

A Case Series of Six Children with Primary Pulmonary Hypertension

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Abstract

Introduction: Primary pulmonary hypertension is an uncommon but serious disease in children. Management is difficult despite recent advances in pharmacotherapy. **Clinical Picture:** We reviewed patients with this condition with respect to their presenting symptoms, investigations, treatment and outcome. **Treatment:** These children were treated with individualised combinations of oxygen, diuretics and calcium antagonists. **Outcome:** In our follow-up of 5 children, 4 had died. **Conclusion:** This condition is irreversible and progressive with a high mortality rate. A better understanding of, and research into, the pathogenesis would hopefully lead to the formulation of improved therapeutic strategies for this condition.

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Introduction

Pulmonary arterial hypertension¹ (PAH) is an uncommon but serious and debilitating disorder seen in children and adults. By definition, it is an elevation of the pressure in the pulmonary artery to above a mean of 25 mmHg at rest, or 30 mmHg during exercise. It has to be differentiated from pulmonary venous hypertension, which arises from obstruction of the left heart, such as in conditions of mitral stenosis, cor triatriatum or obstructed pulmonary veins.

PAH can be further subdivided into primary/idiopathic pulmonary hypertension (PPH) where no known cause of the hypertension is evident, or secondary pulmonary hypertension where a predisposing factor for the raised pressure can be identified. Some of these causes include large intracardiac or systemic-to-pulmonary shunts, pulmonary disease or drugs like fenfluramine. PPH^{2,3} is a rare condition with a poor prognosis; and with an incidence of 1 per 1,000,000, it is less common than secondary pulmonary hypertension.

Case Series

We reviewed our series of patients who were diagnosed to have PPH over a 5-year period from 1995 to 2000. There

were 6 patients (females = 5, males = 1) seen with this condition. The average age at presentation was 10.3 years (range 3 to 21 years).

Presenting Symptoms

Among the most common presenting symptom was effort intolerance. Many of these patients were unable to keep up with their peers in terms of play and/or exercise. Subjective complaints of dyspnoea and easy fatigability also featured prominently in all patients, particularly during the severe stages. In addition, they also experienced chest pain and syncope. These symptoms reflected an inadequate ventricular output in the face of a stressed right heart.

Physical examination in all revealed active praecordial impulses with ventricular heave suggestive of right ventricular hypertrophy. There was an accentuation of the pulmonic component of the second sound, to the extent that most times, it was palpable. A soft systolic murmur of tricuspid regurgitation was often audible. Interestingly, 1 patient's father also has idiopathic pulmonary hypertension on follow-up with our adult cardiology colleague, although the severity of involvement is less than the patient.

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Investigations

All of these patients were referred to a cardiologist and had chest X-ray, electrocardiogram (ECG) and echocardiogram performed. With these non-invasive methods, the diagnosis could be accurately made. Most of these patients were already in fairly advance stages of the disease at presentation. The chest X-ray revealed cardiomegaly in all cases (Fig. 1). In addition, there was a prominent pulmonary conus from dilatation of the pulmonary artery as a result of the hypertension.

The ECGs of our patients revealed the presence of right ventricular hypertrophy. This would be suggested by right axis deviation, increased R amplitudes and upright T waves in the right praecordial leads and deep S wave in the left praecordial leads. A right ventricular strain pattern with ST segment depression and T wave inversion was also noted (Fig. 2). These patients were given an individualised combination of medication, comprising some or all of these: oxygen therapy, diuretic therapy, aspirin and calcium antagonists.

The diagnosis was made on echocardiography in all patients. There was obvious dilatation of the right heart (Fig. 3) in all patients. The raised pulmonary pressure was suggested from Doppler interrogation of the tricuspid and pulmonary regurgitant jets, which were markedly elevated. There was also flattening of the ventricular septum. In 3 of the patients, right to left shunting across a patent foramen ovale could be seen on colour flow mapping. Importantly,

other intracardiac causes for the pulmonary hypertension were excluded in the studies.

