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

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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.

Introduction
G6PD deficiency affects more than 400 million people worldwide. It is highly prevalent in Africa, Asia, and especially in Mediterranean countries. Iran is one of the countries with the highest prevalence of G6PD deficiency according to the World Health Organization (WHO) reports. 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.

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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 pneumonia17 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.23,24 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>
<thead>
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<th>Table 1: Risk factors of hemolytic crisis in G6PD deficient patients</th>
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<tbody>
<tr>
<td><strong>Risk Factor</strong></td>
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<tr>
<td>Fava bean ingestion</td>
</tr>
<tr>
<td>Fava bean and Drug exposure</td>
</tr>
<tr>
<td>Fava bean and URI</td>
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<tr>
<td>Fava bean and Hepatitis</td>
</tr>
<tr>
<td>Fava Bean, Drug exposure and URI</td>
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<tr>
<td>Infections</td>
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<tr>
<td>Gastroenteritis</td>
</tr>
<tr>
<td>URI</td>
</tr>
<tr>
<td>Drug exposure</td>
</tr>
<tr>
<td>Drug exposure and URI</td>
</tr>
<tr>
<td>Total</td>
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</tbody>
</table>
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. 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. Multiple mutations of G6PD are described in different areas of Iran. Noori reported to be the most common agent. As a result in Afghanistan as antimalarial agents and aspirin were the most important episodes had evidence of viral infections. This data is common trigger of hemolytic episode in G6PD deficient patients.

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

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of study population</th>
<th>Hemolysis risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jordan</td>
<td>428</td>
<td>Young age, Negative family history, Male</td>
</tr>
<tr>
<td>Jordan</td>
<td>258</td>
<td>Fava bean, URI, Drug exposure</td>
</tr>
<tr>
<td>Iraq</td>
<td>102</td>
<td>Fava bean, Spring time</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>6</td>
<td>Fava bean, URI, Herbal drugs</td>
</tr>
<tr>
<td>Thailand</td>
<td>225</td>
<td>Dried Fava bean</td>
</tr>
</tbody>
</table>

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. 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.

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.

References

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