

Pulmonary hypertension in pulmonary agenesis-a report of five pediatric cases and review of previous cases.

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Abstract

Pulmonary Agenesis (PA) is a rare congenital malformation of lung development, and patients with comorbid Pulmonary Hypertension (PH) have substantially increased morbidity and mortality risks. We describe five pediatric cases born with unilateral PA who developed PH. By integrating our findings with those of 7 previously published case reports, we aim to provide a more complete description of disease features, prognosis, and the most effective treatment strategies. We found that male PA patients and those with right-side agenesis were more likely to develop PH. Moreover, half of these comorbid patients had congenital heart disease with left-to-right shunt. Early diagnosis and treatment, including surgical and medical interventions, are critical for preservation of cardiopulmonary function. All PA cases should receive regular cardiopulmonary function tests starting at an early age.

Keywords: Pulmonary agenesis, Congenital malformations, Pulmonary hypertension, Co-existing anomalies.

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Introduction

Pulmonary Agenesis (PA) is a rare congenital defect of lung development first described by De Pozze at autopsy of an adult female. According to the classification of Schneider and Schwabbe [1], pulmonary agenesis patients are divided into three groups: type 1 with agenesis (complete absence of lung, bronchus, and vascular supply), type 2 with aplasia (absent lung tissue and pulmonary artery, but a rudimentary bronchus projecting from the trachea), and type 3 with hypoplasia (hypoplastic lung and a rudimentary bronchial tree).

Bilateral PA is incompatible with life, while unilateral cases may survive in the absence of other fatal malformations. Pulmonary agenesis is associated with numerous additional congenital abnormalities of the cardiovascular, musculoskeletal, genitourinary, and gastrointestinal systems that may negatively impact prognosis. Pediatric PA patients also present with varying degrees of Pulmonary Hypertension (PH) [2-8], but effects of PH on disease course and prognosis are uncertain, and there are no widely accepted treatment standards. Therefore, we describe five pediatric cases born with unilateral PA who developed PH, and review already published cases for a more complete description of disease features, clinical course, and treatment options.

Patients and Methods

Patients meeting the Schneider and Schwabbe definition of PA [1] were enrolled from two institutes in Guangzhou, China: Guangzhou Children's Hospital and Guangzhou Institute of Respiratory Disease and State Key Laboratory of Respiratory Disease. The following information was collected: maternal and parental history, sex, co-existent malformations, treatment history, imaging features, and outcomes. Mutations in *BMPR2*, *ALK1*, and *SMAD9* were also examined. Follow-up duration ranged from one month to five years depending on outcome.

All five patients fulfilled diagnostic criteria A and (or) B [9,10]: (A) mean pulmonary artery pressure (mPAP) \geq 25 mmHg and Pulmonary Vascular Resistance Index (PVRI) $>$ 3 Wood units as measured by right heart catheterization; (2) right ventricular hypertrophy, dilated Main Pulmonary Artery (MPA), and tricuspid regurgitation with maximum velocity $>$ 2.5 m/s as measured by echocardiography. A systematic literature search of PubMed using the terms "pulmonary/lung agenesis and pulmonary hypertension", "pulmonary/lung agenesis and right ventricular failure", and "pulmonary/lung agenesis and dilated pulmonary artery" was also performed to find similar pediatric cases (0-18 y old). Information from these published cases and our five new cases was compiled to evaluate demographics, co-anomalies, interventions, and outcomes.

Results

We identified five pediatric PA cases with PH by institutional record review. The clinical presentations were all atypical, with most presenting with varying degrees of tachypnea, cyanosis, and thoracic asymmetry. No mutations in *BMPR2*, *ALK1*, or *SMAD9* were found. The imaging features of these five patients are shown in Figures 1-4.

