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Detection of occult kidney injury in glucose 6 phosphate dehydrogenase deficiency anemia.

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Abstract

Patients with Glucose-6-Phosphatase Dehydrogenase (G6PD) enzyme deficiency may develop hemolysis after administering different food, drugs, and herbs. Renal damage could be mild, resolving after administration of high-volume hydration and alkylating agents, or be severe and life-threatening due to acute renal failure.

Materials and Methods: All children older than 28 days of age who were experiencing the first episode of the hemolytic crisis were enrolled in this prospective cohort study. In a period between February to May 2017. An acute hemolytic crisis is defined as the acute presence of pallor or jaundice, tea-color urine, normochromic normocytic anemia, reticulocytosis, indirect hyperbilirubinemia, and normal liver function test. Demographic information and laboratory investigation were taken to assess renal damage.

Results: Totally, fifty children were included in the study, there was a significant decrease in GFR during the hemolytic crisis (mean=56.1 ml/min/1.73 m^2), but the value increased to reach near normal (but still less than normal) during the next three weeks (mean=82.9 ml/min/1.73 m^2). Surprisingly, the serum creatinine and BUN during the crisis and three weeks later were in the normal range.

Discussion: In the recent survey, we found that the mean of GFR increased but did not reach the normal range three weeks after the hemolysis, although sCr levels were in the normal range. Therefore, we thought that G6PD deficiency per se might have an adverse outcome on the kidney functions. This finding was consistent with the study conducted by Hakeem et al., showing that the damage to the kidneys persisted even after the cessation of hemolysis, while the level of cystatin C was significantly higher compared to the control group fourteen days after hemolysis.

Keywords: Renal injury, G6PD enzyme deficiency, Hemolysis.

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Introduction

Glucose-6-Phosphatase Dehydrogenase (G6PD) enzyme is the cornerstone of the Pentose Phosphate Pathway (PPP) that protects the cells from oxidative stresses through the production of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) [1]. Patients with G6PD suffer from a variety of clinical manifestations. They are asymptomatic throughout their lives, but hemolysis could occur after administering different food, drugs, and herbs [2,3]. Renal damage could be mild, resolving after administration of high volume hydration and alkylating agents, or be severe and life-threatening due to acute renal failure [4].

Previous studies stated that kidney damage in patients with G6PD is mainly caused by hemolysis and hemosiderin toxicity in renal cortices and tubular cells [4,5]. However, recent surveys claimed that the G6PD deficiency per se might damage the kidney; the prevalence of G6PD was higher in participants with chronic kidney disease of unknown etiology than biopsy-proven healthy ones. Of note, GFR was lower in patients with concomitant Diabetes Mellitus Type 2 (DMT2) and G6PD deficiency compared to patients with DMT2 alone [6-8]. In the present survey, we aimed to evaluate the pediatric patients regarding whether G6PD deficiency per se could damage the kidney.

Materials and Methods

Patients' enrollment

All children older than 28 days of age who were experiencing the first episode of the hemolytic crisis were enrolled in this prospective cohort study. They were admitted to Al-Zahraa teaching hospital, Iraq, from February to May 2017. An acute hemolytic crisis is defined as the acute presence of pallor or jaundice, tea-color urine, normochromic normocytic anemia, reticulocytosis, indirect hyperbilirubinemia, and normal liver function test. The exclusion criteria were past medical history of known kidney diseases, renal transplantation, and any congenital renal anomalies, known autoimmune diseases with renal involvement, malignancies, metabolic disorders, and any hematologic diseases other than G6PD deficiency. All parents filled out the informed consent. The study was conducted

according to the declaration of helsinki. The patients were also followed and re-evaluated 3 weeks after the crises.

Demographic information

A qualified doctor gathered the patients' demographic and clinical information at the time of admission, and three weeks later. These included thepatients' age, gender, weight (kg), height or length (cm), his or her vital signs on arrival, the presence of the possible family history of fauvism, and any possible triggering factors.

