Cobalamin-C Methylmalonic Acidemia and Homocystinuria in Neonate Presenting as Persistent Pulmonary Hypertension Requiring Extracorporeal Membrane Oxygenation

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ABSTRACT:

Introduction:

Introduction: Inborn errors of metabolism (IEM) represent a small, yet unknown, fraction of idiopathic causes of persistent pulmonary hypertension of the newborn (PPHN). The treatment of a neonate presenting with PPHN follows a well-described pattern until standard medical therapies do not improve the patient's condition. Once these therapies are exhausted, and pulmonary hypertension, as well as acidosis, persists, the search for a more unlikely etiology of PPHN is undertaken. Extracorporeal membrane oxygenation (ECMO) allows for the treatment of PPHN and respiratory acidosis while allowing time for diagnosis and treatment of the IEM.

Case Presentation:

This is the case of a term Hispanic female exhibiting symptoms consistent with PPHN. After initial stabilization with CPAP, antibiotics and inhaled nitric oxide, she deteriorated, requiring intubation. Serial echocardiograms demonstrated worsening pulmonary hypertension along with hemodynamic instability and severe acidosis. Given the failure to respond to maximal medical therapy, she was placed on venovenous ECMO. Despite achieving hemodynamic stability on ECMO, the acidosis persisted leading to exploration of a metabolic cause. A thorough evaluation revealed a diagnosis of methylmalonic acidemia, an inborn error of metabolism. Treatment was started with levocarnitine, hydroxocobalamin, and cessation of proteins. Once treatment was initiated, the patient's metabolic acidosis resolved rapidly, and she was weaned from ECMO support twenty-four hours after initiation. Ultimate diagnosis after genetic testing was cobalamin-C methylmalonic acidemia (Cbl-C) and homocystinuria.

Discussion:

There is evidence that IEM's like Cbl-C represent a subset of idiopathic causes of PPHN, and early diagnosis is crucial to prevent rapid, progressive deterioration. Recognition of an association between IEM, pulmonary hypertension, and the need for ECMO support would lead to a search for underlying IEM and aggressive treatment.

Key Words:

Cobalamin-C Methylmalonic Acidemia, Cbl-C, Homocystinuria, Inborn Error of Metabolism, IEM, Persistent Pulmonary Hypertension, PPHN, Extracorporeal Membrane Oxygenation, ECMO

Introduction:

Persistent pulmonary hypertension of the newborn (PPHN) complicates the course of over ten percent of neonates with respiratory failure and is responsible for over 30% of neonatal mortality.1 More common causes of PPHN include meconium aspiration syndrome, pneumonia, respiratory distress syndrome, sepsis, and congenital diaphragmatic hernia. Idiopathic PPHN is seen in 10-20% of cases; however, an inborn error of metabolism (IEM) is rarely reported as the cause. (1) The rarity of metabolic causes of PPHN can lead to a lag in the initiation of appropriate treatment, placing the patient at significant risk of morbidity/mortality.

Extracorporeal support of the infant with PPHN is considered the last option in infants who have failed all other medical management. Over the last 5 years, (Jan 2013 - Dec 2017) Extracorporeal Life Support Organization (ELSO) reported approximately 4000 neonatal respiratory patients with 40% listed as PPHN or 'other' for diagnosis. (2) It is unclear how many of these patients were eventually diagnosed with a metabolic etiology, but given the lack of case studies reported, it is suspected to be a small subset. Significant, early metabolic acidosis can cause complications such as severe PPHN; whereas extracorporeal membrane oxygenation (ECMO) allows for clearing of lactic acid and assists with resolving the severely acidotic state of the patient while allowing an avenue for reduction of harmful ammonia levels. One case report describes a newborn with Methylmalonic acidemia presenting as PPHN treated with ECMO therapy and another case report describes propionic acidemia reportedly causing initial presentation as PPHN. (3,4) This is a case report a neonate with Cbl-C methylmalonic acidemia presenting with persistent pulmonary hypertension requiring ECMO support for survival.

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Case Presentation

This is the case of a term Hispanic female born via cesarean section to a 30-year-old gravida G_4P_4 mother. Apgars were 8 and 9 at 1 and 5 minutes respectively. Weight was at the sixth percentile, length was at the 58th percentile, and head circumference was < 3rd percentile with some molding. She was stable in the newborn nursery for approximately two hours when she was noted to have hypoxia, differential oxygen saturations between right hand and right foot and hypoventilation that required oxygen therapy per nasal cannula. She was transferred quickly to the Neonatal Intensive Care Unit where she was placed on nasal continuous positive airway pressure (nCPAP). Initial arterial blood gas (ABG) was 7.32/34/18/64/-9 ($pH/pCO_2/CO_2/pO_2$/BE). Once on nCPAP, her oxygen saturations were 88-100% with 3-10 point difference in pre and post ductal saturations. Empiric antibiotics were initiated due to concern for pneumonia and possible sepsis due to infiltrates on chest x-ray and worsening respiratory status. An echocardiogram was performed due to increasing and persistent oxygen needs, which demonstrated moderately decreased function (ejection fraction of 41%) and supra-systemic pulmonary hypertension consistent with PPHN. Given these findings, inhaled nitric oxide was started at 20 ppm. This allowed her to stabilize and FiO_2 was weaned to 40% with pCO_2 in the 40's and PaO_2 41-78 for the next twelve hours.

