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RESEARCH ARTICLE

ACQUIRED METHEMOGLOBINEMIA IN AN INFANT

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ABSTRACT

The presentation of methemoglobinemia in emergency care setting can be nonspecific and thereby difficult to diagnose. Cyanosis being a presentation it sometimes leads to unnecessary invasive procedures. Acquired Methemoglobinemia is a common entity and its incidence is much more than documented. Almost 100 compounds have been identified to cause Methemoglobinemia. So, close observation of clinical symptoms with saturation gap between oxygen saturation on pulse oximetry and arterial blood gas analysis, followed by confirmation by methemoglobin levels wherever available can help in diagnosis. Prompt diagnosis and treatment with removal of causative agents leads to good prognosis. Physicians and other health care workers should be made aware and should always consider this in differential diagnosis of cyanosis not responding to 100% oxygen

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INTRODUCTION

A 6 month old infant, resident of rural area in western Uttar Pradesh presented to the emergency department with mother observing cyanosis of lips associated with vomiting and irritability. Patient had tachycardia and tachypnoea on admission. A thorough examination for respiratory and cardiovascular disease was done. Air entry was bilaterally equal and clear. Sample for routine CBC and ABG was drawn which appeared brown in colour. Child was first born child, with no history of consanguinity. He was born after a full term normal vaginal delivery by a midwife at home. Infant was normal at birth and never had cyanotic episodes before this. Pulse oximetry showed oxygen saturation of 87% while ABG showed normal partial pressure of oxygen and saturation as 93%. A simple bedside test was done.1-2 drops of blood on white filter paper were taken, then evaluated for color change upon exposure to oxygen. It remained brown. Deoxygenated hemoglobin changes from dark red or violet to bright red, whereas methemoglobin remains brown. An empirical diagnosis of acquired methhemoglobinemia was made. Treatment was initiated after screening for G6 PD deficiency which consisted of 100% oxygen therapy and intravenous administration of methylene blue at dose of 2 mg/kg body weight over a period of 10 minutes. This improved the condition of the infant. History from mother revealed recent weaning with formula feed. On further questioning it was found that formula was being prepared from water taken from a village hand pump.

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DISCUSSION

Methemoglobinemia should be considered as an important differential diagnosis in a case of cyanosis with normal arterial oxygen tension and no underlying cardiopulmonary Disease. Hemoglobin can accept and transport oxygen only when the iron atom is in ferrous form. When hemoglobin loses an electron and becomes oxidized, the iron atom is converted to the ferric state (Fe_3+), resulting in the formation of methemoglobin. Methemoglobin lacks the electron that is needed to form a bond with oxygen and thus is incapable of oxygen transport. Free ferrous heme in the blood is rapidly oxidized to ferric heme. However, as part of the hemoglobin molecule the heme moiety is embedded in a hydrophobic pocket that provides protection from rapid oxidation. It is estimated that approximately 3% of hemoglobin is autoxidized to methemoglobin daily. However, the concentration of methemoglobin is normally maintained below 1% of the total hemoglobin by two separate enzymatic reducing systems.

Foremost is the reduced nicotine adenine dinucleotide (NADH)-dependent cytochrome b5 methemoglobin reductase system in which NADH generated during glycolysis donates its hydrogen ion to cytochrome b5, which in turn reduces methemoglobin to hemoglobin.This system is responsible for almost 95% of the normal methemoglobin reducing activity in the body. Secondly, the reduced nicotine adenine dinucleotide phosphate (NADPH)- dependent methemoglobin reductase system which reduces flavin; the reduced flavin in turn reduces methemoglobin. This pathway normally accounts for less than 5% of the normal methemoglobin reduction in the body, but in the presence of methylene blue this system is dramatically potentiated and can reduce large quantities of methemoglobin. The NADPH needed for this reaction is generated by the hexose monophosphate shunt. Cellular antioxidants such as ascorbic acid and glutathione can directly reduce methemoglobin without the presence of any enzyme system, but under normal circumstances contribute little to methemoglobin reduction. (Mansouri, 1985; Jaffe, 1985) Methemoglobinemia can be hereditary or acquired. Hereditary/ Congenital is due to presence of Hemoglobin M, cytochrome b5 reductase deficiency (NADH deficiency)—responsible for 95% of Methemoglobin reduction, NADPH deficiency of the HMP shunt and acquired can be due to exposure to multiple drugs and toxins including aniline dyes, benzene, chloroquine, dapsone, local anesthetic agents, naphthalene, nitrites, primaquine, phenazopyridine, and sulfonamides. Acquired methemoglobinemia incidence may be much higher than is documented. Often, this is associated with the use of or exposure to oxidant drugs, chemicals, or toxins, including dapsone, local anesthetic agents, and nitroglycerin. More than 100 compounds have been implicated (Coleman and Coleman, 1996; Curry, 1982). Nitrates are also an important cause of methemoglobinemia but they need to be converted to nitrite by nitrate reductase producing bacteria (such as Escherichia coli, Pseudomonas aeruginosa, and Aerobacter aerogenes) in the gut or on the skin (Donovan, 1990). Infants and children are more susceptible than adults. The most common sources of nitrate exposure are well water, which is mixed with infant formula, consumption of some vegetables with high nitrate concentration, administration of oxidant drugs, and the presence of diarrheal episodes. After ingestion, nitrates are converted to nitrites by fecal organisms, rapidly absorbed from the intestine by passive diffusion reaching the systemic circulation without undergoing first-pass metabolism in the liver (extrahepatic metabolism). Nitrites are potent oxidant agents of ferrohemoglobin. Infants younger than 6 months old are particularly susceptible to nitrate-induced methemoglobinemia because fetal hemoglobin is more easily oxidized to methemoglobin; 2) newborns have lower levels of NADH-methemoglobin reductase and glutathione peroxidise activity than adults; 3) the pediatric exposure to the inducing agent represents a greater dose per kg body weight compared to adults; and 4) infants have higher gastric pH due to limited acid secretion, which allows bacterial proliferation and may thus increase conversion of nitrates to nitrites (American Academy of Pediatrics, 1970; Kross *et al*., 1992)

