Congenital Methemoglobinemia Identified by Pulse Oximetry Screening

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abstract

Congenital methemoglobinemia is a rare condition caused by cytochrome b5 reductase deficiency, cytochrome b5 deficiency, or hemoglobin M disease. Newborn pulse oximetry screening was developed for the early detection of critical congenital heart disease; however, it also enables the early identification of other hypoxicemic conditions. We present the case of a term neonate who was admitted to the neonatal unit after a failed pulse oximetry screening at 3 hours of age. Oxygen saturations remained between 89% and 92% despite an increase in oxygen therapy. Chest radiograph and echocardiogram results were normal. A capillary blood gas test had normal results except for a raised methemoglobin level of 16%. Improvement was seen on the administration of methylene blue, which also resulted in an increase in oxygen saturations to within normal limits. Further investigation revealed evidence of type I hereditary cytochrome b5 reductase deficiency as a result of a CYB5R3 gene mutation with 2 pathogenic variants involving guanine-to-adenine substitutions. Although mild cyanosis is generally the only symptom of type I disease, patients may later develop associated symptoms, such as fatigue and shortness of breath. If an early diagnosis is missed, these patients are likely to present later with a diagnostic conundrum and be subject to extensive investigation. This case represents the success of pulse oximetry screening in the early identification of subclinical hypoxemia in this infant. After the exclusion of other pathologies, a routine investigation of capillary blood gas provided the information that led to a diagnosis, which allowed for early and effective management.

Methemoglobinemia is a rare condition in which there is an abnormally high level of methemoglobin in the blood. In methemoglobin, the iron in the heme group is in the ferric rather than the ferrous state of normal hemoglobin, meaning that it cannot bind oxygen. Therefore, methemoglobin is not functional in oxygen carriage.

In contrast with acquired methemoglobinemia caused by environmental oxidizing agents, innate reductase deficiency resulting in congenital methemoglobinemia is a rare condition, with only a few cases reported in the literature. Nevertheless, cyanosis (the leading symptom) may present early, the diagnosis of congenital methemoglobinemia is often delayed in affected children because of a failure to recognize due to its low incidence. In other cases, cyanosis may be mild and clinically not apparent.

Pulse oximetry screening was developed for the early detection of critical congenital heart disease and has become a standard screening tool for neonates in several countries. However, pulse oximetry also allows for the identification of other forms of hypoxicemic conditions, such as...
respiratory disease, infection, and metabolic conditions.\textsuperscript{6}

In this article, we present the case of a term neonate who was admitted to the neonatal unit after a failed pulse oximetry screening. The initial diagnosis of methemoglobinemia was established within the first 24 hours of life. To our knowledge, this is the first case of congenital methemoglobinemia in which the diagnosis was facilitated by neonatal pulse oximetry screening.

**CASE REPORT**

The patient was born postterm by normal delivery as the third child of nonconsanguineous parents. The delivery was uncomplicated, and there were no risk factors for sepsis. The patient presented to the neonatal team within 3 hours of birth after routine pulse oximetry screening because both preductal and postductal saturations were found to be low (right hand 92% and foot 94% and right hand 93% and foot 97% on repeat). There was no evidence of respiratory distress, but because of the unexplained low saturations, the infant was screened for possible infection and commenced on antibiotics. The oxygen saturations improved to within normal limits at the time of commencing antibiotics, so the patient was transferred back to the postnatal ward for routine care. After a few hours, the patient had an additional pulse oximetry assessment in the postnatal ward, at which time the oxygen saturations were between 89% and 92%. The infant was otherwise asymptomatic but was transferred to the neonatal unit for low-flow nasal prong oxygen therapy and further investigation.

The oxygen saturations remained unchanged despite oxygen therapy. Despite an escalation of oxygen therapy to 100% high-flow oxygen, the saturations remained between 89% and 92%. A chest radiograph and echocardiogram revealed no abnormality. A capillary blood gas sample was taken, revealing normal results except for a raised methemoglobin level of 16%. The methemoglobin level in a maternal capillary blood sample taken at the same time was 1.1%.

Following the advice of the pediatric hematology team, the patient was given a 1 mg/kg intravenous dose of methylene blue, which resulted in the methemoglobin falling to 1.1% in the first 24 hours. This resulted in an improvement in oxygen saturations, and oxygen was weaned. In addition, regular ascorbic acid was commenced at a dose of 30 mg/kg per day orally divided into 4 doses. The methemoglobin again gradually increased, reaching a maximum of 18%, and additional doses of methylene blue were required every 3 to 4 days. A limit of 10% methemoglobin was set before giving additional methylene blue. A lower threshold for oxygen saturations of 80% was tolerated, and oxygen was discontinued.

