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Clinical Manifestations of Acute Hemolysis in Children with Glucose-6-Phosphate Dehydrogenase Deficiency in Fars Province, Iran

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Abstract

Background: Absence or deficiency in Glucose-6-phosphate dehydrogenase (G6PD) enzyme in patients with G6PD deficiency presents with a wide spectrum of symptoms. This study evaluates the clinical features of acute hemolysis in children with G6PD deficiency.

Materials and Methods: Seventy G6PD deficient children younger than 18 years old were included in this cross sectional study in Dastgheib Hospital of Shiraz in South West of Iran. Complete blood count, zinc level, reticulocyte count, peripheral blood smear, liver function tests and coombs test were performed for all patients. Subject were observed for multiple clinical manifestations such as paleness, Yellow sclera, Dark Urine, abdominal pain, back pain, vomiting, diarrhea or constipation, liver tenderness, hepatomegaly, splenomegaly, changes in level of consciousness according to Glasgow Coma Scale.

Results: All of the G6PD deficient children developed paleness at the time of admission. The next frequent manifestations in our population were yellow sclera and dark urine that were present in 69 and 68 patients, respectively. The least prevalent features were diarrhea and constipation. Liver tenderness, hepatomegaly and splenomegaly were not found in our population. There were no significant differences in age distribution between the boys and girls ($p>0.05$). There were not any significant correlation between each clinical manifestation and the primary Hemoglobin (Hb) level, number of needed transfusion, severity of hemoglobinuria and hospitalization duration ($p>0.05$).

Conclusion: In this study, pallor, icterus and dark urine were the three important symptoms in G6PD patients with acute hemolysis. There was no correlation between the primary clinical symptoms and severity of the hospital course characteristics of the patients such as Hb level, hemoglobinuria and number of needed transfusion.

Key Words: Acute hemolysis, Children, Glucose-6-phosphate dehydrogenase deficiency, Iran.

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1- INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD), as a cytoplasmic enzyme in red blood cells, plays a major role in the metabolism and modulation of oxidative stress by detoxification of free radicals (1-3). The gene of this enzyme transmitted in an X-linked recessive pattern (4). A missense mutation or deletion in this gene results in G6PD deficiency disorder. G6PD deficiency affecting near to 35 million people globally (5), and also is highly prevalent in Iran especially in the Fars and Isfahan provinces (4). The incidence of G6PD deficiency in Iranian people varying between 10% to 14.9% and the prevalence of G6PD deficiency in Fars province is about 12% in male and 0.9% in female population (6). G6PD deficiency is associated with a wide spectr um of biochemical and clinical manifestations (7, 8).

Majority of individuals with G6PD deficiency are asymptomatic although remain presents a variety of symptoms such as neonatal jaundice, neonatal hyperbilirubinemia and hemoglobinuria, chronic nonspherocytic hemolytic anemia and acute hemolytic anemia (AHA) (9-13). Acute hemolytic anemia (AHA) may occurs through exposure to oxidative stressors such as some certain drug consumption, infections, diabetic ketoacidosis (DKA), and some types of foods (10, 14-16).

Ingestion of fava bean is an important predisposing factor for acute hemolysis (15). However, in the absence of all known risk factors, patients with G6PD deficiency are potentially prone to hemolysis and hyperbilirubinemia (8). AHA usually begins with typical symptoms such as; malaise, weakness, abdominal pain and/or lumbar pain after the rise in unconjugated bilirubin (9). Jaundice and dark urine appears after several hours or even days due to hemoglobinuria (12). The other characteristics of G6PD deficiency due to acute hemolysis include fatigue, unconjugated hyperbilirubinemia, Reticulocytosis, and increased level of lactate dehydrogenase (LDH) (12, 17). In present study we evaluate the prevalence of each clinical manifestation in G6PD deficient children presented with acute hemolysis in Fars province, Iran.

2- MATERIALS AND METHODS

2-1. Study Participants

This cross sectional study has been performed on seventy G6PD deficient patients with acute hemolysis gradually referred to emergency ward of Dastgheib Hospital, Shiraz, Fars province, in South West of Iran during February 2015 to March 2016. Only patients with definite diagnosis of acute hemolysis caused by G6PD deficiency were included in this study. Inclusion criteria were aged 18 years or less and diagnosis of G6PD deficiency by a positive rapid florescent spot test. Exclusion criteria were no previous history of kidney or hepatic diseases, systematic disorders, other hematologic diseases, and no history of using special medications.

