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ACUTE PRESENTATION OF HEMOLYSIS AND CYANOSIS IN A HEALTHY CHILD. CASE REPORT AND LITERATURE REVIEW

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ABSTRACT The G6PD enzyme is part of pentose monophosphate shunt. It catalyzes the oxidation of glucose 6 phosphates to nicotinamide adenine dinucleotide phosphate (NADPH) that maintains the glutathione in its reduced form. Most cases of (G6PD) reported developing acute hemolytic anemia after ingestion of fava bean related foods, certain medication or even during stressful situations. Here, we report a case of acute hemolytic anemia occurred after ingestion of FALAFEL sandwich (a fava bean product), that was associated with methemoglobinemia. This rare coexistence of both diseases with only 5 cases reported in pediatric age group. Mother was informed about the diagnosis of G6PD in primary health care center when the patient was two years old but wasn't sure about it. After reviewing the literature for similar cases, we concluded that there were no other reported cases with the same presentation and good outcome.

KEY WORDS : Hemolysis and cyanosis, FALAFEL sandwich, NADPH, methemoglobin

INTRODUCTION

Glucose-6-phosphate dehydrogenase deficiency is a disorder which it's linked to X chromosome, Where the red blood cells break down when the body is exposed to certain types of food, drugs, stress or even infection.

G6PD could lead to an acute hemolytic anemia if exacerbated by a trigger. In this case, it coexisted with methemoglobinemia, a condition develops when methemoglobin a form of oxygen-carrying hemoglobin present with the iron in the ferric state rather than the ferrous state. This will lead to a reduction in the O2 binding capacity causing oxygen desaturation (1).

We report a case of known G6PD deficiency developing hemolytic anemia with methemoglobinemia after ingestion of FALAFEL (a fava bean product).

Case report

A previously healthy 7-year-old boy presented to the Royal Commission Hospital's ER with yellowish discoloration of sclera and skin, dark brown urine, shortness of breath, and a history of fever for 3-days relieved by paracetamol. Cyanosis was noticed by the attending ER physician upon presentation. (Figure1)

Mother reported a history of eating FALAFEL (a fava bean product) prior to symptoms.

There was no history of similar attacks, previous admissions or drug ingestion.

On examination, patient looks lethargic, mildly distressed, febrile 38.8C, with a respiratory rate of 30 breath/min, SPO2 of 82% measured with the pulse oximeter, and mild jaundice of both sclera and skin. Height was: 129 cm, Weight: 25.4 kg (centile). The patient was tachycardic with a heart rate of 145 b/m, blood pressure 119/75mm Hg slightly elevated on the upper limit for age.

Cardiac examination revealed normal finding apart of Ejection systolic murmur (hemic murmur grade 1/6 mainly at the apex), with a clear chest. The abdomen was soft, lax with no organomegaly In ER the patient's oxygen saturation was initially 82% on room air, despite being supplied with a non-rebreathing oxygen mask 15 L/Min his oxygen saturation did not exceed 86%, which alert the diagnosis of methemoglobinemia. A bedside test was performed comparing the blood sample taken from the patient with a blood sample taken from one of the staff. The first impression of both blood samples was the clear difference in color between the two with the blood sample taken from the staff becoming brighter in color, in the other side, the sample taken from the patient continued to display a dark red color. (Figure 2)

Initial venous blood gases analysis was obtained; the results came as the following:

PH: 7.39, PCO2: 43, PO2: 11, HCO3: 26, Met Hb: 10.6.

Blood count test, showed hemoglobin (Hb) 6.7 g/dl; mean corpuscular volume (MCV) 87.21fL; Reticulocytes 1.7 The serological test revealed the following abnormalities: Conjugated serum bilirubin 26.2, total serum bilirubin 175.1, Lactate dehydrogenase (LDH) 1317, serum creatinine 47, and C- reactive protein 30. G6PD screening test showed marked Deficient. Direct COOMBS test was negative.

A chest x-ray showed no abnormalities.

