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A Study of Glucose-6-Phosphate Dehydrogenase Deficiency among Children attending the Emergency Hospital in Zakho City Kurdistan Region, Iraq

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ABSTRACT:

Background: G6PD deficiency, which affects 400 million individuals globally, is an X-linked hereditary enzymopathy that causes acute hemolysis after exposure to specific oxidative agents such as fava beans, more than 37 drugs, and infections viral or bacterial. Neonatal jaundice worsened by kernicterus is one of the condition's significant consequences. It can be prevented by avoiding the oxidative factors that cause a hemolytic episode alongside neonatal screening programs for early detection of afflicted individuals.
Objectives: This research aimed at investigating the variability in clinical and biochemical manifestations among children with G6PDD. This is the first study to be carried out in the Zakho area.
Methods: A cross-sectional study was used, recruiting 112 children attending Zakho Emergency Hospital from January 2022 to April 2023. Laboratory aids involved in obtaining CBC, liver enzyme activities, and blood grouping were all investigated. The IBM SPSS 26 program was used to analyze the obtained data.
Results: There was no statistically significant difference between male and female patients in terms of age, time of admission, hemoglobin level, WBC count, and liver enzymes. The majority of cases who visited Zakho Emergency Hospital within 72 hours of exposure to the triggering agent were males (67.9%), with the most common clinical features being jaundice, dark urine, and abdominal pain.
Conclusion: In this study, the three main symptoms in G6PD deficient patients with acute hemolysis were pallor, jaundice, and black urine. These signs appeared several hours or even days after consuming fava beans. The primary clinical symptoms and the patient's gender, family history, or prior newborn jaundice were not related, according to our research.
Keywords: Glucose-6-phosphate dehydrogenase deficiency, G6PD, hemolysis, children, Zakho, Kurdistan-Iraq.

1. INTRODUCTION

Glucose 6 phosphate dehydrogenase deficiency (G6PDD), is the most common inherited X-linked enzymopathy resulting in hemolytic anemia(1,2). Hence, it is more common in males (3). There are 400 million people with G6PD deficiency worldwide(4).
G6PD has an important role in the pentose phosphate pathway that provides nicotinamide adenine dinucleotide phosphate NADPH for the erythrocytes which help maintain glutathione in a reduced form to protect hemoglobin from being damaged by oxidative agents, knowing that erythrocyte lacks nucleus and mitochondria, and NADPH is the only source available against oxidative damage(5,6). Based on the level of deficiency in enzyme activity, there are 5 classes of G6PD deficiency. With regards to classes I and II, enzyme activity is < 10% of normal, making the most severe forms. Class II is the most common in the Mediterranean region. Class III has an enzyme activity of 10-60%. Classes IV and V have enzyme activity of > 60% and therefore are insignificant clinically(7,8).
Neonatal jaundice and acute hemolytic anemia are the most common manifestations of G6PD Deficiency (9,10), a patient can present with malaise, weakness, abdominal pain, lumbar pain, pallor, jaundice, dark-colored urine (hemoglobinuria)(11). Neonatal jaundice is one of the most serious and life-threatening consequences of G6PD deficiency, as it can result in kernicterus, cerebral palsy, and the neonate ending up needing an exchange transfusion(12,13). WHO recommends neonatal screening programs to help detect this condition early in life(14,15).
It is worth mentioning that G6PD Deficiency patients are usually asymptomatic until exposed to a triggering agent such as fava beans, more than 37 drugs, and viral or bacterial infections (7,16). Fava beans specifically can result in hemolysis among people with G6PDD due to their toxic chemicals vicine, convincing, divicine, and isouramil(17). Many drugs used in treating infections are incorrectly blamed for resulting in hemolysis among G6PDD patients when in fact infection itself is the cause of hemolysis, but the mechanism through which infection can cause hemolysis in G6PDD is not fully understood(13). Not all G6PD-deficient individuals develop hemolysis after exposure to a trigger, which means other factors are involved(18).
The G6PDD hemolysis can be self-limiting, in other patients' fluid management and blood transfusions are required, and avoidance of the triggering agent helps prevent the condition(19). This study aimed to have an idea about the variability in biochemical and clinical presentations among children with G6PDD in the Kurdistan Region, Zakho City. This is the first study to be carried out in the Zakho area.

