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Glucose 6 phosphate dehydrogenase deficiency: A single-center experience

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What is already known on this topic?

- *Glucose 6 phosphate dehydrogenase (G6PD) deficiency is the most common erythrocyte enzyme deficiency worldwide.*
- *It is inherited as an X-linked recessive disorder and is estimated to affect more than 400 million people. G6PD deficiency is common in Africa, Asia, the Mediterranean Region, and the Middle East where malaria is endemic.*

What this study adds on this topic?

- *Although G6PD deficiency is more common in boys, it can also be seen in girls.*
- *G6PD deficiency should be considered in patients presenting with prolonged jaundice.*
- *As variants with chronic hemolysis are not common in Turkey, the need of regular blood transfusion, splenectomy and cholecystectomy are low.*

ABSTRACT

Objective: This study aims to evaluate the demographic information, clinical and laboratory findings of patients with glucose 6 phosphate dehydrogenase deficiency.

Material and Methods: We collected data by reviewing files and electronic records of 65 patients with glucose 6 phosphate dehydrogenase deficiency under the age of 18 years who were followed up in our clinic between 2007 and 2019. Demographic, clinical, and laboratory features, family history, complications of the disease, and history of splenectomy and cholecystectomy were evaluated. Mean, standard deviation, and median values were used when descriptive analyses were presented.

Results: The age of diagnosis ranged between 1–192 months and the median age of diagnosis was two months. Fifty-nine patients (90.7%) were boys and six (9.2%) were girls. The mean value of glucose 6 phosphate dehydrogenase enzyme on admission was 1,9±1,4 U/g of hemoglobin (Hb). Family history was pesent in 40% of patients in whom information was avaliable. The most common presentation was prolonged jaundice and the most common physical finding was jaundice. Splenomegaly was detected in none of the patients. Cholelithiasis was present in one of 21 patients who were evaluated with ultrasonography. None of the patients required splenectomy, cholecystectomy, and regular erythrocyte transfusion during follow-up.

Conclusion: As G6PD variants with chronic hemolysis are not usually seen in Turkey, patients who required splenectomy, cholecystectomy, and regular erythrocyte transfusion were not detected. Although glucose 6 phosphate dehydrogenase deficiency is more common in males, it can also be seen in girls. In Turkey, glucose 6 phosphate dehydrogenase deficiency should be considered in patients presenting with prolonged jaundice.

Keywords: Glucose 6 phosphate dehydrogenase deficiency, hemolytic anemia, prolonged jaundice

Introduction

Glucose 6 phosphate dehydrogenase (G6PD) deficiency is the most common erythrocyte enzyme deficiency worldwide. It was first described in patients with hemolytic crisis after taking primaquine in 1956 (1). Glucose 6 phosphate dehydrogenase shows X-linked recessive inheritance and is estimated to affect more than 400 million people. The gene coding for the G6PD enzyme is on the long arm of the X chromosome and about 400 variants have been identified uptodate. (2).

Glucose 6 phosphate dehydrogenase is the rate-limiting enzyme of the pentose phosphate pathway (2, 3). The purpose of the pentose phosphate pathway is to provide the organism nicotine adenine dinucleotide phosphate (NADPH) and ribose phosphates. Nicotine adenine

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dinucleotide phosphate enables the oxidized glutathione to be reduced in erythrocytes. In G6PD deficiency, sufficient NADPH cannot be produced in the cell and hemolysis occurs in the presence of oxidative factors (3).

Glucose 6 phosphate dehydrogenase deficiency is usually asymptomatic, it may present with severe jaundice in the neonatal period, acute hemolytic anemia after ingestion of certain food like fava beans, or exposure to various drugs and infections, depending on the degree of enzyme deficiency (4). Hemolytic anemia, jaundice, pallor, hemoglobinuria, decreased haptoglobulin, coombs test negativity, Heinz bodies and blister cells on the peripheral smear, and reticulocytosis can be seen during acute attacks caused by drugs and infections. Jaundice that may cause kernicterus may be observed in the neonatal period. According to the World Health Organization (WHO) G6PD variant classification, class I variant patients may have chronic hemolysis (5). Diagnosis is made by measuring the G6PD enzyme activity in erythrocytes (6).