Because of a raised C-reactive protein level at 24 hours of age (maximum 17 mg/L), the patient received 5 days of antibiotics; however, the blood culture result was negative. Hemoglobin electrophoresis revealed a fetal hemoglobin of 71.6%, which is normal for a newborn (range 60%–80%). Hemoglobin DNA studies revealed heterozygosity for the 3.7 kilobase single \(\alpha\)-globin gene deletion, resulting in a carrier state of \(\alpha\) plus thalassemia, which is a benign and common condition.\textsuperscript{7} There is no evidence to suggest any link between this gene deletion and methemoglobinemia, and this is an incidental finding. Glucose-6-phosphate dehydrogenase revealed normal activity.

Gene analysis was performed on the \(CYB5R3\) gene from which the cytochrome b5 reductase enzyme is transcribed. This enzyme exists in 2 isoforms, soluble and membrane bound, and the soluble form is involved in converting methemoglobin to hemoglobin. It does so by converting the ferric iron in the heme group to ferrous iron so that hemoglobin can function. The patient’s gene analysis revealed 2 pathogenic variants involving guanine-to-adenine substitutions. One of these variants has previously been reported in the literature as being pathogenic in congenital methemoglobinemia type 1.\textsuperscript{8}

The patient was discharged from the hospital at 2 weeks of age. She was breastfeed and generally well at the time of discharge. She was managed after discharge and continued to have twice-weekly measurements of methemoglobin levels and to receive methylene blue as required. The 2 older siblings as well as both parents of the patient had normal methemoglobin levels.

**DISCUSSION**

Standard pulse oximeters measure oxygen saturation by passing 2 wavelengths of light through the tissues into a detector. By measuring the changes in absorbance at each wavelength, they can identify the absorbance caused by hemoglobin bound to molecular oxygen in the pulsing arterial blood. However, pulse oximetry only measures the percentage of bound hemoglobin, resulting in a false reading when hemoglobin binds to something other than oxygen. The finding that postductal saturations were initially found to be higher in our patient may be related to this inaccuracy. Because standard pulse oximeters are not capable of differentiating between different forms of bound hemoglobin, including dyshemoglobins, they do not necessarily distinguish between severe and mild methemoglobinemia. A noninvasive method that allows for the continuous measurement of dyshemoglobins is co-oximetry. This device employs a greater number of wavelengths, allowing researchers to
determine carboxyhemoglobin and methemoglobin levels.

Congenital methemoglobinemia is rarely diagnosed, and the true incidence remains unknown. It has a distinct pathology and is unrelated to acquired methemoglobinemia, which occurs as a consequence of exposure to toxins. The causes of congenital methemoglobinemia can be cytochrome b5 reductase deficiency, cytochrome b5 deficiency, and hemoglobin M disease.\(^9\) In the case described, there is evidence of type I hereditary cytochrome b5 reductase deficiency as a result of a \(\text{CYB5R3}\) gene mutation.

Hereditary cytochrome b5 reductase deficiency is mainly classified into 2 phenotypes. Both are inherited in an autosomal recessive pattern. Type I is caused by an enzyme deficiency that is only present in the erythrocytes, which results in mild cyanosis in homozygotes and is generally well tolerated. Methemoglobin levels typically range from 10% to 35%. Patients have a normal life expectancy, and methemoglobin levels can be well controlled with methylene blue and ascorbic acid.\(^10\) Type II disease is less common and is caused by an enzyme deficiency in all tissues, leading to both cyanosis and neurologic impairment. Life expectancy is significantly reduced because treatment has no effect on the neurologic dysfunction.\(^11\)

Although mild cyanosis is generally the only symptom of type I disease, patients may later develop associated symptoms, such as fatigue and shortness of breath. If an early diagnosis is missed, these patients are likely to present later with a diagnostic conundrum and be subject to extensive investigation. This case represents the success of pulse oximetry screening in the early identification of subclinical hypoxemia in this infant. After the exclusion of other pathologies, a routine investigation of a capillary blood gas provided the information that led to the diagnosis of methemoglobinemia, which allowed for early and effective management. Performing a capillary blood gas analysis can therefore be routinely recommended after a positive pulse oximetry screen result to aid in differential diagnosis.

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