Jeanne A. Krick, MD,* Tendo Kironde, MD,† Melinda Hendrickson, MD*

*Division of Neonatology and †Department of Pediatrics, University of Washington, Seattle, WA

PRESENTATION

A term male infant is born via spontaneous vaginal delivery at 40 2/7 weeks’ gestational age to a gravida 2 para 2 mother. Her pregnancy was complicated by maternal tobacco use and inadequately treated group B Streptococcus colonization. The infant is vigorous at birth with Apgar scores of 7 and 9 at 1 and 5 minutes, respectively. The infant has growth parameters appropriate for gestational age and examination in the delivery room reveals bilateral clubfeet, but is otherwise normal.

At 11 hours of age, the infant is noted to have cyanosis with breastfeeding and is found to have an oxygen saturation of 83% measured in the right upper extremity with pulse oximetry. His breathing is unlabored and lung sounds are clear to auscultation. Heart rate and rhythm are normal and no murmurs are appreciated. Blood pressures in all 4 limbs, peripheral pulses, and perfusion are also all appropriate.

The infant receives oxygen supplementation via nasal cannula, which is subsequently escalated to nasal continuous positive airway pressure (CPAP) of 6 cm H₂O with a fraction of inspired oxygen (FiO₂) of 1.00. Despite these interventions, his pulse oximetry saturations remain between 70% and 80%. Chest radiography reveals a normal cardiac size and silhouette, with clear bilateral lung fields. A complete blood cell count with differential and blood glucose concentrations is also unremarkable. Blood culture specimens are obtained and the infant starts broad-spectrum antibiotics for empirical treatment of possible early-onset neonatal sepsis.

Given the concern for congenital cyanotic heart disease, the infant is transported via air ambulance to our tertiary care children’s hospital. Echocardiography performed on admission at 16 hours of age reveals normal ventricular size and function, as well as an expected patent ductus arteriosus and foramen ovale with small left-to-right shunt. An arterial blood gas measurement is obtained while the patient is receiving an FiO₂ of 1.00, which reveals a partial pressure of arterial oxygen (Pao₂) of 279 mm Hg, while the measured oxygen saturation via pulse oximeter on the right upper extremity reads only 78%. The remainder of the blood gas value is within normal limits. Repeat arterial blood gas measured while the patient is breathing room air shows a Pao₂ of 73 mm Hg.

In the midst of the medical workup, the patient’s mother and maternal grandfather arrive. A detailed family history is obtained and the team learns that the infant’s mother herself was hospitalized in the NICU shortly after birth for cyanosis that persisted until 5 weeks of age. The patient’s grandfather states that the mother was later diagnosed with a novel fetal hemoglobinopathy that resolved over time. Her diagnosis is subsequently confirmed and a presumptive diagnosis for the patient is made.
DISCUSSION

Diagnosis

The differential diagnosis for cyanosis in a newborn is broad, but it can be delineated into 2 major categories: conditions that result in deoxygenated hemoglobin and those that are due to an abnormality in the hemoglobin molecule itself. (1) Often a first diagnostic step, the hyperoxia test is a simple clinical test that can be helpful in differentiating cardiac etiologies of hypoxemia from other causes, such as pulmonary or hematologic. For the patient in the current case, because of the presence of a high PaO2 with a low pulse oximetry reading in the setting of an FiO2 of 1.00, along with a normal echocardiogram and cardiac examination, it is unlikely that his cyanosis is of a cardiac or pulmonary origin. With the added family history, there is a high index of suspicion for the presence of a hemoglobinopathy, specifically a methemoglobinemia. On further review of the mother’s records, it is determined that she was diagnosed with Hb FM-Fort Ripley, a fetal hemoglobinopathy. Based on this information, a presumptive diagnosis is made, “which is later confirmed by the newborn screen (Fig).” The nasal CPAP is discontinued and the infant is discharged from the hospital and continues to receive close follow-up. Over the course of the next 2 months, his cyanosis completely resolves.

