Article

Unexplained neonatal cyanosis: don't forget the dyshemoglobinemias

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Keywords

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Abstract

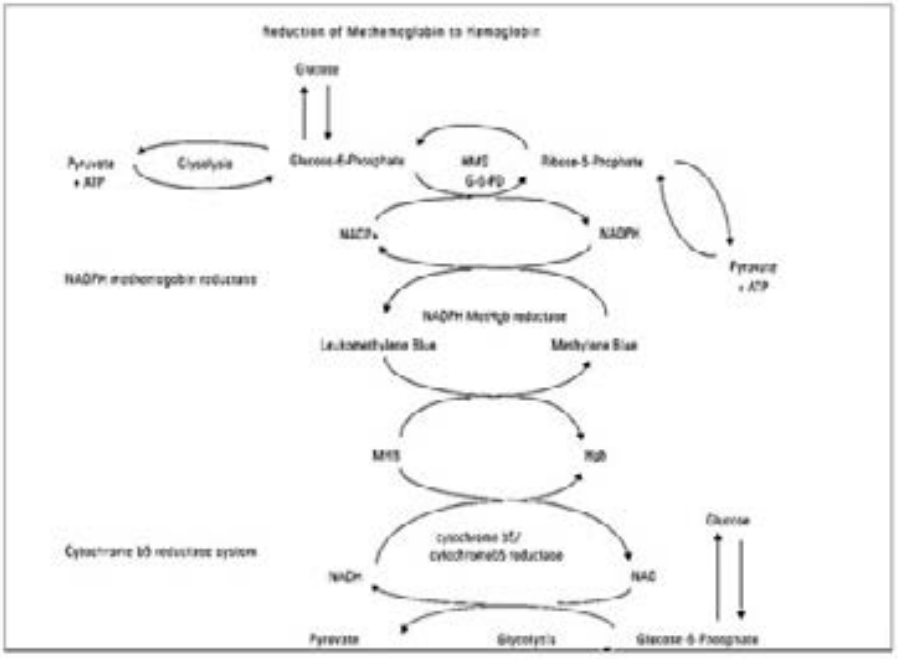
The diagnosis of dyshemoglobinemias is a challenge. A high index of suspicion is required in neonates with central cyanosis out of proportion to the oxygen saturation, not responding to supplemental oxygen and an oxygen saturation gap exceeding 5%. Gold standard for the diagnosis is co-oximetry. We report two neonates with rare forms of dyshemoglobinemias. The first neonate has a, probably congenital, methemoglobinemia and was treated with methylene blue (rescue treatment) and vitamin B2 (maintenance therapy). The second neonate had a sulfhemoglobinemia due to Escherichia coli and was treated with blood transfusions. Early recognition of dyshemoglobinemias is vital because early therapy is life-saving.

Introduction

The differential diagnosis of central cyanosis in a newborn infant not only includes respiratory, cardiac, pulmonary and neurological causes, but also dyshemoglobinemias or hemoglobinopathies have to be considered. Dyshemoglobinemias are disorders in which the oxygen-carrying capacity of hemoglobin is impaired due to alterations in its structure (1).

In methemoglobin, hemoglobin is oxidized from the ferrous (Fe2+) to the ferric state (Fe3+) in response to oxidative stress (1). Normally protective counteracting mechanisms keep the methemoglobin level below 1% of the total hemoglobin level (3). The most important pathway is the cytochrome b5-methemoglobin reductase (CYB5R) pathway which converts methemoglobin to hemoglobin (1, 3, 4). The second pathway is the nicotinamide adenine dinucleotide phosphate (NADPH)-methemoglobin reductase pathway (4-5) (see Figure 1). Other pathways, which need an exogenous medium, are the flavine reductases (6). Furthermore, intracellular glutathione and ascorbic acid reduce oxidant compounds (4). Whenever these counteracting mechanisms fail to keep the methemoglobin below 1%, methemoglobinemia occurs (7). The pathophysiology of sulfhemoglobinemia is not completely understood. Sulfhemoglobin is formed when there is a second reaction in methemoglobin which irreversibly incorporates sulfur into heme (3). The diagnosis of dyshemoglobinemias is a challenge as neonates can present with various vague or life-threatening symptoms.

