



## Porto Pulmonary Syndrome in Children

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### Abstract

**Background:** Porto pulmonary hypertension (PoPH) is combination of portal hypertension and pre capillary pulmonary arterial hypertension (PAH). Prognosis is poor in pediatric patients. To evaluate incidence, clinical profile, investigational profile and outcome of pediatric PoPH, the following study was done.

**Method:** The children (age 3 – 12 years) who had portal hypertension and respiratory distress were admitted in pediatric gastro enterology ward of PGIMER – Chandigarh from July 1993 to June 2003. History and clinical examination (Ascites, GI Bleed, Jaundice, dyspnea, fatigue, chest pain, syncope etc.), investigations (USG whole abdomen, LFT, UGI Endoscopy, pulse oxymetry, echocardiography, contrast echocardiography, chest X-ray etc.) were noted.

Simplified Bernoulli equation is used to detect PAP by echocardiography. Contrast echocardiography is done to rule out hepato pulmonary syndrome.

**Results:** Out of 10 cases of portal hypertension, 6 were male, 4 were female. Age was 3 – 12 years (mean 8 year). Out of 10 cases, 6 were cirrhosis, 4 were non cirrhotic portal hypertension. Invasive procedure like cardiac catheterization was not done. PAP (measured by echocardiography) was 40 – 55 mm Hg. 4 patients who had non cirrhotic portal hypertension improved after portal systemic shunt and reduction of portal hypertension. 6 patients who had cirrhosis and pulmonary hypertension could not survive. Symptomatic treatment of pulmonary hypertension was done. (IV prostaglandins etc.)

**Conclusion:** Porto pulmonary hypertension is a rare but serious problem in children. Research is still going on to get best management.

**Keyword:** Porto Pulmonary Syndrome in Children.

### Introduction

Mantz and Craig reported a case called porto pulmonary (PoPH) syndrome in 1951, where there is combination of portal hypertension and pulmonary hypertension. Mean pulmonary arterial hypertension (mPAP) remains > 25 mm Hg, pulmonary capillary wedge pressure (PCWP) < 15 mm Hg and pulmonary vascular resistance (PVR) > 3 wood units (WU).<sup>(1)</sup>

Histopathology of pulmonary artery in porto pulmonary syndrome is similar to that of idiopathic pulmonary hypertension. Findings are vasoconstriction, endothelial and smooth muscle proliferation, plexogenic arteriopathy, in situ thrombosis and fibrosis.<sup>(2)</sup>

In adults with liver cirrhosis, incidence of porto pulmonary hypertension (PoPH) is reported to be 2 – 8%.<sup>(3)</sup>

Various studies have shown that patients with PoPH have poorer survival rate and all cause hospitalization rates compared to that with Ideopathic pulmonary arterial hypertension (IPAH).<sup>(4)</sup>

A diagnosis of PoPH in a cirrhosis is associated with high mortality even after liver transplantation. PoPH may be a contraindication to liver transplantation.<sup>(5)</sup>

Adult patients with PoPH are recorded in literature in most cases. But pediatric PoPH are scanty in literature. In an autopsy series of children with portal hypertension, 5.4% had histologic evidence of pulmonary arterial hypertension.<sup>(6)</sup>

PoPH is disorder which has high mortality in pediatric patients. Due to limited experience, there is under recognition and delayed diagnosis. Condino et al reported high mortality in a series of 7 patients where 4 (4/7) died.<sup>(7)</sup>

Syncope is most common presenting symptom of PoPH in children. Risk of death is three fold higher in pediatric PoPH than IPAH patients.<sup>(8)</sup>

In adult series, alcoholic liver disease and hepatitis are common cause of cirrhosis.<sup>(9)</sup>

In children with PoPH, congenital causes of liver cirrhosis are more common (e.g. Billiary atresia) but in pediatric PoPH, there are cases where there is portal hypertension without cirrhosis (porto systemic shunt)<sup>(10)</sup>

Porto systemic shunt and hepatic failure leads to increased circulating vasodilators.<sup>(11)</sup>

This condition leads to splanchnic vasidilation and low systemic vascular resistance.<sup>(12)</sup>

Volume overload into splanchnic vasculature leads to bowel wall congestion and liberation of endotoxins and cytokines. In addition, higher cardiac output and increased flow within pulmonary vasculature causes increased shear forces and increased mPAP (mean pulmonary artery pressure).<sup>(13)</sup>

Pulmonary vasculature's response to hyper dynamic state is variable. A vasodilatory response may lead to hepato pulmonary syndrome. Vasoconstriction may lead to PVD (pulmonary

vascular dilatation) similar to precapillary PH (pulmonary hypertension).

