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Original Research Article

Idiopathic acute onset pulmonary artery hypertension in infancy need for research

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ABSTRACT

Background: The aim of this study was to study the clinical outcome of infants beyond neonatal period who presented with acute onset pulmonary artery hypertension of unknown etiology.
Methods: This is a retrospective case record analysis of all the babies admitted to pediatric intensive care unit between January 2013 to March 2017 at Rajarajeswari Medical College with signs and symptoms of Pulmonary Arterial Hypertension on clinical examination and ECHO. Descriptive and inferential statistical analysis has been carried out in the present study.
Results: Out of 49 infants beyond neonatal period who presented with Pulmonary Arterial Hypertension, 9 were females and 40 were males. 43 babies required ventilator support and 6 babies required only supplemental oxygen. Out of 33 babies who expired, cardiogenic shock and severe hypoxia was the main cause of death in 19, pulmonary hemorrhage in 4, acute kidney injury and fluid overload in 2, multi organ dysfunction in 1, septicemia in 4 and disseminated intravascular coagulation in 3. Babies who survived less than 72 hours cardiogenic shock and severe hypoxia was the main cause of death and babies who survived more than a week, pulmonary hemorrhage, acute kidney injury and fluid overload, multi organ dysfunction, septicemia and disseminated intravascular coagulation were the main cause of death.
Conclusions: There is a need for research in infants beyond neonatal period with pulmonary arterial hypertension, to find out the etiology.

Keywords: Infancy, PAH, Unknown etiology

INTRODUCTION

Pulmonary arterial hypertension is a serious progressive condition with a poor prognosis if not identified and treated early. Because the symptoms are nonspecific and the physical findings can be subtle, the disease is often diagnosed in its later stages. Remarkable progress has been made in the field of pulmonary arterial hypertension over the past several decades pathology is now better defined, and significant advances have occurred in understanding the pathobiologic mechanisms. Risk factors have been identified, and the genetics have been characterized.[1]

Advances in technology allow earlier diagnosis as well as better assessment of disease severity. Therapeutic modalities such as new drugs, e.g., epoprostenol, treprostinil, and bosentan, and surgical/interventional options, e.g. transplantation and atrial septostomy, which were unavailable several decades ago, have had a significant impact on prognosis and outcome.[2] Despite of the above progress in the diagnosis and management of pulmonary arterial hypertension many babies beyond the neonatal period presented with vague symptoms and signs, where in the etiology remained obscure and uncertain leading to late diagnosis and treatment.

METHODS

The aim of the study was to study the clinical outcome of babies with acute onset Pulmonary Arterial Hypertension of unknown etiology. This is a retrospective case record analysis of 49 babies who presented with Pulmonary Arterial Hypertension of unknown etiology but behaved similarly in clinical manifestations. The cases were evaluated in terms of signs and symptoms, duration of illness, need for ventilator support, ECHO findings, blood gas analysis at the time of admission, duration of hospital stay, and the short-term outcome after the acute illness and follow up at 3 months. All the babies who presented with acute onset Pulmonary Arterial Hypertension were included. ECHO was done by pediatric cardiologist and pulmonary pressures were classified as:

- Mild (pulmonary pressures 30-60 mm of hg)
- Moderate (pulmonary pressures 60-90) and
- Severe (pulmonary pressures >90 mm of hg).

Babies with congenital heart disease with pulmonary arterial Hypertension, babies with neonatal onset PPHN were excluded.

Statistical methods

Descriptive and inferential statistical analysis has been carried out in the present study. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver. 2.11.1 were used for the analysis of the data. Results on continuous measurements are presented on Mean±SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for qualitative data analysis.

RESULTS

Out of 49 babies, males were affected more compared to the female babies. All the babies presented with clinical signs and symptoms of PAH before the age of 6 months with most of them within first 3 months. Refusal of feeds (69.4%), fast breathing (65.3%), cough (40.8%), vomiting (36.7%), decreased urine output (26.5%) were the predominant symptoms, were as change of voice, seizures were reported by few mothers.

