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Beyond the Lungs: Rare Causes of Persistent Pulmonary Hypertension of the Newborn – A Three-Case Series

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Abstract

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a serious and potentially life-threatening condition, characterized by elevated pulmonary vascular resistance leading to right-to-left shunting and hypoxemia. It is typically associated with common neonatal pathologies such as meconium aspiration syndrome, perinatal asphyxia, or sepsis. However, a subset of neonates present with refractory PPHN that does not respond to conventional treatment, prompting a deeper evaluation for less obvious underlying causes. These rare etiologies, though infrequent, carry significant diagnostic and therapeutic implications and may easily be missed without a high index of clinical suspicion.

In this case series, we present three neonates diagnosed with PPHN secondary to uncommon underlying conditions. The first case involves a vein of Galen malformation—a high-flow cerebral arteriovenous anomaly causing high-output cardiac failure and severe pulmonary hypertension, detected antenatally but clinically evident postnatally. The second case describes a neonate with an antenatally undiagnosed congenital diaphragmatic hernia (CDH), manifesting as severe PPHN due to pulmonary hypoplasia and compromised lung perfusion. The third case highlights a nutritional etiology: thiamine deficiency (Shoshin beriberi) in a breastfed neonate, resulting in myocardial dysfunction, shock, and PPHN, with dramatic improvement following parenteral thiamine administration. Each case outlines a distinct pathophysiological mechanism converging on the same clinical presentation—refractory pulmonary hypertension in the newborn.

These cases illustrate the importance of considering vascular, anatomical, and metabolic causes when evaluating neonates with unexplained or treatment-resistant PPHN. Early neuroimaging,
targeted echocardiography, and metabolic workup can facilitate timely diagnosis and appropriate intervention. A broadened diagnostic approach can be life-saving in such scenarios and is essential for optimizing outcomes in neonatal intensive care settings. This series aims to raise awareness among neonatologists and pediatricians about these atypical yet clinically significant contributors to PPHN.

Keywords: Persistent Pulmonary Hypertension of the Newborn (PPHN), Vein of Galen Malformation, Congenital Diaphragmatic Hernia, Shoshin Beriberi, Thiamine Deficiency, Neonatal Cardiac Failure, Refractory PPHN

Introduction

Persistent Pulmonary Hypertension of the Newborn (PPHN) is a serious cardiopulmonary condition that arises due to the failure of pulmonary vascular resistance to fall after birth. This sustained elevation in

pulmonary pressure leads to right-to-left shunting through the foramen ovale or ductus arteriosus, resulting in significant hypoxemia. Commonly, PPHN is associated with underlying pulmonary conditions such as meconium aspiration syndrome, respiratory distress syndrome, pneumonia, or sepsis. These causes are well documented and generally respond to standard therapies including oxygen supplementation, mechanical ventilation, and pulmonary vasodilators.

However, in a subset of neonates, PPHN persists despite appropriate conventional management, suggesting an underlying atypical etiology. In such cases, the diagnosis can be easily missed if clinical evaluation remains limited to respiratory or infectious causes. Identifying rare systemic, vascular, or metabolic contributors is critical, as early recognition and targeted treatment can significantly improve outcomes and prevent complications from prolonged hypoxia or misdirected therapy.

In this case series, we describe three neonates presenting with severe PPHN secondary to rare causes: a Vein of Galen malformation leading to high-output cardiac failure; a congenital diaphragmatic hernia compromising lung development and vascular transition; and a case of thiamine deficiency (Shoshin beriberi), manifesting with cardiac dysfunction and shock. These cases represent distinct but clinically important contributors to PPHN, and through their discussion, we aim to emphasize the importance of a broadened diagnostic approach when managing neonates with unexplained or refractory pulmonary hypertension.

Case Reports

Case 1: Vein of Galen Malformation Presenting as PPHN

Clinical Presentation

An early-term male neonate was delivered via emergency lower segment cesarean section (LSCS) at a tertiary care center due to fetal distress. The mother, a 23-year-old primigravida, had an uneventful antenatal course until the 36th week of gestation, when an ultrasound revealed a large midline cystic lesion measuring approximately 2.0 × 2.3 cm, located posterior to the cavum septum pellucidum. Color Doppler demonstrated venous flow within the lesion, with a peak systolic velocity (PSV) of 27 cm/s, suggesting a vein of Galen malformation (VOGM). Mild fetal cardiomegaly and hyperdynamic cerebral circulation were also noted. Prior ultrasounds at 12 and 20 weeks were unremarkable.

