Article published online: 2024-04-05

Methemoglobinemia as a Cause of Unexplained Hypoxia in Neurosurgical Patients: A Report of Two Cases

Sonia Bansal[1] Bharath Srinivasaiah[1] Vidya Sriram[1] Vishal Baradwad[1] Parthiban Giribabu[1] Rajeeb K. Mishra[1]

[1] Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, Karnataka, India

Address for correspondence Rajeeb Kumar Mishra, MD, DM, Department of Neuroanaesthesia and Neurocritical Care, National Institute of Mental Health and Neurosciences, Bengaluru, 560029 Karnataka, India (e-mail: litu86@gmail.com).

J Neuroanaesthesiol Crit Care

Abstract

In methemoglobinemia, ferrous iron in the hemoglobin is oxidized to a ferric state. Hemoglobin in this state cannot carry oxygen resulting in hypoxemia, which manifests as low peripheral oxygen saturation (SpO_2). Bedside co-oximetry can identify this condition. We present here two cases of methemoglobinemia. Our experience with the first case enabled swift diagnosis of the second case. This also enabled us to prepare ourselves better in the second case if worsening of hypoxemia had occurred. Therefore, we learn here that whenever there is low SpO_2 with a normal partial pressure of oxygen, methemoglobinemia should be suspected and diagnosis should be confirmed using co-oximetry.

Keywords
- methemoglobinemia
- methemoglobin
- hypoxia
- co-oximetry

Introduction

Methemoglobin (metHb) is an abnormal hemoglobin where the ferrous iron in the hemoglobin is oxidized to a ferric state. Hemoglobin in this state cannot carry oxygen, resulting in hypoxemia that does not respond to oxygen supplementation. Congenital methemoglobinemia occurs due to deficiency of cytochrome-5-reductase and the acquired variant occurs due to the ingestion of oxidizing agents. The normal level of metHb is less than 2%.

Few anesthesiologists are aware of this condition and do not know when to suspect it. In patients with methemoglobinemia, there is a discrepancy between peripheral oxygen saturation (SpO_2) and partial pressure of oxygen (PaO_2) by arterial blood gas (ABG) analysis. The pulse oximeter gives erroneous values as it recognizes only wavelengths of oxyhemoglobin and deoxyhemoglobin.[1] In this case series, we present two patients of undiagnosed methemoglobinemia with primary neurological pathology who had intraoperative hypoxemia, which were misdiagnosed or nearly missed.

Case 1

A 9-year-old child presented with complaints of headache, projectile vomiting, and weakness of the right-sided upper and lower limbs (Medical Research Council [MRC] grade ⅘). Magnetic resonance imaging of the brain showed multiple serpiginous flow voids in the cervicomedullary junction. Bilateral vertebral artery angiogram showed arteriovenous malformation (AVM) measuring 19.5*13 mm, in the cervicomedullary junction, with feeders from both right and left posterior inferior cerebellar arteries (PICA), right and left vertebral arteries and draining via dilated latero-medullo-pontine veins into the petrosal vein, superior petrosal sinus, bilateral cavernous, and transverse sigmoid sinus. The patient had initially visited another hospital, where SpO_2 of 85% was documented. Chest X-ray and two-dimensional echocardiogram with bubble test for the evaluation of the cause of hypoxia were unremarkable. Given the diagnosis of brainstem AVM, hypoxia was attributed to central

DOI https://doi.org/10.1055/s-0043-1776389.
ISSN 2348-0548.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