On examination, all the babies had varying degree of respiratory distress, 37 babies had central and peripheral cyanosis, 18 babies presented with shock, and 15 babies were brought with gasping and acute respiratory failure. None of the babies had features of lower respiratory tract infection clinically or radiologically. Initial septic workup including blood cultures were negative in all the babies. Chest X-ray was suggestive of oligemic lung fields with right ventricular hypertrophy in most of the babies, in addition 5 babies developed pulmonary edema suggestive of biventricular failure. Echocardiography showed severe PAH in 43 babies, moderate PAH in 5 and 1 baby had mild PAH. 43 babies required inotropic support in the form of dopamine and adrenaline, 25 babies required blood transfusion to improve hypoxia. All the babies were given oral sildenafil, intravenous fallowed by oral sildenafil in 4 babies.

Table 1: Clinical profile of babies with acute onset pulmonary arterial hypertension.

		No. of babies)n=49(	%
Gender	Female	9	18.4
	Male	40	81.6
Age	<3 months	30	61.2
	3-6 months	19	38.8
Symptoms	Cough	20	40.8
	Fast breathing	32	65.3
	Vomiting	18	36.7
	Refusal of feeds	34	69.4
	Decreased urine	13	26.5
	Change of voice	4	8.2
	Fever	3	6.1
	Seizures	6	12.2
Signs	RDS	49	100.0
	Hepatomegaly	42	85.7
	Cyanosis	37	75.5
	Gasping	15	30.6
	Shock	18	36.7
Chest x-ray	Normal	5	10.2
	Right Ventricular Hypertrophy	40	81.6
	Pulmonary oedema	5	10.2
	Oligemic lungs	44	89.8
Echo-PAH	Mild	1	2.0
	Moderate	5	10.2
	Severe	43	87.8
ABG	Metabolic acidosis	14	28.6
	Respiratory alkalosis	4	8.2
	Respiratory alkalosis with metabolic acidosis	30	61.2
	Normal	1	2.0
Mechanical ventilation	Yes	43	87.8
	No	6	12.2
	Inotropic support	43	87.8
	Blood transfusion	25	51.0
Outcome	Survived	16	32.7
	Expired	33	67.3

43 babies required ventilator support and 6 babies required only supplemental oxygen. Out of 16 babies who survived pulmonary pressures normalized by 2-4

weeks and sildenafil was tapered and stopped by 3mths of age. One baby required more than a week peritoneal dialysis for acute kidney injury and fluid overload, though renal parameters settled within 2weeks baby developed neurological sequela in the form of microcephaly, spasticity, developmental delay on follow-up. Out of 33 babies who died, cardiogenic shock and severe hypoxia was the main cause of death in 19, pulmonary hemorrhage in 4, acute kidney injury and fluid overload in 2, multi organ dysfunction in 1, septicemia in 4 and disseminated intravascular coagulation in 3. Babies who survived less than 72 hours cardiogenic shock and severe hypoxia was the main cause of death and babies who survived more than a week, pulmonary hemorrhage, acute kidney injury and fluid overload, multi organ dysfunction, septicemia and disseminated intravascular coagulation were the main cause of death.

Table 2: Clinical outcome of babies with acute onset pulmonary arterial hypertension.