2. METHODS

2.1. Selection of subjects.

In conducting this research, a cross-sectional study design was used to analyze data collected from a sample of 112 children (76 males, and 36 females) attending Zakho Emergency Hospital in Zakho City, Kurdistan region of Iraq during the period from January 2022 to January 2023.

2.2. Patient information.

Parents of the patients provided consent to participate in this study and were asked to answer questions from a questionnaire aiming to collect data regarding their sociodemographic (age, gender) and the current and past episodes of hemolysis caused by

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G6PD deficiency (number of hemolytic episodes, time from exposure to trigger resulting in clinical and biochemical manifestations, family history of G6PDD, history of neonatal jaundice). Parents were also asked about the triggering agent (a drug, fava beans, and whether it was fresh, cooked, or dried), and the symptoms of their children (lethargy, yellowish discoloration, dark urine, poor oral intake, itching, vomiting, abdominal pain)

2.3. Ethical Approval.

The ethics committee at the College of Medicine at the University of Zakho, Kurdistan Region, Iraq, authorized the study proposal. Before collecting samples, parents of children were contacted for permission to participate in the study, and informed written agreements were obtained from all the participants.

2.4. Sample collection.

Five milliliters of peripheral venous blood were drawn from each patient using the appropriate sterile venipuncture technique and divided equally between K2 ethylenediaminetetraacetic acid (EDTA) tube (BD Vacutainer, Franklin Lakes, NJ), and vacuum gel tube.
The K2-EDTA tubes are well mixed by inverting 10 times (or by putting on a rotator mixer).
Vacuum gel tubes are allowed to stand at room temperature for 30 minutes and centrifuged at 5000 rpm for 10 minutes to obtain the serum.

2.5. Laboratory procedures.

The K2-EDTA tubes were used to perform complete blood count parameters using a fully automated blood analyzer (Medonic M-series- Sweden) instrument, which was calibrated daily using quality control reagents obtained from the manufacturer.
The CBC included WBC (total and differential count), RBC count, RBC size (mean cell volume [MCV]), Hb content (mean corpuscular hemoglobin [MCH] and mean corpuscular hemoglobin concentration [MCHC]), total Hb concentration (HGB), hematocrit test (HCT), and platelet count (PCT). Quality controls were run every day before the analysis of samples.
Hemoglobin of less than 11g/dl was regarded as anemia according to WHO (20), and a WBC count of more than 11 × 10^9/L was regarded as leukocytosis.
The serum from gel tubes was used to determine liver functions including total bilirubin, AST, and ALT levels using the Cobas c311analyzer- Roche Diagnostics USA instrument which was calibrated daily using quality control reagents obtained from the manufacturer. Liver enzymes AST and ALT levels were measured, and levels more than 45 IU/L, and 50 IU/L were regarded as elevated respectively (21). Blood group analysis by slide method was performed for all the children participating in the research.
After 3 months of hemolytic episodes, three milliliters of peripheral venous blood were drawn from each patient using the appropriate sterile venipuncture technique and put in an (EDTA) tube (BD Vacutainer, Franklin Lakes, NJ), and well mixed by inverting 10 times (or by putting on the rotatory mixer). G6PD enzyme assay was determined using the U.V. Kinetic method (Biolabo-France) Reagents were used for G6PD enzyme assay.

2.6. Statistical Analysis.

Data were collected on the IBM SPSS 26 statistics program, which was used for statistical analysis, the chi-square test was used to determine the significance of qualitative data, and a P value of 0.05 or less was regarded statistically significant.

3. RESULTS

This research included 112 children, all were from Zakho City, Kurdistan region of Iraq. The majority of the cases were between the ages of 9 months and 6 years, the youngest age was 9 months, and the oldest was 18 years, as shown in Figure 1.

