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CASE REPORT

Acquired methemoglobinemia due to ultraprocessed food

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Abstract

Tissue hypoxia and even death from methemoglobinemia occur when its levels exceed 2%, and the higher the level, the more severe the symptoms presented by the patient. Its mechanism occurs through the oxidation of hemoglobin from ferrous to ferric state, making the iron in the heme unable to bind to oxygen. It is a congenital or acquired pathology, the latter when there is exposure to certain oxidizing agents, such as pesticides, fertilizers, topical anesthetics, and nitrates, as in the case described. The symptoms are variable, from just grayish pigmentation of the skin to central cyanosis, browning of the blood, syncope, dyspnea, convulsions, and even cardiovascular failure due to tissue hypoxia. But, the main sign is the disparity between saturation on pulse oximetry and arterial oxygen saturation, refractory to oxygen therapy. The agility in the diagnosis and in the institution of the adequate treatment are essential for a good outcome, having as the main curative measure the administration of methylene blue. This paper presents a case report of an adolescent patient with methemoglobinemia acquired after ingestion of ultra-processed food. Structured report from the analysis of the medical record and literature review on the subject. No conflict of interest or external funding source.

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INTRODUCTION

Methemoglobinemia is characterized by high levels of oxidized hemoglobin in the blood, resulting in inadequate oxygen transport. This condition is an uncommon and potentially fatal cause of cyanosis in the pediatric population [1,2]. It should be considered in patients with cyanosis and hypoxia refractory to oxygen therapy, who present discrepancies between oxygen saturation levels measured by pulse oximetry and arterial blood gas. [3] Congenital and acquired methemoglobinemia result from exposure to substances that oxidize hemoglobin. Among the oxidants found in clinical practice are nitrites, which are used as preservatives in foods of animal origin, such as processed meat. [2,4] This article reports the case of an adolescent who developed acquired methemoglobinemia after she ate ultra-processed food of dubious origin (hot dogs), in which early diagnosis and adequate treatment contributed to a satisfactory outcome.

CASE REPORT

A 13-year-old female patient was admitted to the emergency unit of a tertiary hospital in southern Brazil, presenting with cyanosis and desaturation. She reported eating a hot dog of dubious origin, purchased at a bus station, approximately five hours earlier. Approximately one hour after eating it, she developed nausea, vomiting, chest pain, and cyanosis, which prompted her to seek care. She denied having other symptoms, using medications, having experienced similar episodes previously, or having comorbidities or allergies.

On admission, the patient was drowsy but attentive to verbal cues, with painful facies, central cyanosis, and an oxygen saturation (SpO2) of 79% on room air. She was refractory to oxygen therapy with a non-rebreather mask at 15 L/min. The following were observed on physical examination: heart rate 120 bpm; respiratory rate 32 bpm; blood pressure 123x80 mmHg; temperature 36.2ºC; capillary blood glucose 102; cardiac and pulmonary auscultation without noteworthy alterations; absence of respiratory effort; central cyanosis (Figure 1); warm extremities with good perfusion; wide and symmetrical pulses.

In light of the observed signs and symptoms, laboratory tests were ordered, and samples of arterial blood were taken (Table 1), which showed very dark-colored blood. Chest X-ray images did not reveal alterations. An electrocardiogram showed sinus tachycardia and a computed tomography pulmonary angiogram was negative for pulmonary thromboembolism.

During observation, the patient's precordial pain worsened, and she entered into a state of altered level of consciousness, with periods of drowsiness from which she awakened only to tactile stimulation. Due to the diagnostic hypothesis of acquired methemoglobinemia secondary to the ingestion of nitrite and nitrate and the deterioration of clinical signs and symptoms, we decided to perform a methylene blue test. The serum methemoglobin level was measured before medication and sent to a laboratory outside the hospital. Methylene blue was administered intravenously at a 1 mg/kg dose, diluted in 100 ml of a 5% glucose solution, for 5 minutes. Partial improvements were observed in cyanosis and SpO2, and the medication was repeated at the same dose. After the second infusion of methylene blue, the patient



Figure 1. Patient with central cyanosis.

Table 1. Arterial blood gas analysis results and other laboratory tests performed on admission.

