Pattern of Hemolytic Anemia Among Egyptian Pediatric Emergency Department Patients

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Objectives: The emergency department is considered the backbone of the medical service offered in any hospital. Yet, the data on the frequency of pediatric hematological presentation is scanty. Anemia occurs in 9% to 14% of pediatric emergency department (ED) patients. Glucose-6-phosphate dehydrogenase (G6PD) deficiency affects more than 400 million people worldwide. Unfortunately, we do not have screening program for G6PD deficiency in Egypt. The aim of this study is to assess the burden of hemolytic crisis among Egyptian children visiting ED.

Methods: This is a prospective cross-sectional study among children presenting with acute hemolytic crisis in the ED of New Children Hospital, Cairo University from March to June 2016. Cases underwent full history taking, clinical examination, and laboratory tests based on clinical judgment of the resident. We categorized the presenting hemolytic anemias into 3 groups: G6PD deficiency, acute hemolysis in previously diagnosed patients with chronic hemolytic anemia, and acute undiagnosed hemolytic anemia.

Results: Our study included 143 patients, 109 males (76.22%) and 34 females (23.76%), with a mean age 36 months (range, 3–188 months), who presented with hemolytic anemia in the ED. Seventy-six cases (53.1%) were diagnosed as G6PD deficiency, 36 (25.2%) were diagnosed as chronic hemolytic anemia, and 31 (21.7%) were diagnosed as undiagnosed acute hemolytic anemia.

Conclusions: Hemolytic anemia is very common presentation in ED. G6PD deficiency is the most common cause, representing 53.1% of the hemolytic anemia.

Key Words: G6PD deficiency, hemolytic anemia, acute hemolytic crisis

(*Pediatr Emer Care* 2020;36: 153–157)

Anemia occurs in 9% to 14% of pediatric emergency department (ED) patients.[1,2]

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme defect, which affects more than 400 million people worldwide.[3] Several factors predispose to acute hemolytic anemia (AHA), such as certain drugs or infection. However, the commonest trigger is fava beans ingestion.[4] Our aims in this study are to detect the pattern of hemolytic crisis among Egyptian children visiting ED, New Children Hospital, Cairo University as we believed this will give us valuable information that we will need in planning and prioritizing our provided health services, and to study the burden of G6PD deficiency among Egyptian children visiting ED with acute hemolysis.

METHODS

This is a prospective cross-sectional study of children presenting with acute hemolytic crisis in the ED of New Children Hospital, Cairo University from March to June 2016. A verbal consent was obtained from the patients or their legal guardians before enrollment in the study.

We included all patients presenting with evidence of acute hemolytic crisis (acute pallor, jaundice ± dark urine), age ranging from 0 to 12 years and both sexes.

All patients were subjected to full history taking with focusing on history of fava bean ingestion, previous blood transfusion, family history of G6PD deficiency, previous similar attack, and repeated blood transfusion. Thorough clinical examination was done with stress on vital signs, pallor, jaundice, dark urine, fever, hepatomegaly, splenomegaly, or both.

Laboratory examination routinely done in the ED based on clinical judgment of the resident including complete blood cell count and bilirubin level. Blood samples were obtained from each patient in a sterile tube.

We categorized the presenting hemolytic anemias into 3 groups according to their presentation:

1. G6PD deficiency (either previously diagnosed with G6PD deficiency or positive family history plus ingestion of fava beans).
2. Acute hemolysis in previously diagnosed case with chronic hemolytic anemia.
3. Acute undiagnosed hemolytic anemia requiring additional investigations: as measuring G6PD activity levels during acute attack can give false normal results, because only nonhemolyzed, younger cells are assayed.[5]

