CASE REPORT

DOI: 10.4274/jcrpe.galenos.2022.2021-11-10

J Clin Res Pediatr Endocrinol 2023;15(4):417-420

Hemolytic Anemia due to Glucose 6 Phosphate Dehydrogenase Deficiency Triggered by Type 1 Diabetes Mellitus

Burçe Orman[1], Semra Çetinkaya[1], Nergiz Öner[2], Meltem Akçaboy[3], Ali Fettah[2], Naz Güleray Lafcı[4], Şenay Savaş Erdeve[1]

[1]Dr. Sami Ulus Obstetrics and Gynecology, Children's Health and Diseases Training and Research Hospital, Clinic of Pediatric Endocrinology, Ankara, Turkey
[2]Dr. Sami Ulus Obstetrics and Gynecology, Children's Health and Diseases Training and Research Hospital, Clinic of Pediatric Hematology, Ankara, Turkey
[3]Dr. Sami Ulus Obstetrics and Gynecology, Children's Health and Diseases Training and Research Hospital, Clinic of Pediatrics, Ankara, Turkey
[4]Hacettepe University Faculty of Medicine, Department of Genetics, Ankara, Turkey

What is already known on this topic?

Glucose 6 phosphate dehydrogenase (G6PD) deficiency is the most common enzymopathy in humans and is among the important causes of hemolytic anemia. Severe hemolytic anemia due to G6PD deficiency has rarely been reported in association with newly diagnosed diabetes. No genetic analysis of the *G6PD* gene has been published in these cases.

What this study adds?

Rapid correction of blood sugar in diabetic individuals may induce severe hemolytic anemia due to G6PD deficiency. In the present case a previously reported missense pathogenic variant (c.653C > T; p.Ser218Phe) in the *G6PD* gene was found.

Abstract

Glucose 6 phosphate dehydrogenase (G6PD) is expressed in all tissues and is necessary to maintain oxidant stress capacity of cells. G6PD deficiency is the most common enzymopathy in humans and is among the important causes of hemolytic anemia. It has been reported that severe hemolytic anemia due to G6PD deficiency may develop in newly diagnosed diabetes, especially during the correction of hyperglycemia. To date, nine cases have been published. Genetic analysis was not performed for G6PD deficiency in these published patients. We present a case of hemolytic anemia due to G6PD deficiency secondary to newly diagnosed type 1 diabetes mellitus. Genetic testing was performed for the index patient and revealed a previously reported missense pathogenic variant (c.653C > T; p.Ser218Phe) in the *G6PD* gene.

Keywords: Diabetes mellitus, G6PD, anemia

Introduction

Glucose 6 phosphate dehydrogenase (G6PD) is expressed in all tissues and is necessary to maintain the oxidant stress capacity of cells. G6PD is a cytoplasmic enzyme involved in the hexose monophosphate pathway and protects erythrocytes against oxidative damage by producing NADPH. G6PD deficiency is the most common enzymopathy in humans and is among the important causes of hemolytic anemia (1). Medications, certain foods (such as broad beans) and acute infections can cause hemolysis in individuals with G6PD deficiency (2). In G6PD deficiency,

Address for Correspondence: Burçe Orman MD, Dr. Sami Ulus Obstetrics and Gynecology, Children's Health and Diseases Training and Research Hospital, Clinic of Pediatric Endocrinology, Ankara, Turkey
Phone: +90 312 305 65 10 **E-mail:** burceayvazoglu@gmail.com **ORCID:** orcid.org/0000-0002-2737-7815

Conflict of interest: None declared
Received: 17.11.2021
Accepted: 11.01.2022

the severity of hemolysis is variable, and this hemolysis resolves when the normal metabolic balance is restored (3). It has been reported that severe hemolytic anemia due to G6PD deficiency may develop in newly diagnosed diabetes, especially during the correction of hyperglycemia, but this is very rare (4,5).

