

## A Rare Case Report of Acquired Methemoglobinemia

Apoorva M<sup>1</sup>, Vinod Khandait<sup>2</sup>

### ABSTRACT

Methaemoglobinaemia is a rarely diagnosed, life-threatening pathology and involves the presence of more than 1% of oxidised haemoglobin in the blood that is unable to carry oxygen.

We report the case of a 25-year-old male who consumed “Bloom Flower”(Nitrobenzene 20%) compound and developed fulminant symptoms of acute hypoxaemic respiratory failure and in whom acute and chronic cardiovascular and respiratory conditions had been ruled out. The discrepancy between oxygen saturation determined by pulse oximetry and oxygen partial pressure determined by capillary blood gas analysis, as well as the evident lack of response to oxygen therapy, were important indicators suggestive of methaemoglobinaemia. His methaemoglobin level was 3.4%. The symptoms resolved after treatment.

This case stresses upon the knowledge of the reasons for discrepancies in blood oxygen saturation values assessed by pulse oximetry and blood gas analysis for the correct diagnosis and a favourable treatment outcome.

### Introduction :

Haemoglobin, the principal pigment of the blood, is found in red blood cells and accounts for about 90% of their dry mass. The haemoglobin molecule consists of globin, which is made up of two pairs of polypeptide chains forming a tetramer, and four haem molecules. The globin chains differ in the number and sequence of constituent amino acids. Their synthesis is controlled by genes located in chromosomes 11 and 16. Each of the chains binds with a haem molecule, which is composed of a porphyrin ring containing a centrally placed iron atom. This association confers the ability to carry oxygen and stabilises the haemoglobin molecule. Oxygen is bound without changing the valence of the iron, as it occurs thanks to forces of side valences. Hence the process is referred to as “oxygenation” and the resulting form of haemoglobin is called “oxyhaemoglobin”. Oxidation of haemoglobin can, however, occur when the divalent iron undergoes oxidation to the trivalent form with the resulting product being methaemoglobin (MHb). The trivalent iron ion,

which is found in methaemoglobin, does not have any oxygen-carrying capacity.

In natural conditions, the blood methaemoglobin level is up to 1%<sup>1</sup>. Erythrocytes are constantly exposed to oxidative stress and oxidation to MHb. Two enzyme systems are involved in the defence mechanism : a larger one involving the Cytochrome B5 Reductase system, and a smaller one involving NADPH-dependent Methaemoglobin Reductase. Exposure to drugs or drug metabolites that show potent oxidising properties results, upon the exhaustion of the defence capacities of these enzyme systems, in increased methaemoglobin levels accompanied by the signs and symptoms of acute tissue hypoxaemia<sup>2</sup>.

Methaemoglobinaemia is diagnosed when the oxidised haemoglobin level exceeds 1%. The clinical manifestations depend on blood methaemoglobin levels and co-morbidities. Levels of 10-20% result in blue discolouration of the mucous membranes and the skin. When methaemoglobin levels exceed 20% headache, anxiety, and dyspnoea develop. At levels exceeding 30%, malaise, arrhythmias, and confusion ensue, which progress, at 50-70%, to coma, severe arrhythmia, acidosis, and death<sup>2-4</sup>.

Below is a presentation of a case of paroxysmal methaemoglobinaemia of unclear origin in an adult male with manifestations of acute tissue hypoxia.

<sup>1</sup>Junior Resident, <sup>2</sup>Associate Professor,  
Department of Medicine, Government Medical College, Nagpur

#### Address for Correspondence -

Dr. Apoorva M.  
E-mail : apoorva.medico7@gmail.com

Received on 29th June 2020

Accepted on 3rd July 2020

**Case Report :**

A 25-year-old man presented with the alleged history of consumption of “Bloom Flower” (Nitrobenzene 20%) (*Fig. 1*) compound at his residence, following which he had 2-3 episodes of vomiting and complained of dyspnea. Patient's relatives also give history of drowsiness and unconsciousness for a period of 30 minutes post consumption. Patient gave history of stressor being present. His past medical history was unremarkable. He did not have history of any psychiatric illness or previous suicidal attempts.