Statistical Methods

- Quantitative data were presented as mean, median, minimum, maximum, and standard deviation (SD) values. Qualitative data were presented as frequencies and percentages.
- For parametric data, Student *t* test was used for comparisons between 2 groups. One-way analysis of variance test was used for comparisons between more than 2 groups. Scheffé post hoc test was used for pair-wise comparisons between the groups when one-way analysis of variance test is significant.
- For nonparametric data, Mann-Whitney *U* test was used for comparisons between 2 groups. Kruskal-Wallis test was used to compare between more than 2 groups. Mann-Whitney *U* test was used for pair-wise comparisons between the groups when Kruskal-Wallis test is significant. χ^2 Test was used for studying the comparisons and associations between different qualitative variables.
- The significance level was set at $P \leq 0.05$. Statistical analysis was performed with IBM SPSS Statistics Version 21 for Windows.

RESULTS

Our study included 143 patients presenting with hemolytic anemia who were visiting the ED in New Children Hospital. The study included 109 males (76.22%) and 34 females (23.76%) with

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Disclosure: The authors declare no conflict of interest.
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ISSN: 0749-5161

male-to-female ratio 3.2:1, with a mean age 36 months (range, 3–188 months). Clinical data of the cases is illustrated in Table 1.

Regarding the comparison between the 3 diagnoses as shown in Table 2, we found that male predominance, history of fava bean ingestion, family history of G6PD deficiency, jaundice, and dark urine are statistically significantly higher in acute G6PD deficiency than in chronic hemolytic and acute undiagnosed hemolytic cases. Hepatomegaly and splenomegaly are statistically significantly higher in chronic hemolytic anemia than in acute G6PD deficiency and acute undiagnosed hemolytic cases.

Mean corpuscular volume and platelet count are statistically significantly lower in chronic hemolytic anemia than in acute G6PD deficiency and acute undiagnosed hemolytic cases. Total leukocytic count (TLC) is statistically significantly higher in acute G6PD deficiency than in chronic hemolytic anemia.

In our study, 76 patients were diagnosed with G6PD deficiency, 66 of them (86.8%) were precipitated by ingestion of fava beans, 4 (0.05%) appeared to be related solely to a concurrent infection, and 6 (0.07%) had no identifiable cause (no drug or fava bean ingestion or infection).

Sixty-two males (89.9%) with G6PD deficiency required blood transfusion and only one of them developed febrile reaction. On the opposite side, 7 (9.2%) of our G6PD deficiency patients were females. Two of them were clinically stable and did not require transfusion, whereas 5 who presented with moderate to severe hemolytic anemia required packed RBC transfusion. One Patient developed febrile reaction during transfusion.

One hundred twenty-five (87.4%) of 143 cases who presented with hemolytic anemia required packed RBC transfusion. Four patients (3.2%) developed adverse reaction (2 developed febrile reactions and 2 developed allergic reactions), and accordingly, they stopped the transfusion and received intravenous corticosteroids and antihistaminic shot.

TABLE 1. Clinical Data of Studied Cases

	n (%)
History	
History of fava bean ingestion	89 (37.8%)
Family history of G6PD deficiency	45 (31.5%)
Previous similar attack	70 (49%)
Previous blood transfusion	48 (33.6%)
Examination	
Jaundice	104 (72.7%)
Dark urine	101 (70.6%)
Fever	63 (44.1%)
Hepatomegaly	3 (2.1%)
Splenomegaly	18 (12.6%)
HSM	12 (8.4%)
HR	
Mean	129.42
SD	28.45
RR	
Mean	32.93
SD	11.4
Diagnosis	
G6PD deficiency	76 (53.1%)
Chronic hemolytic anemia	36 (25.2%)
Acute undiagnosed hemolytic anemia	31 (21.7%)

HR indicates heart rate; RR, Respiratory rate.

On the opposite side, 18 patients did not receive blood transfusion, 9 of them were G6PD deficiency, 3 were chronic hemolytic anemia, and 6 were undiagnosed hemolytic anemia. Those who did not transfuse were clinically stable not requiring transfusion and referred to the hematology clinic for further investigations and follow-up.