Test	Value	Reference value
Ph	7.41	7.34 to 7.45
pCO_2 (mmHg)	38	32 to 48
pO_2 (mmHg)	184	83 to 108
HCO_3 (mmol/L)	24.1	21 to 28
Base excess (mmol/L)	-0.3	-3 to +3
O_2 saturation (%)	100	95 to 99
Lactate (mmol/L)	2.3	0.6 to 2.2
Creatinine (mg/dL)	0.6	0.4 to 1.0
Urea (mg/dL)	29	7.8 to 21.6
Hemoglobin (g/dL)	14.8	11.5 to 15.5
Hematocrit (%)	42.7	33 to 46
Troponin (pg/mL)	5.4	<11.6
CK-MB (U/L)	8	<16

improved completely, corroborating the idea that she had methemoglobinemia. The patient was referred to the intensive care unit for observation; additional methylene blue treatment was unnecessary.

She was discharged after 48 hours of observation, with a SpO2 of 97% on room air, normal vital signs, and no complaints. Serum methemoglobin levels determined by UV/Vis spectrophotometry were available six days after the patient was discharged and read 1.74% (reference value <1.5%), confirming the central diagnostic hypothesis.

DISCUSSION

Methemoglobinemia is an uncommon and potentially fatal cause of cyanosis in children [1,2] in which ferrous hemoglobin (Fe^{2+}) is oxidized to ferric hemoglobin (Fe^{3+}), making it impossible for it to bind to oxygen. [1,2,5] Tissue hypoxia is further exacerbated since methemoglobin shifts the oxygen dissociation curve to the left, which causes the remaining normal hemoglobin to bind more strongly to oxygen, impairing its release to tissues. [1,2,3] This process results in acute functional anemia and impaired oxygen delivery to tissues. [1]

Under normal physiologic conditions in healthy individuals, hemoglobin is constantly exposed to the oxidative stress of normal metabolism, and approximately 1% of total hemoglobin exists in the form of oxidized methemoglobin. [3,5] Protective enzyme systems, such as cytochrome b5 reductase and NADPH methemoglobin reductase, neutralize the spontaneous formation of methemoglobin. [2,5] In congenital methemoglobinemia, hemoglobin's synthesis or metabolism is altered, which makes this protective system ineffective or deficient. [3] In the acquired form of the disease, exposure to exogenous oxidants and their metabolites may accelerate the rate of methemoglobin formation by up to 1,000 times, overloading the protective enzyme systems and acutely increasing methemoglobin levels. [5]

Acquired methemoglobinemia is the most commonly observed form in clinical practice. It can be caused by oxidants found in industrial chemicals, medication, well water, and food. [2,4] The authors of a systematic review including 568 cases of food-related methemoglobinemia found that the main oxidizing agents were nitrites and nitrates. [2]

Sodium and potassium nitrite salts have historically been added to foods of animal origin (processed meat products), and the concentrations accepted by health regulatory agencies are only slightly higher than those needed to preserve these foods. The Food and Drug Administration allows up to 200 mg/kg to be added to final food products sold in the United States. In the European Union and Brazil, the accepted limit is 150 mg/kg [2,6], and the doses needed to preserve meat range from 50 to 100 mg/kg. The recommended daily intake of nitrites is up to 0.07 mg/kg of body weight, and poisoning symptoms may occur with doses above 0.4 mg/kg. [2,7] Nitrates are commonly found in vegetables and are less toxic than nitrites, presenting a lower oxidative potential. [4,8] The potential danger of nitrate lies in its conversion to nitrite before or after ingestion. [9] The literature has few case reports of methemoglobinemia acquired via the ingestion of hot dogs, as in the case reported in this article.

Hypoxia and cyanosis occurring concurrently with discrepancies in oxygen saturation measured with pulse oximetry and arterial blood gas in individuals refractory to oxygen therapy, especially after contact with oxidizing agents, should elevate methemoglobinemia in the list of differential diagnoses. [3] Clinical presentation consists of a constellation of signs and symptoms due to tissue hypoxia. It depends on methemoglobin fractions, the patient's intrinsic ability to eliminate it, and the patient's underlying functional status. [2] The main findings are cyanosis, pallor, fatigue, headache, central nervous system depression, metabolic acidosis, seizure, arrhythmia, coma, and death. [2,3]

The diagnosis of methemoglobinemia is eminently clinical. Pulse oximetry is not accurate enough to assess the level of hypoxemia since the device measures light at wavelengths of 660nm and 940nm. Oxyhemoglobin and deoxyhemoglobin absorb light at these wavelengths but at different levels, and the reading is produced based on the relevant absorbance ratios. Methemoglobin, however, absorbs both wavelengths equally, which explains the false pulse oximetry reading and lack of improvement with oxygen therapy. The gold standard noninvasive measurement of the methemoglobin fraction in blood is obtained by co-oximetry, which measures four different wavelengths (600 nm and 631 nm are added), thus differentiating methemoglobin from oxyhemoglobin and deoxyhemoglobin. [2,3]

