Case Report

Severe Methemoglobinemia Secondary to *Ferula asafoetida* Ingestion in an Infant: A Case Report

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Abstract

Methemoglobinemia is an increase in the methemoglobin levels in the blood. Infants are more susceptible to develop secondary methemoglobinemia because of the limited activity of methemoglobin reductase B enzyme. We report a case of life-threatening methemoglobinemia secondary to ingestion of *Ferula asafoetida* herbal remedy in an infant who presented with cyanosis and severe respiratory distress. The patient had two brothers who had a glucose-6-phosphate dehydrogenase deficiency and the patient’s deficiency status was unknown, and thus, methylene blue was not initiated whereas ascorbic acid was unavailable. Accordingly, the patient was successfully treated with hyperoxia. Based on this case, the authors suggest that the use of *F. asafoetida* as an herbal remedy should be avoided in infants, and pediatricians should be aware of such toxicity and inform parents appropriately.

Keywords: *Ferula asafetida*, glucose-6-phosphate dehydrogenase deficiency, heltit, hyperoxia, infant, methemoglobinemia

INTRODUCTION

Methemoglobinemia occurs when there is an increase in methemoglobin (Met-Hb)¹ levels in the blood, either because of congenital changes in hemoglobin (Hb) synthesis or metabolism or due to exposure to various chemical agents that increase the production of Met-Hb more than the capacity of the reduction system.¹,² Met-Hb exceeds normal level as a result of the increase in the ferric form of iron, instead of ferrous form. Met-Hb is an abnormal Hb, which lacks the ability to bind oxygen and interferes with oxygen delivery to the tissues.³ In normal conditions, body mechanisms protect against oxidative stress, mainly NADPH, that keeps Met-Hb within normal ranges.⁴ However, when exposed to an oxidizing agent or its metabolites, the conversion of Hb to Met-Hb may be increased more than the capability of these protective mechanisms, causing clinically significant Met-Hb.⁵ Among those oxidizing agents, medications are the most common cause of Met-Hb including local anesthetics (benzocaine and procaine), antibiotics (dapsone) and nitrites (nitroglycerin/nitric oxide).⁶

Here, the authors report a very rare cause of acquired methemoglobinemia secondary to ingestion of gum resin of *Ferula asafoetida* as an herbal remedy (commonly known in Saudi Arabia as heltit) for treating infantile colic. To the best of the authors’ knowledge, this is
only the second reported case of methemoglobinemia secondary to F. asafoetida remedy toxicity[7] and the first case of lethal methemoglobinemia successfully treated with hyperoxia (inspired fraction \( O_2 \) of 1.0).

**CASE REPORT**

A 3-month-old Saudi boy, who was in a good health before, presented to the emergency department of our maternity and children hospital with grayish-blue discoloration of the skin and respiratory distress that started 6 h before admission. There was no history of aspiration or abnormal movements. The mother had noticed some degree of abdominal distension without vomiting or diarrhea, but the infant had no fever. He was on breastfeeding plus formula milk, which was prepared using bottled water. In terms of family history, the patient had two brothers with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The initial physical examination included mottling of the skin with central and peripheral cyanosis. The patient was irritable, tachypneic with a respiratory rate fluctuating between 80 and 90 breaths/min. Furthermore, he was tachycardic and hypoxic, with an oxygen saturation of around 65% in room air and 76% with 10 L of oxygen with a nonbreathing mask. His initial blood pressure was 85/43 mmHg, which was normal for the age and gender. The patient was found to have poor peripheral perfusion, cold extremities with capillary refilling time exceeding 4 s. Other systemic survey was unremarkable.

Because of the persistent hypoxia and tachypnea, a decision of intubation was made and the patient was connected to mechanical ventilation (synchronized intermittent mandatory ventilation mode). The initial laboratory results included Hb (10.4 g/dl), hematocrit (32.9%), white blood cell count (≥24,000/mm) and platelet count (≥455,000/mm). The renal function tests and levels of electrolytes were within normal range. In addition, his chest X-ray was normal. The first venous blood gas showed very high methemoglobinemia (66.9%) with pH 7.137, \( pCO_2 \) 28.7 mmHg and \( HCO_3^- \) 10.4, with a base defect of 18.0 matching the picture of metabolic acidosis with lethal methemoglobinemia. Based on this, the parents were asked if any medication or toxic material was given to the child before onset of the symptoms, when they revealed that he was given a gum resin of F. asafoetida, which is locally known as heltit, as a treatment for infantile colic.