Our results showed improvement in 138 cases (96.5%). They did not require hospitalization and were referred to hematology clinic. On the opposite side, 5 (3.5%) only required inpatient hospital admission for follow-up due to ongoing hemolysis (3 were diagnosed as G6PD deficiency and 2 were undiagnosed AHA).

DISCUSSION

Widespread neonatal screening programs for G6PD and hemoglobinopathies is established in developed countries.[6] In Egypt, as well as other developing countries, these programs are lacking. That is the reason why we performed this study to detect the cost benefit of screening program in Egypt. One hundred nine males (76.2%) and 34 females (23.5%) were included in the study with male-to-female ratio 3.2:1, with a mean age 36 months (range, 3–188 months).

Among our cases, 76 cases (53.1%) were diagnosed as G6PD deficiency, 36 (25.2%) were diagnosed as chronic hemolytic anemia, and 31 (21.7%) were undiagnosed AHA. This high percentage of G6PD deficiency cases highlights the cost benefit of screening of G6PD, which represent 53% of the cases agreeing with Khneisser et al and Parashar.[7,8] Some countries in Asia (Malaysia, Philippines, Taiwan, Hong Kong, and Singapore) were able to reduce the morbidity and mortality associated with this G6PD deficiency after the introduction of a neonatal screening program.[6]

Forty-nine percent of the total number of cases experienced a second attack of hemolytic anemia. The relatively high number of patients presenting with second attack can be due to the lack of screening or awareness or lost follow-up in the hematology clinic in the contrary to other studies that showed less than 10% presenting with second attack.[9]

Mean corpuscular volume was statistically significantly lower in chronic hemolytic anemia than in G6PD deficiency, which could be explained by nature of thalassemia.[10] Thalassemia represents the most common cause of chronic hemolytic anemia in Egypt (85.1%).[11]

Jaundice, dark urine, and tachycardia were statistically significant in G6PD deficiency than in chronic hemolytic anemia, which could be explained by the acute hemolytic crisis presentation in G6PD deficiency. Bilirubin was higher in G6PD deficiency than in chronic hemolytic anemia yet not reaching statistical significance, which may be explained by the small number of cases that required measuring total and direct bilirubin.

Hepatosplenomegaly (HSM) was more statistically significant at chronic hemolytic anemia. This could be explained by chronic nature of the disease and extramedullary hematopoisis.[12] Platelets were significantly lower in chronic hemolytic anemia than in G6PD deficiency, and this could not be explained, but there is a postulation based on the data, that 21 (58.3%) of 36 cases of chronic hemolytic anemia had either splenomegaly or HSM, and this predisposed them to hypersplenism, especially that the majority of the patients with thalassemia major ultimately develop hypersplenism and accordingly lower platelet count.[13]

Total leukocytic count was statistically significantly lower in chronic hemolytic anemia than in G6PD deficiency and acute undiagnosed hemolytic anemia. Higher TLC count in G6PD deficiency could be elaborated by 2 explanations. First, infection precipitates hemolysis with secondary lecocytosis,[14–16] the mechanism by which infection triggers hemolysis postulated by that,

