inhibitor and ERA) over the past 5 years. His growth is normal, with a height of 116 cm and a weight of 22.5 kg at 6 years old. On his last follow-up visit, his echocardiography revealed a moderate dilatation with mild hypertrophy and preserved function of the right ventricle, a dilated right atrium, a cardiac index of 4.2 L/min/m², and the absence of a pericardial effusion. Estimation of systolic PAP was not feasible using tricuspid regurgitation. His last NT-proBNP level fell to 588 pg/ml. His hemoglobin and hematocrit levels spontaneously fluctuated over time and the former is currently at 15.5 g/dl, in the context of marked iron deficiency. In that regard, phlebotomy was never performed.

DISCUSSION

Using clinical exome sequencing in parent-child trio, we found compound heterozygous *VHL* mutations c.162G>C (p.Met54Ile) and c.376G>A (p.Asp126Asn) in a patient presenting with severe PAH at an early age, associated with splenomegaly, polycythemia, and an exceedingly elevated EPO levels. *VHL* is a tumor suppressor gene located on chromosome 3.⁹ Heterozygous loss-of-function *VHL* mutations are associated with VHL syndrome, a dominantly inherited familial cancer syndrome leading to the development of highly vascularized tumors.¹⁰ pVHL acts as the recognition component of the ubiquitin ligase E3 complex for oxygen-dependent proteasomal degradation of the alpha-subunit of the hypoxia-inducible factors (HIF-1, HIF-2, and HIF-3).¹¹ The HIF family of transcription factors coordinate the intracellular response to hypoxia. In the context of *VHL* mutations, HIFs are stabilized at normoxia, leading to the upregulation of their targets such as EPO.¹¹ Elevated EPO level is one of the hallmarks of Chuvash polycythemia, an autosomal recessive disorder caused by the *VHL* mutation R200W, and very high EPO levels have been previously described in carriers of the p.Met54Ile and p.Asp126Asn mutations.^{5-7,12} Also, organomegaly, including splenomegaly, has been previously reported in carriers of similar or other *VHL* mutations including the Chuvash mutation.^{6,13} Extramedullary hematopoiesis

occurring in the spleen has been shown in mice models of Chuvash polycythemia, which could explain the associated splenomegaly.¹⁴

This case is the second *VHL*-associated PAH case being treated at our hospital. The first was previously reported by our team in 2015.⁴ He is also a boy of Moroccan Berber ethnicity, who was diagnosed with congenital polycythemia and PAH at 11 years old due to a homozygous c.162G>C (p.Met54Ile) mutation.⁴ Mutations in *BMP2*, *ACVRL1*, *ENG*, and *KCNK3* were excluded in this patient as well. This patient has been treated by monotherapy using macitentan (an ERA) for 15 years, as well as with a vitamin K antagonist and recurrent phlebotomies, and is currently in a low-risk category according to the European Society of Cardiology guidelines.¹ He is now 27 years old and does not present with any symptoms suggestive of *VHL* syndrome-associated tumors.

Both our patient's *VHL* mutations have been separately linked to polycythemia and PAH.³⁻⁷ However, our patient's combination of *VHL* mutations has never been reported so far. As mentioned above, our team previously reported the first documented case of PAH in a Moroccan Berber carrier of the homozygous c.162G>C (p.Met54Ile) mutation.⁴ This same mutation was also described in other patients of Moroccan ethnicity: in a 19-year-old female presenting with mild polycythemia and associated PAH, as well as in three children with polycythemia but without documented PAH.^{6,7} These three latter cases shared the same haplotype and ethnicity, suggesting a founder mutation in the Moroccan ethnicity.⁷ This mutation might be more frequent in the Moroccan population, potentially due to a heterozygous advantage regarding anemia as it has been previously suggested for the Chuvash mutation.¹⁵ Furthermore, a boy from Bangladesh developed severe PAH at 16 months old and unfortunately died at 2 years of age. He was shown to carry the homozygous c.376G>A (p.Asp126Asn) *VHL* mutation.³ Also, compound heterozygous c.376G>A (p.Asp126Asn) and c.548C>T (p.Ser183Leu) *VHL* mutations were reported in a 2-month-old boy presenting with severe PAH.⁵ In addition to these two cases of affected infants, this current report reinforces the hypothesis that the p.Asp126Asn *VHL* mutation leads to early-onset and severe PAH.^{3,5}

In addition to previous reports, the *VHL* mutation c.162G>C (p.Met54Ile) was shown to impact the translation of the short isoform of VHL (VHLp19).⁷ It was also shown to segregate with erythrocytosis in two families.⁷ Functional studies were performed for the c.376G>A (p.Asp126Asn) variant using *VHL*-null renal carcinoma cells stably transfected to express this mutant. The study showed increased levels of HIF-1 α and increased

expression of its target genes in mutant cells compared to wild-type cells.⁵ This same study also suggested a decreased stability of the mutant protein and the amino acid 126 was suggested to form electrostatic interactions with Glu160 and Arg167 to maintain a correct α -domain fold.^{5,16} This could potentially explain the severity of the phenotype observed in our patient as well as in the two previously reported cases.^{3,5} Finally, raised EPO levels in the patients strongly suggest a deficiency in the regulation of the oxygen-sensing pathway, and no other mutations were identified in this pathway in our patient. Moreover, the role of the VHL/HIF oxygen-sensing pathway has been implicated in the pathophysiology of PAH (mechanisms recently reviewed by Pullamsetti et al.¹⁷).

