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Seizure following acute hemolysis caused by Glucose-6-phosphate dehydrogenase Deficiency

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Abstract

Background: Storage of platelet concentrates (PCs) at room temperature (20-24°C) limits its storage time to 5 Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common inherited enzyme deficiency of the human red blood cells . Most of G6PD deficient individuals are asymptomatic, but acute hemolytic anemia may be presented with nausea, vomiting, abdominal pain, headache, jaundice, pallor, discoloration of the urine, chills, and fever. Seizure is reported as a rare symptom, as well. The present study aimed to investigate seizure following acute hemolysis caused by Glucose-6-phosphate dehydrogenase deficiency.

Material and Methods: This analytic cross-sectional study was conducted on all consecutive patients aged 1-12 years with G6PD deficiency hospitalized for hemolysis in 17 Shahrivar children hospital, Rasht, Iran, in 2016. Demographic characteristics and other variables such as place of inhabitants, type of drinking water, history of seizure in the patients and family, cause of hemolysis, hemoglobin level and hemoglobinuria on admission, and infection history prior to hemolysis were recorded. Data were analyzed by Mann-Whitney U test and Fischer Exact Test. P-value < 0.05 indicated statistical significance and data were assessed by SPSS (version 20).

Results: The youngest patient was one year old and the oldest was 11 years old. Most of them were males (68.9%). Out of 244 patients, 8 ones (3.3%) experienced seizure. There was a significant correlation between seizure occurrence and family history of seizure (p=0.03) as well as fava bean consumption (p=0.019) as the causes of hemolysis; but not with infection as the cause of hemolysis, hemoglobin or hemoglobinuria level on admission, types of drinking water, place of living, and gender. Methemoglobinemia was considered as the main cause of the seizure.

Conclusion: Although the rate of seizure was not so high (3.3%), it seems that seizure can be a critical and potentially life-threatening complication in these patients. Environmental factors may also play a role in the pathogenesis of the seizure in these patients.

Key words: Glucosephosphate Dehydrogenase Deficiency, Hemoglobin, Hemolysis, Seizures

Introduction

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme defect in human which affects more than 400 million people worldwide (1). Mediterranean region, Middle East, India, China, and Africa are mostly affected areas (2). However due to the global migration, this disorder is increasingly prevalent in north and South America and in parts of northern Europe (3). Most of G6PD deficient individuals are asymptomatic, but there are 3 types of clinical manifestations including acute hemolytic anemia, neonatal jaundice, and congenital non-spherocytic hemolytic anemia. Severity of the manifestations depends on the levels of enzyme activity and the burden of oxidative stress (4). Nausea, vomiting, abdominal pain, headache, jaundice, discoloration of the urine, chills, and fever are the most reported symptoms in acute hemolysis of G6PD deficiency (5). Fava bean ingestion has been considered as the most prevalent cause for hemolysis in G6PD deficient populations either in Iran (6) or in the world (7). Infections such as hepatitis A

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(8) and typhoid fever (9) may also trigger hemolysis. Antibiotics (10), anti-malarial agents (11), aspirin (12), and sulfonamides (1) also can induce hemolysis in these patients. Seizure is not a common symptom of acute hemolysis attack caused by G6PD deficiency. To the best of our knowledge and based on the literature, there were only rare case reports on this issue. Investigators of those case reports noted methemoglobinemia as the cause of the seizure. It is noteworthy that over production of methemoglobine can be detected during oxidative damage caused by G6PD deficiency as well as exposure to nitrite (13,14). Therefore, the present study aimed to investigate seizure following acute hemolysis caused by G6PD deficiency.

Materials and Methods

This analytic cross-sectional study was conducted on patients aged 1-12 years old with G6PD deficiency who were hospitalized for hemolysis in 17 Shahrivar children hospital, Rasht, Guilan province, Iran, in 2016.

Ethical approval was obtained from Mazandaran University of Medical Sciences, International Branch (no: IR.MAZUMS.REC.95.2187 date:30 JAN 2017).

Acute hemolysis caused by G6PD deficiency was diagnosed through its clinical manifestations, including nausea, vomiting, abdominal pain, headache, jaundice, discoloration of the urine, chills, and fever in conjunction with characteristic peripheral blood smear findings such as bite cells, schistocytes, blister cells, micro spherocytes, and finally reduced plasma level of G6PD enzyme. All patients with acute hemolysis caused by G6PD deficiency were included in this study. The occurrence of discontinued treatment, or G6PD deficiency with clinical conditions other than acute hemolysis was noted as the exclusion criteria. The data of patients who received routine management, including hydration +/- alkalinization and packed red cell transfusion according to the local guideline were recorded. Demographic characteristics, namely age and sex as well as other variables such as place of inhabitants, type of drinking water, history of seizure in the patients and family, cause of hemolysis, hemoglobin level and hemoglobinuria on admission, and infection history prior to hemolysis were recorded. All data were extracted from patients' medical records and then patients were divided into seizure and non-seizure groups.