TABLE 2. Comparison Between the 3 Diagnoses

	G6PD Deficiency	Chronic Hemolytic Anemia	Acute Undiagnosed Hemolytic Anemia	*P*
Sex, n (%)				
Males	69 (90.8%)	21 (58.3%)	19 (61.3%)	<0.0001
Females	7 (9.2%)	15 (41.7%)	12 (38.7%)	
Age, mo mean ± SD	30.03 ± 30.28	57.21 ± 44.88	31.39 ± 28.06	<0.0001
History				
History of fava bean ingestion, n (%)	66 (86.8%)	8 (22.2%)	15 (48.4%)	<0.0001
Family history of G6PD, n (%)	31 (40.8%)	8 (22.2%)	6 (19.4%)	0.037
Previous similar attack, n (%)	22 (28.9%)	34 (94.4%)	14 (45.2%)	<0.0001
Previous blood transfusion, n (%)	26 (34.2%)	14 (38.9%)	8 (25.8%)	0.520
Examination				
Jaundice, n (%)	63 (82.9%)	19 (52.8%)	22 (71%)	0.004
HR mean ± SD	136.84 ± 29.65	114.69 ± 22.19	129.59 ± 25.55	0.001
RR mean ± SD	33.61 ± 12.03	31.24 ± 11.48	33.48 ± 9.67	0.543
Dark urine, n (%)	62 (81.6%)	18 (50%)	21 (67.7%)	0.003
Fever, n (%)	36 (47.4%)	11 (30.6%)	16 (51.6%)	0.156
Hepatomegaly, n (%)	0 (0%)	3 (8.3%)	0 (0%)	0.011
Splenomegaly, n (%)	2 (2.6%)	13 (36.1%)	3 (9.7%)	0.001
HSM, n (%)	2 (2.6%)	8 (22.2%)	2 (6.5%)	0.002
Laboratory investigations				
Hb, mean ± SD, g/dL	5.59 ± 1.67	5.04 ± 1.35	4.97 ± 1.63	0.166
MCV mean ± SD	81.69 ± 13.27	68.75 ± 6.73	77.77 ± 20.40	0.031
Microcytosis, n (%)	13 (25.5%)	8 (66.7%)	8 (30.8%)	0.023
HCT mean ± SD	17.93 ± 5.71	16.54 ± 5	16.55 ± 5.65	0.570
MCHC mean ± SD	30.77 ± 3.04	31.98 ± 4.32	30.57 ± 3.49	0.456
MCH mean ± SD	26.09 ± 10.25	22.59 ± 2.31	26.01 ± 6.02	0.080
Platelet, mean ±SD, $\times 10^3$ per mm^3	397.19 ± 147.28	291.5 ± 162.36	363.59 ± 207.88	0.039
TLC, mean ± SD, $\times 10^3$ per mm^3	16.43 ± 7.61	9.27 ± 4.69	23.45 ± 22.25	0.005
Total bilirubin, mean ± SD, mg/dL	5.83 ± 5.12	2 (0)	4.13 ± 1.89	0.440
Direct bilirubin, mean ± SD, mg/dL	1.09 ± 1.02	0.4 (0)	0.77 ± 0.19	0.345
Transfusion				
Transfusion of packed RBCs, n (%)	67 (88.2%)	33 (91.7%)	25 (80.6%)	0.383
Adverse reaction occurred, n (%)	2 (2.6%)	2 (5.6%)	0 (0%)	0.462
Outcome				
Improved, n (%)	73 (96.1%)	36 (100%)	29 (93.5%)	0.341
Hospitalized, n (%)	3 (3.9%)	0 (0%)	2 (6.5%)	0.341

P values ≤ 0.05 are significant.

Hb indicates hemoglobin; MCV, mean corpuscular volume; HCT, hematocrit; MCHC, mean corpuscular hemoglobin concentration; MCH, mean corpuscular hemoglobin; RBCs, red blood cells.

during phagocytosis, leukocytes damage erythrocytes in their environment by discharging active oxygen species during phagocytosis.[16,17] The second explanation is that G6PD deficiency impairs immunity. Many hypothesis have been postulated that individuals with severe G6PD deficiency may have neutrophil dysfunction due to an impaired respiratory burst, with impaired bactericidal activity and recurrent infections with catalase-positive organisms.[18] This agrees also with Abu-Osba et al[19] who concluded that neonates with G6PD deficiency are more susceptible to late sepsis and to infection with catalase-positive organisms and secondarily to infection they developed fever.

