Favism
Experience in Al-Elwia Pediatric Teaching Hospital Caused by Ingesting Raw or Cocked Fava-beans

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Abstract

Background: G6PD deficiency very common disease in our country with variable presentation (mysterious disease) with ingestion of fava beans was the most common cause.

Patient&method: Prospective study involving One-Handered Twenty Three cases of patient who were admitted to Emergency Room in AL-Elwia Pediatric Teaching Hospital and were diagnosed as G6PD deficiency between the 1st of February 2016 and 31st of May 2016.

Results: One Handed-One were males and Twenty-Two were females, 66.7% were due to ingestion of raw fava beans and 33.3% were due to ingestion of cooked fava beans. Negative family history of hemolysis was found in 56.9% and only 4.1% had positive drug history without fava beans ingestion. Pallor and jaundice with dark urine were the commonest presenting features. Hematocrit level was ≤ 20 in 83.8%. Blood film showed normochromic normocytic anemia in 95.9%, blister cells in 86.2% and fragmented cells in 11.4%, and 2.4% of patients showed spherocyte. Significant reticulocytosis was seen only in 84.6% of patients. Hyperbilirubinemia was universal in all the cases and renal function was normal in all cases. Some patient need more than one time blood transfusion. G6PD enzyme was deficient early in 76.4% of cases. All the patients recovered well after intravenous fluid or blood transfusion. There is No Death.

Conclusion: Boys were more affected than girls in terms of presentation and severity and intoxication with raw fava beans were more dangerous than cooked beans. Blood transfusion is the most used therapeutic measure.
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Introduction

Definition: Favism is an acute hemolytic anemia, usually in persons of Mediterranean area descent, occurring when an individual with G6PD deficiency of erythrocytes eats fava beans or inhales the pollen, of Vicia faba (1). The term ‘favism’; however, is used rather broadly for symptoms caused by a reaction to a number of different substances including, but not limited to, favas (2).

General Considerations: G6PD deficiency is the most common human enzyme deficiency in the world (2,3). It is considered to be the most important disease of what is known as hexose monophosphate pathway of RBC metabolism (4).

Favism has been known to exist since antiquity; the Greek philosopher and mathematician Pythagoras was said to have warned his disciples against the dangers of eating fava beans (3). However, the recognition of G6PD deficiency was a direct result of investigations of the hemolytic effect of the antimalarial drug primaquine, carried out in the early 1950s (5). These early studies defined G6PD deficiency as a hereditary sex-linked enzyme deficiency that affects primarily the erythrocytes, older cells being more severely affected than newly formed ones (5, 6). As well, they showed that this disease represents an example of “balanced polymorphism” in which there is an advantage of resistance to falciparum malaria (4).

From clinical point of view, G6PD deficiency is responsible for two syndromes, an episodic hemolytic anemia induced by infection, certain drugs or fava beans, and a spontaneous chronic nonspherocytic hemolytic anemia (4, 6). So, favism is a variety of the first (episodic) one. Fortunately the second form (chronic nonspherocytic) is very rare (2, 7).

Electrophoretic variants of G6PD enzyme, that are valuable in studies of gene regulation and population biology, have been identified (3, 5).

The prevalence of G6PD deficiency is most evident in people of African, Mediterranean, and Asian ancestry (2, 3, 8), but it could be found in virtually any population (9). Importantly, not all G6PD-deficient families appear at risk for favism, indicating the additional need for a single, probably autosomal, gene to create the susceptibility to favism of G6PD-deficient persons (10).

Etiology and Pathogenesis: The gene for G6PD located on the terminal end of long arm of X-chromosome (3,6). A G6PD-like locus, possibly a pseudogene, has been identified on chromosome 17 (6.9). The enzyme function is determined mainly by the sequence and size of G6PD gene, and the mRNA encoded by the gene, which are 18,500 and 2,269 base pairs in length, respectively (3). G6PD cDNAs from normal subjects and those with some mutations have been sequenced (9, 11).

