

Hemolysis Induced by Glucose-6-Phosphate Dehydrogenase Deficiency and Its Association with Sex in Children

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Abstract

Background: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme disorder in human. The aim of this study was to determine the prevalence of G6PD deficiency among children and evaluate its association with ABO/Rh blood groups.

Method: Blood samples of 3401 asymptomatic children were analyzed and compared with 317 children who were admitted to hospital because of hemolysis resulted from G6PD deficiency.

Results: Among asymptomatic children 375 (11%) were G6PD deficient. Male to female ratio for this group was 4.2:1 and for the hemolytic group was 2.5:1 ($P=0.004$). Two hundred and sixty-seven (84.2%) of the patients with hemolysis were younger than 2 years, with the peak age of hemolysis between 2 and 3 years (27.7%). The overall rate of hemolysis caused by G6PD deficiency was 12.3% during the 3 consecutive months of fresh Fava bean consumption. Blood groups O⁺, A⁺, and B⁺ together constituted 87.1%, 87.7%, and 84% of the blood groups among normal children, asymptomatic G6PD deficient subjects, and those with G6PD deficiency related hemolysis respectively ($P=0.367$). Seven percent of the normal children and asymptomatic G6PD deficient subjects were Rh⁻ vs 9.7 % of G6PD deficient children with hemolysis ($P=0.16$).

Conclusion: The prevalence of G6PD deficiency among the children was 11%. Male to female ratio was greater in non-hemolytic vs hemolytic group so that the female share was higher in hemolytic group than in the other two groups ($P=0.004$).

The distribution of ABO blood groups was similar among asymptomatic non-G6PD deficient, asymptomatic G6PD-deficient, and G6PD-deficient children with hemolysis. The distribution of Rh⁻ types among the G6PD-deficient children with hemolysis and the other two groups was similar (9.7% vs 7%, $P=0.16$).

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Keywords • Glucose-6-phosphate dehydrogenase • enzyme
• RBC

Introduction



Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzyme disorder in human affecting more than 400 million people worldwide.^{1,2}

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G6PD is a highly polymorphic enzyme encoded by a human X-linked gene (Xq2.8). This enzyme catalyses the first step of pentose phosphate pathway, which converts glucose 6-phosphate to 6-phosphogluconate with production of NADPH₂. The deficient cell is vulnerable to oxidative injury to membrane and cytoplasmic proteins.^{3,4} The main clinical manifestations of G6PD deficiency are acute hemolytic anemia and jaundice, triggered by infection or ingestion of Fava beans or oxidative drugs. A variant of G6PD, named Mediterranean, is the most frequent allele found among patients in Southern Iran.¹ And is often associated with favism.

The relationship between G6PD deficiency and ABO/Rh blood group is still controversial.^{5,6} The aim of the present study was to review the epidemiologic aspects of G6PD deficiency (with or without hemolysis) among asymptomatic outpatient and inpatient children with Favism in Southern Iran and to find an association with ABO, or Rh blood groups.

Patients and Methods

During a 9-year period (1994-2003), tests for ABO blood groups, Rh typing, and G6PD activity were conducted on 3401 children in Shiraz (south of Iran). All the children were Muslim and selected randomly among the visitors of the first author's (E.S) outpatient clinic. The included children were asymptomatic children aged 1-14 years referring for routine checkup, with no history of hemolysis, and with normal blood count and peripheral smear. Informed consents were obtained from the parents. Blood samples were drawn in the early morning with EDTA anticoagulant. G6PD activity assay was performed in a clinical laboratory affiliated to Shiraz University of Medical Sciences, using dye reducing (Brilliant cresyl blue) test and carried out on 0.1 ml of hemolysed blood.⁷ Blood group and Rh typing were also performed on the samples at the same time.

In addition, we reviewed hospital records of 317 G6PD deficient patients with hemolysis, among a total of 2567 patients, who admitted to the Pediatric Emergency Department of Nemazee hospital affiliated to the same University during the season of heavy Fava bean consumption (April, May, and June) in years

1996 to 1998. Blood group and Rh were found in records of 226 of these patients.

Data were analyzed by Chi-square test using SPSS software (version 12.0) for the PC, (SPSS Japan Inc, Tokyo). A P value of less than 0.05 was considered statistically significant.

Results

Of the 3401 children visited in outpatient clinic, 375 (11%) were G6PD deficient. There were 304 (81%) male and 71 (19%) female patients with the male to female ratio of 4.2:1.

There were 317 (12.3%) G6PD deficient children with hemolysis among 2567 children admitted to the Emergency Department in the three months of fresh Fava bean consumption period. Of them, 228 (72%) were male and 89 (28%) were female patients, with male to female ratio of 2.5 to 1. There were more females in this group compared with the G6PD deficient children in the outpatient group (P=0.004). The monthly distribution of G6PD deficiency related hemolysis in fava bean consumption season is shown in table 1 and figure 1.

Figure 2 depicts the age distribution of the patients with hemolysis. Most (84.2%) of the patients admitted to the Emergency Department with G6PD deficiency related hemolysis, were younger than five years old. The peak age of hemolysis was between 2 and 3 years (27.7%).