Clinical features & Diagnosis

The hallmark of methemoglobinemia is central cyanosis. The cyanosis is more brown than blue and has classically been described as “chocolatecolored.” It usually becomes apparent at concentrations of methemoglobin above 15%. The pulse oximeter cannot be used to accurately assess oxygen saturation in a patient with methemoglobinemia (Eisenkraft, 1988). The ABG will typically show a normal arterial oxygen tension since it is dependent on the amount of dissolved oxygen and not on oxygen molecules bound to haemoglobin. Large saturation gaps (≥5%) in arterial blood are almost always due to methemoglobinemia or carboxyhemoglobinemia and less commonly sulfhemoglobinemia and it does not respond to 100% oxygen therapy. Co oximetry actually measures the various forms of hemoglobin in the blood and will not only provide a more accurate oxygen saturation but also measure methemoglobin level (Ralston *et al*., 1991). But it is not available widely. A simple bedside test is to place a drop of the patient’s blood on a filter paper or paper towel. Dark blood due to deoxyhemoglobin will redden on exposure to air, whereas dark blood due to methemoglobin will not. Using a drop of control blood for comparison is helpful (Harley and Celermajer, 1970). In general, there appears to be a low index of suspicion for this condition, which can result in considerable delay in diagnosis, unnecessary invasive investigations, and even therapeutic misadventure. Harley and colleages (Harley and Celermajer, 1970) described two neonates with acquired methemoglobinemia who typify this difficulty. Both infants had undergone cardiac catheterization for persistent cyanosis, with normal findings, before the diagnosis of methemoglobinemia was entertained. To summarise Cyanosis not responding to 100% oxygen, low hemoglobin oxygen saturation on pulse oximetry (typically 85-89%), normal PaO_2 on ABG, “chocolate blood”, should raise the suspicion of methemoglobinemia. Diagnosis should be confirmed by multiple-wavelength cooximetry wherever available.

Treatment

Prompt recognition of the condition and initiation of treatment, as indicated (especially in acquired methemoglobinemia), are critical in the management of methemoglobinemia. Supportive care should be implemented as soon as methemoglobinemia is identified, including supplemental (100%) oxygen, ensuring airway patency and hemodynamic support. Further absorption of the toxic agent should be prevented. In asymptomatic or mild cases only close observation is required along with supportive measures. The half-life of methemoglobin is approximately 55 minutes (Wright *et al*., 1999; Herman *et al*., 1999). Once the inducing agent has been cleared, the methemoglobinemia will resolve in most cases, usually within 36 hours, due to the normal reducing mechanisms. Intravenous (IV) methylene blue is the first-line antidotal agent used after screening for G6PD deficiency. It greatly accelerates the NADPH-dependent methemoglobin reductase system by acting as a cofactor. One to two mg/kg of a 1% solution is administered intravenously over 5 minutes. The slow infusion helps prevent a painful local response, and flushing the intravenous line after administering the drug also helps. A marked reduction in the methemoglobin concentration is usually seen within 30 to 60 minutes. Repeat doses may be given for persistent or recurrent methemoglobinemia, but the total dose should not exceed 7 mg/kg. Methylene blue is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency for two reasons, first as patients with G6PD deficiency have

insufficient NADPH thus making methylene blue therapy ineffective; and secondly G6PD deficient individuals are more prone to methylene blue induced hemolysis. Also Identification/ avoidance/ discontinuation of offending agents is critical (Mansouri, 1985). Exchange transfusion and hyperbaric oxygen treatment are second-line options for patients with severe methemoglobinemia whose condition does not respond to methylene blue or who cannot be treated with methylene blue (e.g. with G-6PD deficiency). Vitamin C has also been used in such cases to act as electron acceptor. (Jaffe, 1985)

Conclusion

The presentation of patients with methemoglobinemia in emergency room can be nonspecific and thereby difficult to diagnose leading to unnecessary invasive procedures. So, close observation of clinical symptoms with saturation gap between oxygen saturation on pulse oximetry and arterial blood gas analysis, followed by confirmation by methemoglobin levels wherever available can help in diagnosis. Prompt diagnosis and treatment with removal of causative agents leads to good prognosis .Physicians and other health care workers should always consider this in differential diagnosis of cyanosis not responding to 100% oxygen.

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