Although VHL's implication in PAH has been demonstrated, not all carriers of homozygous *VHL* mutations seem to develop PAH. The exact incidence of PAH, documented by RHC, in Chuvash and other VHL-related congenital polycythemia cases is unknown. Elevated basal ventilation and pulmonary vascular tone were demonstrated in Chuvash patients in normoxic conditions, as well as marked pulmonary vascular sensitivity to hypoxia.¹⁸ Also, a study performed in a cohort of 120 adult and pediatric Chuvash patients showed these patients had increased tricuspid regurgitation velocities compared to wild-type patients.¹⁹

Strikingly, patients with Chuvash polycythemia do not seem to develop tumors. In a study including 96 Chuvash patients, 67 underwent an imaging study (of whom only 33 underwent magnetic resonance imaging of the brain) highlighting the presence of cysts, yet no tumors were found.²⁰ Furthermore, no tumors were described in the VHL-associated polycythemia cases reported in the literature, although many were children or young adults, and there was no family history of VHL-related tumors in the present case.^{3,5,6} Although the genotype–phenotype correlation is incompletely understood, there are reports suggesting VHL could follow a continuum model of tumor suppression, where gene-dosage sensitivity and tissue-specificity are at play.^{21,22} Another report suggested that other HIF-independent functions could also intervene.¹⁶ Due to the rarity of VHL-associated PAH cases and the many unanswered questions on the genotype–phenotype correlation, there are no recommendations on the adequate follow-up for VHL-associated polycythemia patients regarding their tumor risk.

There is also no evidence-based data on the appropriate management of VHL-related PAH cases. Some patients undergo venesection to maintain hemoglobin levels in the high normal range. However, iron depletion resulting from venesection could lead to worsening of PAH due to iron's

implication in HIF-2 α hydroxylation and degradation.¹⁹ Moreover, relative depletion of the red blood cell mass could potentially decrease oxygen transport to the tissues, further inducing HIF signaling.¹⁹ Therefore, performing phlebotomy can be debated in this context. Regarding pharmaceutical treatments, there is a rationale for using PAH-approved therapies in VHL-associated PAH based on the fact HIFs can modify vasomotor tone and upregulate ET-1, among others.¹⁷ However, these therapies work on the vasoconstrictive component of PAH rather than the remodeling itself. Recently, inhibitors of HIF-2 α were shown to have a potential beneficial effect on vascular remodeling in PAH rodent models.²³ The efficacy and safety of this therapeutic strategy need to be further studied.

In conclusion, VHL-associated PAH is a rare disease, although the exact prevalence of PAH due to *VHL* mutations is unknown, and the genotype–phenotype correlation is still incompletely understood. On the basis of this report and two others, the *VHL* mutation c.376G>A (p.Asp126Asn) seems to lead to severe and early-onset PAH, with exceedingly elevated EPO levels.^{3,5} Despite a theoretical tumorigenic risk in VHL-associated PAH patients, there are no data suggesting a clinically significant risk of tumor in these patients so far, underlining the need for further research to understand this observation. Also, further collaborative studies are needed to better determine the clinical management for this rare subset of PAH patients.

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CONFLICTS OF INTEREST

Outside the submitted work, Antoine Bondue received consultancy fees from Amicus, Baeyer, Boehringer Ingelheim, Sanofi, Pfizer, and Alnylam; speaker fees from Pfizer, Sanofi, and Alnylam and reports travel grants from Abbott, Pfizer, and Takeda. Jean-Luc Vachier received consultant fees from Actelion, Bayer, Bial Portela, PhaseBio, Respira Therapeutics, United Therapeutics, and SoniVie and reports speaker fees and travel grants from Actelion, Acceleron, Bayer, Merck, Novartis, United Therapeutics. Laura Chomette reports travel grants from Sanofi and Pfizer. Remaining authors declare that there are no conflicts of interest.

ETHICS STATEMENT

The legal representatives gave their written consent for the publication of the clinical data.

AUTHOR CONTRIBUTIONS

Laura Chomette, Jean-Luc Vachieri, and Antoine Bondue interacted with the patient and his family. Laura Chomette collected clinical data. All authors participated in the interpretation of data. Laura Chomette drafted the manuscript and all authors revised it critically for important intellectual content. All authors approved the final version of the article.

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