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Case Report

Interferon alpha: A rare cause of persistent pulmonary hypertension of newborn

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Introduction

Persistent pulmonary hypertension of newborn (PPHN) is a relatively common disease of full term and post term infants¹ with an incidence of 1–2 per 1000 live births. PPHN mimics foetal circulation as these infants continue to have supra-systemic pulmonary arterial pressures with right to left shunting of blood. Till now few etiological agents have been defined like birth asphyxia, meconium aspiration syndromes, respiratory distress syndrome and delivery by caesarean section. Few drugs like selective serotonin reuptake inhibitors (SSRIs), non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin consumed during pregnancy² have resulted in PPHN. However, we are presenting a rare case of Persistent pulmonary hypertension of the newborn caused by administration of interferon alpha during pregnancy. Diagnosis of such cases is important for timely treatment to prevent various complica-

tions like chronic pulmonary disease, neurodevelopment disabilities, hearing impairment and brain injury among the survivors.

Case report

Male baby, born at term by elective LSCS with birth weight of 3500 g, presented with central cyanosis on day 2 of life. Baby was born to 28-years-old booked, second gravida who was a diagnosed case of chronic myeloid leukaemia on interferon alpha therapy. Mother was taking 10 million IU of interferon alpha subcutaneously thrice weekly. There was no history of oligohydramnios or polyhydramnios, gestational diabetes mellitus, pregnancy induced hypertension, premature rupture of membranes, urinary tract infection, and prolonged fever during pregnancy. There was no history of prolonged labour, meconium stained liquor or foetal distress. Baby cried at birth with normal Apgar score. His Vitals on day one – HR-140/min, RR-42/min, CFT-<2 s, SpO₂-94–96% at room air. There was no cyanosis or respiratory distress at birth or on day one. Sucking reflex was good and baby was put to breast feeding, but there was inadequate Lactation on day one. However, baby developed cyanosis on day 2 of life. Clinical examination revealed presence of central cyanosis, parched skin, heart rate – 130/min, respiratory rate – 40/min, capillary refill time < 2 s, Mean arterial pressure 45 mm Hg and Downe's score – 2/10. His peripheries were warm, all peripheral pulses well felt. Preductal SpO₂ at room air was 88–90% and postductal SpO₂ at room air was 82–84%. There was no lethargy, frothing/excessive salivation, no evidence of poor feeding, no dysmorphism and no obvious congenital anomaly. Fontanelles

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Table 1 – ABG values on admission.

Preductal ABG on admission	Postductal ABG on admission
pH – 7.32	pH – 7.364
PO ₂ – 68.6 mmHg	PO ₂ – 24.7 mmHg
PCO ₂ – 45.9 mmHg	PCO ₂ – 54.2 mmHg
HCO ₃ – 27.2 mmol/l	HCO ₃ – 29.9 mmol/l
BE – 2.3 mmol/l	BE – 3.4 mmol/l

were not bulging. There was no evidence of choanal atresia as nasogastric tube was readily inserted. Sucking/swallowing reflex was present. Systemic examination was essentially normal. Laboratory tests found haemoglobin count of 18.4 g %, PCV of 54%, WBC count of 7300/cm, platelet count 218,906/cumm. All markers of sepsis were negative. Blood culture was sterile. Serum electrolytes and blood sugar levels were within normal limits. Radiograph chest and abdomen did not reveal any abnormality. However when subjected to hyperoxia test, baby did not pass the test. Following this, echocardiography was done which suggested the presence of dilated right ventricle, dilated right atrium with mild tricuspid regurgitation with no structural abnormality. ABG done on admission suggested the presence of PO₂ gradient > 40 mmHg between preductal and postductal blood samples (Table 1). In view of central cyanosis and increased PO₂ gradient of more than 40 mmHg between preductal and postductal ABG samples and absence of structural heart disease, a diagnosis of Persistent pulmonary hypertension of the newborn (PPHN) was made.