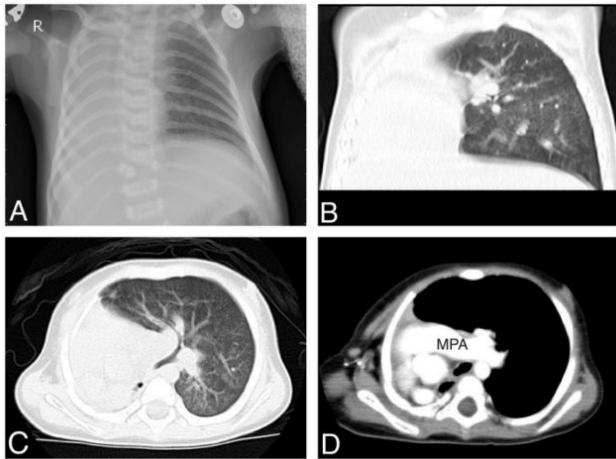


Figure 1. (A) X-ray (posterior-anterior view) from case 3 revealing homogenous right-side opacity. (B-D): CT scans from case 4 showing right lung, right bronchus, and pulmonary vasculature absence with hyper-inflated left lung, enlarged Main Pulmonary Artery (MPA), cardiac displacement to the right, and thoracic asymmetry.

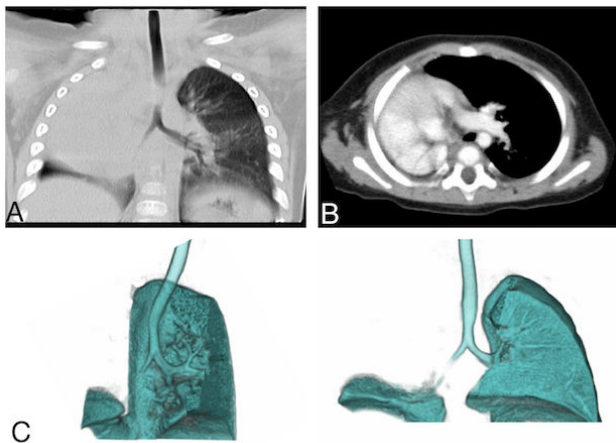


Figure 2. (A and B) CT scans from case 2 showing absence of right pulmonary artery and right upper and middle lobes. (C) Three-dimensional reconstructed images showing right bronchial stenosis with the lower right lobe.

Other clinical features, co-existing anomalies, treatments, and follow-up results for the institutional population (Cases 1-5) and the seven previous cases retrieved from PubMed are summarized in Table 1. Except for case 3 (the female twin of a healthy male conceived by *in vitro* fertilization, born by cesarean delivery at 32 w' gestational age and weighing 1,480 g), all patients were full-term with normal maternal and perinatal histories.

Male PA patients (M: F=2:1) and those with right-sided agenesis (right: left=3:1) were more likely to develop PH. Moreover, 50% of PA patients with PH had congenital heart disease with left-to-right shunt, mainly Patent Ductus Arteriosus (PDA) and/or Arterial Septal Defect (VSD), one in sixth had diaphragmatic hernia, and one in twelve presented with bronchopulmonary fistula and bronchopulmonary foregut malformation. Five cases died before two years of age from repeated respiratory infection or unresolved PH. The seven surviving patients are doing well with normal growth and development. Congenital anomalies (congenital heart disease or diaphragmatic hernia) have been repaired and PH controlled by drugs.

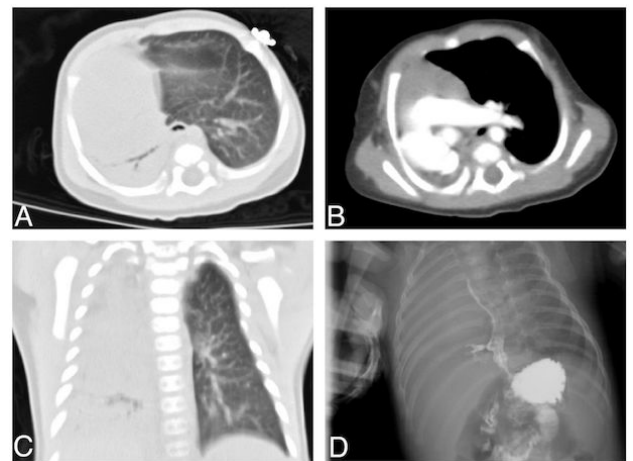


Figure 3. (A-C) CT scans from case 1 showing cardiac displacement to the right and left lung hyperinflation, absence of right bronchus and right pulmonary artery, and a small volume of residual lung tissue in the right hemi-thorax. (D) Upper gastrointestinal contrast image from Case 1 showing bronchopulmonary foregut malformation.