Cardiac catheterisation was performed in 3 of our 6 patients. One patient was a foreigner who came for a second opinion and was subsequently lost to follow-up. Two other families did not consent to the procedure. In the remaining 3 patients, the pulmonary pressures were confirmed to be elevated (mean pulmonary artery pressure 86.7 mmHg, compared to systemic mean pressure of 92.7 mmHg). The mean pulmonary vascular resistance was 19.9 (+/- 5.7) units.m². During the catheter study, 100% oxygen for at least 20 minutes was given to these patients. There was no significant drop in pulmonary pressure (defined as decrease of 20% or more). In addition, 1 patient was challenged with a calcium antagonist and 100% oxygen, and there was a drop of about 21% in the mean pulmonary artery pressure. Unfortunately at the time when this study was conducted, nitric oxide and prostacyclin were not readily available and we were unable to test the response using these agents. Our protocol would now include challenge with oxygen and vasodilators (inhaled nitric

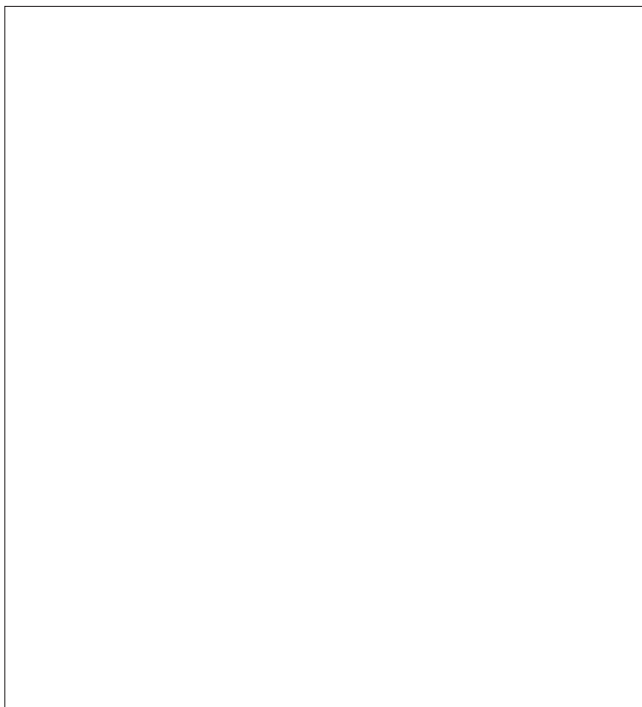


Fig. 1. Chest X-ray of a child with pulmonary hypertension.

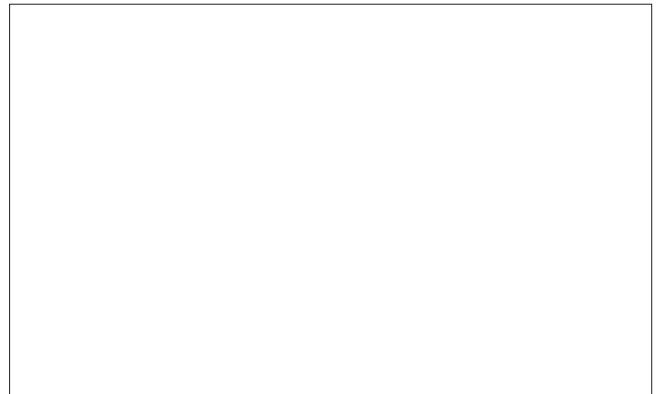


Fig. 2. Echocardiogram demonstrating right ventricular hypertrophy and strain pattern reflecting high lung pressures.