Figure 1: *Pathways for the reduction of methemoglobin to hemoglobin. Figure from Wright RO et al. (3)*
(ATP: Adenosine triphosphate; HMS: hexose monophosphate shunt; MHB: methemoglobin; Hgb: hemoglobin. NAD: nicotinamide adenine dinucleotide; NADP: nicotinamide adenine dinucleotide phosphate; NADPH: nicotinamide adenine dinucleotide phosphate hydrogenase.)



Materials and methods

This narrative review, illustrated with case descriptions, gives an update on the pathophysiology, diagnosis and treatment of two rare dyshemoglobinemias.

Cases

The first case is a girl born at 35 weeks of gestation. Her birth weight was 1930 grams (< 10th percentile), her length and head circumference were within normal ranges. She was the third child of healthy non-related parents. One sibling died suddenly, at the age of 22 days, due to a cardiogenic shock with an unexplained hyperchloremic metabolic acidosis.

On day of life (DOL) 7, the girl vomited and had a decreased state of consciousness. Further physical examination and cardiorespiratory parameters were normal. Venous blood gas analysis showed hyperchloremic metabolic acidosis with a pH of 7,24 (reference range 7,35-7,45); base excess (BE) of -10,9 mmol/L; lactate of 1,23 mmol/l (normal < 2 mmol/l); chloride of 134 mmol/l (reference range 101-109 mmol/l) and bicarbonate of 15,6 mmol/l (reference range 21-35 mmol/l). An intravenous bolus of NaCl 0,9% and sodium bicarbonate were given with normalization of the pH and neurologic status. C-reactive protein (CRP) was negative. Gastro-intestinal and renal losses of bicarbonate were excluded. On DOL 14, the girl developed central cyanosis with arterial saturations measured by pulse oximetry around 85-90%. There was tachycardia with normal capillary refill and no respiratory distress. Her neurological status was normal. Capillary blood gas analysis showed metabolic hyperchloremic acidosis (pH 7,29; BE -2,7 mmol/l; lactate 2,7 mmol/l; sodium 146 mmol/l, chloride 124 mmol/l, bicarbonate 22 mmol/l). Blood examination showed a hemoglobin of 10,9 g/dl, no leukocytosis and CRP was negative. Lactate increased to 8,2 mmol/l. Administration of 100% of oxygen through nasal cannula had no effect on the oxygen saturation. Echocardiography showed a hyperdynamic heart without structural abnormalities. Because we thought of a hemoglobinopathy, methemoglobin level was determined using a blood gas analyzer (ABL90 FLEX PLUS, Radiometer Medical ApS, Bronshoj, Denmark). Methemoglobin level was 72% (normal < 1%). Urgently methylene blue was administered intravenously (1 mg/kg). Saturation raised within 20 minutes to 100%. There were no arguments for provoking medications or feedings that can cause acquired methemoglobinemia. Because of the young age and the unexplained death of the sibling, it is likely that this is a congenital form of methemoglobinemia. Nevertheless, there were no pathogenic mutations in the CYB5R3, CYB5A, HBB, HBA1, HBG1 and HBG2 gene. Glucose-6-phosphate deficiency (G6PD) and hemoglobinopathy M were excluded. Hemoglobin electrophoresis of both parents was normal. During hospitalization, the girl needed administration of methylene blue twice more because of symptoms and recurring elevated methemoglobin of 28% and 39%. Maintenance therapy with vitamin B2 (4 mg/kg/day) was started. At the age of 6 weeks, she was discharged home. Currently, she is ten months old and her methemoglobin levels remains low.

The second case is a girl born at 28 weeks of gestation. She received endotracheal surfactant administration through a less invasive surfactant application because of respiratory distress syndrome. Thereafter, her respiratory parameters were stable on non-invasive continuous positive airway pressure without supplemental oxygen. On DOL 10, her oxygen saturations dropped to 85-90% and did not respond to supplemental oxygen. Radiography of the chest, abdomen and echocardiography were normal. Antibiotics were started because of suspicion of a late onset sepsis with a CRP of 15 mg/l (normal < 10 mg/l) and diarrhea. Culture of the stools were positive for two different Escherichia coli species (without Shiga producing toxins). Hemoculture was negative as well as viral cultures. Total hemoglobin level was 9,1 g/dl (reference range 10-17 g/dl). Arterial blood gas analysis showed a partial oxygen pressure of 143 mmHg after oxygen administration (with a simultaneous pulse oximetry oxygen saturation of 86%) and detected sulfhemoglobin. Hemoglobin electrophoresis showed that 3,5% of the hemoglobin was sulfhemoglobin. As cause of the sulfhemoglobinemia we considered the E. coli. The girl nor her mother received sulfur containing medications or were exposed to sulfites. Breast milk tested negative for sulfites. The girl was treated with two packed cell transfusions. Her oxygen saturation gradually improved and respiratory support was ceased on DOL 56.

