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Do favic patients resume fava beans ingestion later in their life, a study for this, and a new hypothesis for favism etiology

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BACKGROUND AND OBJECTIVES: The etiology of favism remains unclear and the fate of favic patients has not previously been studied. Therefore, individuals who had experienced an episode of favism were studied regarding subsequent fava bean ingestion, including the reason for fava bean ingestion after the initial favic attack and any adverse reactions. In addition, a new hypothesis for the etiology of favism is proposed.

PATIENTS AND METHODS: From June 2005 to June 2012, a total of 38 patients with a history of favism were included in this study. Circumstances regarding the initial favic attack were obtained from medical records and patient interviews, and subsequent fava bean ingestion and recurrence of symptoms were investigated.

RESULTS: Three of the 38 patients (7.9%) were female, and 35 (92.1%) were male. The mean age was 27.9 years (14–63 years). The first attack of favism occurred before 10 years of age for 31 patients (81.6%) and in the springtime for 35 patients (92.1%). Thirty-three patients (86.7%) regularly ate fava beans before the attack, and 35 (92.1%) resumed eating fava beans within 1–17 years after the attack without symptoms. Two patients (5.2%) experienced a single recurrence of symptoms. No evidence of hemolysis was found in the four patients checked after fava bean re-ingestion.

CONCLUSIONS: Patients resumed eating fava bean for various reasons, and the recurrence of symptoms was uncommon. An infectious agent such as a virus may play a role in the development of favism.

Favism, which is a severe hemolytic anemia that occurs after ingesting fava bean (FB), has been known since ancient times.1 In the mid-20th century, a link between this disease and glucose-6-phosphate dehydrogenase (G6PD) deficiency was discovered.2 Since then favism has been considered to be simply a manifestation of G6PD deficiency3 rather than a distinct disorder.

Favism occurs most often in children aged 1–5 years who have the Mediterranean type of G6PD deficiency. It is uncommon in adults and those with other types of G6PD deficiency.4–7 Although all patients with favism are G6PD-deficient, not all G6PD-deficient individuals develop hemolysis after eating FB. Even in the same person, favism attacks show a striking variability from one exposure to another.8–10 Furthermore, favism does not recur in most favic patients who later resume eating FB.5,7,11–13 Many favic patients ingest FB for years without any harm before they develop favism.5,13 Although familial aggregation of favism has been reported,5,7,11 another study reports that family members of a favic patient ate the same FB without ill effects, and these individuals were later found to be G6PD-deficient.14

Epidemics of favism occur in the spring and during FB harvest, with only sporadic cases occurring during the rest of the year.4,5,11 It is most common after eating fresh FB, especially raw beans, but can occur after eating frozen or dried FB.4,11 However, there are no reports of favism associated with eating canned FB. Favism has also occurred after inhaling fava pollen, in lactating children a few days after their mothers ate FB, and in neonates whose mothers ate FB a few days before delivery.5,15–17 Clinical symptoms of hemolytic anemia in favism occur 24–48 hours after eating FB and can last up to 5 days.5,8,18 Favism does not always cause severe symptoms; milder or “abortive” forms exist and may be widespread.19 Various causes have been proposed for the pathogenesis of hemolysis in favism, such as toxic substances in the...
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A NEW HYPOTHESIS FOR FAVISM ETIOLOGY

FBs (e.g., vicine and convicine or their active aglycones divicine and isouramil), hereditary factors, and immunological factors. However, the clinical and epidemiological evidence does not appear to be consistent with these explanations. Thus, no convincing hypothesis exists that can explain the erratic hemolytic episodes seen in favism. The pathogenesis of favism appears to be complex, suggesting that factor(s) other than G6PD deficiency are involved. Few authors have raised the possibility that favism could be a distinct disease, and that the hemolysis that occurs in G6PD deficiency may be a severe form of the disease.

To better understand this complex disease, I studied non-pediatric patients with a history of favism, recurrence of symptoms after subsequent exposure to FBs, and the reasons for subsequent FB ingestion if occurred. In addition, I propose a new hypothesis for the pathogenesis of this disease.

PATIENTS AND METHODS

This study was conducted at the Al-Ramadi General Teaching Hospital in Al-Ramadi city, western Iraq from June 2005 to June 2012. Patients with a history of favism were recruited from the outpatient clinic. For patients who agreed to participate, all available records in the Al-Ramadi Pediatric Teaching Hospital and Al-Ramadi General Teaching Hospital were reviewed. The purpose of the study was explained to all participants, their addresses and cell phone numbers were obtained for interviews. All participants were screened for G6PD deficiency by the fluorescent spot test; those with negative test results were excluded from the study. A detailed history was obtained from all patients regarding their favism attack(s), including time of onset, hospital admission, any blood transfusions, consumption of FB before and after the initial attack, recurrence of favism, hemolysis after drug ingestion, and family history. All available records related to the illness or laboratory tests were reviewed. In addition, complete blood counts, including reticulocyte count and blood film, were obtained for all participants at the time of the study. Four male patients, who resumed FB ingestion at a previous date, agreed to have a single blood test after ingesting fresh FB. They contacted me after ingesting FB to arrange the blood test. All these patients were tested during the time of FB harvest and all had ingested a moderate amount of fresh boiled FB. Hemoglobin levels, reticulocyte count, and serum bilirubin levels were checked for these four patients within 2.5–5 days after ingestions.