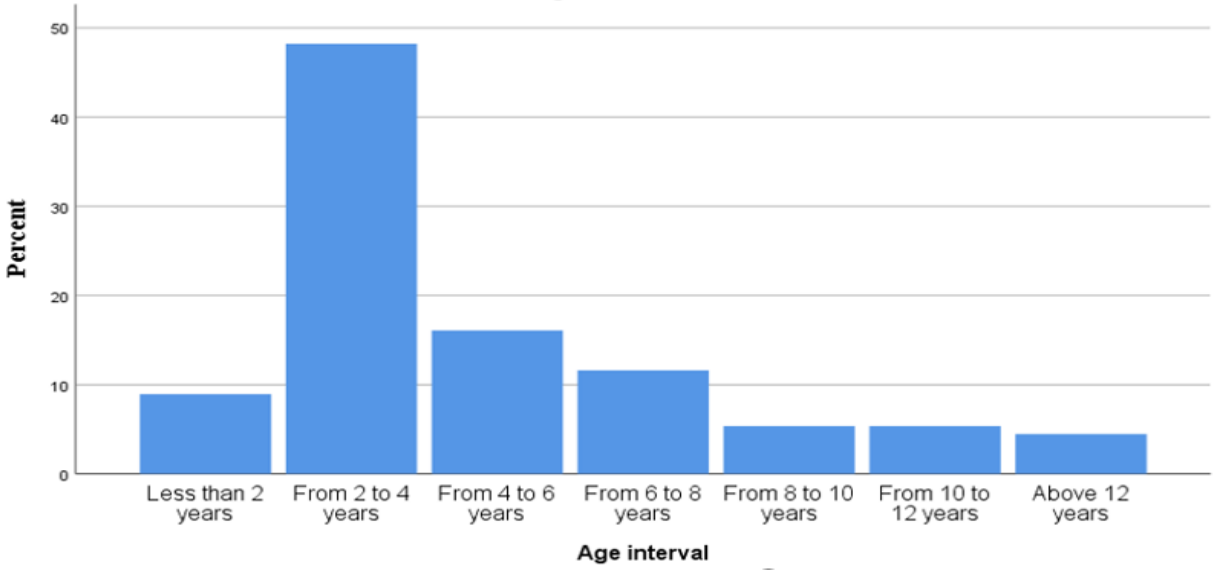

Figure 1 Frequency distribution of G6PD deficiency according to age interval

The majority of the cases presented to the hospital had clinical manifestations within 72 hours of exposure to the oxidative triggering agent, with 7 cases presenting within the first 24 hours and only 4 cases presenting after 4 days. The participants were divided into 76 males (67.9%) and 36 females (32.1%). In 91.17% of cases, all patients were Rh-positive. In terms of ABO blood grouping, group O accounts for 40.19% of all cases, followed by group A (34.31%), B (19.61%), and AB (5.88%).
For tabulated parameters, mean values (+/- standard deviation), were 5.39 +/-3.37 age in years, 47.46 +/- 27.98 duration of exposure in hours, 7.56 +/- 1.74 hemoglobin level, 13.67 +/- 5.98 WBC count, 23.55 +/- 11.69 S. ALT, 54.99 +/- 27.6 S. AST, as shown in Table 1.

Table 1: The mean and standard deviation of a specific variant

Variable	Mean	SD
Age in years	5.39	3.37
Duration of exposure (hours)	47.46	27.98
Hemoglobin level gm/dl	7.56	1.74
WBC count X 10^9/L	13.67	5.98
S. ALT IU/L	23.55	11.69
S. AST IU/L	54.99	27.6

Male patients had an average age of 5.52 years, duration of exposure of 47.69 hours, hemoglobin levels of 7.51 mg/dl, WBC counts of 14.33, S. ALTs of 24.08, and S. ASTs of 56.54. Females had an average age of 5.11 years, a duration of exposure of 46.99 hours, and hemoglobin levels of 7.66, 12.43, 22.56, and 52.06 s. ALT and AST, respectively, as shown in Table 2. There was no significant difference between males and females regarding age, time of admission, hemoglobin, WBC count, and liver enzymes.

