Cobalamin C Defect Presenting With Isolated Pulmonary Hypertension

abstract

Cobalamin C (cblC) defect is the most common inborn error of vitamin B₁₂ metabolism. Clinical features vary as does the severity of the disease. In most cases, the clinical symptoms of cblC defect tend to appear during infancy or early childhood as a multisystem disease with severe neurologic, ocular, hematologic, renal, and gastrointestinal signs. The neurologic findings are common and include hypotonia, developmental delay, microcephaly, seizures hydrocephalus, and brain MRI abnormalities. We report a case of a young boy with cblC defect, who did not undergo newborn screening, presenting at the age of 2 years with isolated pulmonary hypertension as the leading symptom. This novel way of presentation of cblC defect enlarges the spectrum of inherited diseases that must be considered in the differential diagnosis of pulmonary hypertension. *Pediatrics* 2013;132:e248–e251

AUTHORS: Francesca G. Iodice, MD,a Luca Di Chiara, MD,a Sara Boenzi, MSc;b Chiara Aiello, MD,c Lidia Monti, MD,d Paola Cogo, MD, PhD,a and Carlo Dionisi-Vici, MDb

aUnit of Pediatric Cardiac Anesthesia and Intensive Care, Department of Pediatric Cardiology and Cardiac Surgery, bDivision of Metabolic Diseases, Department of Pediatric Medicine, cUnit of Neuromuscular Diseases, Department of Neurology, and dDepartment of Radiology, Children’s Hospital Bambino Gesù IRCCS, Rome, Italy

KEY WORDS

cobalamin C defect, pulmonary hypertension

ABBREVIATIONS

cblC—cobalamin C
CoA—coenzyme A
CT—computed tomography

Dr Iodice anesthetized the patient, drafted the initial article, and approved the final article as submitted; Dr Di Chiara was part of the anesthetics team and approved the final article as submitted; Dr Boenzi performed biochemical testing, reviewed and revised the article, and approved the final article as submitted; Dr Aiello performed the molecular analysis of Cobalamin C defect, reviewed and revised the article, and approved the final article as submitted; Dr Monti supervised the radiological images, reviewed and revised the article, and approved the final article as submitted; Dr Cogo reviewed and revised the article and cared for the patient in the ICU; and Dr Dionisi Vici diagnosed the Cobalamin C defect, reviewed and revised the article, and approved the final article as submitted.

doi:10.1542/peds.2012-1945

Accepted for publication Mar 21, 2013

Address correspondence to Francesca G. Iodice, MD, Children’s Hospital Bambino Gesù, Piazza San Onofrio 4, 00195, Rome, Italy. E-mail: fgiovanna.iodice@opbg.net or francesca_iodice@yahoo.it

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2013 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Dr Dionisi-Vici was supported by the grant “CCM 2010: Costruzione di percorsi diagnostico-assistenziali per le malattie oggetto di screening neonatale allargato” from the Italian Ministry of Health.
Cobalamin C (cblC) defect is the most common inborn error of vitamin B12 (cobalamin) metabolism and is responsible for the impaired conversion of dietary cobalamin into its 2 metabolically active forms, methylcobalamin and adenosylcobalamin. Methylcobalamin is the cofactor for methionine synthase, which catalyzes the conversion of homocysteine into methionine in the cytosol; adenosylcobalamin is the cofactor for methylmalonyl-coenzyme A (CoA) mutase, which converts methylmalonyl-CoA into succinyl-CoA in the mitochondria. The impaired activity of these enzymes results in accumulation of homocysteine and methylmalonic acid and reduced synthesis of methionine. The gene responsible for the defect was identified as MMACHC, and mutations have been found in over 300 cases.

In the absence of newborn screening, cblC defect is difficult to recognize clinically due to the wide variety of symptoms. Based upon the severity and timing of the presentation, 2 distinct clinical forms can be identified. Early-onset, which usually manifests as a multisystem disease with severe neurologic, ocular, hematologic, renal, gastrointestinal, and cardiac symptoms within the first year after birth, and a late-onset form, which usually presents with a milder phenotype with predominantly neurologic disturbances, dementia, myelopathy, and thrombembolic symptoms. More recently, cblC defect has been found in some countries included in the panel of diseases detectable with expanded newborn screening. However, management and outcome of asymptomatic patients with cblC detected by newborn screening has not yet been extensively studied.

We report a case of a young boy with cblC presenting with isolated pulmonary hypertension as the leading symptom. This novel way of presentation of cblC defect enlarges the spectrum of inherited diseases that must be considered in the differential diagnosis of pulmonary hypertension.