Hospital management and outcome:

The diagnosis confirmed to be acute hemolytic anemia with methemoglobinemia. The patient was managed initially with high O2 mask and IV fluids. Two packed red blood cells transfusion was given as definitive treatment.

Repeated venous blood gasses analysis showed PH 7.39, PCO2: 41, PO2: 31, HCO3: 24.8, Met Hb:

Hemoglobin (Hb) rises up to 8.8mg/dl, followed by a second attack of hemolysis with (Hb) level of 7.3 mg/dl. The patient was given a second transfusion of 10 ml/kg. After that Hb rises to 11.2 mg/dl, associated with improvement of urine color.

Blood tests post-transfusion was: conjugated bilirubin 29, total bilirubin 152, LDH 2062, creatinine 44.8 and urea blood 6.4.

The patient became stable and was discharged home within 1 week of admission.

His mother was informed about the diagnosis. An arrangement was made with the dietician and health educator to educate the parents

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about his condition.

DISCUSSION

This case report represents a previously healthy 7-year-old boy who is known to have G6PD. There was a history of ingestion fava bean products in the past but no similar symptoms were reported. He presented to the hospital with an acute attack of hemolytic anemia with hemoglobin reaching 6.67 mg/dl associated with methemoglobinemia 10.6 that decrease his oxygen saturation to 86%. Despite the severe presentation, the patient improved significantly returning to his daily life activity within 1 week of admission. Unlike other case reports in this case, the coexistence of the two conditions leading to a good outcome with early diagnosis and management.

Hemolytic diseases involve disorders that affect the structure of erythrocytes itself such as disorders of the erythrocyte's membrane, deficiency of enzymes, for example, glucose- 6-phosphate dehydrogenase, or the functional hemoglobin unit in erythrocyte including hemoglobin abnormality leading to hemolytic anemia. Most cases are due to congenital anomalies, but others can happen due to acquired causes such as autoantibodies, drugs, and infection. (2) Glucose-6-phosphate dehydrogenase deficiency or G6PD is defined as an X-linked enzymatic defect leading to variable degrees of antioxidant dysfunction involving erythrocyte membrane. (3) As erythrocytes have a principal role in oxygen transport to peripheral tissues they are exposed to the variable oxidative stressor, nictitating the presence of antioxidant mechanisms for erythrocyte protection. (2) The enzyme G6PD catalyzes the reduction of nicotinamide adenine dinucleotide phosphate (NADP) to NADPH. This form of NADP maintains a constant supply of reduced glutathione into the cell, this component in return plays a critical role in the defense of the cell against variable oxidative stress and free radicals through the cytochrome- b5- methemoglobin reductase system. Without this mechanism, erythrocytes are vulnerable to damage caused by an oxidative stressor and free radicals leading to hemolytic anemia and Methemoglobinemia. (4) Methemoglobinemia is a condition in which the normal globin molecule that contains four ferrous (Fe2+) ions is oxidized into ferric (Fe3+) form or hemoglobin M, a form that is unable to carry oxygen resulting in shifting of the oxygen dissociation curve to the left. This will lead to cells hypoxia and lactic acid formation. (5) The relation between these two conditions is justified by the fact that Methemoglobin is a normal product of the human body at a level that should not exceed 1% of the total hemoglobin. It's strictly regulated by the NADH cytochrome 5b reductase (methemoglobin reductase) enzyme. As for, any oxidative burden for a G6PD patient can be the trigger leading to high level of Methemoglobin and hypoxia. (5, 3)

Diagnostic consideration:

In cases where G6PD and Methemoglobinemia present in one patient, the symptoms of one disorder can mask the other. Methemoglobinemia should be suspected when there is unexplained low saturation of oxygen not responding to the high flow of O2 after the exclusion of cardiac and respiratory causes. (5) In our case, the patient presented mainly with symptoms of dark urine and yellowish discoloration of the eyes and skin. Total bilirubin level showed to be 175.13 upon admission. Despite following the recommended guideline for hemolytic anemia management, the patient continues to have low O2 saturation reaching to 86% with high flow O2. The readings of O2 saturation using Pulse oximetry can sometimes be misleading, as Methemoglobin absorbs all wavelengths equally leading to misinterpretation of the results. In contrast, co-oximetry that used for blood gas analysis in most hospital laboratories can give accurate results for both SatO2 and metHb levels. (3) Other clinical signs that may help in the diagnosis of Methemoglobinemia is the color of the blood giving a dark chocolate color with no change in color with O2 exposure. (5) In our case, the blood sample giving the characteristic chocolate color was sent to the lab for analysis. It gave an initial level of met Hb=10.6 and Hb level of 5.6.

In any patient with Methemoglobinemia and G6PD observing the met Hb level and Hb level is critical for management and anticipation of any complications. It was reported in the literature that elevated levels of met Hb could be associated with serious complications. Pediatric patients can be symptomatic with levels of met Hb equal to 30%. Higher level can be associated with Dyspnea, cyanosis, nausea, and tachycardia. Serious complications may include heart failure, renal failure, shock, seizure, coma, and sometimes death with levels reaching up to 70%. (4, 6) Patients can become symptomatic with lower levels in cases of anemia as result of decrease O2 carrying capacity. This becomes more apparent in cases of G6PD as they are vulnerable to oxidative stressors. (3) In our case, the renal function tests showed creatinine levels of 47.1, and Blood urea nitrogen of 7.5 upon presentation, but the patient was asymptomatic. Met Hb level recorded to be 10.6 a level that is usually tolerable by children with Methemoglobinemia only. But in our patient, it resulted in the symptoms of lethargy, dyspnea, and tachycardia taking into consideration the coexisting G6PD hemolytic anemia.

Therapeutic consideration:

Treatment of G6PD anemia associated with Methemoglobinemia depends on the level of met Hb and clinical presentation. In asymptomatic patient with Methemoglobinemia, the target of met Hb should be up to 30%. This level becomes lower in symptomatic patients and cases with concomitant G6PD anemia. The drug of choice for Methemoglobinemia is methylene blue, which is oxidized through the NADH system so it can act as trigger worsening the anemia in G6PD patients. Based on the literature review done in combined cases of both conditions. They suggested that if Methemoglobinemia presented with acute life-threatening symptoms, methylene blue should be administered with critical monitoring of the hemolysis. Worsening of the hemolysis indicate abandoning the treatment and administration of blood transfusion (Backed RBC)(3). In cases of chronic or mild to moderate conditions Backed RBC transfusion and vitamin C are the mainstay of management. (4, 5) Other associated symptoms should be monitored along with met Hb levels. In our case, the patient was transfused backed RBC twice. His symptoms improved with the met Hb level reduced to 5.6 and hemolysis improved with Hb level of 11 mg/dl. Total bilirubin recorded to be 152.97a, BUN reaches to 6.4 and creatinine levels declined to 44.8. The patient showed significant improvement and was discharged home within 1week.

He was followed two weeks later in the hematology clinic. Repeated blood analysis showed Hb level of 13.66 and met Hb level of 1%. The patient was doing well returning fully to his daily activity.

CONCLUSION:

In summary, G6PD anemia associated with Methemoglobinemia can be a life-threatening condition. High index of suspicion is needed as one of them can overlap with the other. Early diagnoses and critical monitoring of the disease can lead to a remarkably good outcome.

Appendixes:

Figure1: Initial urine sample was taken in the ER showing dark brown urine.

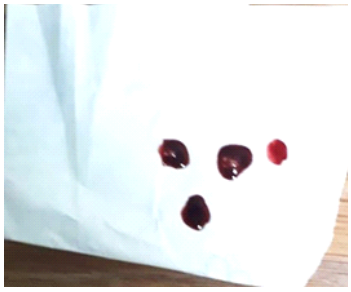

Figure 2: A bedside test comparing the blood sample taken from the patient with a blood sample taken from one of the staff. Bloods ample shows dark chocolate color with no change with O2 exposure.

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