G6PD deficiency related hemolysis began with a sharp increase in April, gradually decreased in May and declined to the lowest point in late June, as the fresh Fava bean consumption period ended. No case of G6PD deficiency related hemolysis caused by Fava bean consumption was reported during the remaining 9 months of the years. Although the frequency of hemolysis almost doubled for the corresponding months of 1997 compared with 1996, the rate of decline was similar for the corresponding months of the consecutive years.

The results of blood groups and Rh typing performed on asymptomatic children and those with G6PD deficiency related hemolysis are shown in table 2. The patients with partially deficient G6PD are not included in the table 2. Blood groups of O⁺, A⁺, and B⁺ together constituted 87.1%, 87.7%, and 84% of the blood groups among normal children, asymptomatic G6PD

Table 1: Distribution of G6PD deficiency related hemolysis in months and years of Fava bean consumption*

	April	May	June	Overall
1996	50/292 (17%)	29/307 (9.4%)	3/170 (1.7%)	82/769 (10.6%)
1997	69/218 (31.6%)	65/378 (17.1%)	14/401 (3.4%)	148/997 (14.8%)
1998	49/256 (19.1%)	33/308 (10.7%)	5/237 (2.1%)	87/801 (10.8%)
Total	168/766 (21.9%)	127/993 (12.7%)	22/808 (2.7%)	317/2567 (12.3%)

*Hemolysis/Total patients.

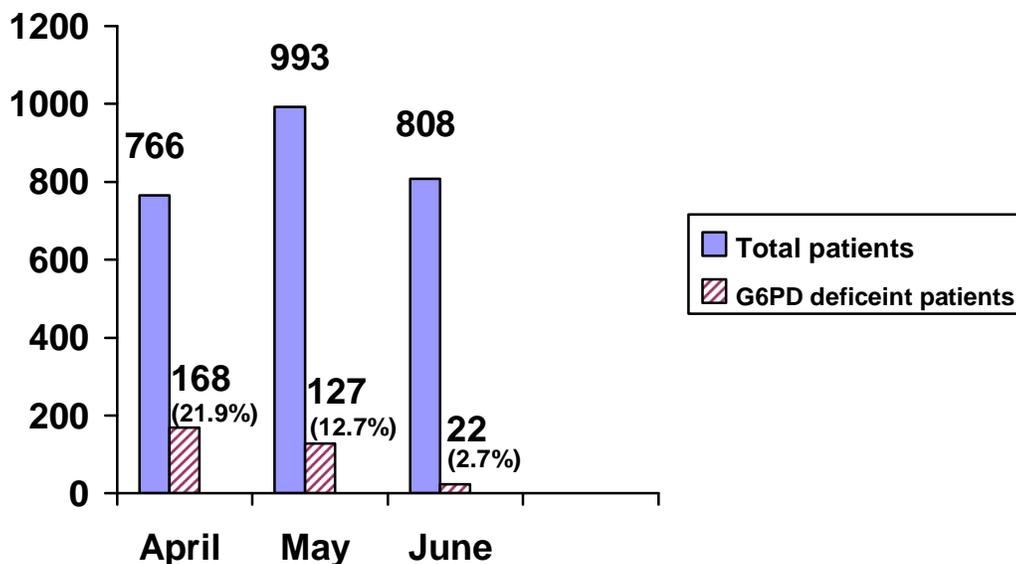


Figure 1: Cumulative monthly distribution of G6PD deficient patients in three consecutive years (1996-98).

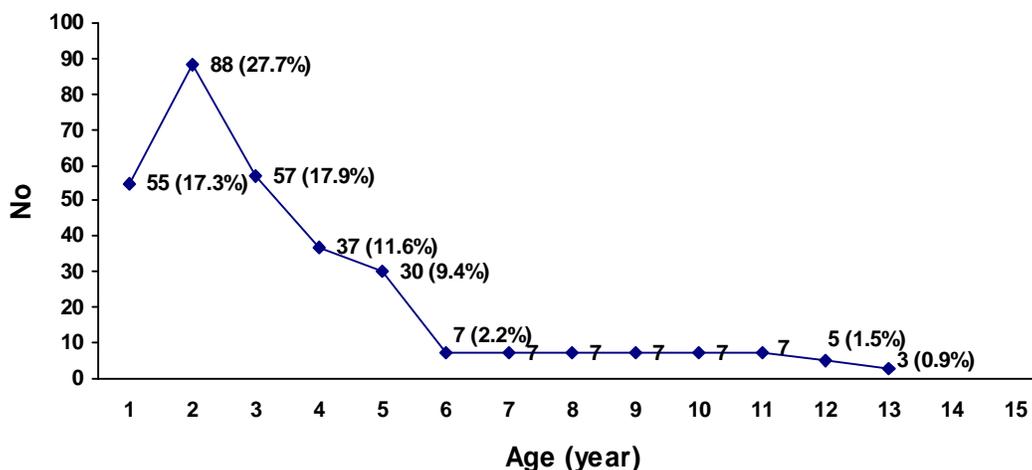


Figure 2: Age distribution of children referred to Emergency Department with G6PD deficiency related hemolysis.

