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Case Report

New-onset type 1 diabetes mellitus in an adolescent boy with glucose-6-phosphate dehydrogenase deficiency

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Abstract

Background and Aims: Glucose-6-phosphate dehydrogenase (G6PD) deficiency and diabetes mellitus could aggravate each other when they co-exist.The aim of this report is to raise the awareness of clinicians regarding the possibility of co-existence of diabetes mellitus and G6PD deficiency in adolescents with an additional history of passage of dark-colored urine. **Case Report:** We report a case of a 16-year-old Nigerian boy with newly-diagnosed type 1 diabetes mellitus (T1DM) co-existing with glucose-6-phosphate dehydrogenase deficiency which manifested as hemoglobinuria. **Conclusion:** The index case suggests that in the initial period of T1DM, even without ketoacidosis, patients with G6PD deficiency are predisposed to hemolysis, manifesting as hemoglobinuria. Additionally, patients with T1DM, presenting with hemoglobunuria should be investigated for G6PD deficiency.

Keywords: Diabetes mellitus, glucose 6 phosphate dehydrogenase, hemoglobinuria, Nigeria.

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is a cytoplasmic enzyme that catalyzes the first step in the production of reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) in the pentose phosphate pathway. G6PD deficiency is an X-linked recessively inherited enzyme defect and the defect gene has been mapped at Xq28 [1]. The World Health Organization has classified G6PD deficiency into five variants, classes I to V, based on level of enzyme activity and the severity of the hemolytic episode and its clinical manifestations. Class-I variant, residual enzyme activity less than 10%, is associated with chronic hemolysis. In the Mediterranean basin, it is usually the class II variant with residual enzyme activity less than 10% with intermittent acute haemolysis. Class III deficiency has moderate residual enzyme activity (10–60%) with intermittent acute haemolysis and is due to gene G6PD A (African variant). Classes IV and V are of no clinical significance [2]. The two most common mutations of G6PD are the G6PD Mediterranean and G6PD African.

In the red blood cells, defense against oxidative damage is heavily dependent on G6PD, which is the only source of NADPH [3]. This protection is achieved via maintenance of intracellular pool of reduced gluthathione. Majority of individuals are asymptomatic and do not have hemolysis in the steady state. They have neither anemia, nor evidence of increased red blood cell destruction or an alteration in blood morphology [1]. Occurrence of symptoms has been associated with exposure to some drugs and food (e.g., antimalarials and fava beans), severe

bacterial infections and diabetic ketoacidosis [1, 2, 4, 5]. The clinical manifestations of G6PD deficiency include prolonged neonatal jaundice and hemolytic anaemia, which may be acute or chronic. The reported prevalence of G6PD deficiency among Nigerian children is 15.3% [6].

The results of some studies suggest that G6PD deficiency is a risk factor for diabetes mellitus (DM) [7, 8]. Additionally, diabetic ketoacidosis may trigger hemolysis in G6PD-deficient individuals [4, 5]. Diabetes mellitus (DM) is characterized by high blood glucose level which is a major source of free radicals through several mechanisms [9]. Although hamolysis has been reported in newly-diagnosed type 1 diabetes (T1DM), it is uncommon [10, 11]. In European literature, majority of the reports on the subject focus on the Mediterranean variant of G6PD deficiency [4, 5, 12]. However, the African variant has been shown to trigger hemolysis in diabetic ketoacidosis [13].

Case Report

We report a case of a 16-year-old Nigerian boy who presented with fever and occasional vomiting, polyuria, weight loss, and generalized weakness all of one week duration. Four days after his parents administered an antimalarial (artemeter-lumefanthrine) procured from a patent medicine shop, he started passing dark-colored urine. He has had two similar episodes in the past following fever and administration of an antimalarial. This change in urine color prompted his presentation to a private clinic where random blood glucose was performed and found to be elevated (247 mg/dl). HbA1C was elevated by 7.6%. There was a positive family history of DM. His maternal grandmother reportedly had occasional episodes of passage of dark-colored urine. However, there was no similar history in maternal uncles. History of neonatal jaundice was negative. Physical examination revealed moderate dehydration, bilateral pitting pedal edema, evidence of weight loss, and blood pressure of 130/70 mmHg (90th centile for age, gender, and height). There was no jaundice. Other physical examinations were unremarkable. A provisional diagnosis of T1DM with G6PD deficiency was made. Acute glomerulonephritis and urinary tract infection were also considered. G6PD assay was markedly reduced at 1.047 U/gHb (reference interval 7.9–16.3g/Hb), representing 8.7% of mean normal enzyme activity. Full blood count and serum E/U/Cr were essentially normal. The cold agglutinin test and Coomb's test were negative. The hemoglobin concentration was 10.7g/dl. Urine microscopy did not show red blood cells (RBC) or RBC casts. Peripheral blood smear revealed bite cells, Heinz bodies and spherocytes. Serum bilirubin (both total and direct) was slightly elevated. The other laboratory findings are summarized in table 1.

