International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Index Copernicus Value (2015): 78.96 | Impact Factor (2015): 6.391

Favism Clinical Experience in Al-Elwia Pediatric Teaching Hospital in Iraq

Muthanna Falah Athab[1], Anwer Sabeeh Al-Zubaidy[2], Hayder H Al-Momen[3]

[1, 2] Ministry of Health, Al-Rusafa Health Directorate, Al-Elwia Pediatric Teaching Hospital

[3]University of Baghdad, Al-Kindy College of Medicine, Department of Pediatrics

Abstract: ***The glucose-6-phosphate dehydrogenase (G6PD) gene is an X-linked disease, and its deficiency is common throughout the world.Acute hemolytic anemia is the main feature, usually during infection, after treatment with certain drugs, and after eating fava beans. A target of studying favism clinically in a sample of Iraqi patients was performed, including (but not limited to) the commonest involved age, gender,and a presumable disease-triggering discrimination between raw and cooked fava beans. All cases with suggestive symptoms and signs of acute hemolysis following exposure to fava beans, were studied retrospectively, resulted in 123 patients enrolled, 101 males and 22 females. The most common age on presentation was between 2-3 years (21.95%), row fava beans were about double than that of cooked ones asthe most popular risk factor even in small amounts (66.7% versus 33.3%). In a conclusion; male toddlers ≤ 5 years` age had the highest chance of hemolysis due to G6PD deficiency, which was induced by fava beans ingestion, only a small amount of raw beans could be enough, while larger deal was required if these fava beans were cooked.***

Keywords: favism, hemolysis, and fava beans (row or cooked)

1. Introduction

Favism is an acute hemolytic anemia, usually affecting persons of Mediterranean area descent, occurring when an individual with glucose-6-phosphate dehydrogenase (G6PD) deficiency within red blood cells swallowed fava beans or inhales the pollen of Viciafaba. [1]

G6PD deficiency is the most common human enzyme deficiency in the world [2,3]. It is considered to be an important disease of hexose monophosphate shunt of a red blood cell(RBC) metabolism. [4]

It is a hereditary sex-linked enzyme deficiency that affects primarily the red blood cell(RBC), older cells were more severely affected than newly formed ones. [5,6]

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], favism is a variety of the first (episodic) syndrome, while the second form (chronic nonspherocytic) is very rare. [2,7]

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]

Most G6PD-deficient persons do not suffer any clinical manifestation from their common genetic trait. [6,11]

Anemia may develop rather suddenly in G6PD-deficient individuals, within a few days of onset of a febrile illness [9,12]. The onset of acute hemolysis results in a precipitous fall in hemoglobin and hematocrit. [4]

Diagnosis of G6PD deficiency is confirmed by a demonstration of decreased enzyme activity through either a quantitative assay or a screening test [13], preferably; testing for the enzyme may be deferred for a few weeks before a diagnostically low level of enzyme can be found. [4]

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]

2. Aim of the Study

To highlight a local Iraqi experience of favism, in link with age, gender, differences between raw and cooked fava beans (if any).

3. Patients and Methods

All cases with suggestive signs and symptoms of acute hemolysis as rapidly progressing pallor, dark urine, fever, and vomiting following exposure to fava beans were studied retrospectively in AL-Elwia Pediatric Teaching Hospital in Baghdad, Iraq, during the period from 1st of February 2016 till end of May 2016.

Children within an age range of 1- 13 years old were included.A full medical history was taken with help of caregivers by the attending pediatrician, which included type of ingested material (fava beans (raw or cooked) or any other precipitating factor), amount of ingested fava beans, color of urine, and means by which fava beans were obtained, either by ingestion, contact and/or smell. Only patients whom succeeded to establish a link with fava beans were recruited.

All patients had a deficient G6PD (glucose 6 phosphate dehydrogenase) enzyme assay-screening test according to hospital laboratory readings on admission.