Lab data

Under the aseptic condition, two venous blood samples were taken during the acute hemolytic phase, and the other two were collected three weeks later. The samples were sent to assess the reticulocyte count, serum creatinine level, and Blood Urea Nitrogen (BUN) level. We used the Schwartz formula to calculate GFR in both phases. Sodium nitrate, dextrose, methylene blue, and distilled water were added to two milliliters of blood to evaluate the efficiency of G6PD. The compound was then incubated for 2.5 hours. If its color turnedbrown, the G6PD level was still deficient. Otherwise, if it remained red, the level was not deficient.

Statistical analysis

Data were analyzed using SPSS version 23.0 for windows (SPSS Statistics, IBM, USA), and the results were expressed as mean ± Standard Deviation (SD). To investigate the relationship between quantitative variables, the Pearson correlation test was used. P-values<0.05 were considered as statistically significant.

Results

Totally, fifty children were included in the study. Mean (± SD) age, weight (kg), and height or length (cm) was 4.35 (± 2.68), 15.71 (± 5.71), and 95.46 (± 24.34), respectively. Table 1 summarized the main demographic features of the participants; the majority of the children was boys (88% *vs.* 12) and did not experience any hemolytic crises before this episode (96%). In almost all children, the ingestion of fava beans was the triggering factor (96%).

Age (yrs); Mean ± SD		4.35 (± 2.68)
Weight(kg); Mean ± SD		15.71 (± 5.71)
Height/length (cm); Mean ± SD		95.46 (± 24.34)
Gender; N (%)		
Male		44 (88%)
Female		6 (12%)
Frequency of blood transfusion; N (%)		
Not need		2 (4%)
One time		38 (76%)
Two times		9 (18%)
Three times or more		1 (2%)
Family history of fauvism; N (%)		18 (36%)
History of fauvism; N (%)		2 (4%)
Triggering factor; N (%)		
Fava bean		48 (96%)
Respiratory tract infection		1 (2%)
Drugs		1 (2%)
Lab data	During crisis	Three weeks after
BUN; Mean ± SD	40.4 ± 14.1	23.2 ± 4
sCr.; Mean ± SD	0.77 ± 0.2	0.4 ± 0.1
GFR; Mean ± SD	56.1 ± 19.2	82.9 ± 21.2

Table 1. Demographical features of children with G6PD deficiency anemia (n=50). BUN: Blood Urea nitrogen; GFR: Glomerular Filtration Rate; sCr: Serum Creatinine

There was a significant decrease in GFR during the hemolytic crisis (mean=56.1 ml/min/1.73 m^2), but the value increased to reach near normal (but still less than normal) during the next three weeks (mean=82.9 ml/min/1.73 m^2). Surprisingly, the serum creatinine and BUN during the crisis and three weeks later were in the normal range.

We evaluated the correlation between the calculated GFR during the hemolysis and three weeks after the attack with other lab data; according to the results of the Pearson correlation test, a statistically significant inverse correlation between GFR during hemolysis and sCr was found at the time of the hemolytic attack and three weeks later (p<0.001). Of note, no correlations between this GFR and BUN, PCV%, and TSB were detected (P-value=0.479, 0.461 and 0.543, respectively), as shown in Table 2. Furthermore,we found inverse correlations of GFR, calculated three weeks after hemolysis, with sCr during the crisis and the one measured three weeks later (P-values=0.005 and <0.001, respectively). Figure 1 shows an inverse correlation between GFR and reticulocyte count, reflecting the degree of hemolysis.