Table 2: Descriptive and inferential statistics based on the sex of the patient

	Males (76)		Females (36)		
Variables	Mean	SD	Mean	SD	p-value
Age in years	5.52	3.47	5.11	3.17	0.556
Duration of exposure hours	47.69	27.78	46.99	28.6	0.380
Hemoglobin gm/dl	7.51	1.7	7.66	1.85	0.143
WBC count 10^9/L	14.33	6.34	12.43	5.08	0.444
S. ALT IU/L	24.08	12.81	22.56	9.45	0.543
S. AST IU/L	56.54	28.49	52.06	26.37	0.162

On average, patients with a family history of G6PD deficiency were 5.86 years old, with hemoglobin levels of 7.5 mg/dl, WBC counts of 13.55, S. ALTs of 26.17, and S. ASTs of 55.65. As indicated in Table 3, patients with no family history had an average age of 4.81 years, hemoglobin levels of 7.63, and WBCs of 13.81, 21.3, and 54.43 s. ALT and AST, respectively. There was no statistically significant difference between the two groups.

Table 3: Descriptive and inferential statistics based on family history

Variables	The mean of characters in patients with		p-value
	+ve Family History	-ve Family History	
Age	5.86 + 3.75	4.81+ 2.73	0.518
Hb	7.5 + 1.78	7.63+ 1.72	0.800
WBC	13.55 + 5.79	13.81+ 6.23	0.204
AST	55.65 + 31.85	54.43+ 23.95	0.505
ALT	26.17 + 13.71	21.3 +9.3	0.513

Patients with a history of neonatal jaundice had hemoglobin levels of 7.4 mg/dl, WBC counts of 13.59, S. ALTs of 20.42, and S. ASTs of 52.29 on average. Patients with no history of neonatal jaundice had an average age of 4.82 years, hemoglobin levels of 7.7, and WBCs of 13.73, 25.07, and 56.3 s. ALT and AST, respectively, as shown in Table 4. Between the two groups, there was no statistically significant difference.

Table 4: The descriptive and inferential statistics based on a history of neonatal jaundice

Variables	The mean of characters in patients with		p-value
	+ve Neonatal History	-ve Neonatal History	
Age	6.04 ±3.95	4.82 ± 2.67	0.710
Hb	7.4 ± 1.78	7.7 ± 1.72	0.079
WBC	13.59 ± 6.6	13.73 ± 5.53	0. 229
AST	52.29 ± 20	56.3 ± 30.8	0. 089
ALT	20.42 ±8.42	25.07 ± 12.82	0. 578

The difference in hemoglobin levels was statistically significant across distinct ABO blood groups, with blood group B having a mean value of 7.16, blood group O having a mean value of 7.6, blood group A having a mean value of 7.51, and blood group AB having a mean value of 7.83, p-value 0.008, as shown in Table 5.

Table 5: The descriptive and inferential statistics based on ABO blood grouping

Variables	Mean				p-value
	O Blood Group	A Blood Group	B Blood Group	AB Blood Group	
Age	5.38 ±3.19	5.45 ± 3.25	5.43 ±3.58	6.3 ± 3.43	0.105
Hb	7.6 ± 1.94	7.51 ± 1.73	7.16 ±0.87	7.83 ±2.09	0.008
WBC	13.97 ± 6.28	13.38±4.48	14.28± 6.49	7.1 ± 1.3	0.205
AST	58.96 ±23.89	55.86±38.46	44.68 ±21.63	35.67±7.23	0.095
ALT	23.46 ±12.35	22.88±12.01	23.55 ±11.01	19 ± 2.65	0.647

The consumption of fava beans caused hemolytic episodes in all individuals who participated in this investigation. A total of 97 instances (86.6%) involved exposure to cooked fava beans, 15 (13.4%) to fresh fava beans, and none to dry fava beans or medicinal products.

Pallor was the most prevalent clinical symptom in 107(95.5%) of the 112 cases, jaundice was present in 105 (93.8%), dark urine was present in 87 (77.7%), and abdominal pain was present in 58 (51.8%) of cases, as shown in Table 6.