The “normal” enzyme found in most populations is designated G6PD B+(4,6). G6PD deficiency results from the inheritance of any one of a large number of abnormalities of the structural gene that codes the amino acid sequence of the enzyme G6PD(9). A normal variant designated G6PD A+ is common in the African-American population (4,9). The latter mutant
enzyme migrates electrophoretically more rapidly than the normal B+ enzyme. In the case of the common deficient African-A- and in Mediterranean mutations the abnormal enzyme formed may be synthesized in normal or near-normal quantity, but has decreased stability in vivo (3,9). Several models have been proposed suggesting possible reasons for why an abnormal enzyme is not fully active, the most popular of them is that the decreased stability of a mutant enzyme results either from a change in the conformation of G6PD molecule or from an increase in its susceptibility to proteolytic enzymes (3, 8). Various combinations of abnormal properties occur, and over 400 variants of this enzyme have been described (10). Favism has been shown to occur most often in the Mediterranean variant which is designated G6PD B (4, 11). The enzyme activity of the red cells of individuals who have inherited this abnormal gene is barely detected, being less than 5% of normal in homozygous females or hemizygous males (4, 9). Many similar but distinct variants exist in the Mediterranean region (12).

The function of the normal G6PD enzyme is critical to human survival; it is present in all human cells but, is particularly important to RBCs (2). The G6PD enzyme catalyzes an oxidation/reduction reaction in the hexose monophosphate pathway (Fig.1)(4). The oxidation involves the conversion of glucose-6-phosphate (G6P) to 6-phosphogluconate (6PG), while the reduction involves the formation of NADPH from NADP+ (6,13). There are other metabolic pathways that can generate NADPH in all cells, except in RBC where other NADPH-producing enzymes are lacking (3). NADPH is a required cofactor in many biosynthetic reactions.

It is necessary to keep glutathione, a tri-peptide, in its reduced form (i.e. GSSG→GSH)(4,14). Reduced glutathione acts as a scavenger for dangerous oxidative metabolites in the cell; it converts harmful hydrogen peroxide to water with the help of the enzyme glutathiones reductase (8). If reduced glutathione cannot be sustained to remove oxygen radicals generated by oxidant substances (e.g. drugs), the hemoglobin precipitates forming Heinz bodies that attach to the RBC membrane leading to increased RBC fragility and early destruction (i.e. shorter life span than normal RBCs)(4). Heinz bodies are particles of denatured hemoglobin and stromal protein formed only in the presence of oxygen (6, 9).

Cells containing Heinz bodies encounter difficulty in traversing the splenic pulp and are relatively rapidly eliminated from the circulation (6). Pending elimination, the RBC morphology during episodes of acute hemolysis is striking. Red cells appear to have “bites” (called cookie cells) taken out of them; these are areas of absent hemoglobin that are produced by phagocytosis of Heinz bodies by splenic macrophages during passage of these cells through the spleen, as a result, the red cells appear blistered (15).

Substances capable of destroying red cell GSH have been isolated from fava beans. They include an unusually high amount of oxidants; these oxidative products, derived mainly from two glucosidic compounds, vicine and covicine, which are hydrolysed to divicine and isouramil respectively, ultimately produce hydrogen peroxide and other reactive oxygen products(4)
Neonatal jaundice in G6PD deficiency may be due to both some shortening of RBC life-span and to inadequate processing of bilirubin by the immature liver of G6PD-deficient infants (7). Hemolysis induced by infection or occurring spontaneously in G6PD-deficient subjects is the least understood mechanism (6). It has been suggested that the generation of hydrogen peroxide by phagocytizing leukocytes may play a role in this type of hemolytic reaction (6,9).

**Mode of Inheritance**

The gene determining the structure of G6PD is carried on the X-chromosome, at the q28 locus (16); so, inheritance of G6PD deficiency is sex-linked. For this reason, the defect is fully expressed in affected males and is never transmitted from father to son, but only from mother to son. In females, only one of the two X-chromosomes in each cell is active (3,6). Therefore, female heterozygotes for G6PD deficiency have two populations of red cells; deficient cells and normal cells (6). The proportion of deficient to normal cells may vary greatly. Favism occurs only in G6PD-deficient subjects, but not all individuals in a particular family may be sensitive to the hemolytic effects of bean (6). Nonetheless, some tendency toward familial occurrence has suggested the possibility that an additional genetic factor may be active (10,18). Genetic testing is available to identify a deficiency in G6PD in both males and females (19).