Case Report

A 4-year-old male patient was admitted with polyuria and polydipsia and was hospitalized with a diagnosis of diabetes when his blood glucose (BG) level was 750 mg/dL. He was not taking any medication. He was tachypneic and weak at admission. Body temperature was 36.8 °C. Height was 105 cm [-0.18 standard deviation score (SDS)], body weight was 13 kg (-2.29 SDS), body mass index was 12.7 kg/m^2 (-2.68 SDS). Other system findings were normal for age. Blood results were: hemoglobin (Hb) 13.1 g/dL (NR 9.6-13.5); white blood cell count (WBC) 6310/mm^3 (5-14.8); platelet count 341,000/mm^3 (150-400,000); C-reactive protein 2.98 mg/L (< 3); blood urea nitrogen 15 mg/dL (0-23); creatinine 0.76 mg/dL (0.3-1.2); BG 750 mg/dL; sodium (Na) 126 meq/L (135-143); corrected Na 137.7 meq/L; potassium 4.55 meq/L (3.1-5.5); aspartate aminotransferase 23 U/L (< 48); and alanine aminotransferase 12 U/L (0-39). The blood tests performed to investigate diabetic ketoacidosis (DKA) showed: pH 7.29 (7.35-7.45); bicarbonate 12.4 mmol/L (18-23); PCO_2 25.8 mmHg (32-46); and base excess -12.3. Urine ketone test was positive. With these results, the patient was diagnosed with DKA. The patient was given intravenous insulin and hydration therapy. Then, intensive insulin therapy was started. Further investigations to confirm the diagnosis showed: HbA1c 15.3%; BG 750 mg/dL (60-110); insulin 2.2 mIU/mL (2-23); C peptide 0.3 ng/mL (0.9-7.1); islet cell antibody positive at 3.38 U/mL (< 1); glutamic acid decarboxylase antibody positive at 1.03 U/mL (< 1); and anti-insulin antibody negative at 4.63% (0-8.2). On the tenth day of admission, while receiving 0.96 U/kg/day subcutaneous insulin treatment, he developed tachycardia with hypoglycemia (heart rate was 160 beats/min while BG was 45 mg/dL). The patient had not previously developed hypoglycemia. The celiac test performed at the time of diagnosis of the patient was negative. Due to hypoglycemia, the dose of insulin was reduced and hypoglycemia did not recur thereafter. The patient, whose tachycardia continued after the hypoglycemia resolved, was examined. There was no jaundice and organomegaly on physical examination. Test results for tachycardia were: Hb 8.3 g/dL (9.6-13.5); mean corpuscular volume 92.8 fL (72.3-90.1); red cell distribution width 23.1% (11.8-15.1); red blood cells 3.06x10^6/L (3.3-5.4); hematocrit 28.4% (28.5-39.5); platelet count 639,000/mm^3 (150,000-400,000); WBC 13,170/mm^3 (5000-14,800). Test results for anemia were: ferritin 136 ng/mL (6-24) and vitamin B12 was 594 pg/mL (200-1080). There were anisocytosis and normoblast in the peripheral smear. There were no atypical cells. The reticulocyte count was 10% (0.2-2). Other results were: prothrombin time 11.7 sec (10-14.7); INR 0.98 (0.8-1.2); activated partial thromboplastin time 23 sec (22-34); total bilirubin 1 mg/dL (0-2) (indirect bilirubin 0.8, direct bilirubin 0.2); and lactate dehydrogenase (LDH) 286 IU/L (140-304). The abdominal ultrasound was normal. The patient was subsequently diagnosed with acute hemolytic anemia. Hb electrophoresis was normal, direct Coombs test was negative, Epstein-Barr virus, cytomegalovirus, brucella and mycoplasma IgM were negative and the G6PD level was low at 0.56 U/g Hb (6.97-20.5). During follow-up, Hb was 7.1 g/dL and erythrocyte suspension was given to the patient whose tachycardia and hemolysis continued. His tachycardia and anemia improved during follow-up. The patient, whose blood sugar regulation was provided, was discharged with intensive insulin therapy. The Hb value measured two weeks after discharge was 12.4 g/dL, and three months after discharge was 12.2 g/dL. Hemogram results are given in Table 1. Genetic examination was performed and a hemizygous mutation (c.653C > T; p.Ser218Phe) was detected in the *G6PD* gene. Genetic analysis was not performed on the patient's parents. Written informed consent for publication of the case was obtained from the parents of the child.

