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Clinical manifestations and long-term follow-up in pediatric patients living at altitude with an isolated pulmonary artery of ductal origin

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Summary

The study aim was to define the clinical manifestations and long-term outcome of pediatric patients living at altitude with isolated pulmonary artery of ductal origin. This was a retrospective cohort study of 17 consecutive cases of isolated pulmonary artery of ductal origin at a single center. All patients lived at modest altitude (median, range; 2050 m, 1700–3050 m). Fifteen children (88%) were symptomatic at presentation. High altitude pulmonary edema was present in 2 patients (12%) at diagnosis and only 1 patient had episodes of hemoptysis during follow-up. Fourteen patients (82%) demonstrated evidence of pulmonary arterial hypertension (PAH). Among 14 patients with PAH, 11 patients had surgical interventions. PAH resolved in 5 of 11 patients (45%) undergoing surgical rehabilitation. One patient died during follow-up and 7 patients are receiving oral vasodilator therapies due to residual PAH; 14 patients remained asymptomatic. Our study showed that early intervention in patients with isolated pulmonary artery of ductal origin at modest altitude can potentially rehabilitate the isolated pulmonary artery and reverse the PAH. Whether surgery is indicated for patients with this disorder in the absence of PAH is unknown.

Keywords

isolated pulmonary artery of ductal origin; unilateral absence of pulmonary artery; altitude; high altitude pulmonary edema; pulmonary arterial hypertension

Introduction

Congenital isolated unilateral absence of a pulmonary artery is a rare entity, with an estimated prevalence of 1 in 200,000 [4]. The term unilateral “absence of a pulmonary artery” is a misnomer and in most cases pulmonary venous wedge angiography has identified a hidden hypoplastic and disconnected pulmonary artery at the lung hilum with normal intrapulmonary distribution [6, 7, 22]. The term isolated pulmonary artery of ductal origin (IPADO) is more appropriate as the native 6th arch vessel is not absent [17, 27].

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Review of published reports identified >160 cases of IPADO [10, 13, 21, 26, 29, 32]. Initially, patients with IPADO can remain asymptomatic for a long period, thus the diagnosis may not be made until adulthood [4]. Over time, however, most of these patients develop severe symptomatology including pulmonary arterial hypertension (PAH), hemoptysis, recurrent pulmonary infections, exercise intolerance, unilateral high altitude pulmonary edema (HAPE) and right heart failure [4,5,12,14,16,21,26,28,29]. Some patients with IPADO are unmasked by PAH associated with altitude exposure and hypoxic pulmonary vasoconstriction [8, 19, 20]. At modest altitude (less than 2500m), minor impairment exists in arterial oxygen transport (arterial oxygen saturation at least 90%) [18]. Preexisting PAH may deteriorate at altitudes greater than 2000 m, particularly during exercise [1]. Patients with IPADO and an underdeveloped pulmonary vascular bed are at increased risk to develop exaggerated PAH and HAPE at lower altitudes [9, 23, 24, 25].

There is limited data published in the literature except isolated rare case reports on long-term outcome of patients with IPADO living at altitude. Consequently, this present retrospective cohort study was undertaken to define the clinical manifestations and long-term outcome of 17 pediatric patients at a single center living at altitude with IPADO.

Methods

In a retrospective cohort study design, we identified 17 consecutive cases presenting with IPADO from 1975 to 2011 from the medical record database at Children's Hospital Colorado. Patients with associated congenital cardiac defects such as tetralogy of Fallot, pulmonary stenosis, truncus arteriosus, anomalous origin of a pulmonary artery from the ascending aorta, pulmonary atresia, coarctation of aorta, transposition of great arteries, or ventricular septal defect requiring surgical repair, were excluded. However, IPADO patients associated with a hemodynamically insignificant small intra-cardiac defect and patent ductus arteriosus (PDA) were included in the study. We reviewed the case records and extracted the clinical data including altitude of residence, gender, age at diagnosis, symptoms, echocardiographic and hemodynamic data, surgical and transcatheter intervention data such as age at the time of surgery, frequency of surgeries, surgical method to connect IPADO, interval and method of transcatheter intervention after surgical procedure, and subsequent pulmonary artery development. To confirm IPADO, cardiac catheterization and pulmonary vein angiography was performed in all cases in combination with computed tomography, and/or magnetic resonance imaging angiography. The clinical outcomes include death and World Health Organization (WHO) functional class status at follow-up. PAH was defined by a mean pulmonary artery pressure (mPAP) of >25 mmHg measured by right heart catheterization. This study protocol was approved by the institutional review board of University of Colorado, which waived patient consent because of the retrospective data analysis. All results are reported as median and range or mean and standard deviation as appropriate.

