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The high incidence of acute hemolysis due to favism in Ahvaz, Iran-clinical features and laboratory findings

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ABSTRACT

Objective: To collect comprehensive information about the features of favic patients in Ahvaz (Capital of Khouzestan, Iran) and analyze the extent of the differences with their corresponding in other regions. **Methods:** A total of 103 patients with acute hemolysis admitted to pediatric division of Abouzar Hospital located in the city of Ahvaz, Iran during 21st of June 2008 to 20th of June 2009 were analyzed retrospectively. **Results:** 95.14% of the patients had favism while 4.86% of them underwent hemolysis due to other reasons. These patients were male (68.93%) and female children (31.06%) admitted mostly during the spring season. The three main symptoms were urine discoloration, jaundice and vomiting. At the admission time, the main hematologic findings were as follows: G6PD sufficient status (45.63%), G6PD deficient status (54.36%) and hemoglobin concentration: 2.5-11.8 (mean±SD: 6.45±2.12) g/dL. **Conclusions:** In conclusion, Ahvaz was determined as a black zone for favism in which the disease can be considered a life threatening health problem. Moreover, slight differences were observed in the three main symptoms compared with favic patients in other regions.

1. Introduction

Glucose-6-phosphate dehydrogenase (G6PD; EC 1.1.1.49) is an intracellular enzyme that plays a key role in the protection of erythrocytes against oxidative stress[1]. Generally, G6PD deficiency is an X-linked disorder. Reduced concentrations of G6PD render erythrocytes susceptible to hemolysis under oxidative conditions induced by oxidant drugs, infection, or ingestion of fava beans[1, 2].

Favism disease is a potentially life-threatening hemolytic anemia that can result from ingestion of fava beans and broad beans (*Vicia faba*) by persons with G6PD enzyme deficiency[3]. Favism can be produced in the following ways: 1) by eating fresh raw beans; 2) by eating fresh cooked beans; 3) by eating cooked dried beans; 4) by walking through a field planted with *Vicia fava*; e) through mother's milk in breast-fed children[4]. In addition, Henna (A traditional cosmetic agent widely used in Khouzestan) and several drugs could result in hemolytic crisis among G6PD deficient individuals[5,6]. The disease is usually characterized by acute hemolysis, hemoglobinuria, anemia and jaundice[1]. Other symptoms such as pallor, weakness, fever, diarrhea and vomitting may also be present[7].

Favism has been noted since antiquity and has occurred on an epidemic scale, particularly in Mediterranean countries, Middle East, Far East and North Africa[8]. In Middle East, particularly Iran, the provinces of Gilan, Mazandaran (Caspian sea littoral) and Khouzestan (Persian gulf littoral) are the three main places where favism has been reported[8]. In the first two provinces, the seasonal peak was reported to be during May to June. This seasonal prevalence coincidence exactly with the maturation and harvesting of the fava beans[4]. Moreover, fava beans form part of many traditional culinary preparations in Khouzestan where *Vicia fava* cultivation is wide-spread.

In spite of several studies on favism disease among the populations of Gilan, Mazandaran and Tehran (published in local journals); the favic patients in Khouzestan have been almost forgotten. Therefore, in this study, we aimed to prepare comprehensive information about the features of favic patients in Ahvaz (Capital of Khouzestan, Iran) and analyze the extent of the differences with their corresponding in other regions.

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2. Materials and methods

Medical records of all patients admitted to the pediatric division of Abouzar hospital (Teaching children hospital) from 21st of June 2008 to 20th of June 2009, with a diagnosis of acute hemolysis were retrospectively reviewed. Acute massive hemolysis was defined as an abrupt onset of symptomatic anemia, clinical jaundice, gross hemoglobinuria and hematological features of hemolysis[9]. A total of 114 medical records were examined. The studied cases were deducted to 103 cases as 11 medical cases were incomplete and excluded from the study.

The patients were initially examined for three classic features of favism including pallor, hemoglobinuria and jaundice[3]. In addition, other features like diarrhea, vomiting, fever, cold symptoms and weakness were examined as well. The histories of fava ingestion prior to admittance, neonatal hyperbilurubinemia, admittance due to hemolysis, favism in the family and blood-relation of parents were also analyzed. Epidemiological studies were carried out based on gender, age and season.

The following hematological features were extracted from the medical records of patients: hemoglobin, reticulocyte, white blood cell, G6PD activity and number of erythrocyte transfusions. Total and direct bilirubin, transaminases (SGOT and SGPT), blood urea nitrogen and creatinine were also analyzed.

3. Results

The patients were 71 male children (68.93%) with 10-164 (mean±SD: 51.74±36.07) months old and 32 female children (31.06%) with 7-119 (mean±SD: 37.5±21.63) months old. Symptoms in 84 cases were observed within 24-72 h after fava ingestion; however, in 9, 4, 1 and 1 of the cases the symptoms were observed in 4, 5, 6 and 7 days after ingestion of fava beans, respectively.