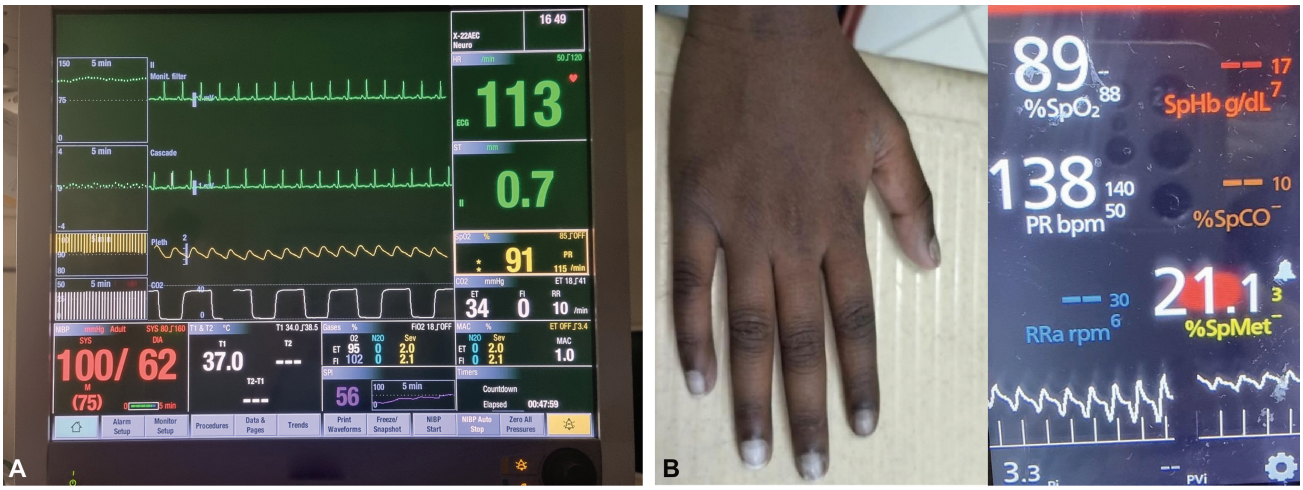

Fig. 1 (**A**) Low peripheral oxygen saturation despite ventilation with fractional inspiratory oxygen (FiO_2) of 100%. (**B**) Cyanosis of hands and high methemoglobin level (21.1%) detected by co-oximetry in the first case.

hypoventilation without any confirmation by polysomnography, ABG, or pulmonary function tests.

The child visited our hospital and was scheduled for the embolization of the AVM. Preinduction, the patient's SpO_2 on room air was 88 to 90%, which improved to 98% after oxygen supplementation. After induction of anesthesia and tracheal intubation, the SpO_2 dropped to 92% and cyanosis of hands and lips was seen, despite ventilation with fractional inspiratory oxygen (FiO_2) of 1 (►**Fig. 1A**). Since the patient was now being ventilated with 100% oxygen, diagnosis of central hypoventilation was ruled out. The color of the arterial blood (drawn for ABG) was chocolate brown. The PaO_2 was 460 mm Hg on two consecutive samples, which were appropriate for FiO_2 of 1. Due to acute angulation of the right distal PICA, navigation until the AVM nidus failed, and the procedure was abandoned. Anesthesia was reversed and the patient's trachea was extubated. In the recovery room, SpO_2 was 89 to 90%, which improved to 94 to 95% with oxygen supplementation. The cause of the mismatch between SpO_2 and PaO_2 and unexplained hypoxemia was evaluated using pulse co-oximetry (Radical-7, Masimo, Irvine, California, United States) and the metHb level was found to be 21.1% (►**Fig. 1B**). Since the child was not on any medications, acquired methemoglobinemia was ruled out and a provisional diagnosis of congenital methemoglobinemia was made.

Case 2

A 30-year-old female presented with a 3 months history of convulsions, headache, and altered sensorium. She had been receiving antiretroviral treatment for the past 4 months. The patient was conscious, with power in right side limbs of MRC grade 3. She had neck stiffness and Kernig sign was positive. A computed tomography scan of the brain showed multiple ring-enhancing lesions in bilateral parietal lobes with significant perilesional edema suggestive of brain abscess. Burr hole and tapping of the abscess were planned on an emergent basis. Laboratory investigations were unremarkable except for the low CD4 count (15 cells per mm^3).

In the operating room, her heart rate was 58 beats/minute with SpO_2 of 85%, without any signs of respiratory distress. Lung and cardiac auscultation were normal. SpO_2 did not rise above 90% despite preoxygenation for 5 minutes.

The tracheal was intubated after induction of anesthesia and the patient was mechanically ventilated with FiO_2 of 1. However, the SpO_2 did not improve beyond 90 to 91%. Arterial blood appeared dark brown with a normal PaO_2 (246 mm Hg) and saturation (98.6%). The difference between PaO_2 and SpO_2 was investigated using co-oximeter, which showed a metHb of 18.7% (►**Fig. 2**).