Results

Clinical characteristics are summarized Table 1. Age at diagnosis ranged from 1 month to 13 years (median; 3 years) with median follow-up period of 10 years (range; 1–46 years). Thirteen patients were male and 4 were female. No patients had a familial history of this disorder. One patient (*patient 8*) had a small muscular ventricular septal defect and 6 patients had a PDA (contralateral, 2 patients; ipsilateral, 4 patients). Extracardiac anomalies were associated with chromosome 22q11.2 deletion syndrome in 1 patient (*patient 6*). The IPADO was of the right pulmonary artery in 10 patients and left pulmonary artery in 7 patients. Aortic arch was opposite the effected pulmonary artery in all patients. Fourteen patients lived in Colorado at moderate to high altitude (median, range; 2050 m, 1700–3050

m) and the remaining 3 patients lived in Wyoming, Montana, and New Mexico (2600 m, 2000 m, 1700 m, respectively).

Clinical symptoms and pulmonary arterial hypertension

Median age at onset was 3 years (ranged from birth to 13 years). Only 2 patients (*patient 9, 12*) were asymptomatic and were investigated because of a heart murmur or abnormal chest X-ray, whereas the remaining 15 patients (88%) were symptomatic due to a cyanotic spell (n=7, 41%), dyspnea (n=5), prolonged cough (n=2), and fatigue (n=1) as the initial symptom. HAPE was present in 2 patients (12%) at diagnosis and 2 patients experienced recurrent infection prior to diagnosis. Only 1 patient (*patient 5*) who has not had surgery experienced hemoptysis at 11 years of age. He was diagnosed at 4 months-old and moved from high altitude (2500m, Colorado) to a lower altitude (1100m, Oregon). The patient underwent coil embolization of three large aortopulmonary collateral vessels, and then experienced an episode of hemoptysis while at altitude 6 weeks after the embolization (2006, 15 years of age). Fourteen patients (82%) demonstrated evidence of PAH preoperatively with a median mPAP of 39 mmHg (range, 25–58 mmHg) by cardiac catheterization and 3 of 14 patients with PAH had congestive heart failure. The remaining 3 patients showed no evidence of PAH at initial catheterization (mPAP; 17–20 mmHg). The median age at onset of symptoms in patients with PAH was 1 year-old (ranged from at birth to 9 years) which was younger than those in patients without PAH (median, range; 6, 4–13 years).

Treatments

All treatment strategies and outcome data are described in detail in Table 2. Surgical intervention was performed in 12 patients (71%) and initial surgery was performed at 2 years of median age (range; 2 months–13 years). The remaining 5 patients did not undergo surgery. The reason for not performing surgery included parental refusal (*patient 4, 5*), asymptomatic (*patient 13*), not a good candidate for surgical intervention because of long distance between main pulmonary artery and IPADO (*patient 12*), and a tiny native pulmonary artery which would be unlikely to grow with surgery in an older patient (*patient 15*).

The surgical approach evolved throughout the years. Initially, a direct anastomosis or anastomosis with tube graft as one-stage surgical correction was performed in 6 patients. However, the attempt to restore blood flow failed due to obstruction of the polytetrafluoroethylene tube graft in 2 patients (*patient 3, 16*). One patient (*patient 3*) underwent surgical re-intervention 5 years later. Another patient (*patient 16*) did not have surgical re-intervention and was initiated on calcium channel blockers due to residual PAH. As a next strategy, ipsilateral modified Blalock-Taussig shunt or central shunt was performed prior to surgery with an interposition tube graft or direct anastomosis in 4 patients. Recently, we attempted stent revascularization of the PDA as a transcatheter strategy instead of surgical systemic-pulmonary shunt prior to surgical intervention in 4 patients, and were successful in 2 patients (*patient 6 at 9 months of age, patient 9 at 4 years of age*). The revascularization of the occluded PDA was unsuccessful in 2 patients (*patient 1 at 6 weeks of age, patient 12 at 5 years of age*). Patient 1 had atrial septostomy performed due to severe PAH and right heart failure (mPAP; 90 mmHg, pulmonary vascular resistance index; 22.1 units $\times$ m²) and a modified Blalock-Taussig shunt was placed for maintaining pulmonary blood flow.