G6PD deficiency is common in regions like Africa, Asia, the Mediterranean, and the Middle East where malaria is endemic (7). G6PD deficiency has been found in studies conducted in Turkey in different frequencies in various regions. Aksu et al. (8) found G6PD enzyme deficiency with a frequency of 7.4% in boys and 1.8% in girls in a study they conducted with 1521 individuals from 375 families between 1986 and 1988 in Antalya. In the study of Acıpayam et al. (9) with 1015 newborns in the Thrace region, G6PD deficiency was found in 133 patients (13.1%). In our study, we aimed to evaluate the demographic information, clinical and laboratory findings, and treatment results of children who were diagnosed with G6PD deficiency and followed up at our center.

Materials and Methods

The data of patients under the age of 18 who were followed up with a diagnosis of G6PD deficiency in the Pediatric Hematology and Oncology Clinic of Kanuni Sultan Süleyman Training and Research Hospital between 2007 and 2019 were investigated by examining patient files and electronic recording systems. Demographic information of the patients, presenting complaints, laboratory characteristics, family history, disease complications, need for erythrocyte transfusion, splenectomy, and cholecystectomy history were evaluated. G6PD enzyme level was determined by the spectrophotometric method. The laboratory normal range for the G6PD enzyme level in our hospital was 7-20.5 U/g of Hb. The disease was diagnosed by clinically and low G6PD enzyme levels.

The study was conducted following the Helsinki declaration principles. Approval was obtained from the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital for the study (May 2018-Subject number: KAEK / 2018.5.02).

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) version 20.0 (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analysis. Numerical data were expressed as mean ± standard deviation and median, and categorical data were expressed as frequency (n) and percentage (%).

Results

The data of 65 patients with G6PD deficiency who were followed up were accessed. Six (9.2%) of the patients were female and 59 (90.7%) were male. The median age at diagnosis was 2 months (Range: 1-192 months). There was consanguinity history in one of the 9 patients whose consanguinity history was obtained. Family history was positive in four of 10 patients with available family history. There were 29 patients included in the study whose reason for the application was known. Twenty-six patients presented with prolonged jaundice, 4 patients with pallor, and 3 patients with pallor after eating fava beans. Physical examination findings of the patients were in the form of jaundice and pallor. Twenty-four of the 32 patients whose physical examination findings are known had jaundice and 12 had pallor. Splenomegaly was not detected in any of the patients (Table 1).

The mean G6PD enzyme level at the time of admission was 1.9±1.4 U/g of Hb, and the mean hemoglobin (Hb) concentration was 10.4±2.4 g/dL (range 3.0-17.2 g/dL). Hemoglobin values were 3 g/dL, 6.9 g/dL, and 7 g/dL, respectively, in three patients who had a history of eating fava beans at the time of admission and who had an acute hemolytic attack. All three patients were transfused with erythrocyte suspension. Two of these patients were siblings. Laboratory findings of the patients are shown in Table 2.

None of the patients had chronic hemolysis and none were transfusion dependent. One of the 21 patients evaluated by ultrasonography had gall bladder stone. None of the patients required splenectomy or cholecystectomy during their follow-up period.

Discussion

Glucose 6 phosphate dehydrogenase deficiency shows X-linked recessive inheritance and the disease is more common in boys. However, it can also be seen in girls in populations where the G6PD mutations are common due to heterozygosity. (10). Atay

Table 1. Clinical and demographic characteristics of patients with G6PD deficiency

Gender n (%)	
F	6/65 (9.3)
M	59/65 (90.76)
The Median age of diagnosis (range)	2 months (1-192 months)
Kinship n (%)	
Yes	1 /9 (11.11)
No	8/9 (88.88)
Family history n (%)	
Yes	4/10 (40)
No	6/10 (60)
Symptoms n (%)	
Prolonged jaundice	26/29 (89.6)
Pallor	4/29 (13.8)
Pallor after eating fava beans	3/29 (10.34)
Physical examination findings n (%)	
Jaundice	24/32 (75)
Pallor	12/32 (37.5)

Table 2. Laboratory findings in patients with G6PD deficiency

	Mean±SD	Interval
G6PD (U/g Hb)	1.9±1.4	0.1-6.2
Hb (g/dL)	10.4±2.4	3.0-17.2
Hct (%)	31.1±6.8	10.0-49.1
RDW (%)	14.2±1.8	10.7-19.4
MCHC (g/dL)	33.4±1.7	30.0-38.0
LDH (U/L)	339.3±167.7	198-737
Total Bilirubin (mg/dL)	6.7±6	0.2-25.4
Reticulocyte (%)	2.3±2	0.7-6.7