**CASE REPORT**

This male child was born at term by an elective caesarean delivery from healthy nonconsanguineous parents of African ancestry. Birth parameters were normal. His eldest brother presented at the age of 3 years with hemolytic uremic syndrome, which was treated with conventional medical treatment.

At the age of 45 days, the patient was admitted to a peripheral hospital because of breathing difficulties, pallor, fever, and anemia (laboratory data are not available). After a few days of hospitalization, the child was sent home. At the age of 2 years, he presented to the emergency department of the Bambino Gesù Children’s Hospital with nonspecific symptoms of feeding difficulties, failure to thrive, and a previous history of anemia treated with iron supplementation by his pediatrician. A first physical examination was overall negative, weight was 9.9 kg (<5th percentile); however, the child was admitted to the pediatric ward. Routine laboratory revealed elevated serum lactate dehydrogenase (1354 IU/l; normal values [n.v.] <600), whereas the remaining blood examinations were as follows: erythrocyte count, 5.05 × 10¹²/L (n.v. 3.6–5.3); red cell volume, 80.7 fl (n.v. 72–88); hemoglobin, 13.0 g/dL (n.v. 13.0–16.0); platelet count, 226 × 10⁹/µL (n.v. 150–450); creatinine, 0.35 mg/dL (n.v. 0.2–0.9); uric acid, 5.0 mg/dL (n.v. 3.4–7.0); total bilirubin, 0.72 mg/dL (n.v. 0.2–0.9); and pH, 7.41 (n.v. 7.35–7.45). Blood electrolytes, liver function, and urine analysis were also within reference limits. Chest radiograph revealed marked interstitial thickening and a normal cardiac size. Although laboratory testing remained unchanged, after a few days clinical conditions rapidly deteriorated. The child began to show signs of respiratory distress, including an increased breathing rate and wheezing, and was transferred to the cardiac ward for further diagnostic testing. A cardiac ultrasound revealed normal pulmonary and systemic venous return, moderate tricuspid insufficiency with a right ventricular systolic pressure of 75 mm Hg (systemic blood pressure 103/70 mm Hg), and moderate left ventricular dysfunction with nonsignificant mitral insufficiency. Z score was −3.4 with an ejection fraction of 38.5%. In the meantime, a chest computer tomography scan was performed, which revealed increased size of the pulmonary artery and signs of pulmonary hypertension (Fig 1). Furosemide 1 mg/kg and enalapril 0.1 mg/kg were soon started.

The presence of a clinical picture that was potentially related to diffuse pulmonary microangiopathic lesions combined with a familial history of hemolytic uremic syndrome in the elder brother prompted us to suspect cblC defect (which had not been considered before in the differential diagnosis of his brother), and to start with metabolic investigations. The child was immediately started on the following therapy: intramuscular hydroxocobalamin 1 mg/day, betaine 250 mg/kg per day, and folic acid 5 mg/day. Metabolic investigations suggested cblC deficiency, revealing increased levels of plasma total homocysteine (66.9 μmol/L; n.v. 4.0–19.0) and of blood propionylcarnitine (9.9 μmol/L; n.v. <2.5), as well as increased urinary excretion of methylmalonic acid. Plasma methionine was borderline low (11 μmol/L; n.v. 10–50), whereas vitamin B₁₂ (531 pg/mL, n.v. 211–911) and folate (6.6 ng/mL, n.v. 1.1–20.0) levels were within normal limits. A cblC defect was subsequently confirmed by molecular analysis of MMACHC gene revealing a compound heterozygous c.271dupA/c.A389G genotype in the proband and in his eldest brother.

A diagnostic catheterization procedure was planned, which was performed under general anesthesia. Anesthesia
was induced with intravenous ketamine 2 mg/kg, midazolam 0.1 mg/kg, fentanyl 1 μg/kg, and vecuronium bromide 0.1 mg/kg. Tracheal intubation and cannulation of a radial artery were performed. Anesthesia was maintained with sevoflurane and remifentanil 0.125 μg/kg per minute. Two serious pulmonary hypertensive crises were recorded during the procedure and both were solved by hyperventilation with administration of 100% oxygen. Inotropic support with dopamine 4 μg/kg per minute was administered throughout the procedure, and blood gas analysis revealed no signs of metabolic acidosis. The child was extubated deeply in the operating room and then transferred to the ICU for postoperative monitoring. The catherization procedure confirmed pulmonary hypertension responsive to oxygen and nitric oxide. The following values were reported in the pulmonary artery: baseline 91/41/25/8 mm Hg (normal values = 15–25/8–15/20), after 100% oxygen 64/44/24 mm Hg, after nitric oxide 51/23/36 mm Hg. Base-line pulmonary arteriole resistances were 15.4 unit woods/m² (normal values 1–3 U.W./m²) after 100% oxygen and nitric oxide; values were lower but remained high respectively at 6.2 U.W./m² and 6.4 U.W./m².