**Prevalence and Geographic Distribution**

The prevalence of G6PD deficiency among white populations ranges from less than 0.1% among northern European people to 50% of males among Kurdish Jews (2,20). G6PD deficiency is also found among certain Chinese population and in Southeast Asia. Several variants appear to be common in Asian population. G6PD deficiency of the A-type is very common in West Africa with an enzyme activity around 5-15% or less of normal and in the USA as well, the incidence among black males is approximately 11%; approximately 16% of American black males carry the non-deficient G6PD A+ gene (9). Italians, Greeks and other Mediterranean, Middle Eastern, and Asian ethnic groups have a high incidence ranging from 5-40% of G6PD Mediterranean (the B-type) variant (4). Favism is most common in this latter group. A higher prevalence of G6PD deficiency in individuals with sickle-cell disease than in the general black population may reflect a favorable effect of enzyme deficiency on the clinical course of the sickling disorders (6).

**Clinical Manifestations**

Most G6PD-deficient persons do not suffer any clinical manifestation from his common genetic trait (6,18). The two major clinical consequences are (1) acute hemolytic anemia following exposure to oxidative stress (22), which may be a drug or chemical, infection,
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or fava beans; and (2) neonatal jaundice. Box 1 shows the drugs and chemicals known to induce hemolysis in G6PD-deficient subjects. A considerable difference exists with regard to the reaction to various drugs among various G6PD-deficient individuals, indicating that the metabolism and excretion of those drugs differ and thus influence the extent to which G6PD-deficient RBCs are destroyed. Since co-existent infection or other stressful situation may precipitate hemolysis in G6PD-deficient individuals, many drugs have been implicated incorrectly as a cause. Fava bean-induced hemolysis in G6PD-deficient individuals may follow either ingestion of fava plant material, beans, pods or foliage; or inhalation of fava pollen. Occasional hemolysis has been reported to occur after ingestion of other foodstuffs such as unripe peaches. Typically, an episode of hemolysis begins 1 to 3 days (called a lag period) after exposure to the offending agent. The urine may turn dark, or even black, described as ‘Coca-Cola’ urine, resulting from hemoglobinuria and urobilinogen in the urine. This may lead to renal dysfunction which can be severe. Headache, dizziness, jaundice, nausea, vomiting, abdominal and/or back pain, and fever may accompany the hemolytic episode. Within 4 to 6 days there is generally an increase in the reticulocyte count, except in instances in which the patient has received the drug in the treatment of an active infection. In severe cases, shock may develop within a short time. The degree of hemolysis varies with the inciting agent, the amount ingested, and the severity of the enzyme deficiency in the patient. Favism has been seen to occur much more commonly in children than adults, and is associated with the most explosive course and all the classical signs of intravascular hemolysis. Anemia may develop rather suddenly in G6PD-deficient individuals, within a few days of onset of a febrile illness. The anemia is usually relatively mild. Jaundice is not a predominant part of the clinical picture here, except in infectious hepatitis, where it can be quite intense. Presumably because of the effect of infection, reticulocytosis is usually absent, and recovery from anemia is generally delayed until after the active infection has resolved.

It has been suggested that hemolytic episode may also occur in association with diabetic ketoacidosis or hypoglycemia as being oxidative stressful conditions. Neonatal jaundice has been observed in many infants with G6PD deficiency and may be severe enough to cause kernicterus or even death if untreated. This is specially common in the Mediterranean type. When a pregnant woman ingests oxidant agents, the may be transmitted to her G6PD-deficient fetus and hemolytic anemia and jaundice may be apparent at birth.

Laboratory Findings

The hemoglobin, reticulocyte count, and blood smear are usually normal in the absence of hemolysis. The onset of acute hemolysis results in a precipitous fall in hemoglobin and hematocrit. Heinz bodies develop in the erythrocytes in the early phases of hemolysis, and are not visible in ordinary Wright’s-stained blood film, but are revealed with supravital stains such as methyl violet. Bite cells (blister or cookie cells) may be seen, in
which the hemoglobin is pushed to one side of the cell, leaving a clear area beneath the membrane on the opposite side (29).

