Malignant Persistent Pulmonary Hypertension in Neonates

Julie Christy Amalraj,1 Sumathy G2

1. Julie Christy Amalraj,

PhD Scholar, Bharath Institute of Higher Education, Seliyur, Tambaram Chennai

1. Sumathy G

Guide , Professor and HOD, Balaji Dental College , BIHER, Chennai

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 neonate. Hypoxia can be due to vascular resistance that progressively decreases during the first few weeks of life. The other abnormalities include the 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.

**Etiology**

Persistent pulmonary hypertension is caused by various perinatal and antenatal reasons. Abnormal lung parenchymal development, Meconium aspiration syndrome, respiratory distress syndrome, sepsis that contribute to the 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 serotonine inhibitor intake, maternal alcohol intake, maternal smoking, congenital diaphragmatic hernia can lead to persistent pulmonary hypertension.

**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 %. Male as a higher predication when compared to female births.2,3 with a risk ratio of 0.8. There is higher incidence African and American births when compared to Asian races.

**Classification**

Persistent pulmonary can be classification in to three types

1. Abnormal adaptation leading to vascular resistance due to lung parenchymal disorders due to meconium aspiration syndrome
2. Underdeveloped vasculature: decreased pulmonary vasculature as seen in small for gestational age or oligohydramnios
3. 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 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 with age zero to a month can develop coagulopathy which is developmental coagulopathy. Developmental coagulopathy can lead to DIC, due to frequent microthrombus formation and altered haemostasias there can bleeding tendencies in a neonate.4

Case Presentation

A full-term neonate was delivered to a mother aged 40 years with a birth weight 2.05 kg, the male neonate was born to a consangious parents, primigravida, IVF conception. Blood group of the mother was B positive, and the neonate was O positive. Antenatal history reveals mother has pregnancy induced hypertension. Mother also had a history of hypothyroidism and was on thyronorm. The neonate was delivered by emergency LSCS (oligohyraminos). Baby cried at birth. He developed respiratory distress within few hours of birth and was admitted in NICU.

History and physical examination

Infants born with difficulty in breathing perinatally admitted at NICU to be examined for oxygen saturation, meconial aspiration. Antenatal history is crucial to know about pregnancy induced hypertension, GDM etc. Perinatal history reveals aspiration of meconium aspiration.There was respiratory distress observed immediately the neonate was shifted to NICU for respiratory support.

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

The baby was started on oxygen support, blood gas analysis showed mild respiratory acidosis. Chest x ray appeared normal. There respiratory distress was worsening requiring C-PAP with higher oxygen flow, baby was intubated and connected to a ventilator/SIMVMode.baby was started on pulmonary vasodilator inj.sildenafil. There increased pulmonary arterial pressure. After 48 hours the baby showed improvement with spontaneous breathing. The extubated and then were placed on C-PAP on day 3. After 72 hours of intubation blood culture showed no growth. The ultrasound abdomen was normal.

The baby was on nasal oxygen upto 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 spontaneoud respiration was present with normal oxygen concentration. Initital Echocadiogram done revealed moderate Patent foramen ovale and large patent ductus arteriosus. Interventricular septum was observed intact. Moderate mitral regurgitation and moderate tricuspid regurgitation observed. Aortic valve and pulmonary valve appeared normal there was no abnormality in the arch of aorta and pulmonary artery. Severe persistent pulmonary arterial pressure. No coractation observed. Ejection fraction was 60%. Situs solitus levocardia.Haemogram showed reduced platelet count, raised MCH, MCV.On the 5th dat the seum 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 bilirubnin 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 were 0.4mg.

**Case presentation 2**

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

A 30-year-old mother with Gestational Diabetes mellitus delivered a boy baby in the ambulance on the way to the hospital. It was a normal vaginal delivery. Neonate cried after birth but the clamping of the umbilical cord was delayed. APGAR score was not available. Down’ s score was 3/10. The baby had severe tachypnea. The umbilical cord was clamped with an elastic rope and cut after reaching the hospital with a time interval of 15–17 min. The baby presented with severe tachypnea, hypoxia, and reduced blood Ph. Inj Vitamin K 1 mg was given intramuscularly. There was no significant congenital anomaly noted, baby was on continuous positive airway pressure (CPAP) with partial pressure of O2 21%, CPAP-5, later 2L/min was given. Blood culture was done using an aerobic bacterial method, no growth was observed after 48 h of incubation. C-reactive protein was also tested negative. The baby was investigated with 2D echo and other blood parameters were evaluated for abnormalities. There was elevated total bilirubin 4.4 mg/dl, while direct bilirubin was normal. Hypocalcemia was noted 7.5 mg/dl. Blood gas analysis revealed reduced Ph 7.314 (slightly acidic) evident hypoxia was noted 42.5 mm/hg. No hypercapnia was noted. Blood electrolyte analysis is done. Hyperkalemia 5.5 mmol/hypernatremia 123 mmol/L, and hypocalcemia 0.88mmol/L (ionized calcium) increased chloride levels. Metabolite levels showed an increase. Increased serum lactose 3.6 mmol/L and decreased glucose level 66 mg/dl ABG analysis revealed reduced O2 saturation 81.2% partial O2 which was 104.6 mm/Hg, and P O2 (a/A)e 40.6% Ph 7.322. C-reactive protein was noted to be reactive. Complete blood count was normal. There were no hemi parasites seen. 2D Echo clearly showed tricuspid regurgitation with pulmonary pressure up to 73 mm/Hg. The baby was administered 2 L/min O2 repeat 2D echo after 6 days revealed pulmonary pressure to be 26 mm/Hg. The serum T4 and thyroid stimulating hormone was normal in repeated evaluation on the 4th and 6th day after birth. There was a reduced ionized calcium level of 0.9 mmol/L. The baby was discharged after giving O2 therapy and reviewed for 3 years. There were no significant breathing difficulties

