ABSTRACT. Cyanosis is a physical finding that can occur at any age but presents the greatest challenge when it occurs in the newborn. The cause is multiple, and it usually represents an ominous sign, especially when it occurs in association with neonatal sepsis, cyanotic congenital heart disease, and airway abnormalities. Cyanosis caused by abnormal forms of hemoglobin can also be life-threatening, and early recognition is mandatory to prevent unnecessary investigations and delay in management. Abnormal hemoglobin, such as hemoglobin M, is traditionally discovered by electrophoresis, so the newborn screen, which is mandatory in several states, is a useful tool for the diagnosis. Although acquired methemoglobinemia, caused by environmental oxidizing agents, is common, congenital deficiency of the innate reducing enzyme is so rare that only a few cases are documented in the medical literature around the world. We present a neonate with cyanosis as a result of congenital deficiency of the reduced nicotinamide adenine dinucleotide-cytochrome b5 reductase enzyme. This infant was found to be blue at a routine newborn follow-up visit. Sepsis, structural congenital heart disease, prenatal administration, and ingestion of oxidant dyes were excluded as a cause of the cyanosis by history and appropriate tests. Chocolate discoloration of arterial blood provided a clue to the diagnosis. A normal newborn screen and hemoglobin electrophoresis made the diagnosis of methemoglobin M unlikely as the cause of the methemoglobinemia (Hb A 59.4%, A2, 1.8%, and F 38.8%). Red blood cell enzyme activity and DNA analysis revealed a homozygous form of the cytochrome b5 reductase enzyme deficiency. He responded very well to daily methylene blue and ascorbic acid administration, and he has normal growth and developmental parameters, although he shows an exaggerated increase in his methemoglobin level with minor oxidant stress such as diarrhea. Pediatrics 2003;112:e158–e161. URL: http://www.pediatrics.org/cgi/content/full/112/2/e158; cyanosis, methemoglobinemia, newborn, NADPH-cytochrome b5 reductase.

ABBREVIATIONS. PRBC, packed red blood cell; NADH, reduced nicotinamide adenine dinucleotide.

Cyanosis is a physical finding of multiple causes that can occur at any age but poses the greatest diagnostic and management challenges when it involves the newborn infant. The clinical manifestation of cyanosis depends on the amount of reduced hemoglobin in the circulation. Approximately 5 g/dL reduced hemoglobin is required to produce the clinical manifestation of cyanosis in disorders involving deoxygenated hemoglobin. However, only 1.5 g/dL is required for disorders involving nonfunctional hemoglobin. The differential diagnosis of cyanosis therefore can be divided into 2 major groups: disorders involving deoxygenated hemoglobin and disorders of abnormal hemoglobin. The former and more common group can be further categorized on the basis of anatomic location of the disorder: the central nervous system and muscle, the upper airway, the lungs, the heart, and the circulatory system. Abnormal forms of hemoglobin such as methemoglobin can also cause cyanosis when present in significant amounts. Methemoglobinemia is an uncommon clinical problem in the newborn infant and when present is usually caused by environmental toxicity from strong oxidizing agents and only very rarely from an inherited disorder of hemoglobin metabolism. Although an autosomal recessive form of methemoglobinemia was described in 1845, it is so rare that no known incidence and prevalence has been established.

CASE REPORT

A 24-day-old 3.4-kg infant was seen in the office for a routine postnatal follow-up appointment. He was born at full term from spontaneous vaginal delivery to a 26-year-old gravida 5 mother with full antenatal care and no perinatal problems. Apgar score was 8 and 9 at 1 and 5 minutes, respectively. He was discharged from the hospital on the second day after his first hepatitis B immunization. He had been well since discharge, taking approximately 4 oz of premixed formula every 4 hours, and his development had been appropriate. His mother did not recognize that his coloration was unusual and denied use of any medications. Parental consanguinity was denied.

Mild central cyanosis was noted on physical examination. Pulse oximetry was 87% in room air, so he was transferred to the emergency department of our regional children’s hospital. In the emergency department, the vital signs were T° 99°F, heart rate 182/min, respiratory rate 36/min, saturation on pulse oximetry 91%, with fraction of inspired oxygen 1.0 and a Dextrostix of 78 mg/dL. Blood pressure measurement could not be obtained, despite rapid infusion of 20 mL/kg crystalloid fluids. His heart continued to appear dusky and cyanotic and was electively intubated with a presumed diagnosis of septic shock. Appropriate cultures were obtained, broad-spectrum intravenous antibiotic coverage was started, and he was transferred to our multidisciplinary pediatric intensive care unit.
Ches...
Type 2 congenital methemoglobinemia does not run such a benign course. It constitutes approximately 10% of all cases and usually causes death within the first few years of life. The severity of disease is a direct consequence of the global deficiency in NADH-cytochrome b5 reductase activity that characterizes this class of the disorder. The distinguishing feature of type 2 and the sine qua non is an unremitting, progressive neurologic deterioration. First described in a paper published in the British Medical Journal, this fulminant disease is associated with mental retardation, microcephaly, opisthotonus, athetoid movements, and generalized hypertonia.14