Genetic and environmental factors determine whether vasodilation and hepato pulmonary syndrome will occur or vasoconstriction and PoPH will occur.<sup>(13)</sup>

Ecochard et al observed that hepato pulmonary syndrome can precede to development of PoPH. Hypoxia secondary to hepato pulmonary syndrome can lead to PoPH.<sup>(14)</sup>

In both pediatric and adult PoPH, histopathological changes are similar to that of IPAH.<sup>(15)</sup>

PAH occurs due to dys-regulation of vasodilators and vasoconstrictors including prostacyclin, nitric oxide, endothelin-I, thromboxam A<sub>2</sub> and serotonin.<sup>(16) (17)</sup>

Due to release of inflammatory mediators, there is continued increase to pulmonary blood flow, sheer stress on pulmonary vascular bed, subsequent vasoconstriction and pulmonary vascular remodeling. In portal hypertension, there is porto systemic shunting and inflammatory mediators escape metabolic degradation by liver. Then they directly act upon pulmonary vasculature.<sup>(18) (19)</sup>

There is no association between severity of portal hypertension and severity of PAH (based on right heart hemodynamic measurements).<sup>(18)</sup>

The most effective therapy for PoPH has not yet established. The use of prostanoids, calcium channel bluchers, endothelin receptor antagonist, phosphodiesterase – 5 (PDE 5) inhibitors have been mentioned. In a study from Mayo Clinic, researchers observed that medical therapy alone or medical therapy plus liver transplant improved survival.<sup>(20)</sup>

No single modality of treatment has shown superiority over others. Treatment with continuous intravenous epoprostenal has been associated with hypersplenism.<sup>(21)</sup>

## Method

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PGIMER – Chandigarh from July 1993 to June 2003. History and clinical examination (Ascites, GI Bleed, Jaundice, dyspnea, fatigue, chest pain, syncope etc.), investigations (USG whole abdomen, LFT, UGI Endoscopy, pulse oxymetry, echocardiography, contrast echocardiography, chest X-ray etc.) were noted.

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## Results

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## Discussion

Splanchnic blood flow is increased in portal hypertension secondary to increase of local and systemic vasodilators. It is potentiated by use of prostacyclin therapy for porto pulmonary hypertension (PoPH).<sup>(12)</sup>

Various studies have evaluated utility of screening all liver cirrhosis patients with echocardiography to detect PoPH. Though echocardiography is useful for screening at risk population, it is insufficient to evaluate PoPH. Cardiac catheterization and targeted medical therapy with closure of intrahepatic shunts should be considered before liver transplantation.<sup>(22)</sup>

In our series of 10 cases of PoPH, 6 had cirrhosis and 4 had non cirrhotic portal hypertension cirrhotic patients could not survive but 4 patients

of non cirrhotic portal hypertension improved with treatment.

Though PoPH is diagnosed 4 – 7 years after diagnosis of portal hypertension diagnosis of PoPH is actually made during hemodynamic monitoring before liver transplantation.<sup>(20)</sup>

Diagnosis of PoPH is made on basis of hemodynamic criteria where patients with portal hypertension and or liver disease (ascites / varices / splenomegaly) have mean pulmonary artery pressure MPAP > 25 mm at rest / pulmonary vascular resistance – PVR > 240 dynes / pulmonary artery occlusion pressure PAOP < 15 mm or transpulmonary gradient TPG > 12 mm where  $TPG = MPAP - PaoP$ .<sup>(23)</sup>

Symptomatic patients of PoPH present with right heart dysfunction secondary to pulmonary hypertension and its consequent dyspnea, fatigue, chest pain and syncope.<sup>(24)</sup>

Sixty percent of patients with PoPH have stage III – IV NYHA heart failure.<sup>(25)</sup>

PoPH is independent of severity of cirrhosis but may be more common in specific types of cirrhosis. Some studies have mentioned that PoPH is more common in auto immune hepatitis related cirrhosis but less in hepatitis C cirrhosis.<sup>(26)</sup>

In PoPH there is imbalance between vasoconstrictors and vasodilator substance. Due to liver cirrhosis, toxic (vasoconstrictors) substances escape metabolism bypassing liver. Moreover, a key pathogenic factor for declining of PoPH status is cirrhotic cardiomyopathy with myocardial thickening and diastolic dysfunction.<sup>(27)</sup>

One autopsy series have shown that cirrhotic patients have thickened pulmonary arteries.<sup>(26)</sup>

Calcium channel blocker, beta blockers, nitrates are all tried but most potent and widely used substances are prostaglandin (and prostacyclin) analogs, phosphodiesterase inhibitors, nitric oxide and most recently, endothelin receptor antagonist. Inhaled nitric oxide (i No) vasodilates, decreases PAP and PVR without affecting systemic artery pressure. It is rapidly inactivated by hemoglobin. It improves oxygenation by redistributing pulmonary blood flow in ventilated area. But i No

requires intubation, it cannot be used for long period due to methenaglobinemia.<sup>(29)</sup>

Prostaglandine like PGE1 (Alprostadil), PGE2 (Prostacyclin) and more stable, long acting Epoprostenol (Iloprost) are tried. Iloprost can lower PAP by 29 – 46% and PVR by 21 – 71%.<sup>(30)</sup>

Phosphodiesterase inhibitors like milrinone causes selective pulmonary vasodilatation, increases myocardial contractile force, increase extent of relaxation.<sup>(31)</sup>

Endothelin I receptor antagonist (Busentan) improves oxygenation and PVR.<sup>(32)</sup>

Imatinib (designed to treat chrome myeloid leukemia) has been shown to reverse pulmonary remodeling associated with PoPH.<sup>(33)</sup>

## Conclusion

Porto pulmonary hypertension is a rare but serious problem in children. Research is still going on to get best management.

**Conflict of interest** – Nil

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