The surgical intervention included main pulmonary artery to IPADO with polytetrafluoroethylene tube graft in 5 patients, anastomosis with homograft in 4 patients, direct anastomosis of distal pulmonary artery to the main pulmonary artery in 2 patients, and

anastomosis with bovine jugular vein graft in 1 patient. Four patients (*patient 1, 2, 6, 7*) had catheter balloon dilatation of the IPADO. Three of 4 patients (*patient 1,2,6*) had balloon dilatation of pulmonary arteries prior to surgical re-anastomosis and 1 patient (*patient 7*) had pulmonary artery dilation after pulmonary artery anastomosis. Table 3 shows the overall results of surgical interventions for pulmonary artery rehabilitation in 12 patients. In 5 patients with available data, the native pulmonary artery diameter increased from 2.3 mm to 6.5 mm after surgical rehabilitation.

Long-term outcomes

On follow-up, 1 patient died due to an asthma attack (*patient 2*). This patient had evidence of PAH at first evaluation and a 2 stage surgical intervention was performed. The hemodynamic data by catheterization after surgery showed mild PAH (mPAP; 32 mmHg), and she was treated with bosentan and calcium channel blockers. During long term follow-up, there was no death due to surgery, hemoptysis, HAPE, heart failure, or PAH. Patient 3 and 15 are in WHO functional class III and II, respectively. The remaining 14 of 17 patients (82%) were asymptomatic in WHO functional class I (2 patients under 2 years-old were asymptomatic) during follow-up. Among 14 patients who had evidence of PAH at first evaluation, 11 patients underwent surgical interventions. In 5 of 11 patients (45%) who underwent surgical rehabilitation, the PAH resolved. In addition, the PAH resolved in 1 of 3 patients (33%) without surgery. Among the 3 patients who did not have PAH at first evaluation, no patient has PAH with or without surgical rehabilitation during follow-up (Figure 1). Although 1 patient (*patient 2*) who received vasodilator therapy after surgery died during follow-up, overall, 7 of 16 patients (44%) are receiving oral vasodilator therapies including prostanoid (iloprost), phosphodiesterase type 5 inhibitor (sildenafil, tadalafil), and endothelin receptor antagonist (bosentan, and ambrisentan) because of elevated pulmonary artery pressures (median, range; 36 mmHg, 26–90 mmHg) and resistance index (median, range; 7.85 units $\times$ m², 3.8–17.7 units $\times$ m²) at cardiac catheterization.

Discussion

This retrospective cohort study demonstrates the clinical characteristics of IPADO in pediatric patients living at modest altitude. We found that 88% of IPADO patients who live at modest altitude were symptomatic at presentation, with a cyanotic spell as the initial symptom in 41% of patients. In addition, the present study demonstrated a higher incidence of PAH compared with previous reports in adults and children with IPADO (82% versus 20–44%, respectively) [12, 21, 26, 29], thus our results suggested that modest altitude increased the risk of developing PAH in patients with IPADO. The high incidence of cyanotic spells in the present study might be associated with hypoxic pulmonary vasoconstriction due to altitude as well. Living at altitude may unmask the presence of IPADO in children.

The risk at altitude likely derives from hypoxic pulmonary vasoconstriction. The level of altitude has an inverse relation to arterial oxygen saturation and a direct relationship to the pulmonary arterial pressure. Increased altitude above 3000 m is associated with important changes of arterial oxygen saturation and pulmonary arterial pressure [20]. When alveolar partial pressures of oxygen falls below 70mm Hg, hypoxic pulmonary vasoconstriction causes a rise in pulmonary vascular resistance and leads to increased pulmonary artery pressure [3]. Even in healthy subjects at high altitude, pulmonary vasoconstriction, pulmonary arterial remodeling, right ventricular hypertrophy, erythrocytosis, and vasoconstriction are observed [15]. PAH at altitude is usually mild with mean pulmonary artery pressures around 25 mm Hg in healthy subjects [20]. Anatomical abnormalities such as IPADO with associated unilateral lung hypoplasia may be risk factors for PAH at

relatively low altitude [9, 23–25]. Previous animal studies demonstrated the hemodynamic effect of unilateral pulmonary artery ligation at altitude (1600 meters) and sea level. In this study, PAH developed in the neonatal calves at altitude, whereas the calves did not have PAH at sea level. The results suggested that altitude might lead to the development of PAH in the condition with unilateral pulmonary artery [31]. Our series of patients includes the longest follow-up period of up to 46 years. Our study is interesting because this is the first case-cohort study to describe and find favorable long-term outcomes in IPADO patients who live at altitude.