The antimalarial was immediately discontinued. He was started on oral amoxicillin-clavulanic acid and subcutaneous insulin. The patient and the care-givers were counseled regarding G-6-PD deficiency, possible triggers, and pointers to hemolysis as well as self-care practices relating to type 1 diabetes mellitus. Following improvement in his clinical condition, he was discharged. He is being followed up in our pediatric endocrinology and hematology clinics. His last clinic visit was a few days ago with good glycemic control and no hemolytic crises.

Discussion

We describe a case of newly-diagnosed T1DM associated with hemoglobinuria/hemolysis. Additional evidence of hemolysis includes the absence of RBC or RBC casts on urine microscopy and the presence of bite cells, Heinz bodies, and spherocytes in peripheral blood smear. The passage of dark-colored urine prompted presentation to hospital where an incidental random blood glucose level check was found to be in a range suggestive of diabetes mellitus. Our patient's HbAIC concentration (7.6%) was also suggestive of DM. The relatively low HbA1C observed in our patient may be due to the simultaneous presence of G6PD deficiency. This may be explained by a reduction in average erythrocyte life span in G6PD deficiency, resulting in younger RBCs in such patients. The implication in clinical practice is that we should suspect G6PD

Table 1: Summary of laboratory results in our patient.

Laboratory test	Results	Comments
Urine glucose	4+	Glycosuria
Urine protein	2+	Moderate proteinuria
Urine blood	+	Hemoglobinuria present
Urine microscopy	No RBC or RBC casts	Hematuria absent
Urine M/C/S	*Pseudomonas aeroginosa*	Urinary tract infection
Urine SG	1.030	High
Serum creatinine	0.6 mg/dl	Normal
Serum cholesterol	243 mg/dl	Elevated
HDL cholesterol	19 mg/dl	Low
LDL cholesterol	187 mg/dl	Elevated
Serum triglyceride	186 mg/dl	Elevated

deficiency in patients with diabetes whose HbA1C concentration is relatively low. Other laboratory results did not reveal acidosis or ketonuria, negating the diagnosis of diabetic ketoacidosis in our patient. The diagnosis of G6PD deficiency in the index case was based on low G6PD activity (representing 8.7% of mean normal enzyme activity) and the presence of evidence suggesting hemolysis/hemoglobinuria. Combined dyslipidemia was present in our patient, suggesting the need to explore the possibility of a link between G6PD deficiency and early development of dyslipidemia in adolescents with diabetes mellitus. Some researchers have demonstrated that G6PD activity was significantly lower in dyslipidemic patients with diabetes mellitus compared to their counterparts without dyslipidemia [14].

In patients with G6PD deficiency, hemolysis may occur as a result of ingestion of oxidant drugs and bacterial infections. An anti-malarial agent was administered to the patient and he also had proven urinary tract infection, both factors might have contributed to the observed hemolysis/hemoglobinuria. Our patient presented with hyperglycemia which, in itself, is capable of causing a reduction the activity of G6PD, resulting in hemolysis. Some researchers have linked the observed decrease in G6PD activity after exposure to high levels of blood glucose to both post-translational mechanisms and decreased gene expression [15]. In the index case, laboratory results did not reveal acidosis or ketonuria, negating the diagnosis of diabetic ketoacidosis in our patient. Various mechanisms have been postulated to explain the hemolysis found in newly-diagnosed T1DM without ketoacidosis. One factor that might potentially weaken the structure of the erythrocyte membrane in T1DM is the associated insulin deficiency. In normal individuals, insulin increases calcium concentration within RBC with a subsequent increase of the activity of phosphofructokinase in the glycolytic pathway. This process increases ATP production, stabilizes the membrane of a RBC, preventing its hemolysis [16]. This protective biochemical process may be compromised in T1DM. Other factors capable of precipitating hemolysis in G6PD- deficient patients are diabetic ketoacidosis and hypoglycemia [4, 5, 16], both of which were absent in the index case.

With regard to prognosis, G6PD deficiency and diabetes mellitus could aggravate each other [17]. The risk of hemolysis in patients with G6PD deficiency would be increased in case of diabetic crisis [4, 5]. Hyperglycemia in itself is known to reduce the activity of G6PD, making such a patient more prone to hemolysis [15, 18]. G6PD deficiency has been linked with increased risk for development of diabetes mellitus [8, 19, 20]. Within this context, West proposed that

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alterations in genes controlling both insulin secretion and G6PD-mediated antioxidant defenses may contribute to predisposition to DM [21]. The implication in clinical practice is that more attention should be paid to avoid severe hemolysis in the treatment of patients with G6PD deficiency, co-existing with DM.

In conclusion, the index case suggests that in the initial period of T1DM, even without ketoacidosis, patients with G6PD deficiency are predisposed to hemolysis, manifesting as hemoglobinuria. Additionally, patients with T1DM and hemoglobunuria should be investigated for G6PD deficiency.

Conflict of Interest

The authors declare no conflict of interest.

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