*Figure 1 : Bloom flower (nitrobenzene 20%)*

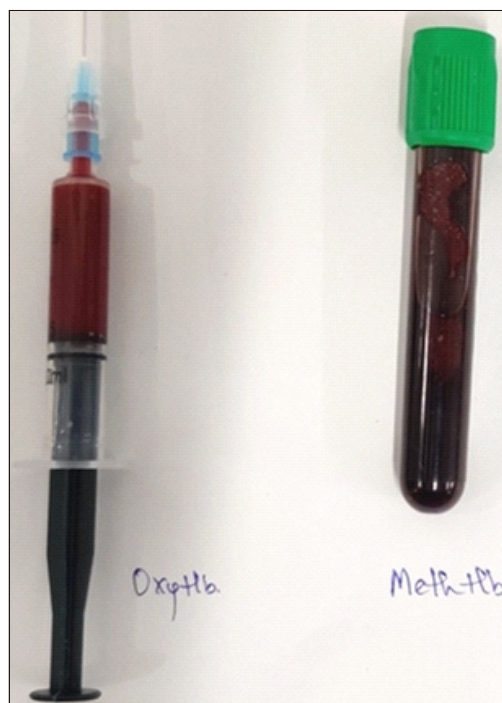
Patient was hypoxic on examination with SpO<sub>2</sub> of 65% at room air and 83% on high flow oxygen. Patient was cyanosed and was passing dark coloured urine (*Fig. 2*). But otherwise, was conscious and oriented to time, place and person with no cardio-respiratory or focal neurological findings and recorded a BP 110/70 mm of Hg.

Laboratory tests including complete blood count, blood urea nitrogen, serum creatinine, liver function tests and electrolytes were normal. Arterial blood gas analysis showed pH-7.49, pCO<sub>2</sub>-34 mmHg, HCO<sub>3</sub>-25.8, PO<sub>2</sub> = 98 mmHg (with Pulse Oximeter reading / SPO<sub>2</sub> of 83% on high flow O<sub>2</sub>). Patient's meth-hemoglobin levels were 3.4%. He tested

negative for G6PD deficiency. Patient's Chest X-Ray and ECG were within normal limits.



*Figure 2 : Passing dark coloured urine*



*Figure 3 : Color difference in blood sample*



**Figure 4 : Recovery of Cyanosis**

Patient was given a gastric lavage with activated charcoal and started on Inj. Methylene blue 1 mg/kg I/V stat dose, Inj. Ascorbic acid 200mg OD, Inj. Lasix 40 mg BD and Tab. NAcetyl Cysteine 600 mg TDS dose.

Symptomatic recovery was observed immediately after the treatment, with improvement of SpO<sub>2</sub> to 93% on high flow oxygen and recovery of cyanosis (**Fig. 4**) and dark coloured urine (**Fig. 5**).

#### **Discussion :**

Dyspnoea and cough are two most common symptoms of respiratory and/or cardiovascular diseases. Measurement of saturation using a pulse oximeter and measurement of arterialised capillary blood saturation are also recognised diagnostic methods for respiratory compromise. In the case we report here, myocardial ischaemia and high risk pulmonary embolism as the causes of dyspnoea and cyanosis of the patient were ruled out. Normal breath sounds over the lungs and normal Chest X-Ray allowed us to rule out respiratory disorders for the same.

