

Young type 1 diabetes mellitus (T1DM) patient with glucose-6-phosphate dehydrogenase deficiency occurring hemolysis: A case report.

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Abstract

Hemolysis during type 1 diabetes mellitus treatment in patients with Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency has been reported, but the underlying pathogenesis is not fully clarified. In this report, we described a girl in whom hemolysis occurred after Diabetic Ketoacidosis (DKA) treatment. Determination of G6PD activity and gene analysis confirmed the diagnosis of G6PD deficiency. We suppose that reducing of G6PD activity by hyperglycemia and decreased source of glucose in the pentose phosphate pathway because of decrease glucose levels may be the mechanism of hemolysis during DKA treatment.

Keywords: Glucose-6-phosphate dehydrogenase, Deficiency, Type 1 diabetes mellitus, Hemolysis.

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Introduction

Glucose-6-Phosphate Dehydrogenase (G6PD) is the key enzyme of the pentose phosphate pathway. In red blood cells, the pentose phosphate pathway is the only source of reduced Nicotinamide Adenine Dinucleotide (NADPH), the main reductant agent, and G6PD provides a source of reducing power against oxidative damage.

G6PD deficiency is X-linked enzymopathy due to mutations of the *G6PD* gene. Mutations cause decrease of *G6PD* activity, and different levels of enzymatic activity can lead to a wide spectrum of biochemical and clinical phenotypes. Many individuals have no symptoms, while some patients could suffer severe hemolytic anemia. The hemolysis usually triggered by some factors, such as the ingestion of fava beans, viral or bacterial infections, or drugs [1].

Hemolysis during type 1 Diabetes Mellitus (T1DM) treatment in patients with G6PD deficiency has been reported. Mechanisms of hemolysis have been supposed to hypoglycemia [2], glucotoxicity [3,4], Diabetic Ketoacidosis (DKA) [5-8], bacterial infections and hemolytic drugs [9]. However, the underlying pathogenesis is not fully clarified. Here we report a girl with G6PD deficiency and diabetes mellitus who developed hemolytic anemia during DKA treatment.

Case Report

In July 2015, a 10 y old girl was admitted to our department, for vomiting once, weight loss (2 kg within 1 w) and for polydipsia and polyuria over a period of 1 w. No precipitating

factor was identified. Physical examination showed mild dehydration. Plasma glucose concentration was 34 mmol/L. Blood ketone bodies were 1.6 g/L and urine ketone bodies were 4⁺. Arterial pH was 7.34 and bicarbonate plasma concentration was 15 mmol/L. Serum potassium concentration was 4.66 mmol/L and serum sodium concentration was 129.9 mmol/L. Glycated haemoglobin (HbA1c) was 13.7% and fasting plasma c-peptide was 148 pmol/L (normal 269-1282 pmol/L). Islet cell cytoplasm autoantibody was positive. Hemoglobin was 125 g/L, hematocrit was 39.7% and total bilirubin was 13.6 μmol/L.

The diagnosis of T1DM was confirmed, and laboratory tests showed a moderate DKA. The patient was treated with fluids replacement and intravenous insulin. She rapidly recovered. Normoglycemia recovery and the disappearance of blood and urine ketone bodies were achieved within 24 h, and subcutaneous insulin injections were introduced, with good glycemic control. On day 9 after admission, the patient appeared transient hypoglycemia (2.7 mmol/L) after heavy exercise, and two days later she developed pallor, jaundice and hemoglobinuria, and blood tests showed hemolytic anemia. Hemoglobin was 58 g/L and hematocrit was 20.2%. Total bilirubin was 60.4 μmol/L and unconjugated bilirubin was 43.2 μmol/L. Direct and indirect Coombs' test were both negative. After the treatment with fluids replacement, alkalinizing urine and transfusion of two packed units of red blood cells, the patient's condition improved that hemoglobin and hematocrit increased to 96 g/L and 32.2%.

