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Fava Bean Ingestion: the Most Important Risk Factor of Hemolysis in G6PD Deficiency in Iran

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ABSTRACT

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is one of the most known enzyme defects in Iran with various genetic mutations. We aimed to study the predisposing factors of hemolysis in children with G6PD deficiency.
Methods: This study was done during 2007-2012 in two referral centers of Mofid Children's Hospital and Baqiyatallah Hospital, Tehran, Iran. The hospital records of the patients were fully reviewed and questionnaires for each patient were filled for the date of admission, initial symptoms, initial laboratory results, family history and history of any drug consumption, infection or fava bean ingestion.
Results: Medical records of 192 children with mean age of 4.2 years (1 month to 14 years) were extracted. 68.2% of the cases were male. Hemolytic crises were significantly more common in spring which is the peak time for fava bean consumption and occurred more frequently in those with a family history of G6PD deficiency especially in females. The most common initial symptoms were jaundice (71%), dark color urine (49%), fever (34.4%), and pallor (24.5%), followed by abdominal pain (16.7%). Fava bean intake (93%) was the first etiological agent triggering hemolysis followed by infectious agents and drug consumption. Initial hemoglobin level was significantly lower in male patients.
Conclusion: Regarding the high prevalence of G6PD deficiency in Iran, we should emphasize on education of parents and physicians about the disease and prevention of fava bean ingestion in people with G6PD deficiency.

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Introduction

G6PD deficiency affects more than 400 million people worldwide. It is highly prevalent in Africa, Asia, and especially in Mediterranean countries.[1] Iran is one of the countries with the highest prevalence of G6PD deficiency according to the World Health Organization (WHO) reports.[2] The prevalence of the disease is reported to be 6.7% in Iran. It seems although neonatal G6PD screening is being practiced in Iran since 2010, the level of education and knowledge of physicians and parents about the nature of the disease and predisposing factors for hemolysis is still essential.[2] Gene frequency for the disease is different from 2.1% in Lebanon[3] to 3.6% in Thailand,[4] 5.1% in Indonesia,[5] and 15.3% in Nigeria.[6] The disease is inherited as an X-linked recessive trait, but the spectrum of the enzyme activity and clinical manifestations are greatly diverse in different populations.[7-9] The most common clinical presentations of people affected with G6PD deficiency are neonatal jaundice and acute hemolytic anemia (favism); while chronic non-spherocytic hemolytic anemia is an uncommon presentation, could be more frequent in geographical areas in which G6PD deficiency is prevalent.[2] Nausea, headache, abdominal pain, chills and fever are the most reported symptoms in acute hemolysis of G6PD deficiency.[10] Prolonged jaundice and Kernicterus may be the other complication of the disease which can cause irreversible effects in the neonates.[6] Hemolysis can in turn cause renal failure or thrombosis as an ultimate risk. All these presentations could impose heavy economical burden on the health system which is avoidable by early neonatal screening of the disease.

Hemolysis is known to be triggered by various environmental factors; the severity of hemolysis is directly related to the degree of enzyme deficiency. Fava bean ingestion is the most common precipitating factor for hemolysis in G6PD deficient populations.[11,12] Infections such as hand-foot-mouth disease, enteroviruses,[13] hepatitis A,[14,15] typhoid fever,[16] and pneumonia[17] also trigger hemolysis in G6PD deficient persons. Consumption of some antibiotics,[18,19] anti-malarial agents,[19] Aspirin,[20] and sulfonamides,[21] also induce hemolysis in these patients.

Overall 1.4 out of 10,000 patients with G6PD deficiency are affected by severe hemolysis, half of which are preventable.[22] WHO recommends neonatal routine screening of G6PD in those countries with higher prevalence than 3-5% of the population.[21,23] This mass screening is being practiced since 2010 in Iran. In this study we investigated the precipitating factors of acute hemolytic attack in patients with G6PD who were admitted to two hospitals, Mofid Children's Hospital and Baqiyatallah General Hospital, Tehran, Iran.