Simple statistical analysis needed in this paper was performed using SPSS version 14.

RESULTS

A total of 44 patients were recruited for this study, but six were excluded because they were not G6PD-deficient. Of the remaining 38 patients, there were three females (7.9%) and 35 males (92.1%). The mean age was 27.9 years (14–63 years). Hospital records for 21 patients were available at the Al-Ramadi General Teaching Hospital and the Al-Ramadi Pediatric Teaching Hospital. Table 1 summarizes the clinical and demographic data of the participants. Thirty-one patients (81.6%; female, n = 2; male, n = 29) experienced their first favism attack before the age of 10 years (2–9 years), whereas seven (18.4%; female, n = 1; male n = 6) experienced their first favism attack after the age of 10 years (14–61 years). Thirty-five patients (92.1%) developed favism in the spring according to patient history or records. Three patients did not remember when the attack of favism occurred, and no hospital records were available for these patients. All patients or their families reported that favism attacks occurred within 1–6 days of eating fresh cooked or uncooked FB. No patient had an attack after eating frozen, dried, or canned FBs. Three patients (7.9%; female, n = 1; male, n = 2) had a positive family history of favism. Only two patients (5.2%) experienced a second attack. The first was a female patient with a positive family history of favism. Her first attack was mild and occurred in spring when she was 2.5 years old; the second attack was severe and occurred in the spring when she was 6 years old. The second was a male patient with a positive family history; he was a relative of the first patient. His first favism attack was moderately severe and occurred at age of 1.5 years, according to his mother. The second attack was mild and occurred at age of 9 years. None of the patients whose first favism attack occurred when they were older than 10 years experienced another attack after subsequent FB ingestion. Thirty-three patients (86.8%) reported that they were able to eat FB without any problems before the first favism attack occurred, and five patients (13.1%) did not know if they had consumed FBs before the attack.

After the initial favism attack, 35 patients (92.1%) consumed FB within 1–17 years (mean 7.1 ± 3.74 years), including one patient who had a second favism attack. She resumed eating FB within 1 year after the first attack, and resumed eating FB 11 years after the first attack.
after the second attack. As shown in Table 2, the reasons given for eating FB after being warned of recurrence of favism were: (1) accidental ingestion (n = 5, 13.1%) for patients younger than 9 years; (2) suggestion of another person (n = 4, 10.5%); (3) intentional gradual reintroduction of FBs into the diet to test whether hemolysis would develop (n = 11, 28.9%); (4) did not believe long-term avoidance was necessary (n = 7, 18.4%); and (5) forgot about the illness or thought it would subside over time (n = 8, 21%).

Three patients avoided FB after the initial favism attack. Two had experienced their first favism attack as adults, and the third had a second favism attack, and avoided FB after that. No patient had a history of drug-induced hemolysis. At the time of the study, all blood counts were within normal limits, including reticulocyte counts.

No significant changes in blood indices and serum bilirubin were found in any of the four patients tested after FB ingestion (Table 3).

**DISCUSSION**

Although favism has long been known, its pathogenesis is not well understood. Few large studies or reviews of this disease have been published. In this study I evaluated non-pediatric patients with a history of favism, concentrating on subsequent FB consumption, to better understand disease behavior over time. The six patients excluded from the study are all male, none of them had G6PD test before, and admitted to hospital as cases of hemolytic anemia at the time of FB harvest. The diagnosis was clinical one, and mostly there was another cause for this hemolysis.

Consistent with results of previous studies, most of the patients were male (92.1%), which was expected because G6PD deficiency is a sex-linked condition,5,13,22,19 and most experienced their first attack of favism during childhood (81.6% were younger than 10 years).5,13,22 Most of the patients had consumed FBs more than once before favism occurred and had the hemolytic crisis during spring, as reported by other researchers.5,7,9,13–16 None of the patients in this study had a history of drug-induced hemolysis.

Although 35 patients consumed FB after the first favism attack, only two patients experienced another attack. Only a few studies have reported the effects of FB ingestion in individuals who previously experienced an attack of favism. Yahya et al. challenged three favic patients with FB, observing no adverse reactions during the 1-month follow-up.13 Kattamis et al. reported that most patients who have favism at first exposure later ingested beans without untoward effects; a second attack of favism occurred in only 10 of the 120 patients studied.5

These findings cannot be explained by the proposed etiologies for favism. Although favism is considered an inherited disease,12 only three study participants had a positive family history of favism. It is of interest that the
only two patients who experienced a recurrence of favism were related to each other. Toxic substances in FB, a predisposing autosomal gene, or immunological causes do not fully explain the features of favism. None of the suggested causes can explain why hemolysis does not occur each time FB is ingested or why favism occurs primarily in children, in the springtime, and after eating fresh FB. If any of the proposed etiologies were true, then all patients should have a hemolytic crisis every time they ingest FBs.

