Acquired methemoglobinemia presenting to the pediatric emergency department: a clinical challenge

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CLINICIAN'S CAPSULE

What is known about the topic?
Methemoglobinemia (MetHb) is an uncommon and potentially dangerous cause of cyanosis in the pediatric emergency department (ED), making its diagnosis a clinical challenge.
What did the study ask?
What are the clinical characteristics of patients with acquired MetHb in our pediatric ED?
What did this study find?
Pediatric ED MetHb presentation is rare but does exist. All our patients had common triggers or underlying conditions associated with MetHb.
What does this study matter to clinicians?
Awareness of key features associated with MetHb can help ED physicians diagnose and manage MetHb in cases of unusual pediatric cyanosis.

ABSTRACT

Objectives: Acquired methemoglobinemia (MetHb) is an uncommon presentation of cyanosis in the pediatric emergency department (ED), making its diagnosis and management a clinical challenge. Through this case series we hope to improve clinician ability to recognize the potential for MetHb in pediatric ED patients and to avoid overlooking this important cause of cyanosis.
Methods: This was a case series using a health records review, investigating patients diagnosed with MetHb at our pediatric ED during 2007–2018. We included only cases with methemoglobin saturation ≥5%.
Results: Ten patients were diagnosed with MetHb in our pediatric ED during the study period. Five had an underlying hematologic disease who received a pharmacologic trigger known to induce MetHb as well (four dapsone, one rasburicase). The other five patients were previously healthy, who presented with a clinical picture of hemolytic anemia, all of whom were diagnosed with previously unknown glucose-6-phosphate dehydrogenase (G6PD) deficiency. Two of the patients received methylene blue, and five patients needed packed red blood cells. All of the patients survived the acute MetHb episode.
Conclusion: Acquired MetHb in the pediatric ED is a rare but important cause of cyanosis. Diagnosis and management of acute, acquired MetHb in the ED requires a high level of suspicion, and a background knowledge of the common precipitants and underlying conditions associated with this condition. We hope this case series will help ED physicians to consider MetHb in pediatric patients presenting with cyanosis and persistent hypoxia. Exposure to known precipitants (e.g., medications and foods), particularly in the setting of active treatment for malignancy or with symptoms of hemolytic anemia should further increase suspicion.

RÉSUMÉ

Contexte et objectifs: La méthémoglobinémie (MetHb) acquise se manifeste par de la cyanose, affection peu fréquente au service des urgences pédiatriques (SUP), ce qui complexifie le diagnostic et le traitement. Aussi espérons-nous, par la présentation d'une série de cas, améliorer la capacité des cliniciens à reconnaître la présence possible de la MetHb chez les enfants, au service des urgences, et éviter que passe inaperçue cette cause importante de cyanose.
Méthode: Il s'agit d'une série de cas reposant sur un examen des dossiers médicaux de patients chez qui avait été posé un diagnostic de MetHb au SUP des auteurs, de 2007 à 2018. Seuls ont été retenus les cas dans lesquels la saturation en méthémoglobinémie était ≥ 5%.
Résultats: Au total, 10 cas de MetHb ont été diagnostiqués au cours de la période à l'étude, au SUP mentionné précédemment. Dans 5 d'entre eux, un déclencheur pharmacologique (dapsone : 4; rasburicase : 1) connu pour provoquer la MetHb avait été utilisé pour traiter une affection hématologique sous-jacente; dans les 5 autres, la MetHb simulait le tableau clinique de l'anémie hémolytique chez des patients, par

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ailleurs en bonne santé, atteints d'un déficit jusque-là inconnu en G6PD. Deux des patients ont reçu du bleu de méthylène, et 5 autres ont eu besoin de concentrés de globules rouges. Tous les patients ont survécu à l'épisode aigu de MetHb.
Conclusion: La MetHb acquise est une cause rare mais importante de cyanose au SUP. Le diagnostic et le traitement de la MetHb acquise, en phase aigüe, au service des urgences exigent une présence constante à l'esprit de cette possibilité de diagnostic ainsi qu'une bonne connaissance des facteurs déclenchants courants de la maladie et des affections sous-jacentes qui y sont associées. Aussi, espérons-nous, par cette série de cas, aider les urgentologues à envisager la possibilité de MetHb chez les enfants qui présentent de la cyanose et une hypoxie persistante. L'exposition à des facteurs déclenchants connus (p. ex. des médicaments ou des aliments), surtout dans les cas de traitement actif de tumeurs malignes ou de symptômes d'anémie hémolytique, devrait susciter encore davantage de doutes.