Four days after the start of treatment, metabolic abnormalities resolved displaying the normalization of plasma total homocysteine (12 μmol/L), methionine (53 μmol/L), and propionyl-carnitine (2.9 μmol/L), along with striking reduction of urinary methylmalonic acid excretion. Despite the improvement of metabolic changes, the child while being maintained under observation in the ICU progressively worsened requiring inotropic support and underwent a fatal pulmonary hypertensive crisis that led to a cardiac arrest.

**DISCUSSION**

We report the results of a young boy with cblC defect and isolated pulmonary hypertension, with a nonneurologic and nonrenal presentation.

In most cases, the clinical symptoms of cblC defect tend to appear during infancy or early childhood as a multisystem disease with severe neurologic, ocular, hematologic, renal, and gastrointestinal signs. The neurologic findings are common and include hypotonia, developmental delay, microcephaly, seizures, hydrocephalus, and brain MRI abnormalities. Cardiovascular signs are increasingly observed in cblC patients with reports of congenital heart disease, such as atrial and ventricular septal defects, pulmonary valve abnormalities, atrial defects, and mitral valve prolapse. Cardiohypertrophy and left ventricular noncompaction have been reported as well. Pulmonary hypertension was the clinical hallmark sign in our patient. In children it has a varied clinical presentation and heterogenous causes and determining its etiology is key to management strategies. Isolated pulmonary hypertension in cblC patients without any other associations has never been to the best of our knowledge described before. Labrune et al reported a child with isolated methionine synthase deficiency, pulmonary hypertension, and hemolytic uremic syndrome. Furthermore, in 3 infants with fatal cblC defect presenting in the first weeks after birth with metabolic acidosis, pancytopenia, lethargy, hepatic dysfunction, respiratory insufficiency, and hemolytic uremic syndrome, lung postmortem findings were dominated by thrombotic microangiopathy. Thromboembolic complications have been reported in cblC defect as the result of hyperhomocysteinemia inducing vascular damage. Brandstetter et al reported an infant with a probable cblC defect, a bronchiolitislike illness, and acute cor pulmonale secondary to pulmonary thromboembolism. However, this patient also showed seizureslike activity and hypotonia. Hemolytic uremic syndrome, which characteristically manifests itself in cblC defect with azotemia, thrombocytopenia, and hemolytic anemia, is caused by a diffuse microangiopathy that represents the underlying mechanism causing both hemolytic uremic syndrome and communicating hydrocephalus. In our patient, the parents refused autopsy and prevented the postmortem examination of the lungs. However, the computed tomography (CT) scan studies
revealed a pattern that confirmed pulmonary hypertension perhaps related to increased levels of homocysteine and subsequent vascular injury. The effects of increased levels of homocysteine on pulmonary vasculature may consist in promoting vasoconstriction and endothelial dysfunction leading to increased pulmonary pressures. 

After the diagnosis, the eldest sibling of our patient received hydroxocobalamin and betaine treatment and revealed the almost complete normalization of metabolic abnormalities (data not shown) without the appearance of neurologic signs at follow-up. Indeed, if expanded newborn screening would have been performed, the 2 brothers would most likely have experienced a different clinical outcome. However, at the time of these cases, this type of screening unfortunately was not available.

**CONCLUSIONS**

We have described a unique case of cb1C defect revealing isolated pulmonary hypertension. Determining the etiology of pulmonary hypertension is essential to evaluate the severity of the disease and the treatment strategy and to assess prognosis. The recent reports associating pulmonary hypertension with mitochondrial diseases and to nonketotic hyperglycinemia underline that when evaluating a pediatric patient with pulmonary hypertension a careful metabolic screening should be included for the differential diagnosis.

**REFERENCES**

Cobalamin C Defect Presenting With Isolated Pulmonary Hypertension
Francesca G. Iodice, Luca Di Chiara, Sara Boenzi, Chiara Aiello, Lidia Monti, Paola Cogo and Carlo Dionisi-Vici

*Pediatrics* originally published online June 10, 2013;

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/early/2013/06/05/peds.2012-1945

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints
Cobalamin C Defect Presenting With Isolated Pulmonary Hypertension
Francesca G. Iodice, Luca Di Chiara, Sara Boenzi, Chiara Aiello, Lidia Monti, Paola Cogo and Carlo Dionisi-Vici
*Pediatrics* originally published online June 10, 2013;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/early/2013/06/05/peds.2012-1945