**Discussion**

Persistent pulmonary arterial hypertension during 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 sequence of hormonal changes that take place.absorption of pulmonary alveolar fluid prepares the alveolus for gaseous transition. The intitial gaseous moevements occur with incrased vascular resistance within the lund while the pulmonary pressure is maintained normal when the pulomnary vascular resistance gradually decreases. In case 1 presented the neonate developed persistent pulmonary hypertension due to meaconium 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 release of inflammatory cytokinins, leading to vascular resistance. Airway obstruction due to meconial aspiration, chemical pneumonitis, persistent pulmonary hypertension etc. Hyperinflation of lungs can be diagnosed with 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, 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 8-10-fold increase in the pulmonary blood flow. Determinant for the gaseous exchange during birth, Alveolus filled with fluid increases the pumonary vascular resistance creating high extraluminal pressure. Alveolar luminal epithelial cell maturation, pulmonary artery smooth muscle expansion enables 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, alveolar expansion. Vasodilators are produced causing vasodilatation in the smooth muscle wall of pulmonary artery, there by expansion of the pulmonary vasculature occurs.9 In case scenario 2, pulmonary vascular resistance occurs due to mechanical factors like delayed umbilical cord clamping. In normal vaginal delivery, the hormonal sequence of events occurring at parturition leads to timely clamping of the umbilical cord after cessation of umbilical cord pulse. There is a rapid decrease in theratio of the pulmonary artery and aorta pressure. This ratio is altered with delay in the cord clamping resulting in increased pulmonaryvascular resistance left ventricular blood flow increases defective. right to left shunt through foramen ovale.10 The case presentation shows that normal vaginal delivery in the ambulance without proper expertise and instrumentation leading to the delayed clamping of the umbilical cord. The umbilical cord was clamped after 15–17 min after delivery after reaching the hospital. The neonate developed hypoxia, malignant tachypnea. There was a reduced oxygen saturation of 81.2% partial Oxygen.

Reference

1. Steurer MA, Baer RJ, Oltman S, Ryckman KK, Feuer SK, Rogers E, Keller RL, Jelliffe-Pawlowski LL. Morbidity of Persistent Pulmonary Hypertension of the Newborn in the First Year of Life. J Pediatr. 2019 Oct; 213:58-65. e4
2. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, Verter J, Stoll BJ, Lemons JA, Papile LA, Shankaran S, Donovan EF, Oh W, Ehrenkranz RA, Fanaroff AA. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. Pediatrics. 2000 Jan;105(1 Pt 1):14-20. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/10617698)]
3. Steurer MA, Jelliffe-Pawlowski LL, Baer RJ, Partridge JC, Rogers EE, Keller RL. Persistent Pulmonary Hypertension of the Newborn in Late Preterm and Term Infants in California. Pediatrics. 2017 Jan;139(1)
4. Bendapudi P, Rao GG, Greenough A. Diagnosis and management of persistent pulmonary hypertension of the newborn. Paediatr Respir Rev. 2015 Jun;16(3):157-61. [[PubMed](https://pubmed.ncbi.nlm.nih.gov/25765845)] [[Reference list](https://www.ncbi.nlm.nih.gov/books/NBK585100/#article-121195.r15)]
5. Lakshminrusimha S, Keszler M. Persistent Pulmonary Hypertension of the Newborn. Neoreviews. 2015 Dec;16(12):e680-e692. doi: 10.1542/neo.16-12-e680. PMID: 26783388; PMCID: PMC4714607.
6. [El Shahed AI, Dargaville PA, Ohlsson A, Soll R](http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD002054.pub3/pdf): Surfactant for meconium aspiration syndrome in term and late preterm infants. *Cochrane Database Syst Rev* 12(CD002054):1–36, 2014. doi: 10.1002/14651858.CD002054.pub3
7. [Natarajan CK, Sankar MJ, Jain K, et al](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4848739/): Surfactant therapy and antibiotics in neonates with meconium aspiration syndrome: A systematic review and meta-analysis. *J Perinatol* 36(Suppl 1):S49–S54, 2016. doi: 10.1038/jp.2016.32
8. Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al.. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. *Pediatrics.* (2000) 105:14–20. 10.1542/peds.105.1.14
9. Martinho S, Adão R, Leite-Moreira AF, Brás-Silva C. Persistent Pulmonary Hypertension of the Newborn: Pathophysiological Mechanisms and Novel Therapeutic Approaches. Front Pediatr. 2020 Jul 24;8:342. doi: 10.3389/fped.2020.00342. PMID: 32850518; PMCID: PMC7396717.
10. Meenakshi m, julie christy a, malignant persistent pulmonary hypertension – A case report. 15, (5) 2022 DOI: <http://dx.doi.org/10.22159/ajpcr.2022v15i5.44260>
11. Tartavoulle TM. Management of Sepsis in Patients with Pulmonary Arterial Hypertension in the Intensive Care Unit. Crit Care Nurs Clin North Am. 2017 Mar;29(1):15-23. doi: 10.1016/j.cnc.2016.09.003. Epub 2016 Nov 15. PMID: 28160954.