Patients and Methods

In this cross-sectional study we reviewed hospital records of all 1 month to 14 years old patients with G6PD deficiency and acute hemolysis admitted to Mofid Children's and Baqiyatallah Hospitals during 2007 to 2012. The study was approved by the Research Ethics Committee of Baqiyatallah University of Medical Sciences, Tehran, Iran.

A questionnaire was designed for every patient to be filled based on their hospital records. The questionnaire included all information about precipitating factors of hemolysis (history of any respiratory or gastrointestinal infection, drug consumption) and clinical signs and symptoms such as icterus, pallor, fever, diarrhea, and dark urine. The season of admission along with any family history of G6PD deficiency or hemolysis was also extracted. Laboratory data such as hemoglobin, total and direct Bilirubin level and G6PD status were also included.

The data gathered from the questionnaires were analyzed using SPSS software, version 18. Data were expressed as means±standard deviations (SD) for quantitative data and percentage for qualitative data. Independent t (or MannWhitney U test for nonparametric amounts) and Pearson's Chi-square (or Fisher's exact test) tests were used as appropriated.

Results

During the study period, records of 192 patients were drawn, consisting of 131(68.2%) boys. The most common signs were jaundice (71.4%), dark urine (49%), fever (34.4%), and pallor (24.5%). Abdominal pain was observed in 16.7% of the patients. Overall 179 (93.2%) patients had a history of fresh or dried fava bean ingestion. Drugs, upper respiratory tract and gastrointestinal infections were the following causes in 12, 9, and 3 patients, respectively. 169 patients had just fava bean exposure; other seven cases had drug consumption along with fava bean eating. One patient had upper respiratory tract infection (URI), one URI with drug consumption and another one had hepatitis and fava bean ingestion. Diabetic ketoacidosis was diagnosed in only one patient with hemolysis. 149 patients out of 179 (83.2%) who had history of fava bean ingestion before their hemolysis attack, reported fava bean ingestion in the past without developing any obvious hemolysis. Eight patients had previous history of hemolysis following fava bean ingestion. Risk factors of hemolysis in the patients are shown in table 1.

Neonatal jaundice was reported in 82 (42.7%) patients. The enzyme activity was reported to be deficient in 41 out of 170 patients tested during the hemolytic attack. The hemolytic episodes mostly occurred in Spring (74.5%), followed by autumn (10.9%), winter (8.9%), and summer (5.7%), respectively.

The initial hemoglobin level was significantly lower in male patients ($P<0.001$); it was higher in those with gastroenteritis and positive family history of favism. Positive family of favism was reported in 69.4% patients. Moreover, 96.5% of the admitted patients received blood transfusion during their admission. The interval between fava bean ingestion and onset of hemolysis was minimally 12 hours and maximally 72 hours (mean: 48 hours).

Discussion

We found that the most common precipitating factor for hemolysis in G6PD deficient children was fava bean ingestion and other factors such as infections and drug exposure played a minor role. In 2007, 6.7% of the world population or 450,000,000 people were affected by G6PD deficiency. It is approved that fava bean ingestion and

Table 1: Risk factors of hemolytic crisis in G6PD deficient patients

Risk Factor		Number of Patients	Percent (%)
Fava bean ingestion		169	88.02
Fava bean and Drug exposure		7	3.64
Fava bean and URI		1	0.52
Fava bean and Hepatitis		1	0.52
Fava Bean, Drug exposure and URI		1	0.52
Infections	Gastroenteritis	4	2.08
	URI	5	2.6
Drug exposure		3	1.56
Drug exposure and URI		1	0.52
Total		192	100

infections are the most common factors to precipitate hemolysis in countries where routine neonatal screening programs are not implemented.