Keywords: Emergency medicine, pediatrics, toxicology

INTRODUCTION

Methemoglobinemia (MetHb) is an uncommon cause of cyanosis in the pediatric population that can cause significant morbidity and even death. MetHb occurs when the iron atom in hemoglobin loses one electron to an oxidant, and the Fe II, or oxidized state, of iron is transformed into Fe III. Because Fe III iron is unable to bind oxygen, and the oxygen affinity of any remaining Fe II in the hemoglobin is increased, a left shift occurs in the oxygen dissociation curve, resulting in functional anemia and impaired oxygen delivery to the tissues.[1] Most cases of MetHb are acquired, induced by agents that cause an increase in the production of methemoglobin, making it a potentially predictable and preventable condition.[1]

MetHb is a rare but potentially dangerous cause of cyanosis in pediatric emergency department (ED) patients. It is important for clinicians to be aware of the key features of patient history and clinical presentation that should raise suspicion for the diagnosis of MetHb. The aim of our study was to improve the clinician's ability to recognize the potential for MetHb in pediatric ED patients and to avoid overlooking this important cause of cyanosis.

METHODS

Study design and subjects

We conducted a case series using a health records review. Records were obtained from pediatric patients with acute acquired MetHb in the ED of the Hospital for Sick Children in Toronto, Canada, from January 1, 2007, to April 30, 2018. This hospital is a large, urban, tertiary pediatric center with approximately 75,000 ED visits per year. Patients were identified by searching for the diagnosis of "methemoglobinemia" in the electronic health record system as well as from laboratory results of methemoglobin levels ordered from the ED. Cases were included only if their presentation and diagnosis were made in our ED and methemoglobin saturation ≥5%. While there is no consensus on the lower limit of methemoglobin that should be considered MetHb, ≥5% reflects the consensus cutoff at our center.

Variables

The following variables were extracted from the electronic health record: date of ED visit, age, gender, medical history, physical findings, vital signs, laboratory results, treatment plan, disposition, and prognosis.

Ethics

The study was approved by the Research Ethics Board of the hospital.

RESULTS

Ten patients were diagnosed with acquired MetHb during the study period. Median age was 5.5 years (IQR = 2.3, 9.5) with seven males and three females. The clinical presentation and management of our patients is presented in Table 1.

Four patients (patients 1, 2, 3, 5) had a known background of underlying disease: three with acute lymphoblastic leukemia, one aplastic anemia, and one newly diagnosed lymphoma. In each of these patients, there was an obvious pharmacological trigger for the MetHb (dapsone). Patient 4 was diagnosed with suspected

Table 1. Clinical presentation and management of patients with acquired methemoglobinemia

Patient Number	1	2	3	4	5	6	7	8	9	10
Age in years/sex	10, Female	2, Female	10, Male	15, Female	7, Male	3, Male	8, Male	2, Male	1, Male	4, Male
Background	Acute Lymphoblastic Leukemia	Acute Lymphoblastic Leukemia	Aplastic anemia, autism	Diagnosed during the ED visit with possible lymphoma	Acute Lymphoblastic Leukemia	Previously Healthy	Previously Healthy	Previously Healthy	Previously Healthy	Previously Healthy
Signs/ symptoms in the ED	Exertional dyspnea, cyanosis	Cyanosis	Cyanosis, fever, vomiting	Cyanosis, abdominal pain	Cyanosis	Fever, dyspnea, hematuria, tachycardia, jaundice	Fever, headache, hematuria, jaundice, leg pain	Jaundice, abdominal pain, vomiting, diarrhea, fever, hematuria, fatigue	Jaundice, pallor, fatigue	Pallor, jaundice, fatigue
Identified triggers	Dapsone (2nd exposure)	Dapsone (1st exposure)	Dapsone (1st exposure)	Rasburicase	Dapsone (1st exposure)	Topical menthol, fava beans	None found	None found	Fava beans	Fava beans
G6PD status	Negative	Negative	Negative	G6PD deficiency*	Negative	G6PD deficiency*	G6PD deficiency*	G6PD deficiency*	G6PD deficiency*	G6PD deficiency*
Nadir in oxygen saturation	81% RA 81% O_2	89% RA 90% O_2	86% RA 96% O_2	79% RA 79% O_2	92% RA 93% O_2	82% RA 82% O_2	82% RA 82% O_2	84% RA 84% O_2	76% RA 76% O_2	82% RA 82% O_2
Hemoglobin (g/dl)	9.7	9.9	10.4	6.6	11.7	6.3	4.7	5.5	6.6	6.4
Peak methemoglobin (%)	22	19	15.5	14	13	10	8	8	8	7
ED treatment and management of MetHb	Methylene blue, hematology admission	Methylene blue, hematology admission	Antibiotics for Pneumonia, fluid bolus, PICU admission	PRBC, PICU admission	Discharge home on vitamin C	Antibiotics, fluid bolus, pain control, PRBC, hematology admission	Fluid bolus, PRBC, pediatric admission	PRBC, hematology admission	Hematology admission	Antibiotics, PRBC, PICU admission

ED = emergency department; G6PD = glucose-6-phosphate dehydrogenase; RA = room air; O_2 = saturation with supplemental oxygen; PICU = pediatric intensive care unit; PRBC = packed red blood cells; *G6PD = deficiency not previously known, diagnosed in the ED.

lymphoma in the ED and given rasburicase in the ED to prevent tumor lysis syndrome; she subsequently developed MetHb. Patient 4 was also found to have a previously unidentified glucose-6-phosphate dehydrogenase (G6PD) deficiency. The remaining five patients (patients 6–10) were previously healthy and presented to our ED with a clinical picture of acute hemolytic anemia including a variable combination of cyanosis, fatigue, jaundice, fever, and dyspnea. They were all found to have previously undiagnosed G6PD deficiency. A probable trigger was found for three of these patients: two were exposed to fava beans, and one was exposed to both topical menthol and fava beans.

