Is it Really PPHN? Think Before Starting Sildenafil!

MUNESH TOMAR AND PANKAJ BAJPAI
From the Departments of Pediatric Cardiology and Congenital Heart Diseases, Medanta-The Medicity, Gurgaon, Haryana. India.

Correspondence to:
Dr Munesh Tomar, Senior Consultant, Department of Pediatric Cardiology and Congenital Heart Diseases, Medanta-The Medicity, Gurgaon, Haryana, India.
drmuneshtomar@gmail.com
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The use of sildenafil has become a common practice in neonatal intensive care unit on clinical ground, because opinion by Pediatric Cardiologist is usually not available especially in peripheral centers. We consider it essential to share our experience that severe pulmonary arterial hypertension can be due to some unusual hemodynamics or extremely rare structural causes which do not require pulmonary vasodilator therapy.

Key words: *Echocardiography, PPHN, Pulmonary veins stenosis, Vein of Galen malformation.*

Following is the description of five cases who were already receiving oral sildenafil when they were referred to us.

CASE REPORTS

Case 1: A 35-days-old baby, product of full term normal delivery with Apgar score of 7,9,9 at 1,5 and 10 minutes, discharged on 2nd day of life, developed severe respiratory distress on 3rd postnatal day associated with vomiting and got hospitalized in a peripheral centre. The sepsis screen showed leucocytosis, high C reactive protein (CRP) and positive blood culture. The child was ventilated and started broad spectrum antibiotics. Chest *X*-ray showed no cardiomegaly but there was patchy atelectesis in lung parenchyma. Echocardiography showed severe left ventricle (LV) dysfunction, severe pulmonary arterial hypertension (PAH) with no mention of any septal defect. As there was difficulty in weaning off from ventilator in spite of repeated attempts till 24th day of life and there was progressive increase in cardiomegaly and pulmonary plethora, he was referred to us. We repeated echocardiography that showed very large patent ductus arteriosus (PDA) shunting left to right with large run-off in descending aorta suggestive of large left to right shunt. LV function was normal. His pulmonary vasodilator therapy was stopped and he was subjected to surgical ligation of PDA.

Case 2: A-45-day old female baby was referred to us for evaluation as there was persistence of cyanosis and respiratory distress since birth; and high PA pressure and moderate-sized PDA with bidirectional shunt on echocardiography. On examination, there were features of CHF, PAH and cyanosis (room air oxygen saturation was 80%). Sepsis screen was negative. Chest *X*-ray revealed decreased pulmonary blood flow, normal lung parenchyma and no cardiomegaly. Repeat echocardiography revealed large PDA with right-to-left shunt and severe PAH. Pulmonary veins could not be profiled. Therefore CT pulmonary angiography was done to define pulmonary veins. CT pulmonary angiography revealed streak like all pulmonary veins and large PDA.

Case 3: A-30-day old male baby, product of full term normal delivery with normal APGAR at birth got discharged on 2nd day of life. On 5th day of life, baby developed bluishness and respiratory distress requiring hospitalization. Echocardiography revealed small ASD with right to left shunt and severe PAH. As the condition of the child did not improve and there was continued requirement for oxygen, he was referred to our centre. On examination, there was tachycardia, tachypnea and mild cyanosis (room air saturation 85%). Chest *X*-ray showed dextroposition of heart, cardiomegaly, smaller right lung volume with no definite lung parenchymal lesion. Repeat echo showed small fossa ovalis ASD right to left shunt, mild TR with peak gradient of 98 mmHg (systemic BP = 88 mmHg), no VSD/AP window/PDA and confluent branch pulmonary arteries with LPA grossly dilated measuring 10 mm (expected= 4mm) while RPA being smaller (3.6 mm). Left sided pulmonary veins were normally connecting while right sided pulmonary veins could not be profiled. CT pulmonary angiography revealed right pulmonary veins very thin in calibre becoming atretic before joining left atrium.

Case 4 and 5: Two full term neonates with normal APGAR at birth, 20 days and 28 days, old respectively were referred to us for persistence of signs of PAH, CHF and oxygen dependency. Chest *X*-ray showed cardiomegaly, pulmonary plethora but no lung parenchymal lesion. Echocardiography revealed moderate tricuspid regurgitation with peak gradient of 70 mmHg, PFO right to left shunt, dilated right atrium and right ventricle with no structural heart defect. Ultrasound head revealed large vein of Galen malformation which

was confirmed on CT head. Vein of Galen malformation is one of the rare form of arteriovenous malformation which can lead to features of CHF even during fetal life.

DISCUSSION

Etiology of pulmonary arterial hypertension in pediatric patients is multifactorial [1]. Persistent pulmonary hypertension (PPHN) in term or near-term infants is reported to vary between 0.43 and 6.8 of 1000 live births [2]. The treatment for PPHN has evolved over the past few years considerably which has reduced its morbidity significantly.

The pulmonary vascular resistance is often increased in sepsis, especially in the presence of acute lung injury. Contributing factors are decreased production of nitric oxide (an endogenous vasodilator) and increased levels in circulating vasoactive substances, such as thromboxane and endothelin. Serotonin contribute to increased pulmonary vascular resistance (PVR) and pulmonary hypertension in sepsis [3-5]. Acute lung injury leads to hypoxic pulmonary vasoconstriction, and this pulmonary pressor response is enhanced by hypercarbia or acidosis. *Case* 1 was an example of increased PVR secondary to sepsis and leading to bidirectional flow across PDA thus giving false impression of PPHN. Sildenafil worsened the situation by inducing CHF in an underlying condition of large PDA as soon as the sepsis got better. Explanation for LV dysfunction in the earlier echo cardiography report could be due to sepsis and PDA might have been missed probably due to right to left shunt resulting from very high PVR. Here hemodynamic implication of large PDA in the setting of sepsis was important to understand.

Pulmonary vein atresia is a rare congenital abnormality resulting from failure of incorporation of the common pulmonary vein into the left atrium [6]. It can involve either lung, and usually presents in infants [7,8]. Pulmonary artery hypertension is a frequent association [9]. Congenital stenosis or atresia of pulmonary veins (Case 2 and 3) are not the conditions where pulmonary vasodilator therapy works due to obvious reasons.

The majority of cases of vein of Galen malformation (94%) are diagnosed in the neonatal period and present with high-output cardiac failure. Severe pulmonary hypertension is a complicating factor [10]. In the past, the mortality rate for this group was close to 100%. Recent advances made in the management of these patients, particularly by the use of endovascular techniques have significantly altered the prognosis [10]. We do USG cranium in all neonates in whom CHF and PAH are unexplained as in the case 4 and 5. Sildenafil will not work in such a situation until the root cause of PAH is addressed.

We conclude, that in clinical suspicion of PPHN, common causes such as pneumonia and septal defects should be excluded. Unnecessary use of pulmonary vasodilators will do more harm than any benefit if given in such conditions.

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