

MALIGNANT PERSISTENT PULMONARY HYPERTENSION IN NEONATES

Abstract

Persistent Pulmonary Hypertension is a crucial condition requiring emergency intervention. Birth is a phase of transition from fetal to neonatal life. Fetal respiration occurs through the placenta. Gaseous Transition occurs from maternal to fetal through the passive ionic movement in the placenta. After birth gaseous transfer occurs through the lung with decreased pulmonary vascular resistance and increased pulmonary blood flow. Vasoconstriction can cause hypoxia in neonates. Hypoxia can be due to vascular resistance that progressively decreases during the first few weeks of life. The other abnormalities include abnormal pulmonary hypoplasia, meconium aspiration syndrome (MAS), respiratory distress syndrome (RDS), Congenital Diaphragmatic Hernia, etc. Circulatory transition during birth can lead to persistent pulmonary hypertension. This chapter explains persistent pulmonary hypertension with two case presentations.

Keywords: Epidemiology, Diagnosis, Hypertension

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I. EPIDEMIOLOGY

Persistent pulmonary Hypertension is 1.8 per 1000 live births. Late preterm birth incidence is 5.4% while in full-term birth the incidence is 1.6 per 1000 live birth.¹ Mortality rate is 7.6% to 10.7 %. Males have a higher prediction when compared to female births.^{2,3} with a risk ratio of 0.8. There is higher incidence in African and American births when compared to Asian races.

1. **Classification:** Persistent pulmonary can be classified into three types

- Abnormal adaptation leading to vascular resistance due to lung parenchymal disorders due to meconium aspiration syndrome
- Underdeveloped vasculature: decreased pulmonary vasculature as seen in small for gestational age or oligohydramnios
- Idiopathic persistent pulmonary hypertension in the newborn, likely due to excessive pulmonary vascular smooth muscle thickness

Increased vascular resistance can lead to decreased blood flow. Pulmonary vascular resistance can lead to ventilation and perfusion mismatch leading to right to left shunting of blood, due to PDA (patent ductus arteriosus) or PFO (patent foramen ovale) causing hypoxemia. Extra cardiac shunting can cause the primary reason for hypoxia. Prolonged hypoxia can lead to respiratory acidosis. Persistent pulmonary hypertension when caused by meconium aspiration syndrome can lead to sepsis leading to dyspnea, hypoxia refractory hypotension, multiorgan failure, and bleeding tendency due to disseminated intravascular coagulopathy. (DIC) Neonates from ages zero to a month can develop coagulopathy which is developmental coagulopathy. Developmental coagulopathy can lead to DIC, due to frequent microthrombus formation and altered hemostasis there can bleed tendencies in a neonate.⁴

II. DIAGNOSIS AND TREATMENT

Diagnosis of pediatric pulmonary hypertension is above 20mm/hg pulmonary arterial blood pressure. The saturation levels in the blood are to be monitored with blood gas analysis. Hypoxia to be prevented with sufficient oxygen therapy. The diagnosis can be made with chest PA view x-ray, ECG, CT scans and 3D Echo to study the effect of pulmonary overload. Mechanical ventilation and ECMO support if there is obstruction suspected.

- ### 1. **Causes:** Persistent pulmonary hypertension is caused by various perinatal and antenatal reasons. Abnormal lung parenchymal development, Meconium aspiration syndrome, respiratory distress syndrome, and sepsis contribute to persistent pulmonary hypertension. Patent ductus arteriosus, patent foramen ovale can also lead to abnormal shunting of blood leading to increased pulmonary pressure. Oligohydramnios, gestational diabetes, SGA, Obesity, preeclampsia, excessive NSAID intake during gestation, selective serotonin inhibitor intake, maternal alcohol intake, maternal smoking, and congenital diaphragmatic hernia can lead to persistent pulmonary hypertension.

III. CASE PRESENTATION I

A full-term neonate was delivered to a mother aged 40 years with a birth weight of 2.05 kg, the male neonate was born to consanguineous parents, primigravida, IVF conception. The blood group of the mother was B positive, and the neonate was O positive. Antenatal history revealed mother had pregnancy-induced hypertension. The mother also history of hypothyroidism and was on T. Thyronorm. The neonate was delivered by emergency LSCS due to oligohyraminos. The baby cried at birth. He developed respiratory distress within a few hours after birth and was admitted to NICU.

1. History and Physical Examination: Infants born with difficulty in breathing are perinatally admitted at NICU to be examined for oxygen saturation, and meconial aspiration. Antenatal history was crucial to know about pregnancy-induced hypertension, Gestational diabetes mellitus, etc. Perinatal history reveals aspiration of meconium aspiration. There was respiratory distress observed immediately, the neonate was shifted to Neonatal Intensive Care Unit for respiratory support.