All data were assessed by SPSS (version 20). Number, percent, mean, and standard deviation were reported as descriptive results. Normality of quantitative data was evaluated by Kolmogrov- Smirnov test and normal distributed data were analyzed by independent T-test. Mann-Whitney U test was used for non- normal distributed variables. In addition, chi_ square and Fischer Exact test were used to compare qualitative data. Statistical significance was noted by P-value < 0.05.

Results

In total, 244 patients were studied. The youngest patient was one year old and the oldest was 11 years old. The mean age of the patients was 3.74±1.97 years old. Most of the patients were males (68.9%). Eight patients (3.3%) experienced an episode of seizure. All of the patients recovered except 1 who had status epilepticus which was refractory to treatment. No one reported previous episode of seizure and 99.2% had no history of seizure in their immediate family. Characteristics of the patients are shown in Table I.

Fava bean consumption (89.3%) was the leading cause of hemolysis. Mean hemoglobin level on admission was 8.49±1.66 (g/dL). Results showed that 60.7% of patients had hemoglobinuria at the time of hospitalization.

Comparison of seizure and non-seizure groups showed that the majority of patients in both groups were males. In the

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seizure group, patients in equal frequency lived in rural and urban areas. Tap water was the main source of drinking water in both groups (Table II).

Although history of seizure in the family was noted in 2 out of 8 patients with seizure, there was not such a history in non-seizure group. As it was expected, fava bean consumption was the most leading cause of hemolysis in both groups. According to results, comparing seizure and non-seizure groups showed that there was no significant relation hemoglobinuria between sex, place of inhabitants, type of drinking water, and infection (p=0.78, p=0.29, p=0.68, p=0.29, and p=0.53, respectively). However, there was a significant association between seizure and non-seizure groups regarding positive history of seizure in the family and cause of hemolysis (p=0.03).

Although higher mean age of patients and lower level of hemoglobin were noted in patients with seizure, results showed that there was no significant difference between seizure and non-seizure groups regarding these variables (Table III).

Table I: Characteristics of the patients

Variable	Status	Number	Percent
sex	boy	168	68.9
	girl	76	31.1
Place of inhabitants	urban	178	73
	rural	66	27
Type of drinking water	tap water	182	74.6
	Well water	24	9.8
	Mineral water	38	15.6
History of seizure in patient	Yes	0	0
	No	244	100
History of Seizure in family	Yes	2	0.8
	No	242	99.2
Cause of hemolysis	Drug consumption	4	1.6
	Fava bean	218	89.3
	Infection	22	9
Hemoglubinuria	yes	148	60.7
	no	96	39.3

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Table II: Comparing groups based on qualitative variables

	Seizure						
	Yes		No		Sum		p- value*
	Number	Percent	Number	Percent	Number	Percent	
sex							
Male	6	75	162	68.6	168	68.9	0.78
Female	2	25	74	31.4	76	31.1	
Place of inhabitants							
Urban	4	50	174	73.7	178	73	0.29
Rural	4	50	62	26.3	66	27	
Type of drinking water							
Tap water	7	87.5	174	73.7	182	74.6	0.68
Well water	1	12.5	23	10.2	24	9.8	
Mineral water	0	0	38	16.1	38	15.6	
History of Seizure in family							
Yes	2	25	0	0	2	0.8	0.03
No	6	75	236	100	242	99.2	
Infection before hemolysis							
Yes	2	25	18	7.6	20	8.2	0.29
No	6	75	218	92.4	224	91.8	
Hemoglobinuria on admission							
Yes	8	100	140	59.3	148	60.7	0.153
No	0	0	96	40.7	96	39.3	
Cause of hemolysis							
Drug consumption	2	25	2	0.8	4	1.6	0.019
Fava bean	4	50	214	90.7	218	89.3	
Infection	2	25	20	8.5	22	9	

*Fischer Exact Test

Table III: Comparing groups based on age and hemoglobin level on admission

	Number	Mean ±SD	p-value*
age			
With seizure	8	3.87±1.35	0.88
Without seizure	236	3.77±1.9	
Hemoglobin level on admission			
With seizure	8	8.05±2.24	0.92
Without seizure	236	8.5±1.65	

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Discussion

G6PD deficiency is the most common inherited enzyme deficiency of the red blood cells in human. As other countries in the Middle East region, Iran is one of the countries with the highest prevalence of G6PD deficiency. The prevalence of G6PD deficiency is reported to be 6.7% in Iran (15) and 6.4% in Rasht (16). Based on the current knowledge, this is the first study investigated seizure as one of the less reported symptom of acute hemolysis due to G6PD deficiency in Iran. Due to lack of comparable studies, in this study a description of the findings and the probable causes of the disorder were presented.