If the hemolytic anemia is very severe, spherocytosis and red cell fragmentation may be seen as well (9).

Early on, the hemolysis usually exceeds the ability of the bone marrow to compensate, so the reticulocyte count may not be elevated for 3-4 days (15). No consistent changes occur in platelets or WBCs (6). Direct antiglobulin test (Coombs’s test) should be negative, as hemolysis is not immune-mediated (31). Varying degrees of hyperbilirubinemia is evident (32).

**Diagnosis**

Diagnosis of G6PD deficiency is confirmed by demonstration of decreased enzyme activity through either a quantitative assay or a screening test (33). Assay of the enzyme is based on measuring the rate of reduction of NADP⁺ to NADPH in an ultraviolet spectrophotometer (9,34). Satisfactory screening tests are based on decoloration of methylene blue, on the reduction of methemoglobin, or on the fluorescence of NADPH (35).

In favism; however, evidence of intravascular hemolysis in persons of Mediterranean area descent, shortly following exposure to fava beans may be enough for diagnosis, particularly if there is a positive family history, because the disease is genetic (2).

**Differential Diagnosis**

Other enzyme defects affecting the pentose-phosphate shunt (syn. hexose monophosphate shunt), such as a deficiency of GSH synthetase, may be similar clinically to G6PD deficiency (8). G6PD assay or the fluorescent screening test will be normal (9).

**Prevention and Treatment**

The most important therapeutic measure is to prevent hemolysis (4,8). When possible, males belonging to ethnic groups with a significant incidence of G6PD deficiency should be tested for the defect to avoid oxidative drugs (Box 1) and fava bean ingestion that might induce hemolytic episodes (4).

If hemolysis occurs, as in the usual case in our society, supportive care is required and includes the following measures:

1. Oxidative agent should be withheld (4).
2. Protecting the kidneys against damage from precipitated hemoglobin by maintaining adequate hydration and urine alkalization (15).
3. Transfusion of whole blood or packed cells (6), if hemolysis is very rapid, as in favism.
4. Human haptoglobin products have been reported in one study to be of some benefit (33).
5. Vitamin E and folic acid (both antioxidants) may help decrease hemolysis in G6PD-deficient individuals (2,6).

Recovery usually occurs within 48-72 hours following initiation of therapy (29). Before discharging the patient home, a list of ‘drugs to avoid in the future’ should be given to his family (Boxes 1&2). Any boy (or girl) suffering from favism should be informed of his (or her) deficiency, so that he (or she) can help himself (or herself) avoid the intake of the forbidden foodstuff and oxidant drugs in various situation where he (or she) is not under supervision (e.g. in the school) (2,3).

Infants with neonatal jaundice due to G6PD deficiency may require exchange transfusion; in areas where
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G6PD deficiency is prevalent, care must be taken not to give G6PD-deficient blood to such newborns (6). Pregnant women, especially in areas where G6PD deficiency is prevalent, should avoid eating fava beans (2). Persons with G6PD B (Mediterranean) enzyme deficiency occasionally have chronic hemolysis, and the hemolytic process may worsen after ingestion of oxidant agents (4). Unless acute hemolysis occurs, usually these patients do not require any therapy (6). Splenectomy is generally ineffective, although some improvement has occasionally been reported following removal of the spleen (6).

Course and Prognosis

With avoidance of hemolysis-inducing triggers, the prognosis is excellent (2). Favism is considered a relatively dangerous, but preventable disease. Prior to the institution of modern hospital therapy, mortality from favism was not uncommon (6). Mortality, which is fortunately now avoidable, was confined to children under 5 yr of age (34). In one study, a decreasing incidence of favism was noted with increasing age of the population (35), a phenomenon may be attributed either to a decreasing incidence of G6PD deficiency with advancing age (18), or increasing awareness of oxidative agents in persons known to have the defect (35). During periods of infections or oxidant drug administration, anemia may increase in severity (6,18). Otherwise the hemoglobin level of affected subjects remains relatively stable (18). Because fava bean is considered as a valuable source of nutrition, researchers are currently genetically engineering it so that the causative agents of hemolysis will be eliminated; this will allow favic individuals to eat fava beans in the future (6).

