Case Report

An unusual case of severe methemoglobinemia

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ABSTRACT

Methemoglobin is a form of hemoglobin containing iron in the ferric state (Fe^{3+}), which reduces oxygen delivery to tissues. Causes can be hereditary or secondary to certain drugs and toxins. It presents with cyanosis and breathlessness. Methylene blue is used for treatment. Majority of literature available has reported levels up to 33%. We came across a case of severe methemoglobinemia (40.2%) that occurred in a full term pregnant female during labor. We got access to only one supporting literature of methemoglobinemia during labor. Hence, this is an unusual case of severe methemoglobinemia during labor.

Key words: Pregnancy, Methemoglobin, Co-oximetry

INTRODUCTION

Methemoglobin (Met-Hb) is an abnormal form of hemoglobin (Hb) containing iron in the ferric form that has reduced ability to transport and deliver oxygen to tissues.[1] Etiology of Methemoglobinemia can be hereditary or acquired. Presentation can be acute or chronic. Clinical presentation correlates well with Met-Hb levels. Concentrations up to 15% are well tolerated, beyond which cyanosis appears. Anxiety, headache, and dizziness appear at 20%; fatigue, confusion, and tachypnea at 30-50%; arrhythmias, acidosis, seizures, and coma at 50%[2,3] and may cause death beyond 70%.[1] Normally methemoglobinemia is prevented by nicotinamide adenine dinucleotide (NADH)-dependent cytochrome b5-Met-Hb reductase and, to a lesser extent, nicotinamide adenine dinucleotide phosphate (NADPH)-dependent met-Hb reductase, which requires glucose-6-phosphate dehydrogenase (G6PD).[4]

CASE REPORT

A 26-year-old woman, gravida 4, para 2, living 2, medical termination of pregnancy 1, 2 previous lower segment caesarean section (LSCS) with 9 months of pregnancy with labor pains was admitted to obstetrics ward of tertiary care hospital. She presented with cyanosis that was not subsiding and complained of shortness of breath, appeared very lethargic. There was no associated chest pain, nausea, vomiting, or chills. The patient was awake and neurologically conversant, and was able to follow commands.

The patient gave H/O episodes of cyanosis in her childhood that subsided spontaneously and was not investigated. She also gave a history of rheumatic heart disease diagnosed 2 years back. During her last LSCS she had cyanosis and acute gastroenteritis with concomitant polycythemia of Hb 17.3 g%. Clinicians at that time were of the opinion that, hemoconcentration due to dehydration caused by AGE resulted in polycythemia. The cyanosis of the patient was thought to be due to exaggeration of rheumatic heart disease in pregnancy and hence was not investigated further.

On examination, the patient had bluish discoloration of skin and lips, fever (103.7°F/39.8°C) and cardiac monitoring revealed atrial fibrillation. Bedside non-invasive pulse oximetry showed a reduced oxygen saturation of 77%. Humidified oxygen inhalation was started immediately. As oxygen saturation improved only to 82% after one hour, Hb fraction estimation was advised.

It was observed that arterial blood sample collected in a heparinized syringe was dark-brown in color. It was processed by co-oximetry in cobas B 221 blood gas analyzer. The report showed increased Met-Hb level at 40.2% (reference interval 0.0-1.0%) with high PO_2 of 164.8 mm of Hg and oxygen saturation of 82.3% (Table 1). G6PD estimated by G6PD assay was 30 min and was within the reference range (reference interval, 30-60 min). All routine biochemical investigations were within the reference interval.

The delivery was planned by LSCS. Bolus dose of IV methylene blue (MB)(1 ml/kg) was administered during intraoperative period followed by additional dose of 80 ml in 100 cc normal saline infusion over 10-15 min after 12 h. Patient was also given vitamin C in the dose of 500 mg OD. Patient's clinical status improved dramatically after administering bolus dose of MB. Arterial blood gas and co-oximetry were repeated twice over a period of 24 h showed reduction in meth-Hb levels with the corresponding rise of oxyhemoglobin (O_2-Hb) and O_2 saturation (Table 1). The clinical features did not demand any further MB dosages. The patient was discharged on 5^W post-operative day. There were no other complications and the mother and the healthy male new-born child were discharged with advice to the mother to continue ascorbic acid and attend emergency if such situations arise any further.