Early identification and initiation of adequate treatment are essential for successfully managing methemoglobinemia. The precipitating agent, when identified, should be immediately discontinued or removed. Support with intravenous hydration and oxygen supplementation should be initiated, and cardiopulmonary support is indicated when necessary. Methylene blue is the main treatment for reducing methemoglobin levels, as it reduces ferric hemoglobin to ferrous hemoglobin. It is administered at an initial dose of 1 to 2 mg/kg, infused intravenously for 3 to 5 minutes, with a repeat dose if the patient fails to improve significantly within 30 to 60 minutes. Other treatments described in the literature include replacement transfusion, hemodialysis, hyperbaric oxygen, and vitamin C as adjuvant treatments. [1,2,3]

Early recognition, identification of the triggering factor, initiating adequate treatment, and reporting cases to public health authorities are essential for successfully managing acquired methemoglobinemia [2]. This is a clinically challenging condition that requires attention. According to the National Health Surveillance Agency regulations, food manufacturers must provide accurate information on the composition of food products.

REFERÊNCIAS

1. Friedman N, Scolnik D, McMurray L, Bryan J. Acquired methemoglobinemia presenting to the pediatric emergency department: a clinical challenge. CJEM. 2020 Sep[citado em maio de 2023];22(5):673-677. Disponível em: https://pubmed.ncbi.nlm.nih.gov/32396060/.
2. McNulty R, Kuchi N, Xu E, Gunja N. Food-induced methemoglobinemia: A systematic review. J Food Sci. 2022 march[citado em maio de 2023];87(4):1423-1448. Disponível em: https://ift.onlinelibrary.wiley.com/doi/full/10.1111/1750-3841.16090.
3. Cefalu JN, Joshi TV, Spalitta MJ, Kadi CJ, Diaz JH, Eskander JP, Cornett EM, Kaye AD. Methemoglobinemia in the Operating Room and Intensive Care Unit: Early Recognition, Pathophysiology, and Management. Adv Ther. 2020 May[citado em abril de 2023];37(5):1714-1723. Disponível em: https://pubmed.ncbi.nlm.nih.gov/32193811/.
4. Zhong L, Liu AH, Blekkenhorst LC, Bondonno NP, Sim M, Woodman RJ, Croft KD, Lewis JR, Hodgson JM, Bondonno CP. Development of a Food Composition Database for Assessing Nitrate and Nitrite Intake from Animal-based Foods. Mol Nutr Food Res. 2022 Jan[citado em maio de 2023];66(1):e2100272. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34792849/.
5. Ash-Bernal R, Wise R, Wright SM. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. Medicine (Baltimore). 2004 Sep[citado em maio de 2023];83(5):265-273. Disponível em: https://pubmed.ncbi.nlm.nih.gov/15342970/.
6. Ministério da Saúde (BR), Agência Nacional de Vigilância Sanitária, Diretoria Colegiada. RESOLUÇÃO DA DIRETORIA COLEGIADA - RDC Nº 272, DE 14 DE MARÇO DE 2019. Estabelece os aditivos alimentares autorizados para uso em carnes e produtos cárneos. Diário Oficial da União. 2019 março[citado em maio de 2023]; 52,1:194. Disponível em: https://www.in.gov.br/web/guest/materia/-/asset_publisher/Kujrw0TZC2Mb/content/id/67378977/do1-2019-03-18-resolucao-da-diretoria-colegiada-rdc-n-272-de-14-de-marco-de-2019-67378770.
7. Chan TT, Leung WCY, Chan CK, Lo HKT, Tso WWY, Tsui SH, Chan TSY, Chang RSK. Clinical experience in diagnosis and management of acquired methaemoglobinaemia: a case report and retrospective review. Hong Kong Med J. 2021 Oct[citado em maio de 2023];27(5):366-369. Disponível em: https://pubmed.ncbi.nlm.nih.gov/34706989/.
8. Kennedy N, Smith CP, McWhinney P. Faulty sausage production causing methaemoglobinaemia. Arch Dis Child. 1997 Apr[citado em maio de 2023];76(4):367-8. Disponível em: https://pubmed.ncbi.nlm.nih.gov/9166036/.
9. Greer FR, Shannon M; American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Committee on Environmental Health. Infant methemoglobinemia: the role of dietary nitrate in food and water. Pediatrics. 2005 Sep[citado em maio de 2023];116(3):784-6. Disponível em: https://pubmed.ncbi.nlm.nih.gov/16140723/