Birth weight was 2.05kg. Neonate had retractions, tachypnoea and grunting. On physical examination right thumb syndactyl was present and the left undecended testis was present palpable at the left inguinal region.

The baby was started on oxygen support, and blood gas analysis showed mild respiratory acidosis. Chest x-ray appeared normal. Their respiratory distress was worsening requiring C-PAP with higher oxygen flow, baby was intubated and connected to a ventilator/SIMV (synchronized intermittent mandatory ventilation) Mode. The baby was started on pulmonary vasodilator inj.Sildenafil. Pulmonary arterial pressure increased. After 48 hours the baby showed improvement with spontaneous breathing. The baby was extubated and then placed on C-PAP on day 3. After 72 hours of intubation blood culture was done. The blood culture showed no growth. The ultrasound abdomen was normal.

The baby was on nasal oxygen up to 6 days with gradual withdrawal of oxygen and spontaneous breathing. The baby was maintaining normal saturation with nasal oxygen. On day 6 nasal oxygen was withdrawn when spontaneous respiration was present with normal oxygen concentration. Initial Echocardiogram revealed moderate Patent foramen ovale and large patent ductus arteriosus. The interventricular septum was observed intact. Moderate mitral regurgitation and moderate tricuspid regurgitation were observed. The aortic valve and pulmonary valve appeared normal there was no abnormality in the arch of the aorta and pulmonary artery. Severe persistent pulmonary arterial pressure. No coarctation was observed. The ejection fraction was 60%. Situs solitus levocardia. Haemogram showed reduced platelet count, raised MCH, and MCV. On the 5th day, the serum bilirubin was observed to be high. Serum indirect bilirubin was 12.5mg/dl (normal range 0-0.2mg/dl). Direct bilirubin was 1mg/dl. Serum indirect bilirubin gradually increased to 14.9mg/dl with decreasing serum potassium and increase in chloride concentration. Total serum protein, albumin and globulin ratio also was decreased. Upper GI bleeding was observed

On the 6th day of life, the neonate. The aspirated meconium was removed and was started on Injection.Piptaz and injection Amikacin, Inj.Ciproflaxacin, Inj.Meropenam.The baby was febrile with signs of sepsis. C-reactive protein was 22mg/L (normal ranges from 0.1-6mg.L). The platelet count was 94,000. There was an increase in prothrombin time and partial thromboplastin time (APPT) 39.2 seconds (while normal ranges from 22-37 seconds) while control APPT was 28 seconds. serum electrolytes were within normal limits. Blood urea was 20mg/dl and creatinine was 0.4mg.

IV. CASE PRESENTATION 2

The case study has been presented as a detailed report after getting prior consent from the parents.

The neonate was born to non consanguineous parents. Maternal age 30 years with a history of gestational diabetes was brought to the emergency with dyspnea. The baby was delivered by normal vaginal delivery in the ambulance on the way to the hospital. The umbilical cord was temporarily clamped with a glove tied around the cord.APGAR score not available. Previous investigations revealed the ultrasound investigation was normal and down's score was 3/10. The baby was presented with tachypnea. The umbilical cord was clamped and removed after reaching the hospital with a time interval of 15 to 17 minutes after the delivery. The baby has severe tachypnea, hypoxia, and reduced blood Ph. Inj.Vitamin K 1 mg was given intramuscularly. There was no significant congenital anomaly detected. The baby was on continuous positive airway pressure (CPAP) with the partial pressure of O₂ 21%, CPAP –5, later 2L/min oxygen was given. Blood culture was done using aerobic bacterial method and no growth was observed after 48 hours of incubation. C reactive protein was tested negative. The baby had normal 2D echo findings and blood parameters. Serum total bilirubin was 4.4 mg/dl, while direct bilirubin was normal. Hypocalcemia was noted. 7.5mg/dl. ABG revealed hypercapnia and Ph was 7.314. evident hypoxia was noted. Metabolites levels such as serum lactose 3.6mmol/L and decreased level of glucose 66mg/dl. Oxygen saturation was 81.2%. Blood culture also appeared normal. Serum thyroxine appeared normal. Serum calcium levels were monitored, and oxygen therapy was given for the next 48 hours. Saturation levels improved after 48 hours. The baby was reviewed for 3 years.

