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Diabetic Ketoacidosis Revealing Severe Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD-D) Deficiency with Methemoglobinemia: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 17
Final Diagnosis: Diabetic ketoacidosis revealing severe G6PD deficiency with methemoglobinemia
Symptoms: Jaundice
Medication: —
Clinical Procedure: None
Specialty: Hematology

Objective: Unusual clinical course

Background: Glucose-6-phosphate dehydrogenase deficiency (G6PD-D) is the most common red blood cell enzymopathy disorder. Severe hemolysis due to G6PD-D may rarely manifest as methemoglobinemia. Although acute hemolytic crises are usually induced by the exposure to certain oxidative stresses, diabetic ketoacidosis may also elicit hemolytic reactions in G6PD deficient persons.

Case Report: A 17-year-old male with type 1 diabetes mellitus presented with diabetic ketoacidosis and features of hemolytic anemia which turned to be G6PD-D related. Interestingly, the arterial blood gas of the patient showed an elevated methemoglobin level (8.1%).

Conclusions: G6PD-D induced hemolysis is conventionally caused by oxidative stress, however, we report here a case of G6PD-D induced methemoglobinemia as a complication of diabetic ketoacidosis that has not been, as far as we know, previously reported.

MeSH Keywords: Diabetic Ketoacidosis • Glucosephosphate Dehydrogenase Deficiency • Hemolysis • Methemoglobinemia

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Background

Glucose-6-phosphate dehydrogenase deficiency (G6PD-D) is the commonest enzyme deficiency in humans [1]. This condition is most prevalent in the Mediterranean and the Middle East areas with male predominance due its X chromosome linked inheritance pattern [2]. The G6PD enzyme plays a role in protection of red blood cells from oxidative injury by generating NADPH (a reduced form of nicotinamide adenine dinucleotide phosphate) [3]. Common oxidative injuries precipitating acute hemolysis in patients with G6PD-D include medications, certain food such as fava beans, acute illnesses like infections, and rarely diabetic ketoacidosis [4,5]. The severity of hemolysis is variable and disappears when the normal metabolic balance is restored [2]. Severe hemolysis due to G6PD-D may rarely manifest as methemoglobinemia [6], in which the heme iron is in the oxidized ferric state rather than the ferrous state [7]. Methemoglobin cannot carry oxygen and the remaining oxyhemoglobin develops increased oxygen affinity resulting in impaired oxygen delivery [8]. Here we report a case of a patient with diabetic ketoacidosis complicated by G6PD-D hemolysis induced methemoglobin.

Case Report

A 17-year-old male with type 1 diabetes mellitus presented to the Emergency Department of our institution complaining of abdominal pain, vomiting, jaundice, tea colored urine, and generalized fatigability started 2 days after missing his insulin injections. The patient also gave a history of fever and symptoms of upper respiratory tract infection that resolved 5 days prior to his presentation. He had 4 previous episodes of diabetic ketoacidosis caused by missing insulin or by an infection. Family history was significant for G6PD deficiency in his brother. His regular home medications include only insulin lantus 30 IU at bedtime and insulin aspart 15 IU before meals. He also took paracetamol for fever prior to presentation.

Upon examination, he was fully conscious, oriented and appeared deeply jaundiced. He was afebrile with normal heart rate and blood pressure. His respiratory rate was 24 breaths per minutes and oxygen saturation was 82% on 15 L of oxygen. Initial arterial blood gases showed a pH of 7.125, $PaCo_2$ of 20.4 mmHg, PaO_2 of 223 mmHg (on oxygen), bicarbonate (HCO3) of 8.8 mmol/L, methemoglobin of 8.1% (normal range, 0.0%–1.5%) and oxygen saturation of 100.6% (Table 1). His random blood sugar was 517 mg/dL. Complete blood count showed hemoglobin of 8.7 g/dL (normal range, 12.0–14.0 g/dL), (2 months back his hemoglobin was 15.2 g/dL), white blood cells count of 35.6 K/uL (normal range, 4.5–13.5 K/uL), red blood cells count of 3.09 K/uL (normal range, 3.8–5.8 K/uL), platelets of 750 K/uL (normal range, 140–450 K/uL). Reticulocyte count was 14.6% (normal range, 1–3%). Peripheral blood film showed polychromasia with significant numbers of bite cells and blister cells. Neutrophilia and shift to the left and toxic changes were also noted. Total bilirubin was 7.2 mg/dL (normal range, 0.2–1 mg/dL) with a direct bilirubin of 1.2 mg/dL (normal range, 0.05–0.2 mg/dL), aspartate aminotransferase of 29 U/L (normal range, 15–37 U/L), alanine aminotransferase of 169 U/L (normal range, 14–63 U/L), and lactate dehydrogenase was 3362 U/L (normal range, 81–234 U/L). BUN was 24 mg/dL (normal range, 7–18 mg/dL), creatinine was 1.10 mg/dL (normal range, 0.6–1.0 mg/dL), sodium was 138 mEq/L (136–145 mEq/L), potassium was 5.10 mEq/L (normal range, 3.5–5.1 mEq/L), and bicarbonate was 7 mEq/L (21–32 mEq/L). Serum osmolality

Table 1. The arterial blood gas (ABG) results of the patient.