Table 2: The distribution of blood groups and Rh factor among normal children, G6PD-deficient asymptomatic children and patients with G6PD deficiency related hemolysis admitted to Nemazee Hospital

	O ⁺	A ⁺	B ⁺	AB ⁺	O ⁻	A ⁻	B ⁻	AB ⁻
Normal children No = 3026	1135 (37.5%) Rh ⁺ = 2808 (92.8%)	789 (26%)	715 (23.6%)	169 (5.5%)	79 (2.6%)	65 (2.1%)	61 (2.0%)	13 (0.4%)
Asymptomatic G6PD Deficient No = 375	150 (40.0%) Rh ⁺ = 348 (92.8%)	95 (25.3%)	84 (22.4%)	19 (5%)	15 (4%)	3 (0.8%)	8 (2.1%)	1 (0.27%)
G6PD Deficient With hemolysis No = 226	86 (38%) Rh ⁺ = 204 (90.2%)	59 (26.1%)	45 (20%)	14 (6.1%)	14 (6.1%)	3 (1.3%)	4 (1.7%)	1 (0.4%)

deficient children, and those with G6PD deficiency related hemolysis, respectively (P=0.367).

The O⁺ type was the most prevalent blood group among all the study participants, ranging

from 37.5-40%, followed by A⁺ type (25-26%), B⁺ type (20-23.6%), and AB⁺ type (5-6%). In addition, 7% of the normal and asymptomatic G6PD deficient children were Rh⁻ (P=0.16). There were

more Rh⁻ types among the G6PD deficient patients who developed hemolysis compared with the other two groups but this difference was not statistically significant (9.7% vs 7%; P=0.16).

Discussion

G6PD deficiency is the most common metabolic disorder of red blood cells, involving more than 400 million people worldwide.² It is more prevalent in the tropical and subtropical areas of the Eastern hemisphere (where, as high as 35% of the population may be affected).⁹ The prevalence of G6PD deficiency may vary in different parts of the world. Frischner and colleagues in 1973 found a prevalence of 10.6% in African-Americans, 9.8% in Iranians, 4.1% in South Vietnamese, and 0.5% in Ethiopians.⁸ Other studies revealed the frequency of G6PD deficiency, 4.3-6% in different population groups of Assam,⁹ 5.2% in Greece,¹⁰ 0.3% in northern and 2.2% in southern Italy,¹¹ 8% in Somalis,¹² and 11.4% in male and 2.5% in female African-American infants.¹³ The frequency of G6PD deficiency may vary among different ethnic groups of a population as well. Study by Hedayat and co-workers in Iran,¹⁴ showed the prevalence of G6PD deficiency to be 9.94% for Moslems, 15.23% for Jews, and 13.39% for Armenians. Frequencies of G6PD deficiency has been reported to be higher in Kurdish Jews than those in any other ethnic population.¹⁵

The present study showed that the overall prevalence of G6PD deficiency among the Moslem children of Shiraz is 11% and remained unchanged when it was monitored repeatedly during a course of 9-year study period. This figure is close to the prevalence rate achieved by some other studies in Southern Iran.^{8,16}

Two recent studies in Iran showed that the frequencies of G6PD Mediterranean were 84.6% in Fars province (southern Iran) and 66.2% in Mazandaran province (northern Iran).^{1,17} The molecular characterization of G6PD deficiency in Fars province of Iran is similar to the finding in United Arab Emirates,¹⁸ and Southeast Asia.¹⁹

The male to female ratio, although may differ in various regions and ethnic groups,^{14,16} remained unchanged during the course of our study. This ratio for the patients with Favism (hemolytic group) was 2.5:1. The female share was higher in hemolytic group than in asymptomatic G6PD-deficient group, with a significant statistical difference (P=0.004). It might be resulted from the fact that females have to inherit two X genes to present with G6PD

manifestations. However, *acquisition* of two defective genes may result in more severe clinical manifestations.

Most of our patients admitted to Emergency Department with G6PD deficiency related hemolysis, were younger than five years old. The peak hemolysis occurrence age was between the ages of 2 and 3 years. Study by Hedayat and colleagues in the Caspian littoral area (north of Iran) also showed the peak of Favism occurrence at the age of 2-3 years.²⁰ Therefore, among our patients, those at pre-school age (2-5 years) seemed to be the most vulnerable for G6PD related hemolysis.

The distribution of ABO and Rh blood groups was quite similar among asymptomatic G6PD-deficient and non-G6PD-deficient children. The same result was also reported by Lesho.⁵ However, in contrary to Tzoneva and colleagues,⁶ we found Rh⁻ more frequently among patients with hemolysis than asymptomatic or non-G6PD-deficient children; although the difference was not significant (P=0.16).

It might be concluded that G6PD deficiency-related hemolysis could relatively be more common among the female patients. Further studies in the endemic areas are recommended to find the possible causes.

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Conflict of Interest: None declared

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