At 18 hours of age, she was intubated and placed on mechanical ventilation due to worsening tachypnea and respiratory distress. She was given a dose of surfactant due to persistently hazy chest X-ray (CXR) and high oxygen needs. The patient then developed hypotension requiring fluid resuscitation and dopamine infusion. A repeat ECHO showed worsening PPHN (estimated RV pressure suprasystemic). She was started on epinephrine and milrinone to assist cardiac function as well as stress dose hydrocortisone. The patient required escalation of respiratory support progressing to high-frequency oscillatory ventilation with ABG of 7.06/67/36/21/-11. She continued to have worsening respiratory and metabolic acidosis with lactic acidemia (lactate 12 mmol/L). At 26 hours of life, ABG was 7.04/70/39/21/-12 with lactic acid of 11.4 mmol/L. Despite maximal therapy including sedation, muscle relaxation, multiple inotropes and fluid resuscitation she continued to have saturations in the upper 70's to low 80's Due to the maximal support required with no improvement, she was then transferred to the Pediatric Intensive Care Unit and placed on ECMO at 37 hours of life.

The patient was placed uneventfully on Veno-arterial ECMO with a rapid turnaround of her respiratory acidosis. She was weaned off dopamine and dobutamine with epinephrine infusion at minimal dosing 2 hours post cannulation. However, over the next 12 hours, she continued to have a marked lactic acidosis with base deficit ranging -10 to -14 meq/L and lactate 9-12 mmol/L despite adequate fluid resuscitation and appropriate blood pressure off inotropes. Due to the lactic acidosis and ammonia of 105 uMol/L, a Metabolic/Genetics consult was obtained. Expedited newborn screen results were obtained by Genetics consultant, and C3 was found to be highly elevated. Newborn screen collected just prior to 24 hours of life showed a significantly elevated C3 propionylcarnitine of 11.88 µmol/L (normal <6, 'alert' value 8.87) and C3:C2 ratio of 0.68 (normal <0.3). Repeat ammonia was 62 uMol/L, Vitamin B12 603 pg/mL, and homocysteine was highly elevated at 85.3 µMol/L (mean 6.8, normal <12.8). Due to the abnormal newborn screen, lactic acidosis and elevated homocysteine, therapy was started with levocarnitine 100mg/kg/day and hydroxocobalamin 2 mg IM daily. Venous nutrition was continued at 120 kcal/kg/day with cessation of intravenous proteins for twenty-four hours. Methylmalonic acidemia cblC type was suspected due to Hispanic heritage. Within eight hours of initiating treatment, the patient's metabolic acidosis resolved and she was quickly weaned off ECMO therapy with decannulation approximately 24 hours post initiation of ECMO.

Labs were reported over the next 2 days showing an acylcarnitine profile with C3 elevated to 3.47 nmol/mL (normal <0.55). Urine organic acids showed a significant increase of excretion of methylmalonic acid at 1086 mmol/mol creatinine (<4) with other propionate metabolites detected. Homocysteine remained elevated at 92.6, total carnitine was 10 nmol/mL (17-41), free carnitine was 3 nmol/mL (10-21), and acylcarnitine to free carnitine ratio was 2.3 (0.2-1.4). Given these results, a disorder of cobalamin metabolism was suspected, and molecular testing of the MMACHC gene was sent. This patient was found to be homozygous for the c.328_331delAACC pathologic variant, consistent with Cobalamin C (Cbl-C) methylmalonic aciduria and homocystinuria.

The patient was extubated on postnatal day of life six. She remained on therapy with hydroxycobalamin, betaine, Leucovorin, Levocarnitine, and folate supplementation and was discharged home on DOL 39. Unfortunately, she developed suspected cardiomyopathy with biventricular hypertrophy with an ejection fraction of 65%. Given social circumstances, she was scheduled for follow-up at a different institution. Follow-up at eleven months of age at this institution reports that the patient was doing well with mild right ventricular hypertrophy, normal growth, and energy for age.