We considered an ingestion of more than one piece of beans as a (large amount), while if only one piece had been eaten or even just had been tasted, it was referred to as a (small amount), but if the child and/ or his/ her family had failed to identify the amount; we assumed it as an (unknown amount).

Patients with any missed needed information in their medical records were excluded from the study.Statistical analysis was accomplished through software package of statistical analysis (SPSS) version 22, all tests were utilized as needed including Z- test, $p \leq 0.05$ was stated to be significant.

4. Results

By applying our specific criteria (mentioned in above section), 123 patients were involved out of 283 children who visited the setting for management, 101(82.1%) were males, and 22 (17.9%) were females.

The peak age of incidence was between 1-5 years of age, and the highest age is 2yr-3yr.

Boys were more affected than girls in terms of presentation with male : female ratio of 4.5:1**,** as shown in table (1).

Table 1: Age and sex distribution

Age	Total		Male		Female	
	No. of patients	%	No. of patients	%	No. of patients	%
12mo –2yr	17	13.8	16	13	1	0.1
> 2yr – 3yr	27	21.95	22	17.9	5	4
> 3yr – 4yr	18	14.6	18	14.6	0	0
> 4yr – 5yr	24	19.5	19	15.4	5	4
> 5yr – 6yr	21	17.1	14	11.4	7	5.7
> 6yr – 13yr	16	13	12	9.8	4	3.3
Total	123	100	101	82.1	22	17.9

Most of patients, precisely 77 cases (62.6%) of the total, had non-consanguineous marriages of their parents, with 63 males (51.2%) and 14 females (11.4 %).Negative family history of G6PD deficiency was found in more than half of cases precisely in 70 cases (56.9%); males included were 62 (50.4%), whiles we had 8 females (6.5%); as shown in table (2).

Table 2: Favism within the same family

Family history of G6PD deficiency	Total		Male		Female	
	No. of patients	%	No. of patients	%	No. of patients	%
Negative	70	56.9	62	50.4	8	6.5
Positive	53	43.1	39	31.7	14	11.4

According to history of drug ingestion, only 5 cases (4.1%) out of the total (whom had known to have had Favisim previously) had history of drug intake without fava beans ingestion. The drugs were nalidixic acid and co-trimoxazole, four of them took co-trimoxazle and only one patient took nalidixic acid. Females were counted in 3 cases (2.4%) while males were only two (1.6%).Recurrent attacks were fortunately uncommon and were represented only in 16 patients (13%); 12 males (9.8%) and 4 females (4%), as illustrated in table (3).

Type and amount of fava beans were studied in relation to time elapsed before symptoms onset, and shown in tables (4-8). Raw fava beans were about double than that of cooked ones, as written in table (4).

Table 3: Frequency of recurrence of hemolysis

Variable	Total		Male		Female	
	No. of patients	%	No. of patients	%	No. of patients	%
1st attack	107	87	89	72.4	18	14.6
Recurrence	16	13	12	9.8	4	3.3

Table 4: Types of fava beans ingested

Types of fava beans	Total		Male		Female	
	No. of patients	%	No. of patients	%	No. of patients	%
Raw	82	66.7	65	52.8	17	13.8
Cooked	41	33.3	36	29.3	5	4.1

Talking about the amount of raw fava beans ingested; we found that what was considered as a (small amount) of ingested favas had been the most popular risk factor occurred in 46 patients (56.1%) with 34 males (41.5%) and 12 females (12%). Please check table (5).

Accordingly; 65 out of 101 male patients representing 64.4% had the disease due to a raw fava beans ingestion, compared to 17 (77.3%) out of 22 female patients.
Z-test between 2 proportions = 2.56 → P-value = 0.014, which was significant from statistical point of view.