Duration of hospital stay	Outcome			Cause of death					
		survived	expired	Cardiogenic shock, hypoxia	Pulmonary haemorrhage	AKI fluid overload	MODS	Septic shock	DIC
<24 hours	16 babie	0)0%(	16)48.5%(	16)84.2%(	0)0%(	0)0%(	0)0%(	0)0%(	0)0%(
24-72 hours	6 babies	1)6.3%(	5)15.2%(	3)15.8%(	2)50%(	0)0%(	0)0%(	0)0%(	0)0%(
3-7 days	17 babies	7)43.8%(	10)30.3%(	0)0%(	2)50%(	2)100%(	1)100%(	3)75%(	2)66.7%(
>1 week	10 babies	8)50%(	2)6.1%(	0)0%(	0)0%(	0)0%(	0)0%(	1)25%(	1)33.3%(
P value		<0.001**		<0.001**	0.074+	0.488	1.000	0.301	0.535

DISCUSSION

Significant progress in the field of pulmonary hypertension has occurred over the past several decades. Advances in technology have also allowed a better diagnosis and assessment of the disease severity with treatment now available that improves quality of life and survival.[1,2] Nevertheless, extrapolation from adults to children is not straightforward for at least several reasons: the anticipated lifespan of children is longer; 2) children may have a more reactive pulmonary circulation raising the prospect of greater vasodilator responsiveness and better therapeutic outcomes; and 3) despite clinical and pathological studies suggesting increased vasoreactivity in children, before the advent of long-term vasodilator/antiproliferative therapy, the natural history remained significantly worse for children compared to adult patients.[3-5]

In the understanding of the pathobiology of primary pulmonary hypertension, the mechanisms which initiate and perpetuate the disease process remain(s) speculative. In the classic studies by Wagenvoort and Wagenvoort in 1970, medial hypertrophy was severe in patients <15 years of age and it was usually the only change seen in infants.[6] Among the 11 children <1 year of age, all had severe medial hypertrophy, yet only three had intimal fibrosis, two with minimal intimal fibrosis and one with moderate intimal fibrosis and none had plexiform lesions. With increasing age, intimal fibrosis and plexiform lesions were seen more frequently. Furthermore, these observations may offer clues to the observed differences in the natural history and factors influencing survival in children with primary pulmonary hypertension compared with adult patients. Younger children in general appear to have a more reactive pulmonary vascular bed relative to both active pulmonary vasodilatation as well as pulmonary vasoconstriction, with severe acute pulmonary hypertensive crises occurring in response to pulmonary vasoconstrictor "triggers" more often than in older children or adults. Thus, based on these early pathological studies, the most widely proposed mechanism for primary pulmonary hypertension until the late 1980s and early 1990s was pulmonary vasoconstriction.[3,7,8]

Subsequent studies have identified potentially important structural and functional abnormalities; whether these perturbations are a cause or consequence of the disease process remains to be elucidated. These abnormalities include imbalances between vasodilator/antiproliferative and vasoconstrictive / mitogenic mediators, defects in the potassium channels of pulmonary artery smooth muscle cells and increased synthesis of inflammatory mediators which cause vasoconstriction as well as enhanced cell growth.[9,10]

Although the diagnosis of primary pulmonary hypertension is one of exclusion, it can be made with a high degree of accuracy if care is taken to exclude all likely related or associated conditions. A thorough and detailed history and physical examination, as well as

appropriate tests, must be performed to uncover potential causative or contributing factors, many of which may not be readily apparent. Hence an attempt is made to enquire about family history of pulmonary hypertension, connective tissue disorders, congenital heart disease, other congenital anomalies, and early unexplained deaths in our study. Previous history of sibling death with PAH at similar age was present in 4 babies, two pair of twins presented with signs and symptoms of PAH to the emergency department one died within 1 hour of admission and one within 24 hours, and one among each pair survived and discharged home.

A similar study was conducted by Rao SN and Chandak GR who investigated 55 such infants who presented with signs and symptoms of PAH. Majority presented with tachypnea, chest indrawing and tachycardia and cardiomegaly with dilatation of right heart and pulmonary hypertension on 2D-echocardiography. Low levels of erythrocyte trans-ketolase activity suggested thiamine deficiency that was confirmed by reversion of several clinical features including cardiologic abnormalities to normalcy on thiamine supplementation. Babies who presented with features of acute lower respiratory tract infection, primary pulmonary hypertension with congestive cardiac failure (CCF) and had remarkable recovery on thiamine administration.