Box (1) Drugs and chemicals that should be avoided by persons with G6PD deficiency

<table>
<thead>
<tr>
<th>Acetanilide</th>
<th>Phenazopyridin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trinitrotoluene (TNT)</td>
<td>Primaqine</td>
</tr>
<tr>
<td>Furazolidone</td>
<td>Sulfaacetamide</td>
</tr>
<tr>
<td>Methylen blue</td>
<td>Sulfamethoxazole</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Sulfanilamide</td>
</tr>
<tr>
<td>Naphthalene</td>
<td>Sulfapyridine</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Thiazolesulfone</td>
</tr>
<tr>
<td>Phenylhydrazine</td>
<td>Toluidine blue</td>
</tr>
<tr>
<td></td>
<td>Chloramphenicol</td>
</tr>
</tbody>
</table>

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Box (2): Drugs that can possibly safely be given in normal therapeutic doses to G6PD-deficient subjects without nonspherocytic hemolytic anemia

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (paracetamol)</td>
<td>p-Aminobenzoic acid</td>
</tr>
<tr>
<td>Acetophenitidin</td>
<td>Phenylbutazone</td>
</tr>
<tr>
<td>Acetylsalicylic acid (Aspirin)</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Aminopyrine</td>
<td>Probencid</td>
</tr>
<tr>
<td>Antazoline</td>
<td>Procainamide hydrochloride</td>
</tr>
<tr>
<td>Antipyrine</td>
<td>Pyrimethamine</td>
</tr>
<tr>
<td>Ascorbic acid (Vit.C)</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Benzhexol (Artane)</td>
<td>Quinine</td>
</tr>
<tr>
<td>Vit. K</td>
<td>Streptomycin</td>
</tr>
<tr>
<td>Chlorguanidin</td>
<td>Sulfacytin</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Sulfadiazine</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Sulfaguanidine</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Sulfamerazine</td>
</tr>
<tr>
<td>Isoniazide (INH)</td>
<td>Sulfamethoxypyridazine</td>
</tr>
<tr>
<td>L-Dopa</td>
<td></td>
</tr>
<tr>
<td>Menadione sodium bisulfite</td>
<td></td>
</tr>
<tr>
<td>Menaphthone</td>
<td></td>
</tr>
</tbody>
</table>


Aim of the Study
To find out the commonest age at risk of hemolysis.
1. To see whether the disease presentation and severity has any relation to gender.
2. To see whether there is any difference between exposure to raw or cooked fava beans in regards to the amount of the ingested beans, time of onset, and severity of symptoms.

Patients And Methods
All cases with suggestive symptoms and signs of acute hemolysis (as rapidly progressing pallor, dark urine, fever, vomiting … etc) following exposure to fava beans, were studied prospectively in AL-Elwia Pediatric Teaching Hospital during the period from the 1st of February 2016 to the 31st of May 2016. The range of their age was from 12 months to 13 years. A full history was taken from their close family members including color of their urine, and history of fava bean ingestion, contact or smell, and a questionnaire paper was used for that and a copy of it is attached in the appendix. Then full systemic examination including checking for enlarged liver and/or spleen was undertaken.
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For all patients, the important investigations done included complete blood count with blood film and Reticulocyte count, direct Coomb’s test, renal function tests, serum bilirubin (total and fractionated), as well as general urine examination (including urobilinogen) and G6PD enzyme assay screening test. 101 of them were males and 22 of them were female. All the patients received supportive measures in the form of intravenous fluids with or without blood transfusion, and all recovered well to be discharged in a good condition. Statistical test done by using Z-test to measure the P value.

Results

1-Age & gender: The peak age of incidence was between 1-5 years of life & Boys were more affected than girls in terms of presentation with Male to Female ratio around 4.5:1 as show in table 1.