One expert technician took 5ml venous blood which were centrifuged, separated and stored at -70°c until analysis in Dastgheib laboratory. The diagnosis of G6PD deficiency was previously established by a rapid florescent spot test. At the time of admission, hemoglobin concentration was measured by using the cyan-methemoglobin method. Other essential laboratory tests include complete blood count (CBC), zinc level, reticulocyte count, peripheral blood smear, liver function tests and Coombs test were performed for all patients. Subject were observed for multiple clinical manifestations such as paleness, Yellow sclera, Dark Urine, abdominal pain, back pain, vomiting, diarrhea or constipation, liver tenderness, hepatomegaly, splenomegaly, changes in alertness and

sleepiness. All patients were managed with standard treatment (hydration and transfusion) to compensate hemolysis (9).

2-2. Ethical Considerations

This study was approved by the Ethics Committee of Shiraz University of Medical Sciences. Since all the participant in this study was under 18 years, they provided assent and their parents provided signed informed consent. Parents were empowered to remain or leave the study and ensured about the confidential archiving of their data.

2-3. Statistical Analysis

Obtained data was evaluated using SPSS version 18.0 software. Qualitative variables were compared using Chi-square tests and 2-sample t-test or by Mann–Whitney test; Also, $p<0.05$ was considered as the significance level.

3-RESULTS

Overall seventy children were recruited in this cross sectional study. The mean age of samples was 5.03± 3.2 years (Ranging from 1 to 15 years of age). Samples were included 34 girl patients (48.5 %) and 36 boy patients (51.5%) (Female: male ratio 0.94). There were no significant differences in age distribution between the boys and girls ($p>0.05$). Acute hemolysis appeared in all patients (n=70) due to fava beans consumption, and the symptoms developed 3.4±1.04 days after fava bean ingestion. Of seventy patients, forty-four (63%) had hemoglobinuria at the time of admission. As shown in **Table.1**, paleness is the most common presentation of acute hemolysis following G6PD deficiency. Furthermore, 97% of the patients had history of dark urine on admission (n=68). Vomiting and abdominal pain appear equally in about 61% of the subjects. There were no significant differences between male and female population in development of these symptoms ($p> 0.05$).

Back pain and anemia occurred equally in 7 children (10%). Seven percent of patients had complaint of constipation (n=5), and 2 patients had diarrhea (2.8%). Twenty four girls and 29 boys experienced drowsiness. Also, in physical examination, none of these patients had liver tenderness, hepatomegaly and splenomegaly. Sixty-five patients were required blood transfusion to compensate the hemolysis. The clinical features and general characteristics of our population summarized in **Table.2**. There was not any significant correlation between each clinical manifestation and the primary Hemoglobin (Hb) level, number of needed transfusion, severity of hemoglobinuria and hospitalization duration

Table-1: Association of acute hemolysis clinical manifestations and primary hemoglobin, hospitalization duration, hemoglobinuria and Number of needed transfusion

Variables	Hemoglobin level on admission(g/dl)	Hemoglobinuria(+)	Number of needed transfusion	Hospitalization Duration(days)
Palor	———	———	———	———
Yellow sclera	———	0.6	> 0.98	0.6
Dark urine	0.8	0.2	> 0.98	> 0.98
Abdominal pain	0.1	0.1	0.2	0.3
Back pain	0.5	0.2	> 0.98	> 0.98
Vomiting	0.4	0.3	0.4	0.5
Diarrhea	0.3	0.7	> 0.98	> 0.98
Constipation	0.6	0.08	0.7	0.4

Liver tenderness	———	———	———	———
Hepatomegaly	———	———	———	———
Splenomegaly	———	———	———	———
Changes in alertness or sleepiness	0.7	0.2	0.8	0.4

Table-2: General characteristics and clinical manifestations of G6PD deficient patients with acute hemolysis (n= 70)