Table 1. Hemogram results of the patient in the follow-up

	First application	In hemolytic crisis	In recovery period
Hb (g/dL)	13.1	7.1	12.2
RBC (10^6/L)	5.53	2.61	4.47
MCV (fL)	71.1	93.5	81
RDW (%)	13.8	23.9	12.3
Hemotocrit (%)	39.3	24.4	36.2
Platelet (10^5/mm^3)	346	499	348
WBC (10^5/mm^3)	6.31	11.83	7.69

Hb: hemoglobin, RBC: red blood cell, MCV: mean corpuscular volume, RDW: red cell distribution width, WBC: white blood cell

Discussion

G6PD protects cells from oxidative damage and is a cytoplasmic enzyme involved in the hexose monophosphate pathway. It reduces glutathione and increases the detoxification of free radicals. G6PD deficiency is inherited in an X-linked fashion and is the most common enzymopathy. G6PD deficiency causes hemolytic anemia in homozygous women and hemizygous men (1). Hemolysis due to G6PD deficiency is a very rare condition in individuals with diabetes. In general, hemolysis occurs while hyperglycemia improves. NADPH production in the hexose monophosphate pathway, the rate-limiting step of this pathway, is G6PD dependent. NADPH is required for reduced glutathione production. In hyperglycemia, erythrocytes shift to the sorbitol pathway. Sorbitol and NADP production increases in erythrocytes. The NADPH/NADP ratio and reduced (GSH) / oxide (GSSG) glutathione ratio decreases. With rapid correction of long-standing hyperglycemia in newly diagnosed diabetes, there is no glucose flow from the sorbitol pathway to the hexose monophosphate pathway, NADPH production decreases, and there is stress in the erythrocyte. Another possible mechanism for hemolysis is increased volume reduction due to hyperglycemia, increased reactive oxygen species (ROS) and oxidative damage, damage to the erythrocyte cell membrane because of increased ROS, and the formation of fragile erythrocytes prone to hemolysis (6). It has been reported that G6PD activity and expression are decreased in islet cells in severe hyperglycemia (7). It has been suggested that the frequency of G6PD deficiency in diabetic patients may be higher than the normal population; similarly, impaired fasting glucose and diabetes frequency may increase in individuals with G6PD deficiency (8). Nine pediatric diabetes cases with hemolysis due to G6PD deficiency have previously been reported. The clinical and laboratory characteristics of the patients are given in Table 2. These cases were between 3.5 and 12 years old. Eight of the cases were male, and two were female. Seven cases were diagnosed with ketoacidosis and one case with hyperglycemia. Hemolytic anemia developed in the first 10 days. In one case, blood transfusion was required, and other cases resolved spontaneously. The distribution of cases were; two Greek, two Egyptian, four Italian and one African American. Most cases were reported from Mediterranean countries and in keeping with this, the presented case was Syrian. Genetic analysis was not performed for G6PD deficiency in previously published patients. Genetic testing was performed for the index patient and revealed a previously reported missense hemizygote pathogenic variant in the *G6PD* gene. The distribution of G6PD activities depended on the type of mutation patterns and genders. Hemizygote, homozygote, and compound heterozygote were predominantly associated with severe G6PD deficiency, whereas heterozygotes with single mutation usually present with moderate enzyme deficiency (9). Thus the hemizygous missense mutation found in the presented case may explain the severe clinical condition.

In addition, an adult case with type 1 diabetes mellitus who was found to have hypoglycemia and hemolytic crisis due to G6PD deficiency has been reported (10). Hypoglycemia was detected in the follow-up of the presented patient and he had tachycardia secondary to hypoglycemia and was diagnosed with G6PD deficiency. In this case, it is not clear whether hemolysis was due to hyperglycemia or a hypoglycemic attack triggered the crisis.

