Case Report

Congenital Methemoglobinemia in Pregnancy

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ABSTRACT

Methemoglobinemia is a well-known but frequently forgotten cause of hypoxia and respiratory distress in patients of all ages. A rare form of methemoglobinemia is divided into congenital or hereditary. There are very few clinical papers and case reports published on literature with regards to this. We report a case of congenital methemoglobinemia in a pregnant woman who presented to us with cyanosis and dyspnea since childhood and worsened during pregnancy.

1. Introduction

Methemoglobinemia is a well-known but frequently forgotten cause of hypoxia and respiratory distress in patients of all ages. It is considered to be a rare "idiosyncratic" reaction to many frequently used medications including nitrates, sulfonamides and topical anesthetics such as benzocaine and lidocaine. Described risk factors include concurrent administration of multiple oxidizing agents, excessive dose of the oxidizing agent, inflammation, irritation or broken integrity of the application site (skin or mucosa), congenital enzyme deficiency (G6PD deficiency or NADH methemoglobin reductase deficiency), extremes of age (infants or elderly), impaired renal or hepatic function and certain underlying health problems including anemia, sepsis, acidosis, cardiopulmonary dysfunction and other reduced oxygen transport states [1].

Congenital or hereditary methemoglobinemia is even a rarer variety [2]. The clinical features and long-term outcome are poorly documented and there are no systematic reviews [3]. Congenital methemoglobinemia is further categorized into two main types with one due to methemoglobin reductase enzyme (diaphorase I) deficiency and the other due to an abnormal oxygen affinity hemoglobin termed hemoglobin M [2].

Cyanosis caused by abnormal forms of hemoglobin can be life-threatening, and early recognition is necessary to prevent delay in management [4]. Diagnosis of the variety with abnormal hemoglobin structure and function is based on clinical suspicion when cyanosis is present with normal oxygen saturation and in the absence of any cardiopulmonary abnormality and response to ascorbic acid therapy [5].

Electrophoresis is a useful tool in the determination of abnormal hemoglobin such as hemoglobin M [4]. The condition is generally asymptomatic even when the methemoglobin level is as high as 40 % of the total hemoglobin [6].

2. Case Report

A 26 year-old pregnant mother in her third trimester with no past medical illness presented to our hospital because of persistent giddiness and breathlessness at rest. She gave a history of being cyanosed since childhood and has been continuously cyanotic with no noticeable fluctuation of degree of cyanosis during all her life. She could not indulge in strenuous exercise because of dyspnoea and experienced easy fatigability and pounding temporal headaches. She denied taking any drugs and had no gastrointestinal symptoms. There was no family history of
similar cyanosis. She had noticed reduction in effort tolerance of late and has been breathless when lying flat and only slept propped up. However, she denied any orthopnea, paroxysmal dyspnoea or leg swelling suggestive of heart failure.

Physical examination disclosed a well developed young mother who is 5 feet 5 inches tall and weighing 56 kilograms. Her skin had a slate blue color which was especially apparent in her lips, ears and finger nail beds. Her conjunctivae and the veins in the optic fundi were dark and dilated. The patient’s venous blood showed dark discoloration due to methemoglobin, compared with venous blood from an adult who does not have methemoglobinemia (Figure 1). There were no abnormalities on examination of her lungs and heart except for a functional murmur which was in keeping with her pregnancy state. Blood pressure was 122/90mmhg. She had no clubbing of her fingers and her spleen and liver were not palpable. Her saturation was 92 % under room air using the pulse oxymeter and improved to 97% with oxygen supplementation using nasal prong 3 liters of oxygen.

Laboratory investigations revealed:

Hemoglobin : 17.3 gm/dl (normal for her age is 11.0-16.0 gm/dl)
Packed cell volume : 52.3% (normal for age 36 - 48%)
Mean corpuscular volume, mean corpuscular hemoglobin concentration were within normal limits.
Platelets, leukocyte count and differential count were also within normal limits.
Arterial blood gases revealed a normal pH with PO2 at 83 % (normal range 80-100%) and O₂ saturation (SO2) of 96.6% (normal range 96 - 100 %).
Liver function tests and thyroid function tests done were essentially normal while antinuclear antibody and C-reactive protein were negative.
ECG and echocardiography were within normal limits.