The intraoperative course was uneventful except for low SpO_2. After surgery and tracheal extubation, with oxygen supplementation at 6 L/min, SpO_2 was maintained at 88%. A detailed history from the patient revealed the ingestion of sulfamethoxazole–trimethoprim for more than a month to treat fever. Methemoglobinemia has been reported with sulfamethoxazole–trimethoprim.[2] The incidentally observed methemoglobinemia is most likely the acquired type due to prolonged use of sulfamethoxazole.

Discussion

In the first case, when low SpO_2 was encountered, the presence of any cardiac and pulmonary causes was ruled out. Hypoxia was present throughout the procedure. Postprocedure, we found the cause of low saturation to be methemoglobinemia by co-oximetry. When hypoxemia occurred again in the second case, after ruling out systemic causes, co-oximetry showed a metHb level of 19%. Now, methylene blue was kept available for emergency use. The early diagnosis and adequate preparation reduced the stress and increased the confidence in managing this case.

Therefore, from these cases, we learnt that abnormal hemoglobin should be suspected whenever PaO_2 is normal, with low SpO_2. Generally, only patients with metHb levels above 30% are symptomatic.[3]

Patients with unexplained hypoxia warrant co-oximetry evaluation. Co-oximetry helps determine the percentages of

Fig. 2 Co-oximetry showing elevated methemoglobin (18.9%) in the second case.

various forms of hemoglobin in the blood in relation to total hemoglobin. These include oxygenated, deoxygenated, carboxy-, and metHb. It uses four to eight wavelengths and therefore is able to distinguish between the different hemoglobin. Blood gas analyzers with integrated co-oximetry modules are available or they can be done using noninvasive technology similar to a peripheral pulse oximeter. Indications for co-oximetry are known or suspected exposure to drugs that cause hemoglobin conversion to metHb or in patients who have been exposed to carbon monoxide. Patients with high levels of carboxyhemoglobin have normal SpO_2 values because pulse oximeters cannot differentiate carboxyhemoglobin from oxyhemoglobin.[4] Drug-induced methemoglobinemia can occur with drugs like nitrates and nitrite derivatives, sulfonamides, and dapsone. Dapsone is administered for the treatment of leprosy, endemic to countries like India. These patients will be asymptomatic preoperatively but will challenge the anesthesiologist intraoperatively with cyanosis and desaturation.[5] Therefore, any history of ingestion of such drugs if positive should alert the anesthesiologist to make arrangements accordingly.

Methemoglobinemia of higher severity can cause tissue hypoxia. In a neurological patient, consequences can range from mild cognitive disturbances, seizures, stroke, to permanent brain ischemia and coma in worst scenarios. If the diagnosis is priorly known, measures can be taken to prevent severe hypoxemia. Methylene blue, which activates Nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) diaphorase, can help reduce metHb to hemoglobin. This can be kept ready for use in life-threatening hypoxemia, as its onset of action is quick. However, methylene blue should not be used in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Known or suspected G6PD deficiency is a contraindication to the use of methylene blue. In fact, methylene blue triggers hemolysis in such patients.[6,7] Dextrose-containing fluids and the administration of vitamin C can help provide substrate to produce NADH. Oxidants like local anesthetics should be avoided.[8] The use of drugs such as fentanyl, dexmedetomidine, nitrous oxide, and drugs metabolized by the P450 system is controversial and these drugs should be avoided. Remifentanil, propofol, benzodiazepines, and inhalational agents are safer choices.[9] Blood transfusion or exchange transfusion can also help in improving oxygen delivery.

Conclusion

The learning point from these cases is that hypoxia in any patient should be thoroughly investigated, and if there is any mismatch between pulse oximetry and arterial oxygen tension, suspicion of abnormal hemoglobin should be raised. This can be diagnosed with a simple bedside co-oximeter. However, availability of co-oximeter may not be possible at many centers. ABG, on the other hand, is more widely and easily available method.

Conflict of Interest

None declared.

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