Table 5: Amount of the ingested raw fava beans

Amount	Total		Male		Female	
	No. of patients	%	No. of patients	%	No. of patients	%
Large	32	39	27	32.9	5	6.1
Small	46	56.1	34	41.5	12	14.6
Unknown	4	4.9	4	4.9	0	0
Total	82	100	65	79.3	17	20.7

In table (6), whatever the amount of ingestion of raw favas was, symptoms started most commonly after one or two days, we had 22 patients (68.7%) between 24-48 hours; 18 (56.3%) of them were males and 4 (12.5%) were females; all these results were about (large amount) of fava beans ingested, but if we take a look over data of the (small amount), we found 26 (56.5%) patients; males` number was 17 (37%), while females were 9 (19.5%). And if we talk about the (unknown amount), we got only 4 males; so; 100% of their group.

Table 6: Time interval between the ingestion of raw fava beans and the onset of symptoms

Time of onset	Large amount						Small amount						Unknown amount					
	Total patient		Male		Female		Total		Male		Female		Total		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 24 hr	8	25	7	21.9	1	3.1	12	26.1	10	21.6	2	4.3	0	0	0	0	0	0
24-48 hr	22	68.7	18	56.3	4	12.5	26	56.5	17	37	9	19.6	4	100	4	100	0	0
49-72 hr	2	6.3	2	6.3	0	0	5	10.9	4	8.6	1	2.2	0	0	0	0	0	0
> 72 hr	0	0	0	0	0	0	3	6.5	3	6.4	0	0	0	0	0	0	0	0
Total	32	100	27	84.5	5	15.5	46	100	34	73.6	12	26.4	4	100	4	100	0	0

In case of cooked fava beans, the story was somewhat different.The ingestion of (large amount) had been the most popular cause with a total number of 25 (61%); 21 (51.2%) males and 3 (7.3%) females. That is clearly shown in table (7).

Table 7: Amount of the ingested cooked fava beans

Amount	Total		Male		Female	
	No. of patients	%	No. of patients	%	No. of patients	%
Large	25	61	21	51.2	3	7.3
Small	11	26.8	11	26.8	1	2.4
Unknown	5	12.2	4	9.8	1	2.4
Total	41	100	36	87.8	5	12.1

Table (8) confirmed that the most common time interval between the ingestion of cooked fava beans and the onset of symptoms was 24-48 hours, just like the raw favas cases.

Based on tables (6 and 8); 46 cases (56.1%) out of 82(66.7%) out of a total 123 cases developed hemolysis after an ingestion (small amount) of raw fava beans compared to 25 (61%) out of 41 (33.3%) out of the total 123 who ingested (large amount) of cooked fava beans.

Z-test between 2 proportions = 2.58 → P-value = 0.024, which touched a level of statistical significance.

Table 8: Time interval between the ingestion of cooked fava beans and the onset of symptoms

Time of onset	Large amount						Small amount						Unknown amount					
	Total patient		Male		Female		Total		Male		Female		Total		Male		Female	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 24 hr	6	24	4	16	2	8	3	27.3	3	27.3	0	0	1	20	1	20	0	0
24-48 hr	15	60	14	56	1	4	7	63.6	5	45.4	1	9.1	4	80	4	80	0	0
49-72 hr	3	12	3	12	0	0	1	9.1	1	9.1	0	0	0	0	0	0	0	0
> 72 hr	1	4	1	4	0	0	0	0	0	0	1	9.1	0	0	0	0	0	0
Total	25	100	22	88	3	12	11	100	9	81.8	1	18.2	5	100	5	100	0	0

5. Discussion

The peak age at presentation was between 1-5 years of life. This gave us a clue that preschool children (2-5 years) including toddlers, were more susceptible to develop the disease if they were enzyme-deficient, it was consistent with finding of other studies done by Beutler E[7], Mark A Belsy[14], and Ibid S[13]. This might be attributed to a decreasing incidence of G6PD deficiency with advancing age. [15]

Since the disease is sex-linked recessive, males were mainly 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; thus; any given red cell in heterozygous females was either normal or deficient. Mean enzyme activity in females who were heterozygous for G6PD deficiency might be either normal, moderately reduced (usual), or grossly deficient, depending on the degree of lionization. [16,17]