The baby was delivered in meconium-stained amniotic fluid and had signs of meconium aspiration syndrome. Apgar scores were 5, 8, and 8 at 1, 5, and 10 minutes, respectively. Intermittent positive pressure ventilation was required immediately after birth, followed by intubation. Birth weight was 2900 grams. On admission, the neonate exhibited respiratory distress with subcostal and intercostal retractions, a respiratory rate of 70 breaths per minute, and preductal oxygen saturation of 91%. Cardiovascular and neurological examinations were unremarkable. Capillary blood gas revealed a metabolic acidosis (pH 7.31, HCO_3 17.4 mmol/L, base excess -8.3), while laboratory parameters including complete blood count, electrolytes, and inflammatory markers were within normal limits.

Diagnostic Workup

A chest radiograph revealed cardiomegaly with a cardiothoracic ratio of 0.7 but no signs of pulmonary infiltrates or consolidation. Cranial ultrasound through the anterior fontanelle showed a well-defined anechoic midline cystic lesion at the confluence of the internal cerebral vein and straight sinus, measuring 1.8 × 2.2 cm. Color Doppler confirmed turbulent biphasic flow with aliasing and a maximum PSV of 52 cm/s—findings consistent with an arteriovenous malformation, most likely VOGM.

Echocardiography revealed cardiomegaly, a closed ductus arteriosus, a patent foramen ovale with left-to-right shunting, and mild tricuspid regurgitation. Pulmonary hypertension was evident, with a peak pressure gradient of 50 mmHg. Notably, there was prominent flow in the superior vena cava, supporting the suspicion of high-output cardiac physiology.

Management

Initial stabilization included pressure-controlled mechanical ventilation (40/5/30/10), umbilical line placement, and inotropic support with noradrenaline and dobutamine. Broad-spectrum antibiotics (meropenem and amoxicillin-clavulanic acid) were

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started empirically. Over the next 72 hours, the infant's oxygen requirement decreased significantly. Blood gases normalized, and

ventilatory settings were tapered to PC mode (21/5/30/10). The patient was successfully extubated on day 4 of life and transitioned to bubble CPAP.

Outcome

The neonate responded well to medical management. By day 4, oxygen requirement had resolved, and the infant was hemodynamically stable on non-invasive support. Follow-up neuroimaging and neurology input were planned to evaluate the need for interventional management of the vascular malformation.

Discussion

Vein of Galen malformation is a rare intracranial arteriovenous anomaly resulting from the persistence of the embryonic median prosencephalic vein of Markowski. The lesion creates a high-flow, low-resistance shunt between cerebral arteries and the venous system, which increases venous return to the right atrium. This leads to high-output cardiac failure, right heart dilatation, and in neonates, can present with features of PPHN. Early postnatal deterioration due to the circulatory burden is well documented, and cranial imaging is essential in neonates with unexplained or refractory PPHN. Prompt diagnosis allows for multidisciplinary planning, including the possibility of staged neurointerventional treatment.

Case 2: Congenital Diaphragmatic Hernia with PPHN Presentation A full-term male neonate (40+1 weeks gestation) was born via cesarean section for

cephalopelvic disproportion to a primigravida mother. The antenatal course was largely unmonitored with no documented anomaly scan. However, a late third-trimester ultrasound done externally at 39 weeks suggested a congenital diaphragmatic hernia (CDH), revealing herniation of the stomach into the thoracic cavity. At birth, the neonate exhibited a weak cry, cyanosis, and hypotonia. He was immediately intubated on the resuscitation table and transferred to the NICU via transport incubator for further stabilization.

Imaging & Echocardiography Findings

Clinical examination revealed signs of respiratory distress, absent air entry on the left side, and a soft, non-distended abdomen. Chest radiography confirmed left-sided CDH with bowel loops occupying the thoracic cavity and mediastinal shift. Echocardiography demonstrated severe pulmonary hypertension with right-to-left shunting across the ductus arteriosus and tricuspid regurgitation. Additionally, cardiac function was compromised, with evidence of right ventricular strain and elevated pulmonary artery pressures, consistent with severe PPHN.