Table 2. Clinical and laboratory characteristics of G6PD deficiency in children with diabetes mellitus

Age	Sex	Country	Presentation at diabetes diagnosis	Time of hemolysis	Hb (g/dL)	Treatment
10	M	African American	Ketoacidosis	9th day	9	Spontaneous
3.5 Twin1	M	Greek	Ketoacidosis	6th day	10.2	Spontaneous
3.5 Twin2	M	Greek	Ketoacidosis	6th day	8.3	Spontaneous
8	M	Sicilian	Hyperglycemia	4th day	7.1	Erythrocyte transfusion
4 Twin 1	M	Egypt	Ketoacidosis	7th day	10.3	Spontaneous
4 Twin 2	M	Egypt	Ketoacidosis	7th day	8.1	Spontaneous
12	F	Sardinia	Ketoacidosis	1st day	Unknown	Unknown
9	F	Sardinia	Ketoacidosis	4th day	Unknown	Unknown
4	M	Italian	Unknown	5th day	Unknown	Unknown
4 Presented case	M	Syria	Ketoacidosis	10th day	7.1	Erythrocyte transfusion

Hb: hemoglobin, G6PD: glucose 6 phosphate dehydrogenase

Conclusion

This case was diagnosed with type 1 diabetes with DKA. The patient had hypoglycemia and tachycardia that developed after his blood sugar was regulated, and his tachycardia continued after hypoglycemia improved. Anemia due to G6PD deficiency was found in the patient who was examined for tachycardia. It should be kept in mind that diabetic individuals may develop severe anemia due to G6PD deficiency when treated for blood sugar regulation.

Ethics

Informed Consent: Written informed consent was provided from the parents.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Burçe Orman, Şenay Savaş Erdeve, Design: Burçe Orman, Şenay Savaş Erdeve, Data Collection or Processing: Burçe Orman, Şenay Savaş Erdeve, Semra Çetinkaya, Meltem Akçaboy, Ali Fettah, Nergiz Öner, Naz Güleray Lafcı, Analysis or Interpretation: Burçe Orman, Şenay Savaş Erdeve, Literature Search: Burçe Orman, Şenay Savaş Erdeve, Writing: Burçe Orman, Şenay Savaş Erdeve.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Beutler E. G6PD deficiency. Blood 1994;84:3613-3636.
2. Wan GH, Tsai SC, Chiu DT. Decreased blood activity of glucose-6-phosphate dehydrogenase associates with increased risk for diabetes mellitus. Endocrine 2002;19:191-195.
3. El-Hazmi MA, Warsy AS. Glucose 6-Phosphate dehydrogenase deficiency genetic, pathophysiological and therapeutic aspects. Ann Saudi Med 1985;5:213-223.
4. Gellady AM, Greenwood RD. G-6-PD hemolytic anemia complicating diabetic ketoacidosis. J Pediatr 1972;80:1037-1038.
5. Aljishi F, Aldarwish M. Glucose-6-phosphate dehydrogenase deficiency induced haemolysis in a woman with newly diagnosed diabetes after normalisation of hyperglycaemia. Diabet Med 2017;34:1318-1321.
6. Piñero-Piloña A, Litonjua P, Devaraj S, Aviles-Santa L, Raskin P. Anemia associated with new-onset diabetes: improvement with blood glucose control. Endocr Pract 2002;8:276-281.
7. Zhang Z, Liew CW, Handy DE, Zhang Y, Leopold JA, Hu J, Guo L, Kulkarni RN, Loscalzo J, Stanton RC. High glucose inhibits glucose-6-phosphate dehydrogenase, leading to increased oxidative stress and beta-cell apoptosis. FASEB J 2009;24:1497-1505. Epub 2009 Dec 23
8. Niazi GA. Glucose-6-phosphate dehydrogenase deficiency and diabetes mellitus. Int J Hematol 1991;54:295-298.
9. He Y, Zhang Y, Chen X, Wang Q, Ling L, Xu Y. Glucose-6-phosphate dehydrogenase deficiency in the Han Chinese population: molecular characterization and genotype-phenotype association throughout an activity distribution. Sci Rep 2020;10:17106.
10. Shalev O, Eliakim R, Lugassy GZ, Menczel J. Hypoglycemia-induced hemolysis in glucose-6-phosphate dehydrogenase deficiency. Acta Haematol 1985;74:227-229.