A 5-Month-Old Infant with Diffuse Cyanosis and No Other Symptoms

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A 5-month-old female infant was sent to the pediatric emergency department (ED) of our hospital by her primary care physician, who reported diffuse cyanosis that began a few hours earlier without any other signs or symptoms.

She was born at full term by vaginal delivery after an uneventful pregnancy.

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Her parents were not related. She lived with her parents in an urban area and had no known allergies or contact with infections. No noteworthy diseases were reported in her family history.

The child was being breast-fed and had regular growth. She had recently started weaning with fruits and vegetables, with good compliance. Her parents reported that no drugs or medicines were being administrated at home.

Upon presentation to the ED the child was in good general condition and without respiratory distress, but she was diffusely cyanotic and slightly irritable. She was afebrile, her pulse rate was 110 beats per minute, and her oxygen saturation was 92% in room air. The physical examination, including neurologic examination, was completely normal except for a capillary refill time of 3 to 4 seconds. Oxygen (12 L/min) by facemask with reservoir was immediately administered, but there was no improvement in her oxygen saturation or in the cyanosis.

An intravenous access and an arterial blood sample were obtained, and the blood was found to be darker than normal.

Blood tests showed only slight thrombocytosis (429×10^9/L), with normal troponin level. In the arterial blood gas, a slight respiratory alkalosis (pH 7.49; partial pressure of carbon dioxide [pCO_2] 29 mm Hg; partial pressure of oxygen [pO_2] 95 mm Hg, and bicarbonate [HCO_3] 21.4 mmol/L) was noted, with methemoglobinemia of 31.6% (normal value <1.5%).

Editor's note: Each month, this department features a discussion of an unusual diagnosis. A description and images are presented, followed by the diagnosis and an explanation of how the diagnosis was determined. As always, your comments are welcome via email at pedann@Healio.com.

Diagnosis:

Acute Methemoglobinemia

Based on the test results, a diagnosis of acute methemoglobinemia was made. In addition to oxygen administration, the child was given intravenous treatment with methylene blue (1 mg/kg).

A few hours after the start of treatment, oxygen saturation increased to 100%, and the cyanosis gradually disappeared. After 4 hours, the control arterial blood gas showed a methemoglobinemia value of 1%, so the methylene blue was discontinued. During the hospitalization, the patient maintained normal vital parameters, and 2 days later she was discharged with good general condition.

To find a possible cause of the methemoglobinemia, the parents were interviewed again with the intention of exploring the possibility that the baby had been exposed to toxic substances. After a detailed investigation, the mother reported that she had begun weaning in the morning, feeding her daughter chard soup. Subsequently, it became clear that the patient suffered from an acute acquired methemoglobinemia due to nitrate poisoning in the diet.

DISCUSSION

Cyanosis is the appearance of a bluish color of the skin and mucous membranes due to an increased concentration of deoxygenated hemoglobin (≥5 g/dL) in the capillary bed.[1] Two mechanisms are involved in cyanosis: systemic arterial oxygen desaturation, and increased oxygen extraction from the tissues. Based on these mechanisms, two types of cyanosis are described: central and peripheral. Central cyanosis refers to the presence of diffuse cyanosis of the skin and also involves mucous membranes, lips, and tongue. Peripheral cyanosis, also known as acrocyanosis, refers to the presence of cyanosis in the extremities and is due to an increased oxygen extraction resulting from sluggish movement of blood through the capillary circulation. Acrocyanosis is often seen in infants as a consequence of transient hypothermia inducing peripheral vasoconstriction. However, other causes of cyanosis, such as vasomotor instability, venous obstruction, polycythemia, and low cardiac output, should be evaluated.[2]

Similarly, central cyanosis may be caused by a wide range of disorders involving one or more systems. Among these, cardiac and pulmonary abnormalities are the most common, but central nervous system impairment, methemoglobinemia (decreasing hemoglobin's affinity for oxygen), infection, and other metabolic abnormalities should be also considered.[2]

To distinguish between congenital or acquired forms and to detect the cause of a diffuse cyanosis it is essential to consider the age of the child, time of onset of the cyanosis, and the associated symptoms. Moreover, the possible intake of drugs or toxic substances, such as nitrates and dapsone, should be investigated. Biochemical investigations, such as a complete blood count and arterial blood gases, and radiologic investigations are useful to achieve the definitive diagnosis. In particular, a chest radiograph, electrocardiogram, and, when available, echocardiography allow the physician to evaluate the heart and the lungs, excluding any other cardiac and pulmonary causes of cyanosis.[3]

The importance of acquired methemoglobinemia should not be underestimated because it can be fatal (methemoglobin level >70%) if not promptly recognized and treated.