During long-term follow-up, no patients died due to PAH in association with IPADO. Most patients with IPADO are in WHO functional class I. In most of the IPADO patients with PAH, surgical intervention during infancy could be performed for rehabilitation and growth of the pulmonary arteries because of their early presentation. The high incidence of PAH due to modest altitude might lead to early diagnosis in our population. Early surgical or catheter intervention can preserve and may rehabilitate the pulmonary vasculature. In recent published literature, an initial repair of IPADO leads to favorable outcomes when performed during the neonatal period and infancy [2, 11, 12]. Therefore, the early diagnosis of IPADO patients may prevent late mortality.

Among patients without PAH at first catheterization, no one with or without surgery has developed PAH during follow-up. In our results, it is unclear whether the patients without PAH should have a staged surgical repair. However, in 11 PAH patients who underwent surgical rehabilitation, 6 patients had residual PAH after surgery. Although mean pulmonary artery pressure measured by catheterization shows mild elevation (median; 36 mmHg), 7 of 16 patients (44%) are still receiving pulmonary vasodilator therapies. Likewise, the previous large case series showed that 30% of IPADO patients with or without surgical intervention had residual PAH during follow-up (mean; 7.7 years) [30]. Our results suggested that milder forms of PAH may be observed regardless of surgery in patients with IPADO during long-term follow-up. In addition, we experienced that one patient with mild PAH had relapse of hemoptysis when visiting to high altitude after coil embolization of collateral arteries. Therefore, even in IPADO patients with mild PAH after surgery, travel to high altitude may not be recommended.

Our study was limited by small numbers because IPADO is a rare pathology and this was a retrospective cohort study from a single center. In addition, we were only able to document pulmonary artery diameter before and after surgery in 5 of 12 patients. A further limitation may also be the lack of comparison data between those patients at modest altitude and at sea level. Despite these limitations, we found that modest altitude was associated with early clinical presentation including PAH in patients with isolated IPADO. In addition, long-term outcome was favorable after surgery, despite the increased risk of PAH.

Conclusions

Most IPADO patients who lived at altitude were symptomatic with a high incidence of PAH. In IPADO patients with PAH who underwent surgical rehabilitation, 55% of patients had resolution of PAH. Our results suggest that early surgical intervention can potentially preserve and grow the peripheral pulmonary vasculature in affected lungs of patients with IPADO. Although 44% of our patients still require medical therapy for mild residual PAH, the long-term outcome was favorable. In conclusion, we recommend surgical revascularization of IPADO in the setting of PAH, but data are lacking in patients without PAH.

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Figure 1. Overall clinical course of 17 patients with IPADO

The diagram shows residual PAH with or without surgery in 17 patients. Among 11 patients who were found PAH prior to surgery, 6 patients (55%) had residual PAH after surgical repair. Among 6 patients who had residual PAH, 1 patient died for asthma attack. In addition, 2 of 3 patients (67%) without surgery had residual PAH. Overall, 7 of 16 patients (44%) require vasodilator therapy due to residual PAH during follow-up. The remaining 9 patients do not receive medication.

PAH; pulmonary arterial hypertension, IPADO; isolated pulmonary artery of ductal origin

patient characteristics

Table 1

patients	gender	Age at onset	Age at diagnosis	IPADO side	Aorta side	Symptoms at diagnosis	HAPE	recurrent infection	hemoptysis	PAH	HF	living altitude (m)
1	M	At birth	1 months	R	L	cyanosis	N	N	N	Y	Y	1700
2	F	2 weeks	3 months	L	R	cyanosis	N	Y	N	Y	Y	3050
3	M	1 month	2 months	R	L	dyspnea	N	N	N	Y	Y	2050
4	M	3 months	3 months	R	L	dyspnea	N	N	N	Y	N	2500
5	M	4 months	8 years	L	R	cyanosis	Y	N	Y	Y	N	2750
6	M	9 months	9 months	L	R	cyanosis	N	N	N	Y	N	1700
7	M	1 year	1 year	R	L	cyanosis	N	N	N	Y	N	2000
8	M	1 year	1 year	R	L	dyspnea	N	N	N	Y	N	2000
9	F	2 years	2 years	R	L	Asymptomatic (abnormal CXR)	N	N	N	Y	N	1700
10	M	3 years	3 years	R	L	cyanosis	N	N	N	Y	N	2050
11	M	3 years	3 years	L	R	dyspnea	N	N	N	Y	N	3000
12	M	4 years	5 years	L	R	cough	N	Y	N	N	N	2600
13	M	6 years	6 years	L	R	Asymptomatic (heart murmur)	N	N	N	N	N	2000
14	F	8 years	8 years	R	L	dyspnea	N	N	N	Y	N	2000
15	F	9 years	9 years	R	L	fatigue	N	N	N	Y	N	1700
16	M	9 years	9 years	R	L	dyspnea	Y	N	N	Y	N	3050
17	M	13 years	13 years	L	R	cough	N	N	N	N	N	2050