The highest incidence of favism disease for both males and females was observed in patients aged 12-36 months old (Figure 1). Most of the patients (72.82%) were admitted during the spring (Figure 2). The complaints of patients were urine discoloration 93 (90.29%), jaundice 88 (85.43%), vomiting 59 (57.28%), weakness 51 (49.51%), pallor 43 (41.74%), fever 31 (30.09%) and diarrhea 7 (6.79%). Hemolysis in 98 (95.14%) of the patients were due to the ingestion of fava beans or inhalation of pollen. However, 5 (4.86%) of the hemolysis in patients were due to other reasons. Noteworthy, two of the cases were exclusively breast-fed infants whose mothers had ingested fava beans. Past history of neonatal hyperbilurubinemia and hemolysis due to ingestion of fava beans was observed in 14 (13.59%) and 4 (3.88%) patients respectively. At least one of the relatives in 34 (33%) of the patients had favism disease. The parents of 59 (57.28%) patients were blood-related.

Hematologic findings at admission were as follows: hemoglobin (Hb) concentration: 2.5-11.8 (mean±SD: 6.45±2.12) g/dL, reticulocyte: 0.5-12% (mean±SD: 3.37±2.42), white blood cell (WBC>15000): 53 (51.45%), G6PD sufficient status: 47 (45.63%) and G6PD deficient status: 56 (54.36%). Hemoglobinurea was detected in 48 (46.6%) patients, of which 17 (35%), 6(12.5%) and 15 (31.25%) had one, two and three plus hemoglubinuria, respectively. An interesting finding was the four and over four plus hemoglobinuria found in 7 (14.58%) and 3 (6.25%) patients. Gender-based analysis showed that 34 (70.83%) and 14 (12.5%) of males and females had hemoglobinurea, respectively. The Hb concentration of most patients was 4-5 g/dL (males) and 5-6 g/dL (females) on the admittance date (Figure 3).

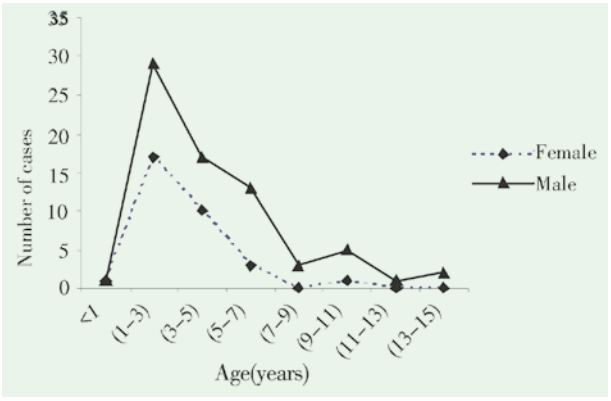

Figure 1. Age and sex distribution of favism patients.

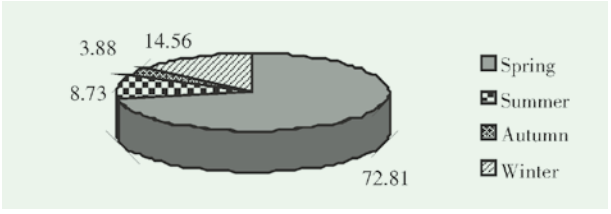

Figure 2. Seasonal incidence of favism disease.

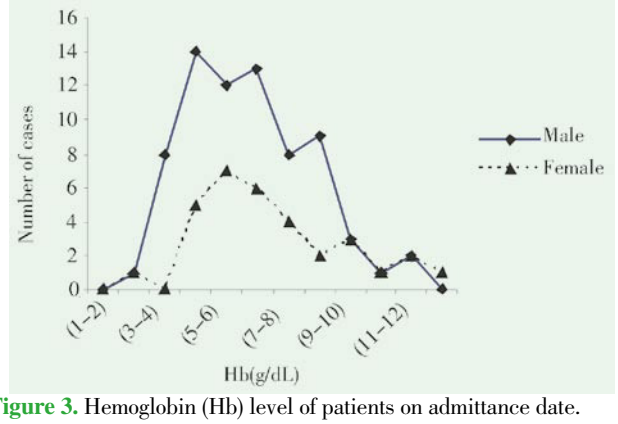

Figure 3. Hemoglobin (Hb) level of patients on admittance date.

Blood (Packed red blood cells) transfusion was given to 99 (96.11%) of all patients, of which 92 (92.94%) underwent 1 or 2 times of erythrocyte transfusion. Gender-based analysis of transfusions showed that all male patients needed transfusion, while only 28(87.5%) of females needed transfusion. Direct and total serum bilirubin levels in this study were (5.79±3.67) mg/dL and (0.69±1.01) mg/dL respectively (Mean±SD). (The bilirubin values for 17 patients were not available). Transaminases (SGOT and SGPT) status was listed in Table 1.

Table 1
Transaminases status of favic patients.

Transaminases	Values		Total casesa
	≥40 N (%)	<40 N (%)	
SGPT	3 (3.33)	87 (96.66)	103
SGOT	65 (72.22)	25 (27.77)	

SGOT: serum glutamic-oxalacetic transaminase, SGPT: serum glutamic-pyruvic transaminase, a: The SGOT and SGPT values for 13 patients were not available.