Individuals with congenital methemoglobinemia will typically present with cyanosis in the neonatal period. In managing a cyanotic patient, physicians will often obtain an arterial blood gas analysis, in addition to monitoring pulse oximetry. Unfortunately, the patient with methemoglobinemia will often have normal values for both. In interpreting arterial blood gas data, the clinician must remember that the PaO₂ refers to the amount of dissolved oxygen in the blood and in no way reflects hemoglobin saturation and thus arterial oxygen content. Patients with life-threatening methemoglobinemia may have a normal PaO₂ and a falsely elevated pulse oximetry reading.19

Unlike a pulse oximeter, which measures light absorbance at 2 wavelengths (660 nm and 940 nm, corresponding to the absorption of oxyhemoglobin and deoxyhemoglobin, respectively), a co-oximeter measures light absorbance at 4 different wavelengths. These wavelengths correspond to the absorption characteristics of deoxyhemoglobin, oxyhemoglobin, carboxyhemoglobin, and methemoglobin. As a consequence, co-oximetry can distinguish between these 4 configurations while providing a more accurate measurement of oxygen saturation. Therefore, in patients who present with cyanosis of uncertain cause, co-oximetry measurements are a valuable diagnostic tool.2

Hemoglobin electrophoresis is also a very helpful adjunct in differentiating the different causes of congenital cyanosis. It will identify hemoglobin M, a hemoglobin variant that causes cyanosis as a result of structural changes in the α or β chains that stabilize the hemoglobin in the ferric state. These structural changes are attributable to amino acid substitutions at positions close to the heme groups in the hemoglobin molecule. Cyanosis is noticed at birth or within 4 to 6 months thereafter.

Once the diagnosis of methemoglobinemia has been made, there are various assays available to quantify NADH-cytochrome b5 reductase activity.20 Adult levels of enzyme function are attained by 2 to 3 months of age, and in the neonate, methemoglobin reductase levels are normally 60% of the normal adult value.2 When congenital methemoglobinemia is suspected, enzyme activity in all immediate family members should be evaluated. As a result of autosomal recessive transmission, by definition our patient must have both alleles, and, accordingly, each parent contributes 1 allele. In heterozygous deficiency, methemoglobin reductase activity is low, as seen in both parents of our patient. Heterozygotes (both parents and the 2 siblings) will have a lower threshold for acquired methemoglobinemia in response to exogenous oxidative stress. However, their level of enzyme activity is not low enough to produce clinical disease under normal circumstances. All other members of our patient’s family had methemoglobin levels below 2%.

In the treatment of hereditary enzymopenic methemoglobinemia, many variables have to be taken into consideration. Often, patients will remain completely asymptomatic. However, methemoglobinemia causes a leftward shift of the oxygen-hemoglobin dissociation curve. Furthermore, in the neonatal period, there is a persistence of fetal hemoglobin and a more pronounced difficulty of oxygen dissociation at the cellular level. These factors, combined with the deleterious effects of reduced arterial oxygen content in the neonatal period, make it reasonable to attempt to keep the methemoglobin level under 10% during this period.2

Methylene blue is the treatment of choice for severe methemoglobinemia.2,21 In the presence of nicotinamide adenine dinucleotide phosphate (NADPH), methylene blue is converted to leucomethylene blue, which results in nonenzymatic reduction of methemoglobin.2,22 Ascorbic acid directly reduces methemoglobin, but the rate of the reaction is too slow for it to be effective when used alone.10 Finally, if the combination of ascorbic acid and methylene blue fails to reduce the methemoglobin level, then hyperbaric oxygen and exchange transfusions are alternative therapy.21

Our patient demonstrated all of the classical features of congenital methemoglobinemia on presentation. He was treated in the emergency department as a child in septic shock as a result of the usual presentation of a rare disease. His initial level of the cytochrome b5 reductase enzyme level was skewed as a result of the PRBC transfusion. A repeat level 3 months after the transfusion revealed his actual enzyme level of 4.2. It is impossible at this point to determine whether he will be classified as having type 1 or 2. This has significant prognostic implications, and full genetic analysis of the family is in progress. In summary, congenital methemoglobinemia is a very rare but treatable cause of neonatal cyanosis that should be considered in the differential diagnosis of cyanosis and septic shock in the neonatal period.

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