Notably, all patients, except patient 3 who also was diagnosed with pneumonia, had a negligible improvement if any in oxygen saturation in response to supplemental oxygen.

Treatment consisted of packed red blood cell transfusion for five of the patients. Methylene blue was given to two patients with methemoglobin saturation of 22% and 19%. One patient received vitamin C upon discharge, and one received supportive care only. In all of our patients, methemoglobin saturation percentages normalized after diagnosis and treatment, and all patients survived the episode of acute acquired MetHb to eventual discharge home.

DISCUSSION

The cases in our series are consistent with previous studies of MetHb, in particular, the clinical features on presentation, the increased risk due to specific triggers, and the persistence of hypoxia despite supplemental oxygen.

Previous pediatric studies reported diverse potential contributors to this condition including: underlying conditions such as G6PD, age <36 months, diarrhea, malnutrition and sepsis, exposure to certain foods and medications such as dapsone (antibiotic), local anaesthetics, rasburicase (recombinant urate oxidase), aniline dyes, and high levels of nitrate in water supplies.[1–4]

The presenting symptoms of acute acquired MetHb depend on methemoglobin saturation percentage.[5] As methemoglobin saturation levels rise, mild symptoms, such as headache, dyspnea, fatigue, dizziness, and anxiety develop. At saturations >40% coma, respiratory depression, convulsions, arrhythmias, and death may occur.[6] The diagnosis is suggested in patients with sudden onset of cyanosis and hypoxia that fails to improve with an increased fraction of inspired oxygen.[7] A dark red, chocolate brown, or blue color of blood observed during phlebotomy and clinical cyanosis in the presence of a normal calculated arterial pO_2 would also be suggestive of MetHb.

Exploring a history of potential MetHb trigger exposures (pharmaceutical agents, precipitating foods) is essential in the early identification of patients presenting with cyanosis. The pharmacologic triggers (rasburicase, dapsone, and menthol) identified in our case series are well-known MetHb triggers. Rasburicase and dapsone are commonly used in the management of pediatric oncology patients but may be less familiar to many emergency physicians. It is important that emergency physicians are aware that pediatric patients with hematologic malignancies may be at increased risk for MetHb due to their treatment medications.

As demonstrated in our case series, pulse oximetry can be misleading and inaccurate in cases of acute MetHb and should not be used to make the diagnosis.[7] High concentrations of methemoglobin may cause the pulse oximeter to display approximately 85% regardless of the true hemoglobin oxygen saturation due to its inability to read true methemoglobin saturation percentage.[7]

The management of acute, acquired MetHb is variable and depends on clinical symptoms, methemoglobin and hemoglobin saturation percentage, and underlying conditions such as G6PD deficiency. The first step is to suspend use of the offending agent(s) if identified. In an asymptomatic patient, with methemoglobin levels <20%, no further action is usually needed; normally metabolizing red blood cells will reduce the methemoglobin within several hours. When intervention is needed, the most widely accepted treatment of MetHb is administration of 1–2 mg/kg methylene blue intravenously over 5 minutes. Methylene blue causes enzymatic reduction of methemoglobin by means of nicotinamide adenine dinucleotide phosphate (NADPH)-methemoglobin reductase. The response is usually rapid, and the dose may be repeated in 1 hour if high saturation percentage of methemoglobin persist. Methylene blue administration in patients with known G6PD deficiency is controversial, due to the risk of hemolytic anemia.[1] Recommendations vary between administering methylene blue in a normal dose,[1] administering it at a low dose combined with ascorbic acid,[1] or not using it at all and providing ascorbic acid only,[8] Severe MetHb may benefit from exchange transfusion and/or hyperbaric oxygen.[9] Patients with severe MetHb should be managed in the intensive care unit.

CONCLUSION

Diagnosis and management of acute, acquired MetHb in the ED requires a high level of suspicion, and a background knowledge of the common precipitants and underlying conditions associated with this condition. Our study highlights the fact that MetHb should be considered in pediatric patients presenting with cyanosis and persistent hypoxia. Exposure to known precipitants (e.g., medications and foods), particularly in the setting of active treatment for malignancy or with symptoms of hemolytic anemia should further increase suspicion. We hope this case series will help ED physicians to recognize MetHb as a potential reversible cause of cyanosis in pediatric patients.

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