

Glucose-6-Phosphate Dehydrogenase Deficiency Unmasked by Hyperglycemia

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disease responsible for moderate to severe hemolytic anemia. This is the most common erythrocyte enzyme disorder, often overpassed. A 14-year-old male patient was admitted to emergency department with hyperglycemia. He was treated initially with fluid therapy, after two hours with subcutaneous ultra-rapid insulin. After five days from hospitalization he showed scleral and skin jaundice were made diagnosis of hemolytic anemia by G6PD deficiency. There was no significant family or prior medical/ drug history. Interestingly, the hemolytic features were evidenced when blood glucose levels were returning to normal values. The insulin mediated NADPH loss may have resulted in increased erythrocyte oxidant sensitivity and a loss of sulfhydryl group's availability, causing hemolysis to manifest.

G6PD deficiency is usually linked to drug which induced oxidative stress. Association with diabetes mellitus is infrequently reported. This case wants to emphasize that the G6PD deficiency has been unmasked by hyperglycemia until now unknown without signs and symptoms.

Keywords: Glucose 6 phosphate dehydrogenase deficiency; Diabetes mellitus type 1; Hyperglycemia; Hemolytic anemia

Case Report

A 14 years-old child was referred to Policlinic Umberto I emergency department, Rome with polyuria, polydipsia started 20 days before and hyperglycemia (494 mg/dl). He was in health until that episode. Firstborn of unrelated parents, born at 40 gestational weeks after an uncomplicated pregnancy his weight and length at birth were appropriated for gestational age. Apgar score was 9 (1') and 10 (5'). The postnatal course was uncomplicated. There was any pathological family history.

Clinical examination revealed the patient was awake and well hydrated.

First line examination on venous blood gas analysis showed: Ph: 7.45; Na⁺: 132 mEq/L; K⁺: 3.6 mEq/L; Pco₂: 28 mmHg; Glu: 482 mg/dl; HC03⁻: 21.7 mEq/L; BE Ecf: -4.5 mMol/L.

Second line examination revealed an HbA1c 9.9% while the other analyses were in the normal range of values. He started fluid therapy with 0.9% NaCl, intensive insulin therapy and potassium supplementation.

After the resolution of mild failure, diagnosis of diabetes mellitus type 1 was revealed by positivity for anti-Insula and anti-GAD antibodies.

Extended investigations have been performed on liver, kidney, coagulation and thyroid functions. Virological examinations were negative.

After five days by hospitalization, patient showed scleral and skin jaundice, urobilinurea and hypo chromic feces. Blood exam revealed signs of hemolysis: red blood counts 3.530.000, hemoglobin 10.7 g/dl,

reticulocytes 4.05 %, total bilirubin 5.94 mg/dl, direct bilirubin 0.53 mg/dl, haptoglobin 10 mg/dl. Coombs test was negative.

Hemolytic episode was resolved without medical intervention. Was studied G6PD activity which revealed slight deficiency: G6PDH 39 mUI/10⁶ GR (164-376 mUI/10⁶), PK 29 UI/gr Hb (7, 4-16, 4 UI/gr), with abnormal erythrocyte osmotic resistance, until now unknown.

As regards diabetes, we had changed ultra-rapid insulin with regular one because of we thought there was an adverse reaction to ultra-rapid insulin. After reviewed literature we have linked the hemolysis to glycometabolic decompensation even if without diabetic ketoacidosis. After therapy, glycometabolic control was excellent without hypoglycemia. Last HbA1c was 5.4%, maybe for slight continue hemolysis without clinical signs.

Discussion

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme deficiency in the world. The disease prevalence is correlated with areas where malaria was and is endemic such as Africa, Mediterranean Europe, South-East Asia, and Latin America [1].

The G6PD is involved in the pentose phosphate pathway. It catalyzes the reaction that products NADPH, which represents the only erythrocytes protection from hemolysis caused by oxidative stress [2]. G6PD also regenerates the reduced form of glutathione which maintains hemoglobin and other proteins in their reduced form [3].