Based on the above clinical history and investigations, hemoglobin electrophoresis was requested, to rule out methemoglobinemia. It revealed band of Hb M in addition to normal HbA2 and HbF which lead to the diagnosis of congenital (Hb M) methemoglobinemia. Hemoglobin electrophoresis revealed bands of HbA and HbM. Quantitation showed 50 % HbA and 50 % HbM (Figure 2). The presence of HbM band confirmed the diagnosis of congenital methemoglobinemia (HbM disease).

Upon the diagnosis of methemoglobinemia made, she was started on oral ascorbic acid and the course of pregnancy was followed up with ultrasound scans. No signs of the intrauterine fetal threat were noticed. The methemoglobin value in the mother's blood ranged from 18.4% at the beginning of pregnancy to 32% at delivery, going down to 2.2% on the third postpartum day. Its reduction was augmented by oral intake of 2.0 to 3.0 g of ascorbic acid per day throughout the pregnancy.

3. Discussion

Causes of cyanosis include those with decreased PaO2 and SO2 including cardiac right-to-left shunts and respiratory disorders and those with normal PaO2 and SO2 including Methemoglobinemia [7-10]. Our patient had cyanosis with normal PO2 and SO2 with no findings on ECG and Echocardiography. These ruled out cardiopulmonary causes and indicated the possibility of a rare etiology of cyanosis. Moreover, our patient had polycythemia, indicating some hematological abnormality. Hypoxic causes of polycythemia include high altitude, hypoxic lung disease, cyanotic heart disease, smoking, and abnormal hemoglobin with altered oxygen affinity including methemoglobin and sulhemoglobin (11).

Methemoglobinemia is a rare disorder of hemoglobin molecule with high oxygen affinity causing tissue hypoxia. Methemoglobin is present in small amounts in normal individuals (< 1.9 gm/dl) and up to 2.8 gm/dl in full-term neonates. The patient is cyanosed when the level is

![Figure 1.](image1.png) The patient’s venous blood (right) showed dark discoloration due to methemoglobin, compared with venous blood from an adult who does not have methemoglobinemia (left).

![Figure 2.](image2.png) Hemoglobin Electrophoresis Pattern of the Patient
more than 10% and may not become symptomatic (breathlessness, headache) even when the level is more than 40 % [6-10], while a level more than 75 % is incompatible with life [9].

Hemoglobin M is an abnormal hemoglobin autosomal dominant condition, usually due to spontaneous mutation [10]. Majority of HbM cases have histidine replaced by tyrosine in the alpha or beta globin chain and tyrosine stabilizes iron in its ferric form [11] which alters oxygen affinity of the hemoglobin molecule. Alpha chain variants presented at birth while beta chain variants presented later in life [12]. This was a possibility in our patient which started to experience the bluish discoloration of lips and extremities at about 8 years of age.

Ascorbic acid (which reduces methemoglobin) and methylene blue (that activates enzyme) are used to treat methemoglobinemia [7-10]. In our patient methylene blue could not be used, so only ascorbic acid therapy was advised and she was followed-up on regular frequent intervals.

Congenital methemoglobinemia was rarely observed in this part of the region, particularly in Malaysia [13]. All previous cases had cyanosis as the basic abnormality as also was seen in our patient. Other presenting symptoms were not well elaborated and comparable in the previous reports as the type of methemoglobinemia in hemoglobin M runs a benign course and the patients are “more blue than sick”. Furthermore, most of the previous reports were of children in neonatal period or early childhood while our patient became symptomatic in adolescence.

4. Conclusions

Congenital methemoglobinemia is a very rare but treatable cause of cyanosis. It is important to consider it as a differential diagnosis in cases of cyanosis with polycythemia.

References