Table 6: The frequency of signs and symptoms of G6PDD among patients

Signs and symptoms	Num. of cases	Percentages
Pallor	107	95.5%
Jaundice	105	93.8 %
Dark urine	87	77.7 %
Abdominal pain	58	51.8 %
Lethargy	52	46.4 %
Fever	52	46.4 %
Poor feeding	50	44.6 %
Vomiting	41	36.6 %
Anorexia	25	22.3 %
Itching	14	12.5 %

4. DISCUSSION

Diagnosing children with G6PDD from the neonatal period through neonatal screening programs and educating the family about G6PDD will assist in preventing kernicterus, and cerebral palsy from the neonatal period, and will help avoid episodes of hemolytic anemias which may increase the rate of hospital admissions and blood transfusions. This is all helpful in avoiding a large economic and load burden on hospitals and governments, in addition to giving the patient a healthy and better lifestyle by earlier diagnosis(22).

G6PD deficiency is not just the most frequent enzymopathy in red blood cells, but it is also the most common of all clinically relevant enzyme abnormalities in human biology as a whole. (1)

Most of the cases of the present study were presented to the hospital within 72 hours, as compared to other research most of the cases were presented within 24 – 48h hours(16,23).

The age of the participants was between 9 months to 6 years, while in another study done in Jordan by Imam, most were between 6 months to 5 years (1). The majority of sufferers (81.6%), according to different research, had their first hemolytic episode before turning 10 years old. (24).

Pallor, jaundice, dark urine, and abdominal pain were the most common clinical features, similar to other research (16) Also, pallor, yellow sclera, and black urine were found to be the most common presenting symptoms in the community, according to another study. These symptoms were almost always present. The next most common symptoms were fatigue (76%), stomach discomfort (61%), and vomiting (61%). (25).

G6PDD was found to be more common in males, as in this research 76 out of the total 112 participants were males, and 36 were females, similar to another research which showed G6PD deficiency in 133 people, from which 82 were males (26). In another study, out of 100 participants, 68 were males (27). Both homozygous females and heterozygous males exhibit complete manifestations of the G6PD deficit. According to another study, male children (76%) were more likely to have an enzyme deficit than female children (24%). The incidence of the severe type of enzyme insufficiency was, however, much lower in female children. (28).

Concerning ABO blood grouping; Group O accounts for (40.19%) of all cases, group A (34.31%), group B (19.61%), and Group AB (5.88%), comparing this to another research which showed ABO blood grouping of group A (6.25%), group B (12.5%), group O (6.25%), and group AB (75%)(19).

In all of the instances studied, the hemolytic episode was caused by eating fava beans rather than by medicine. The findings of our analysis confirmed previous studies since fresh fava beans are known to be the major cause of the development of acute hemolytic anemia and revealed that all incidences of G6PD were caused by fava beans. (1,23).

For liver function tests, the mean AST was 54.99 and S.ALT was 23.55 IU/L in our research. While one study discovered that the average AST was 65.3 and S.ALT was 28.6 IU/L, (29) another discovered that enzyme levels should be equal to or less than 224.5 U/L (S. ALP) and 20 IU/L (S. ALT). (1).

5. CONCLUSION

In this study, the three main symptoms in G6PD patients with acute hemolysis were pallor, jaundice, and black urine. These signs appeared several hours or even days after consuming fava beans.

Ingestion of fava beans was the most frequent method used to cause hemolysis in G6PD deficient individuals. Drug-induced instances are non-existent.

It has been found that the primary clinical symptoms and the patient's gender, family history, or prior newborn jaundice were not related.

Study limitation: To confirm the diagnosis, all G6PD patients should have their G6PD enzyme levels checked after three months, we were unable to locate several of them to validate the diagnosis, some patients bypassed our hospital and traveled straight to a tertiary facility in Duhok.

Recommendation: Future studies should include a larger number of participants, from different cities and countries, to have more accurate data regarding the laboratory results, and clinical presentations including the severity of the disease, amount of blood transfusion, and genetic testing.

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