4. Discussion

G6PD is an intracellular enzyme which protects erythrocytes against oxidative stress. Reduced concentrations of G6PD render erythrocytes susceptible to hemolysis under oxidative conditions induced by oxidant drugs, infection, or ingestion of fava beans. In Ahvaz (Capital of Khouzestan, Iran), favism is becoming a very important health problem.

Throughout the Middle East favism constitutes a major health problem [8]. The high protein content and low price of fava beans render them a valuable element in human diet [4]. In spite of these old reports, favism is still a life threatening disease in Khouzestan and prevention strategies [10] are yet to be applied. Favism has been known to exist in Iran for the past 60 years and the disease has been traditionally linked with the intake of fava beans [4]. The seasonal peak of favism in our study was spring which was in agreement with previous reports [2, 11]. This could be due to the coincidence with harvesting time; in which, many national as well as local fava bean-containing foods are cooked and consumed in Khouzestan. The winter season, however, was the second seasonal peak (14.56%). Noteworthy, in winter, the cases were admitted during the last two weeks of the winter. In climate point of view, the last two weeks of winter in Khouzestan is very similar to the spring season and in some places harvesting time might have started. Dried or freezed fava beans are consumed in Khouzestan as well. Hence, few cases were observed in autumn and summer.

Regardless of gender of our patients, the disease was more frequently found among children aged 12-36 months followed by 36-60 months equal to 1-3 and 3-5 years, respectively. However, in previous studies the age distribution among children with favism was reported within 2-5 years[8, 12]. In the present study favism in males occurred approximately two times more frequently than females. This could be justified considering the X-linked pattern of favism and greater number of hemizygous males than homozygous females[1, 12].

The three main complains of our patients were urine discoloration (93, 90.29%), jaundice (88, 85.43%) and vomiting (59, 57.28%). In our study, however, pallor was replaced by vomiting in the triangle of classic features of favism [3]. In favism, a sudden onset of acute hemolytic anemia within 24-48 hours occurs together with other above-mentioned clinical symptoms[12]. In the present study, these symptoms were observed within 24-72 hours. However, in 9, 4, 1 and 1 of the cases the symptoms were observed in 4, 5, 6 and 7 days after ingestion of fava beans, respectively. This could be due to either different levels of G6PD deficiency of patients or different type of fava beans that had been consumed[4, 13].

Hemolytic onset usually results in sudden fall in Hb concentration even down to 2.5 g/dL[7]. Therefore the favic patients are usually treated with packed cell transfusion up to 20 mL/kg to support the patients with acute hemolysis with Hb concentration of <7 g/dL or $\geqslant 7$ g/dL with continuous hemolysis[3, 7, 14]. Similarly, the peak range of Hb concentration in our study was 4-5 and 5-6 g/dL for males and females, respectively. Erythrocyte transfusion was carried out for 96.11% of the patients. Surprisingly, the need for multiple transfusion was observed in 6 (3 times) and 1 (5 times) of the patients. This could be due to the mismatch of the blood groups of transfused pack cell and patient or G6PD deficiency of red blood cells (RBCs) in the transfused pack cell. As a result the transfused pack cell was undergone hemolysis and the Hb concentration did not reach the desired level[7].

The development of sever hemolytic anemia shortly after ingestion of fava beans raised strong suspicion on the presence of a G6PD deficiency [1]. However, the evaluation of G6PD activity during hemolytic onset is not always reliable as high level of reticulocytes with normal G6PD status might results in false G6PD sufficient status result. Therefore, in our study, the percentage of G6PD deficient patients (54.36%) was not much higher than G6PD sufficient patients (45.63%). Negligible percentage of patients with hemolysis and hyperbilurubinemia in their past history suggested that the majority of our patinet's families were not aware of favism in their children. Therefore, it is of high importance for the families in Ahvaz to be informed about G6PD activity status of their children and get instructed about precautionary measurements.

Although the abnormal function of kidney in patients with favism is rare, it may results in temporary increasing of blood urea nitrogen (BUN) level[15]. In present study, BUN level of 50.48% of the patients was over 20 mg/dL and none of them had serum creatinine over 1 mg/dL.

Hemoglubinoria is very common in favism disease as proteins bound to hemoglobin are saturated and hemoglobin release to plasma and urine[16]. In this study, 46.6% of the patients had hemoglubinuria among which 35% and 31.25% had one plus and three plus hemoglubinuria, respectively. An interesting finding was observing over four plus hemoglobinuria in 3 patients.

In conclusion, Ahvaz showed considerably high prevalence of favism and the features of the patients were determined. The three main complains of the patients with favism disease in our study were urine discoloration, jaundice and vomiting. Favism could be life-threatening in the studied region and it should be reconsidered with higher priority and prevention strategies such as screening of all new borns for G6PD deficiency at delivery and removing of oxidative agents (vicine and covicine) in crops using bacterial as well as fungal hydrolases should be applied.

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