V. DISCUSSION

Persistent pulmonary arterial hypertension during the perinatal period increases the intraventricular pressure leading to right ventricular failure. Ventricular ability to pump blood reduces in septic cases. Increased vascular resistant leads to pulmonary hypertension. During parturition, there are sequences of hormonal changes that take place. absorption of pulmonary alveolar fluid prepares the alveolus for gaseous transition. The initial gaseous movements occur with increased vascular resistance within the lung while the pulmonary pressure is maintained normal when the pulmonary vascular resistance gradually decreases. In case 1 the neonate developed persistent pulmonary hypertension due to meconium aspiration syndrome. The neonate had PFO and PDA which were also factors for increased vascular resistance. During birth when gaseous transition occurs in the lung for the first time instead of placental villous gaseous transfer. There was right to left shunt of blood causing increased pulmonary hypertension. Most of the blood from the right ventricle crosses the ductus arteriosus. 13 –

21% of the blood perfuses through the lung with high vascular resistance⁵. Meconium aspiration syndrome also can lead to pneumonitis. There are 10 –15 % of the neonates pass meconium. 6.75% of the term neonates can be affected by meconium aspiration syndrome. Passing meconium by premature infants may cause serious changes. There may be decreased surfactant release or surfactant activation. There can be the release of inflammatory cytokinins, leading to vascular resistance. Airway obstruction due to meconium aspiration, chemical pneumonitis, persistent pulmonary hypertension etc. Hyperinflation of the lungs can be diagnosed with a chest X ray. Routine suction of the aspirates was meconium-stained amniotic fluid. Mechanical ventilation was preferred to prevent hypoxia. Nasal Oxygen therapy is given. Mechanical factors such as fluid-filled lungs, vasoconstriction due to inflammatory cytokinin, circulating endothelin –1, and prostaglandin levels may cause pulmonary vascular resistance, vascular remodeling also may contribute to the change.⁵ Sildenafil along with glucocorticoids are preferred therapy to induce vasodilatation. Persistent pulmonary hypertension occurs in 2 of 1000 live births but significantly contributes to the mortality rate of the neonate.⁸ After delivery there are sequential changes that happen leading to rapid PVR decrease leading to an 8-10-fold increase in the pulmonary blood flow. Determinant for the gaseous exchange during birth, Alveolus filled with fluid increases the pulmonary vascular resistance creating high extraluminal pressure. Alveolar luminal epithelial cell maturation, and pulmonary artery smooth muscle expansion enable a successful transition from placental respiration to lung ventilation. After delivery PVR declines due to exposure to atmospheric oxygen. The onset of breathing is the greatest stimulant for vasodilation, and alveolar expansion. Vasodilators are produced causing vasodilatation in the smooth muscle wall of the pulmonary artery, where expansion of the pulmonary vasculature occurs.⁹ In case scenario 2, pulmonary vascular resistance occurs due to mechanical factors like delayed umbilical cord clamping. NVD induced a series of hormonal changes that occur while giving birth. Clamping of the umbilical cord after cessation of the umbilical pulse is a crucial factor. There is a rapid decrease in arterial and venous pulse pressure ratio. This pressure gradient is affected during delayed cord clamping resulting in increased pulmonary vascular resistance. Right to left shunting of blood occurs due to patent foramen ovale and patent ductus arteriosus.¹⁰

VI. CONCLUSION

Neonatal persistent pulmonary hypertension occurs due to various causes. Case scenario 1 represented persistent pulmonary hypertension induced by meconium aspiration syndrome. Oligohydramnios antenatally was an added factor. Hypoxia is due to pulmonary vascular resistance. While in Case Presentation 2 persistent pulmonary hypertension was due to delay and improper umbilical cord clamping. Lack of facilities in the ambulance led to the delayed clamping causing an increase in pulmonary arterial pressure. Though there are various treatment modalities followed by the treatment regime iNO is widely preferred and accepted by FDA for pediatric use. Many Cohort studies are required to develop a treatment therapy for persistent pulmonary hypertension, Pulmonary hypertension is a crucial area for future pediatric research.

VII. SUMMARY

1. Persistent pulmonary hypertension can occur due to various reasons involving developmental anomalies of lung. Diagnosis needs to be done with an echocardiogram and 3D echocardiography.
2. Premature birth, bronchopulmonary dysplasia can cause pulmonary hypertension
3. Lung hypoplasia, congenital diaphragmatic hernia, and alveolar capillary dysplasia can also be reasons for pulmonary hypertension.
4. Congenital heart disease can also be a primary reason for persistent pulmonary hypertension.
5. Early diagnosis and intervention can reduce mortality among the affected neonates.
6. Supportive therapy through oxygen therapy, mechanical ventilation, and ECHO has been used as a treatment for persistent pulmonary hypertension.
7. Vasodilatation along with a definite drug regime is to be developed with future randomized control trials.

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