Discussion

Combined methylmalonic acidemia and homocystinuria, Cbl-C type, is an autosomal recessive inborn error of intracellular cobalamin metabolism. It is the most common inborn error of cobalamin metabolism, with an incidence of 1:100,000 live births. (5,6) The gene mutation (MMACHC) ultimately results in the elevation of methylmalonic acid and homocysteine along with decreased production of methionine. (7) Methylmalonic acid is a potent cell toxin inducing excitotoxic cell death in neuronal cells, explaining the classic presentation and progression of this disease. Cbl-C, has a heterogeneous presentation, making diagnosis difficult. (5) Clinical presentations may be as neonates, infants, childhood, or after age twelve. (8)

Early or infantile presentation of MMA consists of rapid deterioration in a term neonate after a symptom-free interval of hours to weeks. (9,10) Cobalamin-C disease is the most frequently diagnosed form of MMA, presenting with neurologic, ocular, hematologic and gastrointestinal symptoms including failure to thrive, developmental delay, microcephaly, somnolence/lethargy, and hypotonia. (5,10) Infants can present with a high anion gap metabolic acidosis, ketonuria, and hyperammonemia. (8) Hemolytic uremic syndrome and megaloblastic anemia can also be seen with relative frequency. (5) Cardiopulmonary signs have

been reported more recently with congenital heart disease such as septal defects, valve abnormalities, and atrial defects with pulmonary manifestations. (5,11) There are reports of patients with Cbl-C presenting with respiratory failure, and cor pulmonale due to pulmonary thrombosis. (3,12,13) ECMO has been reported as a supportive measure in the treatment of metabolic crisis in older children with MMA and propionic acidemia. (6,14) Two case reports highlight the development of pulmonary hypertension in older patients but only one study by Agarwal and colleagues details the rapid progression of isolated pulmonary hypertension in a newborn with MMA requiring ECMO. (3,11,15) This case is the first patient with Cbl-C disease presenting with pulmonary hypertension that highlights the severity of acidosis and PPHN and usefulness of ECMO in stabilizing the patient. ECMO allowed for the time needed to make the diagnosis and begin appropriate treatment.

This infant was born uneventfully with no concerning risk of infection: mother was GBS negative, membranes were ruptured 2 hours, and amniotic fluid was clear. However, she progressed to significant respiratory distress, hypoxia, and acidosis within 3 hours of postnatal life. Escalation of therapy was necessary with the development of significant PPHN, cardiac dysfunction, and lactic acidosis culminating in the need for ECMO therapy. Neonates have a limited ability to respond to illness and differentiating between causes is difficult with a narrow range of clinical signs and symptoms. (9,16) Common neonatal diagnoses associated with PPHN (sepsis, meconium aspiration, and respiratory distress syndrome) that require ECMO support normally have acidosis that responds quickly to the improved hemodynamic stability achieved on ECMO. Despite achieving adequate hemodynamics with ECMO in our patient, the continued acidosis prompted the search for an inciting metabolic condition. With the laboratory studies recommended by the metabolic consultant and the ability to obtain rapid newborn screen results, MMA was suspected early, and treatment was begun within 12 hours of ECMO cannulation. Once treatment was initiated, acidosis improved rapidly, and the patient was able to decannulate from ECMO in twenty-four hours.

This case highlights the importance of newborn care when considering IEMs in the differential diagnosis of critically ill neonates with pulmonary hypertension, especially those not responding to standard therapies. While expanded newborn screens have facilitated early diagnosis of several IEMs, patients can develop symptoms before newborn screen results are available. (17) IEMs must be considered in the differential diagnosis, especially in a term infant with unexplained lactic acidosis. Obtaining an ammonia level and contacting the state newborn screening lab can be helpful.

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In retrospect, this patient did have clinical signs, and exam findings demonstrated in the prenatal and neonatal presentation of Cbl-C disease including intrauterine growth retardation, microcephaly, metabolic acidosis, and hyperammonemia. (18) However these findings are not diagnostic, which is typical with Cbl-C presentation. In neonates, acidosis and hypoxia can produce pulmonary vasoconstriction and maintain pulmonary hypertension (persistent fetal circulation). In this report, however, the patient developed pulmonary hypertension in the absence of an obvious inciting event such as meconium aspiration. It is postulated that physiologic stress of some type, either in utero or in the early postnatal period, triggered the metabolic decompensation. This caused an anion gap acidosis that resulted in the development or exacerbation of PPHN all due to the underlying Cbl-C. It has been suggested that homocysteine or its derivatives have a role in the pathophysiology of vascular disease, causing blood vessel damage, microangiopathy, and thromboembolism leading to pulmonary arterial hypertension. (7,15) Which came first, the acidosis or the pulmonary hypertension is unclear, but the resulting clinical scenario remains difficult.

In summary, to the best of our knowledge, this is the first report of a neonate with Cbl-C disease presenting with persistent pulmonary hypertension requiring ECMO support for survival. While ECMO support of neonates with IEM has been described, this case highlights the rapidity with which an uncommon cause should be suspected when patients do not respond as expected to the classic treatment for PPHN. There is more evidence that IEM's like Cbl-C represent a subset of idiopathic causes of PPHN, and early diagnosis of this is crucial to prevent rapid progressive deterioration, often leading to death. Recognition that there is an association between IEM, pulmonary hypertension, and the need for ECMO support would lead to a search for underlying IEM and aggressive treatment.

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Acknowledgments:
A special thanks to Dr. Huber and Dr. Sandeen for assisting in preparing the article.

Disclosures:
No potential conflicts of interest or financial disclosures relevant to this article are reported.

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