Table (1): Shows the age groups & gender distribution

<table>
<thead>
<tr>
<th>Age</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>&lt;12mo</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12mo –2 yr</td>
<td>17</td>
<td>13.8</td>
<td>16</td>
</tr>
<tr>
<td>&gt; 2yr –3yr</td>
<td>27</td>
<td>21.95</td>
<td>22</td>
</tr>
<tr>
<td>&gt; 3yr –4yr</td>
<td>18</td>
<td>14.6</td>
<td>18</td>
</tr>
<tr>
<td>&gt; 4yr –5yr</td>
<td>24</td>
<td>19.5</td>
<td>19</td>
</tr>
<tr>
<td>&gt; 5yr –6yr</td>
<td>21</td>
<td>17.1</td>
<td>14</td>
</tr>
<tr>
<td>&gt; 6yr –13yr</td>
<td>16</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>123</td>
<td>100</td>
<td>101</td>
</tr>
</tbody>
</table>
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2-The type and the amount of fava beans ingested.

Table (2) : Shows the types of fava beans ingested

<table>
<thead>
<tr>
<th>Types of fava beans</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Raw</td>
<td>82</td>
<td>66.7</td>
<td>65</td>
</tr>
<tr>
<td>Cooked</td>
<td>41</td>
<td>33.3</td>
<td>36</td>
</tr>
</tbody>
</table>

Table (3): Shows the amount of the ingested raw fava beans

<table>
<thead>
<tr>
<th>Amount</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Large</td>
<td>32</td>
<td>39</td>
<td>27</td>
</tr>
<tr>
<td>Small</td>
<td>46</td>
<td>56.1</td>
<td>34</td>
</tr>
<tr>
<td>Unknown</td>
<td>4</td>
<td>4.9</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
<td>100</td>
<td>65</td>
</tr>
</tbody>
</table>

So, 65 out of 101 male patients were having disease due to raw fava beans ingestion, compared to 17 out of 22 female patients.
Z-test between 2 proportions = 2.56 \( \Rightarrow \) P-value = 0.014
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Table (4): Shows the amount of the ingested cooked fava beans

<table>
<thead>
<tr>
<th>Amount</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Large</td>
<td>25</td>
<td>61</td>
<td>21</td>
</tr>
<tr>
<td>Small</td>
<td>11</td>
<td>26.8</td>
<td>11</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>12.2</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>100</td>
<td>36</td>
</tr>
</tbody>
</table>

So, 46 cases (56.1%) from the 82 (66.7) out of 123 cases develop hemolysis after ingestion small amount of raw fava beans compared to 25 (61%) from 41 (33.3) out of 123 who ingest large amount of cooked fava beans
Z-test between 2 proportions = 2.58 \( \rightarrow \) P-value = 0.024


Table (5): Shows the G6PD enzyme

<table>
<thead>
<tr>
<th>G6PD enzyme</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Normal</td>
<td>29</td>
<td>23.6</td>
<td>11</td>
</tr>
<tr>
<td>Deficient</td>
<td>94</td>
<td>76.4</td>
<td>90</td>
</tr>
</tbody>
</table>

The deficiency was screening by decoloration of methylene blue.
So, around 94 (76.4%) of the total cases were having deficient G6PD enzyme; most of them were males 9 (73.4%) compared to 4 out 22 female patient which represent (3.3%).
Z-test between 2 proportions = 2.56 \( \rightarrow \) P-value = 0.02
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4-Treatment: Nearly all patients required blood transfusion, only 4 of them not required Bd.transfusion, since even with higher initial hemoglobin level continuous hemolysis was suspected. Some patient required more than one time of blood transfusion as shown in table 6.