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Table 1: Comparison of patient's ABG report at different time

ABG measured (reference interval)	Before MB*	With MB	At discharge
pH (7.35-7.45)	7.37	7.41	7.45
PCO_2 mmHg (35-45)	34.9	29.5	34.7
PO_2 mmHg (80-90)	164.8	194.3	87.1
O_2 saturation, % (95-100)	99.3	99.6	97.4
Base excess, mEq/L (−2-2)	−4.7	−4.6	0.0
Bicarbonate mmol/L (21.0-28.0)	19.8	18.7	23.5
Hematocrit, % (45-55)	49.4	41	41
O_2 Hb, % (94-98)	55.9	92.2	83.3
HHb, % (1-5)	0.4	0.4	2.2
CO-Hb, % (0.0-14)	3.5	4.1	6.6
Met-Hb, % (0.0-1.0)	40.2	3.2	7.9
Hb, g/dL (14.0-18.0)	14.4	12.3	11.9

MB: Methylene blue, ABG: Arterial blood gas, Hb: Hemoglobin, Met-Hb: Methemoglobin, HHb: Deoxyhemoglobin

DISCUSSION

One of the major hereditary causes of methemoglobinemia is cytochrome b5-Met-Hb reductase deficiency, which is an autosomal recessive condition. Methemoglobinemia may also arise in patients with congenital G6PD deficiency, but this infrequently occurs because the enzyme plays a minor role in maintaining the reduction state of Hb compared to b5-Met-Hb reductase.[2] The acquired causes are mostly exposure to oxidizing toxins, including nitrates and chlorate compounds.[1] Ash-Bernal *et al.*[5] reviewed 138 acquired methemoglobinemia cases, of which 42% were caused by dapsone, followed by the benzocaine (4%) and primaquine (4%). A case report by Krause *et al.*[6] has added that Met-Hb can also be associated with pregnancy and childbirth.

Co-oximetry is one of the sensitive techniques for estimation of Hb species like O_2-Hb, deoxyhemoglobin (deoxy-Hb), carboxyhemoglobin and Met-Hb. Oxygen saturation can be estimated both by non-invasive pulse oximetry and co-oximetry with the latter technique being more sensitive. Pulse oximeters measure only O_2-Hb and deoxy-Hb by using 2 wavelengths (660 and 940 nm) and calculates oxygen saturation indirectly by the same definition as the multiwavelength oximeter in a blood gas instrument. In conditions of methemoglobinemia, the Met-Hb interferes at both wavelengths and falsely lowers oxygen saturation. When the Met-Hb fraction is above 30%, oxygen saturation measured by pulse oximeter plateaus at about 85% even after administration of oxygen, which is another clue for diagnosing methemoglobinemia, which was observed in this patient. The condition can also be diagnosed by determining the oxygen saturation gap (the oxygen saturation difference between the co-oximetry and pulse oximeter).[4] O_2 partial pressure (PO_2) is measured by amperometry on the blood gas instrument and should not be affected by the Hb status. In this case, the PO_2 was 164.8 mmHg, reflecting hyper oxygenation status, and did not correlate with the pulse oximeter oxygen saturation at 82%.

The first-line treatment for methemoglobinemia is removal of underlying cause and wait for chemical reduction of Met-Hb to Hb by NADH-Met-Hb reductase. MB treatment should be considered in symptomatic or asymptomatic patients with high Met-Hb. This drug can accelerate the Hb reduction process through the NADPH-dependent G6PD pathway. In G6PD deficient patients, there is decreased NADPH production leading to inefficient reduction of MB to leuko MB and Met-Hb conversion to Hb[7] thereby increasing the risk of hemolysis and rebound the methemoglobinemia. Hence, G6PD estimation becomes an important parameter to be evaluated, before administering MB. Vitamin C is recommended in moderate dosage in such patients.[8]

MB has a high absorption at wavelength at which Met-Hb is deter-mined, thus can give a falsely elevated value for meth-Hb when estimated by co-oximetry. In such a situation Evelyn–Malloy test can be used as a confirmatory method to measure Met-Hb. The principle of the test is to add cyanide to bind with Met-Hb, which eliminates the absorption at 630-635 nm.[9] The amount of absorption elimination is proportional to the Met-Hb. An alternative confirmatory broad and diffuse optical spectroscopy method has also been developed by including MB spectroscopic features into the deconvolution algorithm to improve Met-Hb absorptive resolution.[10]

CONCLUSION

Although Methemoglobinemia can arise due to multiple etiological factors, the exact cause could not be established in this patient. Limited literature is available suggesting methemoglobinemia during child birth.[6] In the majority of the cases of methemoglobinemia the Meth-Hb levels are below 20-25%.[1] This case study assumes more importance as methemoglobinemia occurred during child birth was of severe degree (40.2%). The detailed history from the patient and her relatives did not reveal any drug or toxin ingestion. G6PD level was with in normal limits. The exact etiology of methemoglobinemia in this patient is not known. So we conclude; this case is one of the severe forms of methemoglobinemia, with unknown etiology, occurring during childbirth. Is it the excess stress during pregnancy and labor leading to aggravation of methemoglobinemia in this patient needs to be studied further.

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