Discussion

Etiology

A variety of medications, chemicals and high nitrate food can cause acquired methemoglobinemia (7). Newborns are at risk for acquired methemoglobinemia because fetal hemoglobin is oxidized more rapidly and their CYB5R activity is only 50-60% of the activity in adults (3,7). Also, individuals with G6PD deficiency are more prone to methemoglobinemia (3,7). Monitoring of the methemoglobin level in neonates treated with higher doses of inhaled nitric oxide is therefore suggested (21). The acquired forms of methemoglobinemia are beyond the scope of this article.

CYB5R deficiency, the most frequent form of congenital methemoglobinemia, is very rare and the actual incidence is not known. In type 1 of this autosomal recessive condition only the red blood cells are deficient (7). These children have a normal life expectancy and have only well-tolerated cyanosis that can cause later on fatigue, headache and dyspnea with exertion (7). In a type 2 CYB5R deficiency all cells are deficient (7). These children have severe neurological damage, failure to thrive and usually die before one year of age (7). Cytochrome b5 deficiency is another, very rare, autosomal recessive form of methemoglobinemia (8). Genetic deficiencies of the NADPH-methemoglobin reductase pathway usually do not result in methemoglobinemia because of the minor role it plays in methemoglobin reduction (3). Another cause of congenital methemoglobinemia is hemoglobin M, in which an amino acid substitution in the alfa or beta (or gamma) chain of hemoglobin makes it more difficult for the enzyme to transform Fe3+ to Fe2+ (9). It is an autosomal dominant condition and most people are asymptomatic (9).

Sulfhemoglobinemia is usually drug-induced (10). But the source of sulfur is not always apparent. Although rare, it can originate from hydrogen sulfide released by intestinal organisms, e.g. in patients with constipation, Morganella morganii or Escherichia coli infection (11-13). Endogenous glutathione may also serve as a sulfur donor (3,14).

Diagnosis

As the ability of heme to bind oxygen is decreased in meth- and sulfhemoglobin, cyanosis is often the first clinical sign (1). Cyanosis develops when methemoglobin or sulfhemoglobin exceeds 15% or 5% of the total hemoglobin level respectively (3,10). As was in our case, the cyanosis is out of proportion to a given oxygen saturation level. Normally, pulse oximetry measures light absorbance at two distinct wavelengths (660 and 940 nm) to determine the ratio of oxyhemoglobin to deoxyhemoglobin (15). Methemoglobin absorbs the light equally at both wavelengths, while sulfhemoglobin has a greater absorbance at 660 nm (10). This distorts the ratio of oxyhemoglobin to deoxyhemoglobin measured by pulse oximetry and give stable saturations around 85% (3,15). There is a poor response of the saturation value measured by pulse oximetry to supplemental oxygen (15). In contrast, supplemental oxygen falsely increases the partial arterial oxygen pressure and the calculated saturation of an arterial blood gas (3). If this oxygen saturation gap exceeds 5%, the patient's hemoglobin may be abnormal (15) (see Table 1). At a neonatal intensive care unit or pediatric ward, there is easy access to point of care capillary blood samples, while obtaining arterial samples is more challenging. In neonates the calculated oxygen saturation range on a capillary blood sample is 80,5±8,5% with a pulse oximetry saturation of 98±1,9% (16). So, the oxygen saturation gap is useless in capillary samples, as in our case. Therefore, we recommend to obtain an arterial blood sample in case of an abnormal pulse oximetry result to aid in the differential diagnosis. Clues for diagnosis of dyshemoglobinemias are summarized in table 1.