We discovered considerable discrepancies between oxygen saturation measured with a pulse oximeter and oxygen saturation calculated in arterial blood gas analysis (these two measurements were conducted simultaneously). This discrepancy and the lack of increase in oxygen saturation measured with a pulse oximeter when oxygen was delivered through a Venturimask, were the most important tips



**Figure 5 : Recovery of dark urine**

that allowed us to establish the correct diagnosis. The significant discrepancy between the saturation value measured by pulse oximetry and the arterial blood oxygen partial pressure (the so-called saturation gap) should prompt the physician to look for the cause of oxygen transport abnormalities, and one such cause is the presence of an abnormal haemoglobin<sup>2,4</sup>.

Measurement of the partial pressure of gases in arterial blood or arterialised capillary blood is based on an electrochemical method and involves the measurement of the difference in the voltage of high-resistance electrodes for the determination of pH and PaCO<sub>2</sub>. PaO<sub>2</sub> is the partial pressure of oxygen dissolved in the serum and not bound to haemoglobin. Patients with methaemoglobinaemia may have normal PaO<sub>2</sub> values despite a high methaemoglobin concentration, which may put their life at risk.

In blood gas analysis, bicarbonate levels and blood oxygen saturation are calculated from pH and PaCO<sub>2</sub> values using the Henderson-Hasselbalch equation with the assumption, however, that normal haemoglobin is present. The presence of abnormal haemoglobins (methaemoglobin, sulphaemoglobin, carboxyhaemoglobin) leads to false results of oxygen saturation measurements<sup>4</sup>. The functioning of the pulse oximeter is based on the absorption of light waves of two wavelengths : 660 and 940 nm.



Both oxygenated and deoxygenated haemoglobin absorbs the waves of both wavelengths, and based on that the pulse oximeter determines oxygen saturation. Methaemoglobin equally absorbs the 660 nm and 940 nm waves. When methaemoglobin concentrations increases, oxygen saturation measured with the pulse oximeter stabilises at a lower level, as was observed in our patient. Oxygen therapy does not change the saturation reading<sup>4,6</sup>. We did not have at our disposal a CO-oximeter, which separately measures, by spectrophotometry, four different wavelengths : for oxy-, deoxy-, carboxy, and methaemoglobin<sup>7</sup>. Methaemoglobinaemia was confirmed by determining the blood concentration of methaemoglobin during an episode, which equalled 3.4%. This result was consistent with the clinical manifestations.

G6PD deficiency not only prevents the reduction of methaemoglobin by methylene blue, but can precipitate a life-threatening haemolysis. It is also ineffective when haemoglobin M is present<sup>8</sup>.

Congenital methaemoglobinaemia is a rare disease which manifests immediately after birth. It is seen in neonates with Cytochrome B5 Reductase deficiencies accompanied, especially in type II deficiency, by numerous congenital anomalies of the nervous system. This also applies to patients with a congenital abnormal haemoglobin structure, the so-called haemoglobin M.

Our patient, who developed his first symptoms at the age of 25, illustrated a case of acquired rather than congenital methaemoglobinaemia. Manifestations of this condition are triggered by exposure to a multitude of drugs, chemicals, or toxins (**Table 1**). Among the very numerous causes of acquired methaemoglobinaemia, inorganic nitrogen is found in insecticides and pesticides is the reason for this condition in our patient.<sup>11,12</sup>

Acquired methaemoglobinaemia is very likely to be under diagnosed, with most of the undiagnosed cases being patients with abortive symptoms. Dyspnoeic and cyanotic patients, however, require immediate evaluation and rapid action. Our patient did not require exchange transfusion or use of a hyperbaric chamber, as these measures are reserved

**Table 1 : Causes of Methemoglobin**

Drugs	
Benzoicaine (spray, ointment, cream)	Metoclopramides
Methylene blue (high doses)	Nitrates
Chloroquine	Nitrofurantoin
Dapsone	Nitroglycerin
Flutamide	Sodium nitroprusside
Phenacetin	Prilocaine
Phenazopyridine	Silver salts
Lidocaine	Sulfonamides
Concomitant diseases	
Sepsis	
Paediatric gastrointestinal infections	
Inhalation of amyl nitrate	
Haemolytic crisis in sickle-cell anaemia	
Other factors	
Paints containing aniline derivatives	
Car exhaust fumes, toxins formed during combustion of wood and plastic materials	
Chemicals: nitrobenzene, nitroethane, glues	
Herbicides, pesticides	
Fuel calorific value enhancers	

for second-line treatment and are utilised when the patient's condition fails to improve or methylene blue cannot be used<sup>6</sup>. Knowledge of the reasons for discrepancies in blood oxygen saturation values assessed by pulse oximetry and blood gas analysis is the key to the correct diagnosis and a favourable treatment outcome.