Since the girl's younger sister was diagnosed with G6PD deficiency after neonatal screening, the same diagnosis was considered. The patient's G6PD activity was 0.12 (normal

1.0-2.3). Both methemoglobin reduction test and heinz body detection were positive. *G6PD* gene analysis showed that the patient was double heterozygous for mutations c.1376G>T and c.1388G>A. The patient's mother was heterozygous for mutation c.1376G>T and her father was hemizygous for mutation c.1388G>A, while both of them had no clinical feature of G6PD deficiency.

This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Sun Yat-sen University. Written informed consent was obtained from all participants.

Discussion

G6PD deficiency is a X-linked recessive enzymopathy. In theory, hemizygous males and homozygous females will suffer from complete deficiency, while heterozygous females will show an incomplete deficiency which clinical manifestation depends on the mosaic proportion of deficient red blood cells.

In this report, we detected two mutations c.1376G>T and c.1388G>A in this family, and both of them are the most common *G6PD* gene mutations in the Chinese population [10-12]. The patient's mother was heterozygous for mutation c.1376G>T, but she had never shown hemolysis. The reason of this phenotype may be that the mosaic proportion of deficient red blood cells is too low. The patient's father, who was detected the hemizygous for mutation c.1388G>A and should have suffered G6PD deficiency in theory, had no symptoms either. Chiu et al. [13] and Jiang et al. [14] found that the enzymatic activity of c.1376G>T was significantly lower than c.1388G>A, so we suppose that the father's enzymatic activity may relatively decrease not obviously.

The patient, who was double heterozygous for mutations c.1376G>T and c.1388G>A, had no symptoms in the past, but suffered hemolysis during diabetic ketoacidosis treatment. The relationship between G6PD and diabetes mellitus is complex. Saha [15] investigated 609 patients suffering from maturity onset diabetes mellitus, and observed a positive association with a higher incidence of G6PD deficiency in Chinese and Indian patients. Monte Alegre et al. [16] found that individuals with G6PD deficiency had glucose intolerance and low insulin release after intravenous and oral glucose tolerance tests. These researches suggest that G6PD deficiency may be a risk factor for diabetes mellitus. On the other hand, diabetes mellitus may also affect G6PD activity. Zhang et al. [17] showed that high glucose decreased *G6PD* gene expression and activity in human islets. Carette et al. [18] suggest that G6PD deficiency and diabetes mellitus could aggravate each other, and the possibility of hemolysis in patients with G6PD deficiency would be increased in case of diabetes crisis.

Before hemolysis, the patient in this report suffered high glucose levels and ketoacidosis at first, then undergone hypoglycemia after DKA treatment. All of these circumstances can aggravate enzymatic activity for an individual with G6PD deficiency. We suppose that the mechanism of hemolysis in this report includes two points. One is that, severe

hyperglycemia reduced G6PD activity so that antioxidant from erythrocyte decreased, meanwhile metabolism disorder of DKA promoted the erythrocyte depletion in antioxidant like glutathione. The other is that, during DKA treatment the glucose levels progressively decreased and even hypoglycemia occurred, making the source of glucose that should have involved the pentose phosphate pathway decreased, and enhancing the inability of the old red blood cells to generate the antioxidant like NADPH. All these factors could lead to the loss of reductant agent, and sensitivity of oxidative damage would increase which occurred in erythrocyte in response to both endogenous and exogenous oxidants, causing red blood cells destruction.