For that reason, we must look for new mechanisms underlying the onset of favism. In 1993 Yahya et al. suggested that a virus may contribute to the pathogenesis of favism. Moreover, Belsey et al. reported that the temporal distribution of favism cases resembles that of an infectious disease, in which the sudden introduction of an agent into a susceptible population leads to the rapid appearance of cases, followed by a less rapid decline. It is clear that G6PD deficiency is necessary for the severe hemolytic crises seen in favism, but most researchers agree that another factor(s) must be involved. Although both G6PD deficiency and FB consumption are common throughout the world, favism is not common. For example, G6PD deficiency was found in 26.4% of Egyptian males, but the incidence of favism is not high in that country even though imported FBs are mixed with local horse beans and consumed by nearly all Egyptians. Ho et al. suggested that G6PD deficiency enhances the cytopathic effects of viral infection and increases the number of progeny viruses, potentially making G6PD-deficient individuals more susceptible to viral infections. Furthermore, infection is the most common cause of hemolysis in G6PD deficiency.

Table 2. Behavior of cases regarding FB re-ingestion in favic patients.

<table>
<thead>
<tr>
<th>Type of behavior regarding FB re-ingestion</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accidental ingestion</td>
<td>5 (13.1%)</td>
</tr>
<tr>
<td>Re-ingestion by suggestion of someone</td>
<td>4 (10.5%)</td>
</tr>
<tr>
<td>Intentional gradual re-ingestion</td>
<td>11 (28.9%)</td>
</tr>
<tr>
<td>Did not believe in avoidance, or think the avoidance is transient</td>
<td>7 (18.4%)</td>
</tr>
<tr>
<td>Forgot the illness over time or thought that the disease disappeared by time</td>
<td>8 (21%)</td>
</tr>
<tr>
<td>Stick to avoidance of FB</td>
<td>3 (7.9%)</td>
</tr>
</tbody>
</table>

Therefore, I propose a new hypothesis for the pathogenesis or etiology of favism that explains all or most of the points mentioned. My hypothesis is that the cause of hemolytic anemia in favism is an infectious agent, probably a virus. The behavior of favism is similar to that of measles in many ways. Measles is viral infection that occurs primarily in the spring, confers permanent or partial immunity, and occurs most often in children (before the era of vaccination) but only sporadically in adults. It is possible that favism is caused by an infectious agent such as a virus that appears in spring in certain regions of the world, and that this infectious agent is associated in some way with the FB plant. Thus an individual with severe G6PD deficiency (especially Mediterranean type) exposed to this pathogen for the first time may develop severe hemolysis. Individuals who survive become completely or partially immune to this infection in the future. If proven, this infectious etiology of favism and the acquired immunity would explain most of the previously unexplained features of the disease. Favism occurs most often in spring, the time of appearance of the supposed pathogen, and the acquired immunity in childhood makes it a pediatric disease. Previous exposure to FBs in the absence of the hypothetical pathogen explains why favism does not always occur the first time FB are ingested, and the acquired immunity explains why hemolysis does not usually recur if FB are eaten after a favic attack. The sporadic cases in adults could be explained by lack of previous exposure to the hypothetical pathogen. The development of favism after pollen inhalation can also be explained by an infectious etiology. If this proposed etiology is true, then FB does not directly cause hemolysis. In support of this hypothesis, first the ingestion of fresh FB in four patients here does not cause any evidence of hemolysis, and secondly in the years 2008–2011, fresh FB were brought to market in the city of Al-Ramadi in early December, but no favism cases appeared until the following spring. Similar to many reported cases, the illness started with mild constitutional symptoms similar to those of an infection.
FB is an important and inexpensive protein source. However, people from Mediterranean countries, and perhaps other regions of the world, are often afraid to eat FB. Therefore, it is important to understand that recurrence of favism is not common. Additional studies needed to better understand the underlying mechanisms associated with this disease.

CONCLUSIONS

Favism does not typically recur after subsequent FB ingestion. The pathogenesis of favism cannot be explained by G6PD deficiency alone but suggests the involvement of an infectious agent such as a virus.

Acknowledgement

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REFERENCES


Table 3. Hemoglobin level, reticulocyte percentage and serum bilirubin after fresh FB ingestion in four patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (year)</th>
<th>Time of blood test after FB ingestion (days)</th>
<th>Hemoglobin gm/dL</th>
<th>Reticulocyte (%)</th>
<th>Total serum bilirubin mg/dL</th>
<th>Hemoglobin before FB ingestion gm/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>4</td>
<td>12.9</td>
<td>0.8</td>
<td>1.1</td>
<td>13.2</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>2.5</td>
<td>14.9</td>
<td>1.2</td>
<td>1.3</td>
<td>14.3</td>
</tr>
<tr>
<td>3</td>
<td>36</td>
<td>3.5</td>
<td>13.5</td>
<td>1</td>
<td>1.3</td>
<td>13.9</td>
</tr>
<tr>
<td>4</td>
<td>39</td>
<td>4.5</td>
<td>13.9</td>
<td>1.3</td>
<td>0.9</td>
<td>13.3</td>
</tr>
</tbody>
</table>

1Hemoglobin level at an older date ranges between three months and 2 years.