Hb, hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width

et al. (11) examined the frequency of G6PD enzyme deficiency in 624 newborns with indirect hyperbilirubinemia between 2001 and 2004, and 18 (75%) of 24 patients diagnosed with G6PD deficiency were male and 6 (25%) were female. In the study where Fotoh et al. (12) examined 202 newborns with jaundice in Egypt, G6PD deficiency was shown in 18 (8.9%) of the cases and all of the cases were male. Six of the patients in our study were girls. Therefore, it should be kept in mind that G6PD deficiency may be present not only in boys but also in girls.

In our study, we found that G6PD deficiency most frequently occurred with prolonged jaundice and was diagnosed in the early childhood. In the study conducted by Bilgin et al. (13) with 100 patients for prolonged jaundice etiology between January 2016 and December 2016, etiology was not determined in 78% of the patients, urinary tract infection was found in 14%, and G6PD deficiency was found in 3%. Currently, G6PD deficiency is screened by neonatal screening programs in some countries. It is not screened in Turkey yet. A study conducted to investigate the relationship between G6PD deficiency and neonatal jaundice in 116 newborns with jaundice in Adana, G6PD deficiency was found in 12.1% of the cases and kernicterus was found in three of these cases (21.4%) (14). Severe jaundice resulting in kernicterus is thought to be caused not only by hemolysis, but also in the presence of conditions that reduced bilirubin glucuronidation resulting from decreased G6PD activity in hepatocytes or Gilbert's syndrome (5, 15). In our study, kernicterus was not observed in any patient. In a study conducted by Katar et al. (16) between 2005 and 2006 with 56 male newborns who needed exhange transfusion due to hyperbilirubinemia in Diyarbakır region, G6PD deficiency was found in 17.8% of the patients. We recommend to test G6PD level in all babies who present with prolonged jaundice and kernicterus.

The mainstay of treatment in G6PD deficiency is to avoid situations that can cause oxidant stress such as drugs, certain food like fava beans, and infections. Also, families and patients should be informed about the symptoms of hemolytic crisis (5). Splenectomy may be recommended in patients with splenomegaly, hypersplenism, severe chronic anemia, and physical restraint, but its benefit is limited. Patients with chronic hemolysis should be closely monitored in terms of iron overload, and cholecystectomy should be considered in cases with cholelithiasis and cholecystitis (5, 17, 18). WHO divided the variants that cause G6PD deficiency into four subclasses according to the degree of enzyme deficiency and the severity of hemolysis. According to this classification, class 1 includes variants causing chronic non-spherocytic hemolytic anemia, class 2 and 3 variants with intermittent hemolysis, class 4 includes variants with normal enzyme activity and no hemolysis (5). Due to the high prevalence of class 2 variants in our Turkey, no cases with chronic hemolysis were detected in our study. Therefore, the need for regular transfusion, splenectomy, and cholecystectomy were not observed during the follow-up.

Hemolysis during acute attacks is usually short-term and temporary and does not require specific treatment. Severe anemia requiring blood transfusion is rarely observed (17). In our study, acute hemolysis that required erythrocyte transfusion was found in three patients after eating broad beans. Favism occurs in areas where G6PD deficiency is relatively high and also where fava beans are consumed (19). Fava beans contain high levels of vicine and convicine compounds. These compounds are transformed into divicine and isouramil which are potent oxidizing agents. Although it has been stated that favism is more associated with certain variants, it is recommended that all patients with G6PD deficiency should avoid fava beans (15).

The limitations of our study are the partial lack of patient data in the patient files and electronic recording systems, and the G6PD gene variant analysis could not be performed.

In conclusion, since variants with chronic hemolysis are not common in Turkey, no patients needing a regular blood transfusion, splenectomy, and cholecystectomy were detected. Although G6PD deficiency is more common in boys, it can also be seen in girls. In Turkey, G6PD deficiency should be considered in patients presenting with prolonged jaundice.

Ethical Committee Approval: Ethical Committee Approval was received from the ethics committee of Kanuni Sultan Süleyman Training and Research Hospital for this study (May 2018- Subject number: KAEK / 2018.5.02).

Informed Consent: Informed consent was not obtained in the study due to the retrospective design of this study.

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