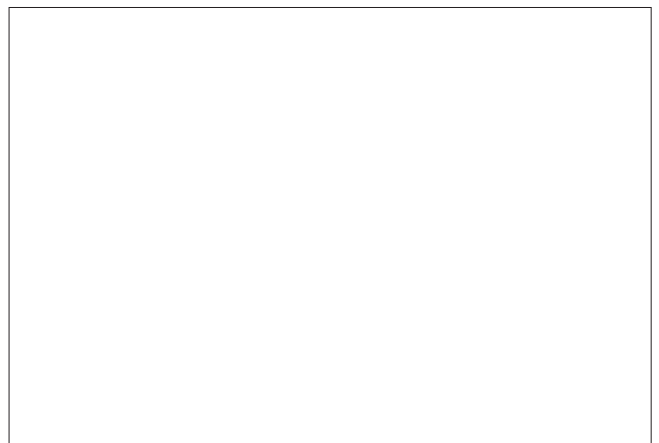


Fig. 3. Echocardiogram demonstrating a dilated right heart in pulmonary hypertension.

oxide, intravenous adenosine or prostacyclin) in the assessment of the reactivity of the pulmonary vascular bed. In the responders, the use of chronic vasodilator agent would be implemented.

Follow-up data (mean duration of 2.2 $\pm$ 2.1 years) were available in 5 children. This included regular visits at the outpatient clinics where the condition of the patients was monitored with serial echocardiography. There was generally no improvement in their condition, and pulmonary pressures continued to remain elevated and even progressed. The pulmonary pressure was estimated non-invasively from serial echocardiography. The clinical condition deteriorated in all the patients. Of the 5, 4 patients had died, within 1 month, 12 months, 13 months and 3 years following the initial diagnosis of the condition.

Discussion

PPH has been a well-recognised entity³⁻⁵ for several decades with an excellent review article by Barst⁶ on this entity. However, it remains an incurable disease with a poor prognosis. Fortunately, the incidence is low, in the region of approximately 1 to 2 per 1,000,000. There is a preponderance of females affected with PPH, and our series appears to suggest a similar trend. Most of these cases are sporadic, although a familial form of PPH^{7,8} has been reported. Recent studies have identified a gene on chromosome 2q 31-32⁹ as being responsible for the familial cases.

Conventional management of these patients includes anticoagulants,^{10,11} oral vasodilator drugs¹² and domiciliary oxygen.¹³ In recent years, several new pharmacologic agents are available. One such potent pulmonary vasodilator, nitric oxide,¹⁴⁻¹⁶ is delivered via the inhalational route. It is one of the best-known vasodilators and can be used in different settings in pulmonary hypertension including persistent pulmonary hypertension of the newborn. However, there are practical problems in its use as a long-term treatment modality for PPH because of its route of administration.

The use of intravenous prostacyclin^{17,18} for PPH has been shown to improve the survival rate of patients. Problems with this include the need for establishing an intravenous route for administration, as well as the need to adjust its dosage frequency with prolonged use. Nevertheless, many reports¹⁷⁻²⁰ have found value in its use and the intravenous route is becoming increasingly accepted. As a bridge to transplant, intravenous prostacyclin could also play a role. More work is also being done to ascertain if the use is associated with beneficial remodelling of the pulmonary bed leading to an improvement in the condition.

Although the disorder can be accurately diagnosed with non-invasive means such as echocardiography, there is a

role for cardiac catheterisation in these patients. The risks involved can be minimised by adequate sedation during the procedure and making sure that the electrolytes are normal. During the study, challenge with oxygen and pulmonary vasodilator can be carried out to ascertain the response of the pulmonary vascular bed. This would help in deciding the value of chronic vasodilator therapy in addition to currently recommended anticoagulation.

The “cure” for PPH is a lung/heart-lung transplant.^{21,22} Expertise and finances aside, the lack of organ donors, especially in children, continues to be a major limiting factor in most countries.

Conclusion

Even as we know of potent vasodilators for this condition, more research into this intriguing condition is necessary. Knowledge of the pathogenesis will lead to a better understanding of the disease, and possibly lead to specific targets for its treatment and even prevention. In familial cases, gene therapy may provide an answer. Meanwhile, the continuing quest to find the most appropriate medication for this condition should continue—this ideal medicine must be easy to deliver, cheap, effective and relatively free of side effects.

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