In the present study, 8 patients developed seizure during the episode of acute hemolysis caused by G6PD deficiency. All of the seizures were tonic- clonic and generalized type which progressed to status epilepticus in two and led to death in one of them. Despite the low prevalence (3.3%), the occurrence of seizure was confirmed for the first time as an important complication and potentially life-threatening hazard inducing by acute hemolysis due to G6PD deficiency.

Patients with G6PD deficiency are susceptible for elevation of methemoglobin level; in addition, methhemoglubinemia has been reported as the causative mechanism for seizure occurrence in these patients (14).

To the best of our knowledge, there are few cases with a report of seizure and G6PD deficiency in the literature. The notewothy finding in the above- mentioned cases were the diversity of clinical presentations. Merdin et al., (2014) reported a 70-year-old female hospitalized for seizure and lethargy. On admission, her hemoglobin was 8 gr/dl. After transfusion, hemoglobin level raised to 11.7 gr/dl but after 2 days again declined to 7.5 gr/dl and G6PD level was low (13). Moreover, Fayazi et al., (2012) reported a 3-year-old boy presented with seizure and cyanosis. Increased methemoglobin level caused by oxidative damage to hemoglobin in the context of G6PD deficiency assumed to be the causative mechanism of this case (14). Furthermore, in 1966, Westrin et al., reported a patient with neonatal juandice, hepatomegaly, splenomegaly, and elevated bilirubin who recovered following blood transfusion and discharged from the hospital two weeks after birth, but finally his G6PD deficiency was manifested by anemia, cataract, and seizure (17).

In the current study, investigators measured methemoglobin level in 2 patients with favism and seizure. The first case was a 2-year-old boy who developed status epilepticus few hours after being hospitalized. Three days after admission, his methemoglobin level was 10.5%. After 2 weeks, its level declined to less than 1% and remained low until last months later. The next patient was a 3-year-old boy who developed seizure after hospitalization. His methemohemoglobin level was 11.2%. Serial assessment during next 2 weeks showed a decline to less than 1%. Thus, it seems that methemoglobinemia should be considered as a cause of seizure. It is expected that many of patients with acute hemolysis experience some degree of increased level of methhemoglobin, but the reason for developing a low frequency of seizure is not known so far. Despite rare case reports such as those mentioned above, there is no report from other centers which consider seizure as a symptom of acute hemolysis due to G6PD deficiency. Therefore, it seems that other parameters such as local environmental factors can be potentially important and could be considered in further investigations.

The level of nitrite in drinking water in some part of Rasht, especially in the east region, is in the upper limit of allowed range (18) Therefore, the question Can whether acute hemolysis due to G6PD deficiency along with environmental factors, such as a high nitrite content of drinking water, lead to brisk elevation of methemoglobin resulting in seizure or not. This hypothesis needs to be answered in

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further investigations. In this study, authors did not find any relation between type of drinking water and seizure.

Another possible explanation for seizure occurrence in these patients is the release of free hemoglobin during hemolytic crisis and resultant the decreased level of nitric oxide. Therefore, sudden decrease of brain blood flow as a result of severe vaso-constriction (secondary to nitric oxide depletion) and resultant cerebral hypoxia may have a role as a cause of seizure. This hypothesis also needs further investigations.

In this study, fava bean consumption was assigned as a risk factor for seizure. More comprehensive studies with larger sample size and complementary studies assessing the strain of consumed bean, place of cultivation, the manner of herbicides usage, etc. are recommended.

Another risk factor in this study was family history of seizure. Since only 2 patients had a family history of seizure, more comprehensive studies with larger sample size should be conducted. Here, no relation was found between seizure and age, place of inhabitants, sex, and history of seizure, doing future research with a larger sample is suggested.

This study had some limitations. Its first limitation was the retrospective nature of the assessment of records. The single center type of the study was the second limitation.

Besides rare published case reports regarding the relation between G6PD deficiency and seizure such as one conducted by Fayyazi et al.,(14), the present study reported an association between seizure and acute hemolysis due to G6PD deficiency for the first time as a case series. The seizure occurred in 3.3% of the studied patients which was tonic colonic and generalized. In 2 cases, seizure led to status epilepticus and in one case led to death. Among the different variables studied here, family history of seizure and fava bean consumption, as the causative agent, had significant associations with the seizure occurrence. Prospective study with larger sample size is recommended to approve or disapprove our findings. Furthermore, since environmental factors may play a role in developing seizure, doing supplementary studies in this regard is recommended. Moreover, routine measurement of nitrite and nitrate in drinking water and detailed investigation of environmental impacts are suggested.

Conclusion

Although the rate of seizure was not so high (3.3%), it seems that seizure can be a critical and potentially life-threatening complication in these patients. Environmental factors may also play a role in the pathogenesis of the seizure in these patients.

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Conflict of interest

None of the authors have any conflicts of interest to declare.

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