Variables		Total n=70	Male 36 (51.4)	Female 34 (48.6)	P-value
Zinc concentration		100.04	106.4	93.3	0.078
Hb concentration on admission (g/dL)		7.2	7.7	6.8	0.05
Needed Blood transfusion (times)	0	5	0	5	0.05
	1	53	30	23	
	2	12	6	6	
Hemoglobinuria	Negative	26	14	12	0.7
	1+	8	4	4	
	2+	16	6	10	
	3+	9	5	4	
	4+	11	7	4	
Palor		70	36	34	—
Yellow sclera		69	36	33	0.5
Dark urine		68	36	32	0.2
Abdominal pain		43	26	17	0.5
Back pain		7	3	4	>0.98
Vomiting		43	25	18	0.5
Diarrhea		2	2	0	>0.98
Constipation		5	4	1	0.6
Liver tenderness		0	0	0	—
Hepatomegaly		0	0	0	—
Splenomegaly		0	0	0	—
Changes in alertness or sleepiness		53	29	24	0.7

4- DISCUSSION

Our study revealed that pallor, yellow sclera and dark urine were the most prominent presenting symptoms in our population. The incidence of these symptoms was close to 100 %. The next prevalent symptoms included drowsiness (76%), abdominal pain (61%) and vomiting (61%).

Back pain, constipation and diarrhea were the least prevalent symptoms occurring in about 10%, 7% and 3% of patients, respectively. The prevalence of diarrhea and constipation, as the two main gastrointestinal symptoms of acute hemolysis, was higher in male than females**,** but the p-value did not reach the statistical significance (p>0.05). Our results also reveal that the vomiting and anemia occurred about equally in either sex. Many previous studies mention the dark urine, hemoglobinuria, nausea and vomiting, liver tenderness, hepatosplenomegaly and cardiac dysfunction as symptoms of patients with G6PD deficiency (18-21), but they didn't report any prevalence for these

manifestations. In a recent study on patients with sickle cell anemia, the prevalence of hepatomegaly and splenomegaly associated with G6PD deficiency estimated to be 18.8% and 37.5 %, respectively (22). However, there were no patients with these symptoms in our population. Similarly to previous report, this study showed that paleness, yellow sclera and dark urine were the prominent symptoms in patients with acute hemolysis (23). Previous reports that G6PD deficiency and Gilbert disease could have a summative effect on rising bilirubin when combined with other factors (24).

Our findings did not reveal any significant correlation between the hemoglobin level, hospitalization, hemoglobinuria, number of transfusion and each clinical manifestation. Also, these relations were not significant in each sex group. Despite the novelty of this study in evaluating the prevalence of each clinical symptom in G6PD patients with acute hemolysis, there are several limitations to our study. Further studies with more subjects over a longer duration are needed to determine the differences between the gender and between different age groups in developing the symptoms of acute hemolysis.

We also speculate that more time is needed to observe some of these clinical manifestations such as hepatomegaly and splenomegaly in G6PD patients with acute hemolysis. To the best of our knowledge, this was the first study to estimate the prevalence of each clinical feature in G6PD deficient children admitted with acute hemolysis in Fars province. However, we had some limitations. The most important one was that it is a subjective study and like other subjective studies it could accompanied with self-reporting bios.

5- CONCLUSION

In this study, pallor, icterus and dark urine were the three important symptoms in G6PD patients with acute hemolysis. These symptoms present several hours or even days after fava bean ingestion. After these symptoms, abdominal pain, vomiting and drowsiness were more frequent in our population. Diarrhea and constipation, as gastrointestinal complications of G6PD deficiency, totally occurred in 10% of patients. Other symptoms were rare in our population. We didn't find any correlation between the primary clinical symptoms and severity of the hospital course characteristics of the patients such as Hb level, hemoglobinuria and number of needed transfusion.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENT

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8- REFERENCES

1. Beutler E. G6PD deficiency. BLOOD-NEW YORK. 1994;84: 3613.

2. Pandolfi PP, Sonati F, Rivi R, Mason P, Grosveld F, Luzzatto L. Targeted disruption of the housekeeping gene encoding glucose 6-phosphate dehydrogenase (G6PD): G6PD is dispensable for pentose synthesis but essential for defense against oxidative stress. The EMBO journal. 1995;14(21):5209.

3. Çimen MB. Free radical metabolism in human erythrocytes. Clinica chimica acta. 2008;390(1):1-11.

4. Noori-Daloii M. Molecular identification of the most prevalent mutations of glucose-6-phosphate dehydrogenase (G6PD) in Fars and Isfahan of Iran. Journal of Sciences, Islamic Republic of Iran. 2009;20(3): 221-25.