Management

The infant required high ventilatory support immediately after birth and was placed on pressure-controlled mechanical ventilation (PC mode 100/5/30/12). Despite maximal respiratory support and the administration of inotropes for circulatory instability, the baby remained hypoxic and hemodynamically compromised. Preductal oxygen saturations ranged between 75–82%, and the baby showed signs of poor perfusion with a capillary refill time of 3–4 seconds. Due to worsening pulmonary hypertension and compromised gas exchange, the patient was considered for extracorporeal membrane oxygenation (ECMO); however, clinical deterioration progressed rapidly.

Outcome

The neonate succumbed within the early neonatal period due to severe refractory PPHN and pulmonary hemorrhage secondary to cardiorespiratory failure. The final cause of death was documented as pulmonary bleed with severe PPHN and cardiogenic shock in the context of congenital diaphragmatic hernia.

Discussion

Congenital diaphragmatic hernia is a developmental defect of the diaphragm, most commonly occurring on the left side, which allows abdominal organs to herniate into the thoracic cavity. This disrupts normal lung development, leading to pulmonary hypoplasia, altered vascular architecture, and subsequent PPHN. The severity of pulmonary hypertension in CDH is a major determinant of outcome, particularly in cases with late diagnosis, large defects, or liver herniation.

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In this case, the absence of prenatal diagnosis delayed perinatal planning and compromised early management. The presence of low lung-to-head ratio (LHR) and significant hypoxemia were poor prognostic indicators. Early prenatal detection, delivery at ECMO-capable centers, and staged surgical management have been shown to improve survival in select cases, although the mortality remains high in severe presentations.

Case 3: Thiamine Deficiency (Shoshin Beriberi) as a Cause of PPHN Clinical Presentation

A young male child, nearly three years old, was admitted to the pediatric intensive care unit with

a two-day history of fever and worsening respiratory distress. He was born to non-consanguineous parents and had no known congenital anomalies. On admission, the child exhibited tachycardia, dyspnea, and signs of cardiogenic shock, including poor peripheral perfusion and elevated jugular venous pressure. There were no focal respiratory signs initially, and auscultation revealed a pan-systolic murmur.

Laboratory Findings

Initial investigations revealed severe microcytic hypochromic anemia (Hb 6.7 g/dL) with supporting iron studies suggestive of iron deficiency. Notably, metabolic acidosis was not overt, but echocardiographic assessment revealed findings consistent with pulmonary hypertension: severely elevated pulmonary artery pressures (estimated at 120 mmHg), right atrial and ventricular dilation, non-collapsing inferior vena cava, and severe tricuspid regurgitation. Mild bilateral pleural effusions were also present, and abdominal ultrasonography indicated congestive cardiac failure.

Diagnosis And Therapeutic Trial

Given the clinical picture of right-sided heart failure, pulmonary hypertension, and dietary history suggestive of a polished rice-based intake, thiamine deficiency (Shoshin beriberi) was suspected. Intravenous thiamine (100 mg once daily) was initiated empirically, alongside standard therapy with milrinone, furosemide, and spironolactone. Remarkably, within four hours of thiamine administration, the child's respiratory distress improved significantly and oxygen requirements decreased. A repeat echocardiogram performed 24 hours later showed a substantial reduction in pulmonary artery pressures (now 30 mmHg), only mild tricuspid regurgitation, and resolution of pericardial and pleural effusions. Despite normal serum thiamine levels reported later, the rapid clinical response confirmed the diagnosis retrospectively.

Outcome And Learnings

The child was weaned off inotropes, continued to improve clinically, and was discharged without the need for ongoing pulmonary vasodilators. No neurological sequelae were noted on follow-up.

Thiamine deficiency, though rare, can manifest as pulmonary hypertension and right-sided heart failure in infants and children, especially in regions where diets are predominantly based on polished rice or other nutrient-depleted staples. Shoshin beriberi—a fulminant cardiovascular manifestation of thiamine deficiency—is characterized by severe myocardial dysfunction, systemic vasodilation, and metabolic acidosis. Thiamine acts as a critical cofactor in oxidative metabolism, and its absence disrupts ATP production, leading to energy failure in myocardial and vascular tissues.