Deficient cells in heterozygous females were susceptible to oxidant injury precisely in the same way as enzyme-deficient cells in males; however; the overall hemolysis amplitude was less because of smaller number of vulnerable cells. [18,19]

This also justified the reduced severity of the disease generally in female patients (13.9%) compared to males (69.9%) with packed cell volume PCV ≤ 20%. Similar results were found by Pai GS [20], and Sawsan S. Abbas. [21]

Most of our patients, namely 77 (62.6%), had non-consanguineous married parents; 63 (51.2%) were male patients and 14 (11.4%) were females; this agreed with the general idea that the disease was purely X-linked and no autosomal element was there, which was consistent with most available studies about the disease like those of Luzzatto L[2],Beutler E [8], and Remez Ethnasios [11]. On the other hand, some researchers suggested an additional need for a single-probably autosomal-gene to create the susceptibility to favism in G6PD-deficient persons. [10,22]

Although a positive family history could be helpful in the identification of favism [2], a negative family history for the same condition in a single family was noted more than the positive one (56.9% versus 43.1%, respectively) in the overall cases collected, a finding that might indicate involvement of other unknown factors. [23]

Regarding history of offending drugs causing hemolysis within this study, we had only 5 (4.1%) patients out of the total 123, which were known cases of favism, 3 (2.4%)

females, and 2 (1.7%) male cases, so they had developed hemolysis after drugs ingestion without the addition of fava beans, those drugs were nalidixic acid and co-trimoxazole. This a relatively low proportion showed that drug-induced hemolysis was not as significant as favism, as said by Beutler E [8], and Derek J King. [22]

Recurrent attacks, luckily, were uncommon (13%), a phenomenon that reflected awareness by most of our families, in line with other workers such as Hassan MK [17], and Sawsan S.Abbas. [23]

Males seemed to have a higher sensitivity to raw fava beansthan females, since 65 out of 101 males (representing 52.8%) had the disease after raw fava beans ingestion, whereas 17 out of 22 females (representing 13.8%) got the disease following raw fava beans ingestion, indicating that females required stronger oxidative effect to induce hemolysis. Statistic calculation of Z-test between two proportions was found to be (2.56), and p-value was (0.014), resulted in a significant difference of risk between the two sexes in regard to the exposure to raw fava beans, that was exactly analogous to what had been found by Ainoon O and colleagues. [24]

Herein this study, a small amount of raw fava beans could induce hemolysis, whereas a large amount of cooked fava beans was needed to start hemolysis. Also; a clinical presentation following ingestion of raw fava beans was earlier matched to that following ingestion of cooked ones, and these findings were mainly in male sex. Other studies like those of Sawsan S. Abbas[21], Ainoon O etal. [24], and Gaskin RS etal. [25],had the same opinion.

6. Conclusion

Male children under 5 years of age were affected more than others, a small amount of raw or undercooked fava beans were relatively more dangerous than a large amount of well-cooked beans; though both can cause a significant disease in susceptible people.