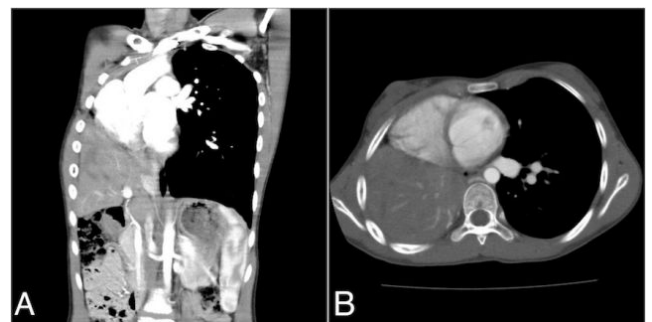


Figure 4. (AB) CT scans from case 5 showing diaphragmatic hernia in right thorax and cardiac displacement to the right.

Discussion

Unilateral PA is an extremely rare congenital anomaly, with an estimated prevalence between 1/10,000 and 1/15,000 live births and a slight preponderance in females (1.3:1) [11]. Genetic anomalies, viral infections, and vitamin A deficiency have all been proposed as causative factors, but etiology is usually uncertain [12].

The exactly incidence of comorbid PH is also unclear. The pathophysiology of PH in PA may involve early aberrant pulmonary vascular remodeling. Changes in pulmonary vasculature begin immediately at first breath. In the healthy developing lung, alveolar dissension, mechanical force, and exposure to oxygen cause a drop in Pulmonary Vascular Resistance (PVR) and an increase in pulmonary blood flow. In PA, however, the contralateral lung may carry markedly increased blood flow, leading to higher shear stress on the endothelium, with subsequent release of vasoconstrictors that increase PVR. Half of all patients with PH presented with VSD and/or PDA, and PH developed more frequently in unilateral right than left PA. Right ventricular overload due to left-right

shunt and greater mediastinal shift due to right-side PA renders pulmonary arterial beds more susceptible to vascular remodeling. We also found that all deaths occurred before 2 years of age due to heart failure. The alveolar stage of human lung development spans the late infant period to age 7-8 y [13]. Remodeling of pulmonary arterioles due to persistent PH may destroy pulmonary vascular beds and adversely affect lung development. Two infants surviving beyond two years (Table 1) had received early intra-cardiac shunts and diaphragmatic hernia repair, suggesting that early protection and preservation of cardiopulmonary function may prevent vasculature remodeling and destruction.

Table 1. Characteristics of pulmonary hypertension in pulmonary agenesis and associated co-existing anomalies, treatments, and outcomes.

Case	Age/sex	Investigation	Side affected	Co-malformation	Recurrent RTI	Surgery and PH-targeted therapy	Outcome and follow-up
Case 1	23 d/M	CATH echo	R	BPMF PDA	yes	No	Died at 7 months
Case 2	8 m/M	CATH echo	R	Tracheal stenosis with right low lobe	yes	No	Died at 14 months
Case 3	9 m/M	CATH echo	R	PDA	yes	Oral bosentan one month	Died at 15 months
Case 4	11 m/F	CATH echo	R	None	no	Oral bosentan two years	At 6 year follow-up with normal status
Case 5	11 y/F	CATH echo	R	CDH	no	Oral bosentan 6 months	At 2 year follow-up with normal status
De-Leno [6]	1 d/M	Echo	R	TEF	no	No	Died at 1 month
Dobremez [4]	1 m/M	dilated pulmonary artery in CT	R	Tracheal stenosis	no	Tissue expander placement	Alive at 3 year follow-up Compatible with normal life
Nakayama [7]	12 d/M	Echo	R	VSD PDA	no	VSD repaired, PDA division	Alive at 1 year follow-up with normal status
Nazir [3]	2 m/M	dilated right pulmonary artery detected during surgery	L	PDA ASD Left kidney absent	no	PDA division	Survived Duration not mentioned
Palma [2]	2 y/M	Echo	L	CDH VSD ASD	no	CDH and VSD repaired	Survived Duration not mentioned
Guo [8]	5 y/F	CATH Echo	L	VSD	no	VSD repaired	Alive at 2 year follow-up with normal status
Muensterer [5]	4 d/M	Echo	R	Tracheal stenosis	no	Tissue expander placement	Died at 5 months

Abbreviations: ASD: Atrial Septal Defect; BPMF: Bronchopulmonary Foregut Malformation; CATH: Catheterization; CDH: Diaphragmatic Hernia; d: day; Echo: Echocardiography; F: Female; L: Left; M: Male; m: month; PDA: Patent Ductus Arteriosus; R: Right; RTI: Respiratory Tract Infection; TEF: Tracheosophageal Fistula; VSD: Ventricle Septal Defect; y: year.