Recent Indian case series have documented similar presentations of thiamine-responsive pulmonary hypertension. While classically seen in 2–5-month-old infants, this case highlights that older children may also be affected. Importantly, normal serum thiamine levels do not exclude deficiency, particularly in acute or functional deficiency states. In such scenarios, a therapeutic trial of thiamine is justified, given the potential for rapid and complete recovery. Early recognition and treatment can be lifesaving and may prevent unnecessary interventions or delayed care.

Discussion

This case series presents three neonates with Persistent Pulmonary Hypertension of the Newborn (PPHN), each stemming from an uncommon underlying cause: a cerebral vascular malformation (vein of Galen malformation), a structural thoracic defect (congenital diaphragmatic hernia), and a metabolic deficiency (thiamine deficiency/Shoshin beriberi). Despite a shared clinical endpoint—severe hypoxemia and

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pulmonary hypertension—the pathophysiological pathways and management strategies varied significantly across the cases, underscoring the importance of broad diagnostic consideration in neonatal PPHN.

A comparison of the cases reveals distinct diagnostic challenges. In the first case, the prenatal identification of a cerebral cystic lesion allowed for early suspicion of a vein of Galen malformation. However, the onset of high-output cardiac failure and PPHN postnatally required timely neuroimaging and echocardiography to confirm the diagnosis. In contrast, the second case of congenital diaphragmatic hernia (CDH) was diagnosed only on a late third-trimester ultrasound and was not anticipated perinatally due to lack of an early anomaly scan. The absence of antenatal preparedness likely contributed to delayed specialized respiratory and surgical planning. The third case posed the greatest diagnostic complexity—no structural anomaly was apparent, yet the infant presented with signs of right-sided heart failure and severe pulmonary hypertension. Only through detailed dietary history, clinical suspicion, and a trial of thiamine therapy was the diagnosis of Shoshin beriberi established.

These cases highlight the importance of considering systemic, vascular, and metabolic causes in the differential diagnosis of PPHN, particularly in presentations unresponsive to standard therapies. While pulmonary disease, meconium aspiration, and sepsis are common culprits, reliance solely on these diagnoses can delay lifesaving intervention in less typical cases. Early neuroimaging should be considered in the presence of unexplained cardiomegaly, prominent superior vena cava flow, or signs of high-output physiology. Likewise, attention to nutritional history and regional dietary patterns can provide valuable diagnostic clues in cases of metabolic origin.

Each case also illustrates a unique mechanism contributing to elevated pulmonary vascular resistance. The vein of Galen malformation produced a high-output cardiac state, overwhelming the pulmonary circulation and causing right heart strain. In CDH, pulmonary hypoplasia and abnormal pulmonary vasculature directly led to persistent pulmonary hypertension. In Shoshin beriberi, thiamine deficiency impaired mitochondrial function and cardiac contractility, resulting in low-output cardiac failure and secondary pulmonary hypertension. These distinct mechanisms emphasize that PPHN is not a diagnosis in itself but a hemodynamic manifestation of a broader underlying pathology.

For neonatologists and pediatricians, the key takeaway from this series is the necessity of a tailored diagnostic approach in refractory PPHN. Clinical improvement may depend on

Recognizing subtle signs, integrating prenatal findings, and initiating targeted therapies—even in the absence of definitive confirmatory tests. Early involvement of multidisciplinary teams, including neurologists, cardiologists, radiologists, and nutritionists, can aid in refining diagnosis and optimizing outcomes.

Conclusion

This case series highlights three rare but clinically significant causes of Persistent Pulmonary Hypertension of the Newborn (PPHN): vein of Galen malformation, congenital diaphragmatic hernia, and thiamine deficiency. Although each case presented with a similar hemodynamic picture, the underlying mechanisms and management pathways were markedly different, reinforcing the heterogeneity of PPHN etiologies.

These cases underscore the importance of maintaining a broad differential diagnosis in neonates with PPHN, especially when conventional pulmonary or infectious causes are absent or when clinical response to standard treatment is inadequate. Vascular anomalies, anatomical defects, and metabolic disorders may all contribute to or mimic primary pulmonary hypertension, and overlooking these less common etiologies may lead to delays in diagnosis and suboptimal outcomes.

A high index of clinical suspicion, guided by prenatal history, imaging, and focused evaluation, is essential in identifying such atypical causes. Prompt recognition and targeted management can significantly improve prognosis, prevent complications, and ultimately save lives. Neonatologists must remain vigilant and adopt a

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multidisciplinary, investigative approach when faced with refractory PPHN in the newborn period.

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