Parameter	Result	Reference range
PH	7.125	7.35–7.45
PaCo2	20.4 mmHg	35.0–45.0
PaO2	223 mmHg	83.0–108.0
Hco3	8.8 mmol/L	22.0–26.0
Met-Hb	8.1%	0.0–1.5
Oxygen saturation*	100.6%	95.0–99.0

* Spo2 of 82% on 15 L of oxygen.

Table 2. Summary of the laboratory tests results.

Parameter	Result	Reference range
Random blood sugar	517 mg/dl	≤140
Hemoglobin	8.7 g/dL	12.0–14.0
WBC	35.6 K/uL	4.5–13.5
RBC	3.09 K/uL	3.8–5.8
Platelets	750 K/uL	140–450
Reticulocyte count	14.6%	1–3%
Total bilirubin	7.2 mg/dl	0.2–1
Direct bilirubin	1.2 mg/dl	0.05–0.2
AST	29 U/L	15–37
ALT	169 U/L	14–63
LDH	3362 U/L	81–234
BUN	24 mg/dl	7–18
Creatinine	1.10 mg/dl	0.6–1.0
Na^+	138 mEq/L	136–145
K^+	5.10 mEq/L	3.5–5.1
$Hco3^-$	7 mEq/L	21–32
Serum osmolality	319 mOs/kg	85–295

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was 319 mOs/kg (normal range, 285–295 mOs/kg) (Table 2). Urine analysis was positive for nitrates, ketones and showed red blood cells of 10–20 per HPF (normal range, 0–3 per HPF). G6PD deficiency screening test was positive. Direct antiglobulin test was negative. Urine and blood culture showed no growth. Chest x-ray was unremarkable. The diagnosis of G6PD-D hemolysis with methemoglobinemia most likely secondary to diabetic ketoacidosis was made. It's worth mentioning that this patient was not aware of his G6PD-D and did not report having previous episode of hemolysis. He also denied taking any medication or having exposure to chemicals that may cause methemoglobinemia.

The patient was managed as per the hospital diabetic ketoacidosis protocol, transfused with 2 units of packed red blood cells, and started on piperacillin-tazobactam empirically. For the methemoglobinemia, he was given 1 g of ascorbic acid orally, as methylene blue should be avoided in patients with G6PD deficiency. He was followed with serial arterial blood gases, electrolytes, CBC, and hemolytic parameters, which showed resolution of the metabolic acidosis and successful decrement in methemoglobin level as well as improvement in hemolytic parameters. The patient was discharged after 5 days with methemoglobin level of 1% and hemoglobin level of 9.8 g/dL.

Discussion

Acute hemolysis in G6PD deficient individuals is caused by several factors via inducing oxidative stress. Certain medications, foods, and medical illnesses such as infections are commonly implicated. The correlation between diabetic ketoacidosis and G6PD-D hemolysis remains controversial. Diabetic ketoacidosis is commonly precipitated by physiological stress. The same fundamentals could be implicated in the hemolysis of the red blood cells in G6PD-D. Diabetic hyperglycemia precipitating G6PD-D hemolysis has been reported in a few case studies, however, the underlying mechanism remains poorly understood [9–11]. Interestingly, an earlier study showed that hyperglycemia was associated with reduction in G6PD activity in rats [12]. More recently, similar observation was obtained from a study involving human and mouse islets cells [13]. In addition, the reverse was shown in the aforementioned study, in which G6PD-deficient mice had smaller islets and impaired glucose tolerance compared with control mice, which suggests that G6PD deficiency *per se* leads to beta-cell dysfunction and death which may provide a mechanistic explanation for the gradual loss of beta cells in patients with diabetes [13].