#### References :

1. Lee D.C., Ferguson K.L. Methemoglobinemia. <http://emedicine.medscape.com/article/815613-print>. 04.11.2009
2. Denshaw-Burke M. Methemoglobinemia. <http://emedicine.medscape.com/article/204178-print>. 20.10.2009
3. Mansouri A., Lurie A.A. Concise review : methemoglobinemia. *Am. J. Hematol.* 1993; 42: 7-12.
4. Wright R.O., Lewander W.J, Woolf A.D. Methemoglobinemia : etiology, pharmacology and clinical management. *Ann. Emerg. Med.* 1999; 34: 646-656.
5. Barker S.J., Tremper K.K., Hyatt J. Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. *Anesthesiology* 1989; 70: 112-117.
6. Tobias J.D., Ramachandran V. Intraoperative diagnosis of unsuspected methemoglobinemia due to low pulse oximetry values. *J. Int. Care Med.* 2009; 24: 273.
7. Rausch-Madison S., Moshenifar Z. Methodologic problems encountered with cooximetry in methemoglobinemia. *Am. J. Med.Sci.* 1997; 314: 203-206.

8. Sankoff J., Louie A.D. Clinicopathologic conference : a 28-year old woman with perioral cyanosis and low oxygen saturation. *Acad. Emerg. Med.* 2008; 15,4: 363-367.
9. Muller J., Murawski K., Szymanowska Z., Koziorowski A., Radwan L. Hereditary deficiency of NADPH2 methemoglobin reductase. *Acta Medica Scandinavica* 1963; 173.2: 243-247.
10. Knobloch L., Salna B., Hogan A., Postle J., Anderson H. Bluebabies and nitrate-contaminated well water. *Environ. Health Perspect.* 2000; 108: 675-679.
11. Linz A.J., Greenham R.K. Fallon L.F. Methemoglobinemia: an industrial outbreak among rubber molding workers. *J. Occup. Environ. Med.* 2006; 48 (5): 523-528.
12. Kane G.C., Hoehn S.M., Behrenbeck T.R. Benzocaine-induced methemoglobinemia based on the Mayo Clinic experience from 28478 transesophageal echocardiograms: Incidence, outcomes and predisposing factors. *Arch. Intern. Med.* 2007; 167 (18): 1977-1982.
13. Yusim Y., Livingstone D., Sidi A. Blue dyes, blue people: the systemic effects of blue dyes when administered via different routes. *J. Clin. Anesth.* 2007; 19,4: 315-321.
14. Largiadier T., Oechslin E., Jenni R. Pulsoxymetrie in der transösophagealen Echokardiographie. *Kardiovaskuläre Medizin* 2006; 9: 230-234.
15. Vasundhara V., Ravinder M., Aziz A., Sandeep K., David L.L. Severe methemoglobinemia after transesophageal echocardiography. *Am. J. Ther.* 2003; 10,3: 225-227.
16. Vallurupalli S., Das S., Manchanda S. Infection and the risk of topical anesthetic induced clinically significant methemoglobinemia after transesophageal echocardiography. *Echocardiography* 2009; 31. [Epub ahead of print].
17. Ash-Bernal R., Wise R., Wright S.M. Acquired methemoglobinemia a retrospective series of 138 cases at 2 teaching hospitals. *Medicine* 2004; 83: 265-273.