	GFR during hemolysis		**GFR three weeks hemolysis**	
Laboratory result	**r**	**P***	**r**	**P***
PCV% before blood transfusion	-0.107	0.461	0.023	0.876
BUN during hemolysis	-0.103	0.479	-0.158	0.274
sCr. during hemolysis	-0.715	<0.001	-0.388	0.005
TSB	-0.88	0.543	-0.034	0.817
Corrected reticulocyte count	-0.722	<0.001	-0.65	<0.001

PCV% after blood transfusion	0.063	0.665	-0.097	0.503
BUN 3wks. after hemolysis	-0.059	0.681	-0.316	0.025
sCr. 3 wks. after hemolysis	-0.438	<0.001	-0.544	<0.001
GFR 3wks. after hemolysis	0.734	<0.001	0.734	<0.001

Table 2. Correlation of GFR during and three weeks after the hemolysis with laboratory result in participants. PCV: Packed Cell Volume; TSB: Total Serum Bilirubin; sCr: Serum Creatinine level; wks: Weeks. *: P-values less than 0.05 were statistically significant.

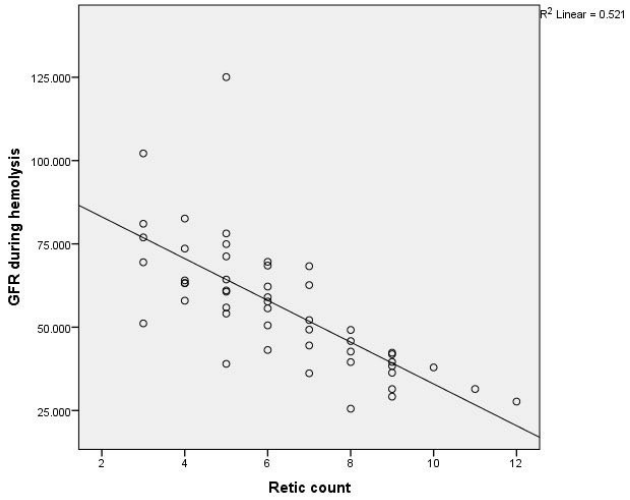

Figure 1. Correlation between reticulocyte count and GFR in participants during hemolysis.

Discussion

Until 2019, G6PD deficiency affected 400 million people throughout the worldand is yet considered the most prevalent enzymopathy [9,10]. Although most affected individuals remain asymptomatic, hemolysis can occur after the administration of several drugs and food [11,12]. Moreover, studies claimed a persistent, insidious adverse effect of the enzyme deficiency on cell survival and growth [13,14]. Four main pathways are responsible for producing NADPH, which is an essential molecule for proper cellular functions. Scientists believe that the most critical pathway is the Pentose Phosphate Pathway (PPP), and the three other pathways cannot provide the appropriate amount of NADPH the cells need [15].

Nowadays, we know that the prevalence of G6PD was higher among patients with chronic kidney disease of unknown etiology, as reported by Sayanthooran et al. and Jayasekara et al. [6,8]. In the recent survey, we found that the mean of GFR increased but did not reach the normal range three weeks after the hemolysis, although sCr levels were in the normal range. Therefore, we thought that G6PD deficiency per se might have an adverse outcome on the kidney functions. This finding was consistent with the study conducted by Hakeem et al., showing that the damage to the kidneys persisted even after the cessation of hemolysis, while the level of cystatin C was significantly higher compared to the control group fourteen days after hemolysis [4]. Unfortunately, we could not measure the level of this marker.

To find the underlying causes of this finding, we should focus on the molecular cascades within the cells. Xu et al. conducted a study on mice,showing that the kidney tissue and endothelial cells had a higher intracellular level of protein kinase C and nuclear factor κB activity, elevated lipid peroxidation markers, and a lower level of glutathione. Surprisingly, they found that the renal tubular cells of G6PD-deficient mice excreted albumin, an index of kidney damage [16,17]. These changes were similar to those of the diabetics.

Our study had some limitations; first, we did not have access to cystatin C to be measured. Several studies proved that cystatin C might be a better predictor of renal function than sCr. [4,18]. Second, we followed the participants for three weeks. Another study with long-term follow-ups is needed to evaluate whether the GFR returns to its normal range.

Conclusion

In conclusion, our study showed that G6PD-deficiency per se may have adverse outcomes on the renal function and may lead to CKD, but the exact mechanisms remain unknown.

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