The gene encoding G6PD is found on the long arm of the X chromosome (Xq28), and consists of 13 exons with a length of 18 kb [4].

This gene is polymorphic, there are at least 400 allele's variants [1]. They are subdivided into five classes based on the functional severity of the deficiency, with Class 1 characterized by severe deficiency

resulting in chronic non-spherocytic anemia ranging to Class 5 with greater than 150% of normal activity [1].

Males expresses the deficiency while female are a mosaic due to the random inactivation of one of the two X chromosome in each cell.

Neonatal jaundice and drug-induced hemolysis, which may follow the ingestion of broad beans and agents with oxidant properties, such as primaquine, sulfonamides, nitrofurantoin, and several anti-inflammatory agents are the most frequent clinical manifestations. Even if hemolysis is often self-limitant some patients requires blood transfusion [2].

Type 1 diabetes (DM1) is an autoimmunity disease caused by a T-cell mediated reaction against pancreatic β -cells. This reaction conducts to insufficient and absent production of insulin [5]. DM1 is characterized by the presence of autoantibodies (anti-Insula and anti-GAD antibodies) that sometimes induce diabetes outset. The disease's etiology is still not clear but it is known that there is an interaction between the environment and polygenic traits [6].

The correlation between diabetes and G6PD deficiency is still in debate. A recent study proposes that alterations in gene controlling both insulin secretion and G6PD-mediated antioxidant defenses may contribute to a predisposition to diabetes [7].

Several clinical observations demonstrate that hypoglycemia can promote the decrease of G6PD activity and also the reverse hypothesis that correlates the presence of G6PD deficiency with the occurrence of diabetes [8]. That is supported by the fact that there is an increased prevalence of G6PD deficiency among diabetic patients [2]. It was hypothesized that blood glucose normalization during treatment of failure induced a stressing glucose deprivation for the energy-dependent function of the red blood cells causing premature RBC destruction [9].

The only characteristic that is common to all the cases of acute hemolysis in diabetic patients is the fact that the hemolysis occurs after diabetes decompensation, whatever the treatment is. This suggests that hyperglycemia may induce hemolysis. Both post-translational mechanisms and decreased gene expression appear to be involved in the decrease of G6PD activity that was observed after exposure to high levels of hyperglycemia [10].

Recently, it has been shown that high glucose also decreased G6PD expression and activity in human islets [11].

Patients with G6PD deficiency have lower HbA1c compared to the normal one. In fact, subjects with DM1 and DM2 and no G6PD deficiency have higher HbA1c than subjects with G6PD deficiency and DM1 or DM2, because the average life of erythrocytes is reduced in the latter patients and RBC are younger. So, we should speculate a G6PD deficiency when patients have low HbA1c and any risk factors [12].

The child had never had clinical signs of jaundice until this episode and neither his parents.

After the hospitalization we tested the patient's parents for G6PD deficiency and his mother resulted positive. The patient's G6PD deficiency is classified as a third type defect: 39% (10-60%) of enzymatic activity that doesn't manifest clinical signs.

Conclusion

Our case report would underline and demonstrate the association between G6PD deficiency and diabetes type 1, until now incompletely known.

In fact our patient, who was in mild glycometabolic decompensation, manifested the hemolysis five days after the diagnosis of DM1. During the first days of recovery he was in health and he had no jaundice. After normalization of glycometabolic parameters with subcutaneous insulin, he had signs and symptoms of hemolysis probably due to the energy deprivation that erythrocytes suffered during hyperglycemia with consequent destruction. Usually hemolysis is showed when associated with diabetic ketoacidosis. In our case hemolysis appeared with hyperglycemia without acidosis.

Until today our patient has good glycometabolic control, last HbA1c: 5.4 %. Although the enzyme remaining activity was low, after a year from the episode we reported, he showed no clinical signs and symptoms of hemolysis.

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