The toxicology center was contacted, and it was confirmed that this herbal medication can cause methemoglobinemia.[7] To stabilize and manage the critical levels of methemoglobinemia, intravenous methylene blue is the preferred treatment option. However, because the patient had a positive family history of G6PD deficiency and the patient’s deficiency status was unknown, methylene blue was not used as it could have caused hemolytic anemia and further aggravated methemoglobinemia. Ascorbic acid is another agent commonly used in the management of methemoglobinemia, but it was not available in our hospital. Therefore, the patient was kept on 100% oxygen plus other supportive care measures, and his oxygen saturation kept fluctuating around 94%. Meanwhile, the patient’s blood samples were sent to determine the level of G6PD enzyme and reductase B enzyme. The level of methemoglobinemia dropped to 37.3% after 3 h and to 24.2% after 4 h of starting hyperoxia. While the patient was ventilated with a fraction of inspired oxygen of 1.0, arterial blood gas analysis showed an oxygen partial pressure of 305 mmHg and an oxygen saturation of 92%–94% on the pulse oximeter, which supported our diagnosis of methemoglobinemia. Furthermore, the level dropped to 7.4% after 10 h and \( FIO_2 \) gradually decreased to 40%. The patient then stabilized and was kept on low ventilator settings. On the 3rd day of admission, he was extubated and discharged to the general pediatric ward. The level of methemoglobinemia gradually dropped to normal. The level of Met-Hb reductase B was 10.7 U/g Hb (reference range 6.6–13.3 U/g Hb), which excluded the possibility of congenital deficiency. The results of G6PD enzyme came as normal. The patient was discharged with no medications and was in good health when followed up in the outpatient department after 1 month.

**DISCUSSION**

The first case of methemoglobinemia in an infant secondary to F. asafoetida gum resin ingestion was reported by Kelly et al.[7] In their report, the patient was a 5-week-old infant who had presented with tachypnea, grunting and cyanosis a few hours after ingestion of F. asafoetida. Their observation indicates that F. asafoetida gum exerts a major oxidative effect on the purified fetal Hb, but not on Hb A.

Infants aged <4 months are at greater risk of developing methemoglobinemia secondary to any oxidizing agent, such as F. asafoetida, because the activity of Met-Hb reductase B is reduced (50%–60% of that in adults) and fetal Hb is more easily oxidized than adult Hb.[2,4] Moreover, the elevated intestinal pH enhances the growth of Gram-negative bacteria, resulting in increase in the reduction of food nitrates into nitrites, which have
higher oxidative capacity. Therefore, infants should not be weaned before 4 months of age because of risk of exposure to nitrate-containing foods, such as carrot, beets, fava beans, green beans, spinach and pumpkin, or to nitrate-contaminated water.

Presentation of methemoglobinemia varies based on the Met-Hb level, ranging from asymptomatic at levels of <15%, cyanosis at ≥15% and death at 70%. At high levels from 50% to 70%, patients usually suffer from tachypnea, metabolic acidosis, cardiac arrhythmias, seizures, central nervous system depression and coma. Our patient presented with severe respiratory distress and metabolic acidosis with poor peripheral perfusion, which can mislead the diagnosis. Although acquired methemoglobinemia is not uncommon, in our case, the high Met-Hb level in the blood gas report, coupled with revised history and the clinical presentation, was the indicator of diagnosis. Methemoglobinemia should be suspected if the patient has central cyanosis and low oxygen saturation on pulse oximetry with high oxygen partial pressure on arterial blood gas analysis in the absence of cardiopulmonary dysfunction.

Severe acquired methemoglobinemia is a medical emergency, and the first step in its management is recognizing the causative agent, eliminating the inducing agent and providing high flow oxygen followed by administrating methylene blue, which is the antidote of methemoglobinemia. However, in the current case, because of the patient’s family history of G6PD deficiency, methylene blue was not given to avoid the risk of severe hemolysis. In addition, intravenous ascorbic acid was not available; therefore, the treating team decided to manage the patient with hyperoxic ventilation. Subsequently, the level of Met-Hb dropped from 66.9% to 24.2% in the first 4 h and the critical level was passed, after which the level dropped further to 7.4% within 10 h of starting the hyperoxic ventilation. To the best of our knowledge, this is the first case of lethal methemoglobinemia successfully treated with hyperoxia. Therefore, the authors recommend that in conditions when methylene blue is contraindicated, hyperoxia treatment may be a viable treatment alternative. In an animal model with lethal acute Met-Hb, hyperoxic pulmonary ventilation has been shown to accelerate the degradation of Met-Hb.

CONCLUSION

Herbal medication with F. asafoetida (heltit) is widely used, but its use in infants should be avoided because it can cause lethal methemoglobinemia. Pediatricians should be aware of such toxicity and should counsel the parents on the same. Hyperoxia can be considered a viable treatment option for lethal methemoglobinemia; however, more research is needed to prove the effectiveness of its outcome in comparison with other treatment modalities.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient’s parents have given their consent for his clinical information to be reported in the Journal. The patient’s parents understand that his name and initial would not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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