G6PD deficiency has been recognized as the most common enzymopathy, affecting near 400 million people worldwide, most frequently in Africa, Asia, the Mediterranean, and the Middle East.[20] In our study regarding the demography of G6PD deficiency in ED of New Children Hospital, Cairo University, it represented 53% of cases of hemolytic anemia, in comparison to 90% of those presenting with acute hemolytic crises in Ain Shams University.[21]

There are no recent documented data for the incidence of G6PD deficiency in Egyptian population due to scarcity of published epidemiological data in developing countries apart from 2 studies: Hussein et al,[22] who stated that the overall incidence was 5.9%, and Ragab et al,[23] who stated the overall incidence was 26.4%. Other populations showed increased prevalence of G6PD deficiency, among Kurdish Jews (60%–70%),[24] South African blacks (20%),[25] and in Thailand (17%),[26] whereas other studies showed lesser prevalence, among African Americans (11%–12%),[27] Greeks (6%),[28] and India (3%).[29]

Mean age of G6PD deficiency cases was 30.03 (30.28) months with 56.2% of the cases were younger than 2 years, 32.9%

ranged from 2 to 5 years, and 10% were older than 5 years. On the contrary, in Greece, 65% of the cases occurred in the 2- to 5-year age group, 7.2% in the 10- to 15-year group, and 5.5% in infants.[9] Similar patterns have been noted in Cyprus[30] and parts of Iran.[31] Earlier presentation of favism in Egypt may be explained by earlier consumption of fava.

Among our G6PD deficiency cases, the male-to-female ratio was 9:1, which was much lower than in studies done by Joannides[30] in which the ratio was 21:1 and more than studies done by Osman et al[32] with male-to-female ratio 4.5:1. These different ranges can be explained by the hypothesis that G6PD deficiency is a sex-linked trait with marked variability for phenotypic expression in the heterozygous female. Five of 7 females in our study presented with moderate to severe hemolytic anemia and required blood transfusion so it is important to consider G6PD deficiency in AHA, not only in males, but also in females, this agrees with van den Broek et al.[33]

An attack of acute hemolysis in an individual with G6PD may be precipitated by oxidant injury including medications, as well as several foods and infections. In our study, 76 patients were known cases of G6PD deficiency, 66 (86.8%) were precipitated by ingestion of fava beans, 4 (0.05%) appeared to be related to a concurrent illness, and 6 (0.07%) had no identified cause (no drug or fava bean ingestion or infection), whereas in Burka et al,[34] 46 cases (39%) were precipitated by a medication alone, and 73 (61%) appeared to be related solely to a concurrent illness.

Fourteen patients (45.2%) presenting with acute undiagnosed hemolytic anemia had history of previous similar attack, and 8 patients (25.8%) had previous blood transfusion. This high percentage can be explained by the lack of the patients follow-up in the hematology clinic after their first presentation leading to undiagnosed of the cause of hemolytic crisis, and this could be due to lack of awareness and poor socioeconomic standard of our patients.

Repeated attacks of favism are not uncommon; second attacks of favism were noted in 22 of 76 patients as opposed to 10 of 120 patients studied by Kattamis et al. This could be explained by lack of awareness of patients. This high percentage of second attack of favism (28.9%) highlights the importance of screening and intensive awareness programs about the disease.[9]

Hemolysis may be mild and self-limiting in some individuals, or severe and life-threatening in others.[35] The mortality from favism varies from country to another. In our study, there was no death, just 3 (3.9%) of 76 required admission for follow-up due to ongoing hemolysis, this finding was similar to many studies where the case mortality was 2 per 10,000 population.[36] In conclusion, G6PD deficiency is the most common cause of acute hemolytic presentation, representing 53.1% of the hemolytic anemia at the ED. Based on our study, we recommend routine neonatal screening program, especially for males. G6PD deficiency in AHA should be considered not only in males, but also in females. Further studies to detect whether G6PD increase incidence of infection or infection triggers hemolytic crisis.

ACKNOWLEDGMENT

The authors thank Mahmoud khaled Hussien, Abeer Mohamed Emam, Zenab Gamal, Zainab Gomaa Gamal, and Yaser Abdulmenem Alsaka for assistance in collecting data from medical records of the patients during their presence in emergency department.

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