The Condition

Methemoglobinemia is a rare cause of cyanosis in neonates. Methemoglobin is the altered state of hemoglobin that occurs when the ferrous iron (Fe2⁺) is oxidized to its ferric state (Fe3⁺) within the heme moiety of hemoglobin. (1) Heme in the ferric state is unable to carry oxygen and leads to the clinical finding of cyanosis. (2)

Methemoglobinemia can be acquired or congenital. Acquired methemoglobinemia can be caused by a number of medications and commercially available chemicals. Acquired methemoglobinemia ranges in severity, but can be life threatening and require acute management. (3)

Congenital methemoglobinemia is very rare and can be caused by deficiencies in an essential methemoglobin reduction enzyme (NADH-cytochrome b5 reductase) or its cofactors, or by abnormal hemoglobin variants. (3) In such cases of abnormal hemoglobin variants, known as M hemoglobins, abnormalities can be found in the α-globin, β-globin, or γ-globin chains. Most patients with hemoglobin M disease are asymptomatic and, in contrast to acquired methemoglobinemia, typically do not have any clinical sequelae and do not require any therapeutic interventions.

Depending on the globin chain affected, cyanosis from hemoglobin M disease may be present at different stages of life. In disorders in which the α-globin chain is affected, cyanosis may appear at any time, because this globin chain is present in both adult and fetal hemoglobins. In disorders affecting the γ-globin chain, cyanosis will appear during the neonatal period and will be transient, resolving when the γ-globin is replaced by β-globin and adult hemoglobin is formed. As such, when the β-globin chain is affected, cyanosis will not appear until a few months after birth when adult hemoglobin has replaced fetal hemoglobin.

Hb FM-Fort Ripley is caused by a single amino acid substitution causing a mutant γ-globin chain, leading to a

Figure. Isoelectric focusing (IEF) from newborn screen performed by the Washington State Newborn Screening Lab. The hemoglobin variant (*) was picked up on the initial IEF test. The variant band is washed out in the Hb C region and did not fully resolve. The hemoglobin variant was highly unstable and was absent on repeat confirmatory testing and so the newborn screen was reported as normal. C=Hb C; S=sickle Hb; F=fetal Hb; A=adult hemoglobin.
functionally abnormal fetal hemoglobin molecule and congenital methemoglobinemia. (4) Because the heme iron remains in the ferric state, it cannot carry oxygen and is relatively resistant to reduction by NADH-cytochrome b5 reductase. (5) This causes slightly elevated methemoglobin levels in affected patients, leading to the primary finding of cyanosis. As it affects the γ-globin chain, it leads to cyanosis exclusively within the first few months of age and gradually improves over time as fetal hemoglobin is replaced by adult hemoglobin. (2)

Hb FM-Fort Ripley has an autosomal dominant inheritance pattern with incomplete penetrance. (6) Such a variant in the γ-globin chain may go undetected on newborn screening because of its unstable nature. The diagnosis of Hb FM-Fort Ripley has been made in some familial cases by next-generation sequencing, where a missense mutation in a single codon was found to be the source of the variant. (7)

Management
Cyanosis in patients with Hb FM-Fort Ripley typically resolves over the first few months of age with the transition to adult hemoglobin. Patients affected by this condition, as well as those with other M hemoglobins who have only mild elevations in methemoglobin levels, are typically asymptomatic. For most patients, there is no clinical sequela and no treatment is required.

Given the rarity of the condition and the challenges of quickly identifying this particular congenital methemoglobinemia, a detailed family history was key to making the diagnosis in a timely manner. Early diagnosis may allow clinicians to pursue fewer interventions after the exclusion of more serious and harmful etiologic factors. Our patient was discharged from the hospital with instructions to follow up with hematology for expectant management of the disease.

Lessons for the Clinician
• The differential diagnosis for cyanosis in a neonate is broad and should consider both disorders that lead to deoxygenated hemoglobin and those that are due to an abnormality involving the hemoglobin molecule itself.
• Methemoglobinemia can be congenital or acquired and differ in management.
• Hemoglobin M disorders can cause cyanosis at different ages, depending on the globin chain affected.
• Obtaining a family history, including the birth history of close relatives, can be critical to the diagnosis of rare conditions in neonates.

American Board of Pediatrics Neonatal-Perinatal Content Specifications
• Know the biochemical characteristics of fetal hemoglobin.
• Know the clinical and laboratory features of neonatal hemoglobinopathies, including the thalassemias.
• Know the indications for and approaches to screening for hemoglobinopathies in the newborn population.

References
Case 2: The Well-Appearing Cyanotic Infant
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