Table 1: Clues for the diagnosis of dyshemoglobinemias in patients with cyanosis

Clues for the diagnosis of dyshemoglobinemias in patients with cyanosis
Cyanosis out-of-proportion to oxygen saturation
Oxygen saturation gap (SaO_2 – SpO_2) > 5%
No change in pulse oximetry with supplemental oxygen administration
Normal arterial oxygen pressure and low SpO_2

SaO_2: calculated arterial oxygen saturation from a blood gas; SpO_2: arterial oxygen saturation read from a pulse oximetry

The gold standard for the diagnosis of dyshemoglobinemias is co-oximetry. Co-oximetry measures the concentration of different types of hemoglobin through spectrophotometry using different wavelengths (3). Not all co-oximeters can differentiate between meth- and sulfhemoglobin as they have spectrophotometrically similarities (17). In our cases an ABL90 FLEX PLUS (Radiometer Medical ApS, Bronshoj, Denmark) was used, which is accurate till sulfhemoglobin exceeds 10%. Diagnosis of sulfhemoglobinemia is confirmed by spectrophotometry or gas chromatography/mass spectrometry (17).

Besides central cyanosis, other symptoms of methemoglobinemia in neonates are dyspnea, discomfort, lethargy and tachycardia. In older children also coughing, headache, dizziness and weakness are reported (3,7). These symptoms appear when the methemoglobin level increases to 20-45%. An increase above 45% causes acidosis, arrhythmias, heart failure, convulsions or coma; levels above 70% are usually lethal (3,7). In contrast, symptoms of sulfhemoglobinemia are usually milder (14). Levels of sulfhemoglobin above 60% are associated with mortality (11).

Another clinical clue is the chocolate-brown color of the blood of a patient with a meth- or sulfhemobloginemia (3). In case of methemoglobinemia, a drop of blood does not change with light exposure (3). In case of application of potassium cyanide, methemoglobin turns bright red while sulfhemoglobin stays dark brown (15).

We found no clear explanation for the hyperchloremic metabolic acidosis in our first patient. Older publications suggest that hyperchloremia facilitates the conversion of hemoglobin to methemoglobin (18,19). Additional suggested risk factors in neonates are: weight below the tenth percentile, as was in our case, immature enzyme systems which are less efficient in acidotic environments and higher intestinal pH which promotes growth of gram-negative bacteria who convert dietary nitrates to nitrites (3,18,20). But others found no association between pH, chloride, dehydration and methemoglobinemia (18).

Treatment

Methylene blue 1-2 mg/kg intravenously is recommended in symptomatic patients with a methemoglobin above 20% and in asymptomatic patients with levels above 30% (3-4). Methylene blue accelerates the reduction of methemoglobin through the NADPH-methemoglobin reductase pathway (7) (See Figure 1). An important contra-indication for methylene blue is G6PD deficiency, as it can induce hemolysis (3,7). Also, in patients with hemoglobin M or flavin reductase deficiency it is ineffective. Maintenance therapy is possible with methylene blue 50-250 mg/d orally (7). There is a variable gastro-intestinal absorption and adverse effects include gastro-intestinal symptoms, discomfort (headache and confusion are reported in older individuals), dyspnea, blue saliva, stool or skin, hemolysis and paradoxical increase of methemoglobin (4,7). Other therapeutic options are vitamin C 200-500 mg/d, which reduces oxidant compounds and decreases methemoglobin production, and vitamin B2 20 mg/d, which activates NADPH flavin methemoglobin reductase (4,5,7). If the patient is unresponsive or unsuitable for methylene blue administration, an exchange transfusion or hyperbaric oxygen therapy can be considered (7). Furthermore, it is important to avoid provoking agents (7).

In contrast, sulfhemoglobin cannot be reduced to hemoglobin because of irreversible sulfur binding (17). Treatment is supportive with removing the cause and giving blood transfusions. In severe cases, exchange transfusion can be necessary. Symptoms resolve over one to six months (3).

Conclusion

The diagnosis of a dyshemoglobinemia should be considered in neonates with central cyanosis out of proportion to the oxygen saturation and not responding to supplemental oxygen. Think of dyshemoglobinemias if the saturation gap exceeds 5%. Nowadays the diagnostic challenge has become less exciting as all modern co-oximeters have the ability to distinguish between common dyshemoglobinemias but clinical suspicion is the rate-limiting step. Early recognition of dyshemoglobinemias is vital as early therapy can be life-saving.

Conflicts of interest

The authors have not disclosed any potential conflicts of interest or financial support from any pharmaceutical company.

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