References

[1] Sybil Parker, Editor, McGraw Hill Dictionary of Scientific and Technical Terms, 4th ed., USA. McGraw Hill, 2001: 751.
[2] Luzzatto L, Glucose-6-phosphate dehydrogenase deficiency. In: Scriver C R, et al., Editors: The Metabolic and Molecular bases of inherited disease, 7th ed. n.p. McGraw Hill, 2000: 3367-98.
[3] George B Segel. Enzymatic defects. In: Behrman R.E., Kliegman R.M., Jenson H.B., Editors: Nelson Textbook of Pediatrics, 17th ed., Philadelphia, 2004, WB Saunders, 455: 1636-38.
[4] Beutler E. G6PD historical perspective and current status; In:Weatherall DJ, et al., Editors: Advances of red blood cell biology, New York: Raven Press; 1999: 297-308.
[5] Mehta A, Mason PJ, Vulliamy TJ. Glucose-6-phosphate dehydrogenase deficiency. Baillieres Best Pract Res ClinHaematol 2000; 13: 21-38.
[6] Tanphaichitr VS, Glucose-6-phosphate dehydrogenase deficiency in the newborn: its prevalence and relation to neonatal jaundice. Southeast Asian J. Trop Med Public Health 1, 2002: 137-41.
[7] Beutler E Red cell enzyme defects. Hematologic Pathology 1999; 4: 103-14.
[8] Beutler E. The molecular biology of G6PD variants and other red cell enzyme defects. Ann Rev Med 2004; 43: 47-59.
[9] Chen E Y,"Sequence of human glucose-6-phosphate dehydrogenase cloned in plasmids and a yeast artificial chromosome" Genomics 10, 1998: 792.
[10] King, Robert C, and William Stansfield, A Dictionary of Genetics: Oxford University Press 1997.
[11] RamezEthnasios, G6PD site; ethnasios@yahoo.com Updated and published by AssociazoneItalianaFavismo-Deficit di G6PD (ONLUS); http://www.favism.org, last access in May 2017.
[12] Peter A Lane, Hematological Disorders, congenital hemolytic anemia. In: William W Hay Jr, et al., editors; Current Pediatric Diagnosis and Treatment, 14th ed., 2006; 25:743.
[13] Ibid S, "Favism: Clinical and Biochemical Data" J. Med. Gen. 6 (2000); 34-35.
[14] Mark A Belsy. "The Epidemiology of Favism", Bull. World Health Org. 48 (2003), 4.
[15] Beutler E, Vulliamy T, Luzzatto L, Hematologically important mutations: glucose-6-phosphate dehydrogenase. Blood cells Mol Dis, 2004; 22: 49-56.
[16] Hilmi FA, Al-Allawi NA, Rassam M, Al-Shamma G, Al-Hashimi A. Red cell glucose-6- phosphate dehydrogenase phenotypes in Iraq. East- Mediterranean Health -2002; 8(1): 20-24.
[17] Hassan MK, Taha J.Y., L.M. AL-Nasama, N.M Widad and S.N. Jasim, et al. Frequency of haemoglobinopathies and glucose-6- phosphate dehydrogenase deficiency in Basrah. Eastern Mediterranean Health.J. 2003; 9(1/2):28.
[18] Nelson DA, Davery FR. Erythrocytic disorders. In: Henry JB, editor, Clinical Diagnosis and Management by Laboratory Methods, Philadelphia: WB Saunders Co.,2007: 660-62.
[19] Sahar K Omar. "Clinical profile of children with favism". Annals of the College of Medicine, Mosul1998; 24 (1,2)27-31.
[20] Pai GS, "Localization of loci for hypoxanthinphosphoriboxyltransferase and glucose-6-phosphate dehydrogenase and biochemical evidence of non-random X-chromosome expression from studies of a human X-autosome translocation" Proc,Natl,Acad, Sci. 77, 2002: 2810.
[21] Sawsan S. Abbas, "G6PD deficiency in a group of Iraqi children". J. Fac. Med. Vol. 47, no.1, 2003: 9-11.
[22] Derek J King. Red cell enzyme defects. In AGM Campbell, Neil McIntosh, ForfarArneil's Textbook of Pediatrics, 5th ed. 1999; 15: 858-59.
[23] Sawsan S. Abbas, "G6PD screening in the newborn babies". J. Fac. Med. Vol. 45, no.3-4, 2003: 203-206.
[24] Ainoon O, Alawiyah A, Yu YH, Cheong SK, Hamidah NH. Semi quantitative screening test for G6PD deficiency detects severe deficiency but misses a substantial proportion of partially-deficient females.

Southeast Asian J Trop Med Public Health 2003;34:405-414

[25] Gaskin RS, Estwick D, Peddi R. G6PD deficiency: its role in the high prevalence of hypertension and diabetes mellitus. Ethn Dis. 2001; 11: 749-59.