The case we present herein is unusual for many reasons. The oxidative stress resulting from the diabetic ketoacidosis had unmasked the G6PD-D and led to hemolysis. Furthermore, this was complicated by methemoglobinemia which has been rarely reported in severe cases of G6PD-D hemolysis [14]. The diagnosis of methemoglobinemia was made based on the methemoglobin level in the arterial blood gases and the difference between the oxygen saturation measured by pulse oximetry and the oxygen saturation calculated from the arterial blood gases analysis (saturation gap). The level of methemoglobinemia in our patient was consistent with what has been reported in the literature for G6PD-D hemolysis related methemoglobinemia (<10%) [7]. The antidote of choice for methemoglobinemia is methylene blue that will be converted to leucomethylene blue by NADPH methemoglobin reductase, which in turn reduces methemoglobin to hemoglobin [15]. However, methylene blue should be avoided in G6PD-D since the reduction of methemoglobin by methylene blue is dependent upon NADPH generated by G6PD. In addition, it might also be potentially dangerous since it has an oxidant potential that may induce hemolysis in G6PD deficient subjects [16]. Another treatment option is ascorbic acid which should be given in moderate doses (300 to 1000 mg/day orally in divided doses) since very high doses of it may also cause oxidant hemolysis in G6PD-deficient patients [8]. Our patient was given a single dose of 1 g of ascorbic acid, which had successfully decrease methemoglobin level.

Conclusions

Hemolytic anemia in the background of diabetes has conventionally been associated with bacterial infections and hemolytic drugs. However, in the absence of these, a search of the root cause is mandatory. In addition to the hemolysis, the presence of methemoglobinemia should rise the possibility of G6PD-D. This case highlights an unrecognized complication of diabetic crises such as G6PD-D hemolysis with methemoglobinemia. As reported in this case, physicians should be aware of the association of all 3 conditions together.

Department and Institution where work was done

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Conflict of interests

None.

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References:

1. Cappellini M, Fiorelli G: Glucose-6-phosphate dehydrogenase deficiency. Lancet, 2008; 371(9606): 64–74
2. El-Hazmi M, Warsy A: Glucose 6-phosphate dehydrogenase deficiency genetic, pathophysiologic and therapeutic aspects. Ann Saudi Med, 1985; 5(4): 213–22
3. Greer J, Arber D, Glader B et al: Wintrobe's clinical hematology. 13th ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins, 2014
4. Constantopoulos A: Fulminant diarrhoea and acute haemolysis due to G.-6-P.D. deficiency in salmonellosis. Lancet, 1973; 301(7818): 1522
5. World Health Organization: Standardization of procedure for the study of glucose-6-phosphate dehydrogenase. Report of a WHO Scientific Group. WHO Tech Rep Ser, 1967; 366: 5–29
6. Clark B, Morrissey R, Blair D: Relation of methemoglobin to hemolysis. Blood, 1951; 6(6): 532–43
7. Skold A, Robin Klein R: Methemoglobinemia: Pathogenesis, diagnosis, and management. South Med J, 2011; 104(11): 757–61
8. Hassan K, Al-Riyami A, Al-Huneini M et al: Methemoglobinemia in an elderly patient with glucose-6-phosphate dehydrogenase deficiency: A case report. Oman Med J, 2014; 29(2): 135–37
9. Agarwal A: Glucose 6 phosphate dehydrogenase deficiency unmasked by diabetic ketoacidosis: An underrated phenomenon. J Clin Diagn Res, 20013; 7(12): 3012–13
10. Silvestri F: Glucose-6-phosphate dehydrogenase deficiency unmasked by hyperglycemia. J Clin Diagn Res, 2013; 7(12): 3012–13
11. Errico MK, Iovane B, Bernardini A et al: Hemolysis during diabetic ketoacidosis treatment in two girls with incomplete glucose-6-phosphate dehydrogenase deficiency. Acta Biomed, 2009; 80(1): 69–72
12. Díaz-Flores M, Ibáñez-Hernández M, Galván R et al: Glucose-6-phosphate dehydrogenase activity and NADPH/NADP+ ratio in liver and pancreas are dependent on the severity of hyperglycemia in rat. Life Sci, 2006; 78(22): 2601–7
13. Zhang Z, Liew C, Handy D et al: High glucose inhibits glucose-6-phosphate dehydrogenase, leading to increased oxidative stress and β-cell apoptosis. FASEB J, 2010; 24(5): 1497–505
14. Rehman A, Shehadeh M, Khirfan D, Jones A: Severe acute haemolytic anaemia associated with severe methaemoglobinaemia in a G6PD-deficient man. BMJ Case Rep, 2018; 2018: pii: bcr-2017-223369
15. Umbreit J: Methemoglobin – It's not just blue: A concise review. Am J Hematol, 2007; 82(2): 134–44
16. Rosen P: Failure of methylene blue treatment in toxic methemoglobinemia. Ann Intern Med, 1971; 75(1): 83–86

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