Similar to our cases all enrolled babies were exclusively breast-fed with an appropriate weight for their age. Mean age of presentation was 3.9 months and mean duration of illness was 7.5 days. All of them presented with tachypnea, chest indrawing and tachycardia. Other major manifestations included hepatomegaly (n ¼ 44; 80%), cough (n ¼ 42; 76.3%) and fever (n ¼ 29; 52.7%), while aphonia (n ¼ 10; 18.2%), external ophthalmoplegia with seizures and altered consciousness (n ¼ 4, 7.3%) were present in few. None of them had anemia or congenital heart disease.[11]

CONCLUSION

Despite of the above progress in the diagnosis and management of pulmonary arterial hypertension many babies beyond the neonatal period present with vague symptoms and signs where in the etiology remains obscure and uncertain leading to late diagnosis and treatment.

- Though etiology of PAH was unknown all the babies behaved similarly in clinical manifestations.
- Apart from definitive vasodilator therapy, supportive treatment in the form of early ventilation, fluid restriction, diuretic therapy, blood transfusion helped the babies to come of acute crisis of PAH.
- Though pulmonary vasoconstriction is the basic underlying pathology in children with idiopathic PAH, the triggers for vasoconstriction like infections mainly viral, genetic, immunological, environmental, nutritional deficiencies necessitates research.

What is already known

Pulmonary arterial hypertension is a serious progressive condition with a poor prognosis if not identified and treated early. Remarkable progress has been made in the field of pulmonary arterial hypertension over the past several decades pathology is now better defined, and significant advances have occurred in understanding the pathobiologic mechanisms.

What this study adds on

- Apart from definitive vasodilator therapy, supportive treatment in the form of early ventilation, fluid restriction, diuretic therapy, blood transfusion helped the babies to come of acute crisis of PAH.
- Though pulmonary vasoconstriction is the basic underlying pathology in children with idiopathic PAH, the triggers for vasoconstriction like infections mainly viral, genetic, immunological, environmental, nutritional deficiencies necessitates research.

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REFERENCES

1. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension: N Engl J Med. 1992;327:76-81.
2. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin: Ann Intern Med. 1994;121 409-15.
3. Yam S, Wagenvoort CA. Comparison of primary plexogenic arteriopathy in adults and children. A morphometric study in 40 patients: Br Heart J. 1985;54:428-34.
4. Sandoval J, Bauerle O, Gomez A, Palomar A, Martinez Guerra ML, Furuya ME. Primary pulmonary hypertension in children: clinical characterization and survival: J Am Coll Cardiol. 1995;25:466-74.
5. D'Alonzo GE, Barst RJ, Ayres SM. Survival in patients with primary pulmonary hypertension: Results from a national prospective registry. Ann Intern Med. 1991;115:343-49.
6. Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension: a pathological study of the lung vessels in 156 clinically diagnosed cases. Circ. 1970;42:1163-84.
7. Barst RJ. Pharmacologically induced pulmonary vasodilatation in children and young adults with primary pulmonary hypertension. Chest. 1986;89:497-503.
8. Rich S, Brundage BH. High-dose calcium channel blocking therapy for primary pulmonary

hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy: Circ. 1987;76:135-41.
9. Barst RJ, Stalcup SA, Steeg CN, Hall JC, Frosolono MF, Cato AE, et al. Relation of arachidonate metabolites in abnormal control of the pulmonary circulation in a child: Am Rev Respir Dis. 1985;131:171-7.
10. Giaid A, Saleh D. Reduced expression of nitric oxide synthase in the lungs of patients with pulmonary hypertension: N Engl J Med. 1995;333:214-21.
11. Rao SN, Chandak GR. Cardiac beriberi often a missed diagnosis. J Tropical Pediatr. 2010;56(4):2010.

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