CXR; chest X-ray, HAPE; high altitude pulmonary edema, HF; heart failure, M/F; male/female, PAH; pulmonary arterial hypertension, R/L; right/left, IPADO; isolated pulmonary artery of ductal origin, Y/N; yes/no

Treatments and outcomes

Table 2

patients	Catheter intervention prior to surgery	Age at first surgery	First operation	Age at second operation	Second operation	Current age	Residual PAH*	Current medication	Current WHO functional class
1	PDA stent (unsuccessful)	2 months	mBTS	1 year	Reconstruction PA with homograft	1 year	Y (90mmHg)	Sildenafil+ Bosentan	NA (asymptomatic)
2	balloon dilatation of PA	3 months	mBTS	6 months	Reconstruction PA with ePTFE	died	Y (32mmHg)	CCB+ Bosentan	NA (died)
3	none	1 year	Anastomosis with ePTFE	6 years	Jump graft from proximal to distal PA	46 years	Y (40mmHg)	CCB	3
4	none	none	none	none	none	15 years	N	none	1
5	coil embolization	none	none	none	none	20 years	Y (26mmHg)	CCB+ Iloprost	1
6	PDA stent, balloon dilatation of PA	2 years	Anastomosis with homograft	none	none	2 years	Y (26mmHg)	Sildenafil+ Bosentan	NA (asymptomatic)
7	none	1 year	Central shunt	2 years	Anastomosis with homograft	10 years	Y (28mmHg)	Sildenafil	1
8	none	2 years	Anastomosis with homograft	none	none	31 years	N	none	1
9	PDA stent	4 years	Anastomosis with bovine jugular vein graft	none	none	7 years	N	none	1
10	none	3 years	Anastomosis with ePTFE	none	none	33 years	N	none	1
11	none	3 years	Anastomosis with homograft	none	none	40 years	N	none	1
12	PDA stent (unsuccessful)	none	none	none	none	6 years	N	none	1
13	none	none	none	none	none	15 years	N	none	1
14	none	8 years	Direct anastomosis	none	none	35 years	N	none	1
15	none	none	none	none	none	15 years	Y (59mmHg)	Tadalafil+ Ambrisentan	2
16	none	9 years	Reconstruction PA with ePTFE	none	none	21 years	Y (52mmHg)	CCB	1
17	none	13 years	mBTS	14 years	Direct anastomosis	21 years	N	none	1

CCB; calcium channel blockers, ePTFE; expanded polytetrafluoroethylene, mBTS; modified Blalock-Taussig shunt, NA; not available, PA; pulmonary artery, PAH; pulmonary arterial hypertension, PDA; patent ductus arteriosus, TRV; tricuspid regurgitant velocity, WHO; World Health Organization

* Residual PAH as evidenced by cardiac catheterization

Table 3

Result of surgical interventions for pulmonary artery rehabilitation

Patient number	Initial PA diameter	Age at first Catheterization (months-old)	PA diameter prior to final surgery	Age at Catheterization prior to final surgery (months-old)	Current PA diameter	Age at last catheterization (months-old)
1	2.0 mm	1	5.5 mm	12	6.5 mm	19
2	3.0 mm	2	4.6 mm	NA	6.0 mm	17
3	NA	NA	NA	NA	NA	NA
6	2.5 mm	11	8.1 mm	31	NA	NA
7	1.5 mm	NA	3.2 mm	21	7.1 mm	75
8	NA	NA	NA	NA	NA	NA
9	4.1 mm	50	9.6 mm	57	NA	NA
10	NA	NA	NA	NA	NA	NA
11	NA	NA	NA	NA	NA	NA
14	NA	NA	NA	NA	NA	NA
16	NA	NA	NA	NA	NA	NA
17	2.1 mm	170	9.8 mm	176	NA	NA
Median	2.3 mm	11 months-old	6.8 mm	31 months-old	6.5 mm	19 months-old

NA; not available, PA; pulmonary artery