5. Khneisser I, Adib SM, Loiselet J, Mégarbané A. Prevalence of G6PD deficiency and knowledge of diagnosis in a sample of

previously unscreened Lebanese males: clinical implications. Journal of medical screening. 2006;13(1): 26-8.

6. Pishva N, Amoozgar H. Hyperbilirubinemia following exchange transfusion with G-6-PD deficient donor blood. Iranian Journal of Medical Sciences. 2015;26(3 and 4):143-5.

7. Vulliamy T, D'urso M, Battistuzzi G, Estrada M, Foulkes N, Martini G, et al. Diverse point mutations in the human glucose-6-phosphate dehydrogenase gene cause enzyme deficiency and mild or severe hemolytic anemia. Proceedings of the National Academy of Sciences. 1988;85(14): 5171-75.

8. Beutler E. G6PD: population genetics and clinical manifestations. Blood reviews. 1996;10(1): 45-52.

9. Frank JE. Diagnosis and management of G6PD deficiency. American family physician. 2005;72(7): 1277-82.

10. Yoshida A. Hemolytic anemia and G6PD deficiency. Science. 1973; 179(4073): 532-7.

11. Au W-Y, Lam V, Pang A, Lee W-M, Chan JL, Song Y-Q, et al. Glucose-6-phosphate dehydrogenase deficiency in female octogenarians, nanogenarians, and centenarians. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences. 2006;61(10): 1086-89.

12. Luzzatto L, Nannelli C, Notaro R. Glucose-6-phosphate dehydrogenase deficiency. Hematology/oncology clinics of North America. 2016; 30(2): 373-93.

13. Mehta A, Mason PJ, Vulliamy TJ. Glucose-6-phosphate dehydrogenase deficiency. Best Practice and Research Clinical Haematology. 2000;13(1): 21-38.

14. Meloni T, Forteleoni G, Dore A, Cutillo S. Favism and hemolytic anemia in glucose-6-phosphate dehydrogenase-deficient subjects in North Sardinia. Acta haematologica. 1983;70(2): 83-90.

15. Burka ER, Weaver Z, Marks PA. Clinical spectrum of hemolytic anemia associated with glucose-6-phosphate dehydrogenase deficiency. Annals of Internal Medicine. 1966;64(4): 817-25.

16. Gellady AM, Greenwood RD. G-6-PD hemolytic anemiacomplicating diabetic ketoacidosis. The Journal of pediatrics. 1972; 80(6):1037-38.

17. Tzounakas VL, Kriebardis AG, Georgatzakou HT, Foudoulaki-Paparizos LE, Dzieciatkowska M, Wither MJ, et al. Glucose 6-phosphate dehydrogenase deficient subjects may be better “storers” than donors of red blood cells. Free Radical Biology and Medicine. 2016;96:152-65.

18. Chhabra A, Raj D, Choudhary PN, Grover A. Interesting case of G6PD deficiency anemia with severe hemolysis. Asian journal of transfusion science. 2013;7(2):147-8.

19. Nabavizadeh SH, Anushiravani.A The prevalence of G6PD deficiency in blood transfusion recipients.Hematology. 2007 Feb; 12(1):85-8.

20. Chisholm-Burns MA, Patanwala AE, Spivey CA. Aseptic meningitis, hemolytic anemia, hepatitis, and orthostatic hypotension in a patient treated with trimethoprim--sulfamethoxazole. American Journal of Health-System Pharmacy. 2010;67(2): 123-7.

21. Drent M, Gorgels AP, Bast A. Cardiac failure associated with G6PD deficiency. Circulation research. 2003;93(8):e75-e.

22. Boutchi M, Ibrahim AI, Daouda A, Zeinabou SA, Ibrahim AT. Sickle Cell Anemia and Glucose-6-phosphate dehydrogenase (G6PD) deficiency: Impact on Biological and Clinical Parameters. International Journal of Biotech Trends and Technology (IJBTT). 2016;15(1):13-7.

23. Devi AS, Kodi M, Devi AM. Living with Glucose-6-Phosphate Dehydrogenase Deficiency. journal of nursing science and practice.2016;6(1):23-26.

24. Saki F, Hemmati F, Haghighat M.Prevalence of Gilbert syndrome in parents of neonates with pathologic indirect hyperbilirubinemia.Ann Saudi Med. 2011;31(2):140-4. doi: 10.4103/0256-4947.77498.