Table (6): Shows the treatment regimen used

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Total</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>%</td>
<td>No. of patients</td>
</tr>
<tr>
<td>Bd transfusion (one time)</td>
<td>102</td>
<td>82.9</td>
<td>83</td>
</tr>
<tr>
<td>Bd transfusion (&gt; one time)</td>
<td>17</td>
<td>13.8</td>
<td>17</td>
</tr>
<tr>
<td>NO Bd.transfusion</td>
<td>4</td>
<td>3.3</td>
<td>1</td>
</tr>
<tr>
<td>I.V.F transfusion</td>
<td>123</td>
<td>100</td>
<td>101</td>
</tr>
</tbody>
</table>

Discussion
The peak age at presentation was between 1-5 years of life. This indicated that the preschool children(2-5 years) including toddlers, are more susceptible to develop the disease if they are enzyme-deficient and is consistent with findings of other studies done by Beutler E (7,8), Mark A Belsy (32) and Ibid S (33). This may be attributed to a decreasing incidence of G6PD deficiency with advancing age (16). Since the disease is sex-linked recessive, males mainly were found to be affected (101 out of 123 cases), with male to female ratio being around 4.5:1. Those 22 female patients affected were explained by Lyon hypothesis, according to which, only one X- chromosome is active in any somatic cell. Deficient cells in heterozygous females are just as susceptible to oxidant injury as enzyme-deficient cells in males; however, the overall magnitude of hemolysis is less because of the smaller population of vulnerable cells (25,36). This also explains the reduced severity of the disease generally in female patients (13.9%) compared to male (69.9%) with Pcv ≤ 20%. Similar results were found by Pai GS (14).

The history of offending drugs which cause hemolysis, as in this study only 5 (4.1%) of the 123, which are akinow cases of favisim previously, 3(2.4%) female and 2(1.7%) male cases had develop hemolysis after drug ingestion without ingestion of fava beans. Males seemed to have a relatively higher sensitivity to raw fava beans than females, since 65 out of 101
males (representing 52.8%) were having the disease following raw fava bean ingestion, whereas 17 out of 22 females (representing 13.8%) were having the disease following raw fava bean ingestion indicating that female required stronger oxidative effect to induce hemolysis. Statistic calculation of Z-test between two proportions (found to be 2.56) and P-value (found to be P=0.014) has shown a significant difference of risk between the two sexes in regard to the exposure to raw fava beans. Here, in this study, a small amount of raw fava beans could induce homolysis, whereas a large amount of cooked fava beans was needed to induce the hemolysis. Presentation following ingestion of raw fava beans was earlier compared to the presentation following the ingestion of cooked ones, and this finding was mainly in male sex. Blister erythrocytes were seen in the blood film of 106 patients (86.2%), fragmented cells in 14 patients (11.4%), and spherocytes in 3 patients (2.4%), mixed appearance of shapes was found in some patients and nearly similar picture was reported by Luzzatto L(13), Yilmaz N.(30).

G6PD enzyme assay was done early in the first day on admission and show early detection of deficient enzyme in 94 cases (76.4%).This consistent with other study done by Mehta A(5).

Finally, all patients recovered well. Recovery in most of them (91.1%), was within the first 3 days, this period is nearly the same as that reported by Hilmi FA.(34) and Ibid S.(33)

Conclusions
1- Children under 5 years of age are affected more than those above this age.

2- Males are affected much more than females in terms of disease presentation.

3- Small amount of raw or undercooked fava beans are relatively more dangerous than large amount of well-cooked ones; though both can cause a significant disease in susceptible people.

4- A significant number of patients with neonatal jaundice may be due the defect responsible for favism, as history of neonatal jaundice is very common among patients with favism.

5- Hemoglobin and blood morphology with hyperbilirubinemia are reliable hematologic indicators of hemolytic process.

6- Renal function is not affected, especially in patients with early presentation followed by early treatment.

7- A significant number of patient show early reduction of G6PD enzyme in the course of disease.

8- Blood transfusion is the most used therapeutic measure, and recovery is expected within 2-3 days.

Recommendations
1. The families can be given instruction about the condition and the offending agents of hemolysis.

2. Detailed printed leaflets about the condition and the offending agents should be available in order to be given to the families.

3. Kits for assessing the level of G6PD should be available all through the year, and specially during the fava season.

4. Blood units should be available in a good supply in all pediatric hospitals, in order that the families will
not suffer a lot in finding compatible blood for their ill children.

References


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Favism
Experience in Al-Elwia Pediatric Teaching Hospital Caused by Ingesting Raw or Cocked Fava-beans

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