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

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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.

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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.¹ 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 mitochondrion. The impaired activity of these enzymes results in accumulation of homocysteine and methylmalonic acid (MMA). The impaired activity of these enzymes results in accumulation of homocysteine and methylmalonic acid (MMA). Plasma methionine as well as increased urinary excretion of methylmalonic acid. Plasma methionine deficiency 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 catheterization procedure confirmed pulmonary hypertension responsive to oxygen and nitric oxide. The following values were reported in the pulmonary artery: baseline 91/41/66 mm Hg (normal values = 15–25/8–15/20), after 100% oxygen 64/24/44 mm Hg, after nitric oxide 51/23/36 mm Hg (53 U.W./m²). The following values were reported (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.¹⁻⁶ Cardiovascular abnormalities 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.⁶ Cardiomyopathy and left ventricular noncompaction have been reported as well.⁶ 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.¹⁰ Isolated pulmonary hypertension in cblC patients without any other associations has never been to the best of our knowledge described before. Labrune et al¹¹ 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.¹² Thromboembolic complications have been reported in cblC defect as the result of hyperhomocysteinemia in inducing vascular damage.¹³ Brandstetter et al¹⁴ reported an infant with a probable cblC defect, a bronchiolitislike illness, and acute cor pulmonale secondary to pulmonary thromboembolism. However, this patient also showed seizure-like activity and hypotonia. Hemolytic uremic syndrome, which characteristically manifests itself in cblC defect with azotemia, thrombocytopenia, and hemolytic anemia,¹¹ is caused by a diffuse microangiopathy that represents the underlying mechanism causing both hemolytic uremic syndrome and communicating hydrocephalus.⁶ 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 our patient received hydroxocobalamin and betaine treatment and revealed a pattern that conformed to 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.

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.

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