Whereas cyanosis can be appreciated for methemoglobin levels between 10% and 20%, other symptoms, such as respiratory distress, dizziness, headache, and fatigue, usually appear at levels between 20% and 50%. Higher levels induce lethargy and stupor. Our patient was slightly irritable, probably because of the high concentration of methemoglobin related to her young age. Moreover, a characteristic finding presented in this patient, and frequently observed in patients with methemoglobinemia, was the chocolate-brown color of the blood due to the hemoglobin's inability to bind oxygen.[4]

Methemoglobinemia is a blood disorder characterized by abnormal levels of oxidized hemoglobin in which the iron in the heme group is oxidized from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state.[5] Therefore, methemoglobin has a greater oxygen affinity; consequently, the oxygen dissociation curve shifts to the left and less oxygen can be released in the tissues. For this reason, methemoglobin is useless as an oxygen carrier, leading to cyanosis.[6] Methemoglobin is primarily reduced through an enzyme system, the nicotinamide adenine dinucleotide (NADH) methemoglobin reductase, which is found in both erythrocytes and somatic cells. Other less important mechanisms that reduce methemoglobin are glutathione peroxidase, superoxide dismutase, and catalase.[7]

Hereditary forms of methemoglobinemia are rare and usually due to hemoglobin variants associated with the production of methemoglobin—generally defined as hemoglobin M—or with NADH methemoglobin reductase deficiency. Hemoglobin M is an autosomal dominant–transmitted disease. It is caused by the replacement of a histidine with a tyrosine on either the alpha or beta subunit of the hemoglobin mol-

Figure 1. Chard, a leafy vegetable that is high in nitrates.

ecule, resulting in stable oxidation of the ferric iron in hemoglobin and, from an early age, consequent cyanosis. NADH methemoglobin reductase deficiency is a recessively inherited disorder due to deficiency of NADH cytochrome b5 reductase and is classified as type I or type II, depending on whether the enzymatic deficiency is present only in erythrocytes (type I) or in all cells (type II). People who are heterozygous with NADH cytochrome b5 reductase deficiency can develop severe cyanosis under conditions of high oxidative stress, such as the ingestion of oxidant drugs.[6,8] In the case reported here, cyanosis was observed only in the mentioned event and did not occur again; thus, a genetic analysis was not considered appropriate.

Acquired conditions of methemoglobinemia due to endogenous (related to systemic acidosis) or exogenous (toxin-induced) causes are more frequent. In all of these cases, methemoglobinemia is directly induced by iron oxidation within hemoglobin, or indirectly through the release of free radicals.[9] Although the disorder can occur at any age, young infants (especially younger than age 6 months)

are particularly prone to developing endogenous methemoglobinemia. They actually have low erythrocyte levels of cytochrome b reductase and high levels of fetal hemoglobin, which is more sensitive to oxidation.[6] Furthermore, infants have low stomach acid production and a higher intestinal Ph, which promotes the growth of gram-negative organisms that convert dietary nitrates to nitrites and induce methemoglobin formation.[10] The combination of food containing nitrate and immaturity or low levels of cytochrome b reductase with higher pH in stomach may be conducive to metemoglobinemia in infants. Although exogenous methemoglobinemia is mainly due to ingestion or exposure to oxidizing agents, such as toxic substances or drugs (among which the most common are local anesthetics such as lidocaine[11]), another common cause is the ingestion of food (in particular, vegetables such as green beans, courgette, carrots, squash, spinach, and chards [**Figure 1**]) or water (used in preparation of infant formula) containing high levels of nitrates.[12]

Although World Health Organization guidelines[13] recommend exclusive

breast-feeding up to age 6 months, several studies show that solid food should be introduced between ages 4 and 6 months to avoid short- and long-term adverse effects.[14,15] Nevertheless, the introduction of particular foods before age 6 months, especially in large quantities and if not properly stored, may represent a risk to a child's health. Because of the above-mentioned anatomic and functional characteristics of infants younger than age 6 months, foods high in nitrates may represent a potential hazard; therefore, they should be avoided. Whereas previous studies have reported the risk of nitrate poisoning in case of intake of infant formula diluted with broth of chards or with rural (ie, untreated) water,[16,17] the risk of intoxication provoked by early introduction of foods rich in nitrates, such as chard, during initial weaning has not yet been described. Because nitrate poisoning often derives from the fact that parents are not properly informed about the risk inherent in food high in nitrates, it is important that pediatricians and other health care providers involved in the care of children recommend parents follow some precautions in preparing an infant's food. In particular, they should use no more than 5 to 10 leaves of leafy vegetables, like chards and spinach, for the preparation of vegetable soup, and they should introduce these preparations in the child's diet only after age 6 months, avoiding multiple administrations during the day.[18] Vegetable soup or broth should be kept in the refrigerator for no more than 24 hours; otherwise they should be frozen, as long intervals between preparation and consumption promote the conversion of nitrates to nitrites.[19]

CONCLUSION

Methemoglobinemia should be suspected when children present with diffuse cyanosis that does not improve

with oxygen administration. Whereas the diagnosis is easily confirmed by measuring the methemoglobin in an arterial blood sample, the cause must be carefully investigated and removed as soon as possible to avoid more severe consequences. Therefore, pediatricians should advise parents to avoid leafy vegetables such as chards and spinach during weaning and to introduce these preparations in a child's diet only after age 6 months, and to avoid multiple feedings during the day.

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