For type 2 PA, it is necessary to determine the origin of the vasculature supplying ipsilateral residual lung tissue. If the supply vessel comes from the systemic circulation, residual lung tissue will have minimal function due to low oxygen tension in alveoli and show repeated infection due to impaired mucociliary clearance and diminished delivery of appropriate inflammatory cells. Hypertrophic collateral vessels from relatively larger systemic vessels also lead to hemoptysis. When recurrent hemoptysis or severe pulmonary infections are

present, lobectomy or pneumonectomy should be considered. In this report, case 3 lacking a right pulmonary artery but retaining a right lower lobe died of recurrent lung infections. Thus, we had no opportunity to further investigate the most effective interventions for such cases.

Right heart catheterization is the gold standard for definitive PH diagnosis (mPAP ≥ 25 mmHg, PVRI>3 Wood units). Echocardiography, cardiac CT scan, and cardiac magnetic

resonance imaging are also fundamental diagnostic tools to screen for PH and assess cardiac anatomy. Right lung agenesis combined with tracheoesophageal fistula is an exceedingly rare but highly lethal combination [14] for which bronchoscopy or upper gastro-intestinal contrast imaging is recommended for diagnosis. Pulmonary angiogram or CTA is also important to define the intrapulmonary supply vessel in type 2 or type 3 PA.

Progressive PH is often responsible for clinical deterioration of PA patients and thus has a major influence on long-term prognosis. Early surgery to repair intra-cardiac shunts could reduce blood volume and diminish the chance of irreversible pulmonary vasculature remodeling. Other measures for timely repair of co-malformations, such as trachea-esophageal fistula and bronchial stenosis, could reduce adverse effects on the cardiopulmonary system. Tissue expanders have been implanted to prevent distortion and rotation of the main bronchus and great vessels caused by right-side agenesis. However, two published pediatric PA cases with PH adopting tissue expander placement yielded completely different outcomes, with one survival and one fatality [3,4]. Further case studies are necessary to confirm the efficacy of tissue expander implantation. For patients exhibiting deterioration despite surgery or other treatments, heart-lung transplantation should be considered.

Medications for PH may delay the structural remodeling process. Vaccines to reduce the frequency of respiratory tract infections and oxygen therapy to maintain suitable ventilation/perfusion ratio are both useful preventative measures. The endothelial receptor antagonist bosentan was used successfully to improve status in two of our cases (Cases 3 and 5, although case 3 ultimately died). Bosentan is considered safe and effective for Pulmonary Arterial Hypertension associated with Congenital Heart Disease (CHD-PAH), whereas there is insufficient evidence for the efficacy of other PH-targeted drugs (such as the PDE5 inhibitor or prostacyclin) [15]. Further studies on animal models and human studies are required to validate the safety, efficacy, and dosage of PH-targeted drugs for this rare condition.

Asymptomatic patients with PA usually do not require intervention, especially in the absence of associated cardiac anomalies. However, pulmonary infection or other cardiopulmonary malformations should be treated as early as possible. Asymptomatic patients should still receive regular cardiopulmonary function tests.

In conclusion, PH is a rare complication of PA requiring early intervention to correct associated malformations and reduce intra-cardiac shunts. Early application of oxygen therapy and medication, including vaccines and PH-targeted drugs, may also preserve cardiopulmonary function by preventing vascular remodeling. Clinicians should recognize that PH associated with PA increases the risks of morbidity and mortality. Early diagnosis is critical to allow for timely initiation of treatment. Every PA case, even if asymptomatic, should receive regular assessments of cardiopulmonary function starting at an early age.

Contributions

Yingkang Jin wrote the manuscript, Li Huang made imaging diagnoses, Zhihao Liang conducted molecular genetic testing, Gen Lu was involved in management of cases, and Jiang Wang will act as guarantor for this paper.

Conflict of Interest

None declared

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