Management: Case was managed on the principle of care bundle approach. The only available vasodilators for treating PPHN at this hospital were oxygen and phosphodiesterase inhibitor 5 (Sildenafil). Liberal oxygen therapy was given under oxygen hood @ 5–7 l/min initially. Sildenafil was given @ 1 mg/kg/day. Patient started improving on therapy. Subsequently the PO₂ gradient reduced to normal and cyanosis disappeared within three weeks (Table 2). Repeat echocardiography showed resolution of tricuspid regurgitation with no dilatation of right atrium or ventricle. Patient was discharged on day 30th of life with discharge weight of 4.2 kg, head circumference of 34 cm and length of 52 cm. He was accepting feeds well. Immunisation was completed on OPD basis during follow up visits.

Discussion

PPHN physiology mimics foetal circulation in which pulmonary vascular resistance (PVR) exceeds systemic vascular resistance (SVR). After birth, pulmonary vascular resistance normally declines. However, neonatal PVR may be increased due to various maladaptive changes that results in profound hypoxaemia from right-to-left shunting with normal to elevated PaCO₂.³ PPHN should be routinely considered in evaluating the cyanotic newborn. A gradient of ≥10% in oxygen saturation between simultaneous preductal (taken from right upper limb) and postductal (lower limb) ABG values or SpO₂ values should suggest a diagnosis of PPHN in the absence of

Table 2 – ABG values during hospitalisation.

Date	Preductal ABG	Postductal ABG
1/8/14	pH – 7.46 PO ₂ gradient = 30 mmHg PO ₂ – 47 mmHg PCO ₂ – 37.9 mmHg	pH – 7.38 PO ₂ – 17 mmHg PCO ₂ – 53.5 mmHg
14/8/14	pH – 7.40 PO ₂ gradient = 25 mmHg PO ₂ – 65 mmHg PCO ₂ – 35 mmHg	pH – 7.33 PO ₂ – 40.5 mmHg PCO ₂ – 45 mmHg
20/8/14	pH – 7.42 PO ₂ gradient = 15 mmHg PO ₂ – 75 mmHg PCO ₂ – 40 mmHg	pH – 7.40 PO ₂ – 60 mmHg PCO ₂ – 50 mmHg

any congenital heart disease. Hence, SpO₂ should be checked routinely in both upper and lower limb in case of cyanotic newborn or even otherwise to avoid missing out on diagnosis of conditions like PPHN. Established perinatal risk factors causing PPHN include intrauterine or perinatal asphyxia, pulmonary parenchymal diseases, meconium aspiration syndrome, congenital diaphragmatic hernia, congenital heart disease, birth by LSCS and drugs used in pregnancy like selective serotonin reuptake inhibitors (SSRIs), aspirin, and non-steroidal anti-inflammatory drugs.

However, interferon alpha is less studied drug known to be associated with pulmonary hypertension in adults on prolonged usage. Prolonged use of interferon alpha during pregnancy is one of the rarer causes of PPHN. The interferons are complex proteins produced by activated macrophages and lymphocytes which are commonly used to treat malignant conditions like chronic myelogenous leukaemia (CML), multiple myeloma, and renal cell carcinoma and chronic infections like hepatitis C. For treating malignancy a relatively higher dose of IFNα is required. Typical dosages range from 10 to 20 million units/day for 12–18 months.⁴

Various authors in their studies have found interferon alpha as causative agent for various respiratory side effects in adults like exacerbation of asthma,⁵ pleural effusion,⁶ bronchiolitis obliterans-organising pneumonia,⁷ pulmonary fibrosis and reversible pulmonary hypertension.^{8,9} Hanaoka et al. in their study on animals have also implicated interferon alpha as a cause of pulmonary hypertension.¹⁰

Conclusion

PPHN is known to occur due to certain drugs like SSRI and NSAIDs during pregnancy. Studies have shown that IFN alpha on prolonged use in adults as a part of treatment of chronic myeloid leukaemia and Hepatitis C has caused pulmonary fibrosis and pulmonary hypertension. However, it may lead to similar changes in foetus when used in pregnancy in high doses for prolonged duration as happened in this case. However further research needs to be done on this subject.

Conflicts of interest

The authors have none to declare.

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