Previous reports show African sub-Saharan followed by Middle East countries were the most prevalent areas for G6PD deficiency. Prevalence of the disease in Iran has been previously reported before and is different in various cities from 3.2% to 19.3% of the population.[24,25] A published study from Iran showed that 38 out of 300 students were G6PD deficient, but only 2% of them had history of favism hemolytic crisis.[26] Multiple mutations of G6PD are described in different areas of Iran. Noori Daloii and colleagues reported Mediterranean mutations to be the most prevalent mutation in Golestan province followed by Chatham mutation; and this recent mutation was higher in this state in relation to other provinces of Iran.[27] It seems that Mediterranean mutations are the most important variant of G6PD to precipitate hemolytic crisis in middle East countries.[28] Another report from Kordestan province of Iran also confirms the predominance of Mediterranean and Chatham mutations in this area.[29] High frequency of Mediterranean mutations has also been reported in other countries such as India.[30] In Spain, among 1139 students studied, only 11 were G6PD deficient which two of them had experienced hemolytic crisis of the disease.[31] Shannon and co-workers described 14 black children with G6PD deficiency and hemolytic episode of whom 11 had infections and three had Naphthalene exposure; only 3 had history of fava bean ingestion. Other oxidant agents were not responsible for any of the hemolytic episodes in their study.[32,33] In India the main triggers of hemolysis were viral hepatitis, malaria and bacterial sepsis.[33] In Nigeria 22% of hemolytic crises were reported following respiratory tract infections.[34] Agarwal and colleagues reported 5 patients with hepatitis and G6PD deficiency all of whom had high fever, severe anemia, and reticulocytosis.[35] In Hong Kong herbal drugs followed by fava bean ingestion were mostly responsible in G6PD hemolytic episodes.[22] A report from North Sardina also indicated fava bean ingestion was the most common trigger of hemolytic episode in G6PD deficient patients.[36] Lou and co-workers also reported fava beans to be the main cause of hemolysis in China.[22]

In our study, only 12 patients with G6PD hemolytic episode had evidence of viral infections. This data is different from many other countries. The most important drugs responsible for hemolytic crisis in G6PD deficient people around the world are antimalarial agents.[37-39] In Turkey antimalarial and antipyretics were the most common drugs to be responsible.[40] This was the same in Afghanistan as antimalarial agents and aspirin were reported to be the most common agent.[41] As a result of success of malaria eradication programs in Iran, antimalarial drugs are not among the common triggers of hemolysis in our country. According to a WHO report in 2015, malaria has been on a declining trend in Iran and now is classified in elimination phase.[42] Cefaperazone/sulbactam could be mentioned among antibiotics that can precipitate hemolytic attack in G6PDdeficient patients.[43,44] Since self-medication with antibiotics is common in Iran, these should be kept in mind as an agent to precipitate hemolysis in such patients.[45] Table 2 shows some published risk factors for hemolysis in G6PD deficient patients in the region.

In our study, 82 out of 109 patients had a history of neonatal jaundice. In 109 Nigerian G6PD deficient children studied, 106 of them described neonatal jaundice.[34] Other reports also showed a significant number of neonatal jaundice occurring in G6PD deficient neonates. There is a global emphasis on importance of neonatal G6PD screening especially in those with prolonged jaundice.[46]

Neonatal G6PD screening program is being practiced in Iran since 2010, albeit still increased level of education and knowledge of physicians and parents regarding the nature of the disease and precipitating factors is essential.

Conclusion

The most common agent to induce hemolysis in G6PD deficient patients was fava bean ingestion. This could be severe enough to compromise the vital condition of the patients. According to eradication programs of malaria in our country and rarity of drug-induced hemolytic crises in G6PD deficient patients, increased level of awareness about the nature of hemolysis and importance of fava bean ingestion is advisable.

Conflict of Interest: None declared.

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Table 2: Different studied populations for G6PD deficiency with their precipitating risk factors in the region

Country	Number of study population	Hemolysis risk factor
Jordan[47]	428	Young age, Negative family history, Male
Jordan[48]	258	Fava bean, URI, Drug exposure
Iraq[49]	102	Fava bean, Spring time
Hong Kong[22]	6	Fava bean, URI, Herbal drugs
Thailand[4]	225	Dried Fava bean

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