Conclusion

G6PD deficiency and diabetes mellitus could aggravate each other, and the possibility of hemolysis in patients with G6PD deficiency would be increased in case of diabetes crisis. Reducing of G6PD activity by reason of hyperglycemia and decrease source of glucose in the pentose phosphate pathway because of decrease glucose levels may be the mechanism of hemolysis during DKA treatment. More attention should be paid to avoid severe hemolysis in the treatment of patient with diabetes mellitus and G6PD deficiency.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet* 2008; 371: 64-74.
2. Shalev O, Eliakim R, Lugassy GZ, Menczel J. Hypoglycemia induced hemolysis in glucose-6-phosphate dehydrogenase deficiency. *Acta Haemat* 1985; 74: 227-229.
3. Messina MF, Lombardo F, Crisafulli G, Salzano G, Rossano M, Di Giorgio RM. Hemolytic crisis in a non-ketotic and euglycemic child with glucose-6-phosphate dehydrogenase deficiency and onset of type 1 diabetes mellitus. *J Ped End Metab* 2004; 17: 1671-1673.
4. Vanelli M, Lucentini L, Picco P, Galanello R, Chiari G, Adinolfi B, Street ME. Blood glucose normalization induced haemolysis in three adolescents with type 1 diabetes mellitus at onset and unknown G-6-PD deficiency. *J Ped End Metab* 1996; 9: 193-196.
5. Haroun M1. G 6 PD deficiency induced hemolysis in diabetic twins. *Indian Pediatr* 2005; 42: 705-707.
6. Galli-Tsinopoulou A, Nousia-Arvanitakis S. Glucose-6-phosphate dehydrogenase deficiency induced hemolysis in newly diagnosed diabetic monozygotic twins. *J Pediatr Endocrinol Metab* 2000; 13: 669-672.
7. Rais N, Churi C, Shah A, Kapoor A. Glucotoxicity and oxidative hemolysis in G-6-PD deficiency. *Diabetes Care* 1993; 16: 1215-1216.

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8. Le Pommelet C, Le Moullec N, Zunic P. Diabetic ketoacidosis revealing glucose-6-phosphate dehydrogenase deficiency. *Diabetes Metab* 2006; 32: 636-637.
9. Shalev O, Wollner A, Menczel J. Diabetic ketoacidosis does not precipitate haemolysis in patients with the Mediterranean variant of glucose-6-phosphate dehydrogenase deficiency. *Br Med J (Clin Res Ed)* 1984; 288: 179-180.
10. Yan JB, Xu HP, Xiong C, Ren ZR, Tian GL, Zeng F, Huang SZ. Rapid and reliable detection of glucose-6-phosphate dehydrogenase (G6PD) gene mutations in Han Chinese using high-resolution melting analysis. *J Mol Diagn* 2010; 12: 305-311.
11. Li Q, Yang F, Liu R, Luo L, Yang Y, Zhang L, Liu H, Zhang W, Fan Z, Yang Z, Cui L, He Y. Prevalence and molecular characterization of glucose-6-phosphate dehydrogenase deficiency at the China-Myanmar border. *PLoS One* 2015; 10: 0134593.
12. Peng Q, Li S, Ma K, Li W, Ma Q, He X, He Y, He T, Lu X. Large cohort screening of G6PD deficiency and the mutational spectrum in the Dongguan District in Southern China. *PLoS One* 2015; 10: 0120683.
13. Chiu DT, Zuo L, Chen E, Chao L, Louie E. Two commonly occurring nucleotide base substitutions in Chinese G6PD variants. *Biochem Biophys Res Commun* 1991; 180: 988-993.
14. Jiang W, Yu G, Liu P, Geng Q, Chen L, Lin Q, Ren X, Ye W, He Y, Guo Y, Duan S, Wen J, Li H, Qi Y, Jiang C, Zheng Y, Liu C, Si E, Zhang Q, Tian Q, Du C. Structure and function of glucose-6-phosphate dehydrogenase-deficient variants in Chinese population. *Hum Genet* 2006; 119: 463-478.
15. Saha N. Association of glucose-6-phosphate dehydrogenase deficiency with diabetes mellitus in ethnic groups of Singapore. *J Med Genet* 1979; 16: 431-434.
16. Monte Alegre S, Saad ST, Delatre E, Saad MJ. Insulin secretion in patients deficient in glucose-6-phosphate dehydrogenase. *Horm Metab Res* 1991; 23: 171-173.
17. 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* 2010; 24: 1497-1505.
18. Carette C, Dubois-Laforgue D, Gautier JF, Timsit J. Diabetes mellitus and glucose-6-phosphate dehydrogenase deficiency: from one crisis to another. *Diabetes Metab* 2011; 37: 79-82.

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