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Original Article

Investigating the Prevalence of Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency among Patients with Favism Symptoms in Kerman City, Southern Iran

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A B S T R A C T

Background and Aims: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is humans' most common erythrocyte enzyme defect. About 400 million people are estimated to be affected by this disorder worldwide. Antimalarial drugs, especially primaquine, and other oxidative stress, can cause hemolytic complications in G6PD deficient individuals. This study aimed to evaluate the prevalence of G6PD deficiency in Kerman City in southern Iran.

Materials and Methods: This descriptive cross-sectional study was conducted from 2016 to 2021. Blood samples were taken from all patients with symptoms of G6PD deficiency who were referred to a general hospital in Kerman City in southern Iran. The G6PD enzyme activity was measured qualitatively by fluorescent spot test.

Results: A total of 6369 patients were included in this study. G6PD deficiency was seen in 424 (6.7%) subjects. Of 424 patients, 359 (84.7%) were severely G6PD deficient, and 65 (15.3%) patients exhibited partial deficiency. G6PD deficiency was seen in 324 (9.3%) males and 100 (3.4%) females ($p < 0.001$).

Conclusion: The results of our study confirmed the existence of G6PD deficiency in a significant percentage of patients in Kerman City. Therefore, many people in this city are exposed to hemolytic complications if they use antimalarial drugs and other oxidative substances. According to our results, testing G6PD deficiency and monitoring the potential primaquine toxicity in patients who receive primaquine are highly recommended.

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Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is a housekeeping enzyme expressed in all body cells [1]. This key enzyme catalyzes the first reaction in the pentose phosphate pathway, converting glucose to ribose-5- phosphate and protecting all cells, especially red blood cells, against oxidative stress in the form of reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) [2]. The gene encoding this enzyme is present on the X chromosome, consisting of 13 exons and 12 introns and encoding 515 amino acids [3]. G6PD deficiency (favism disease) is one of the most common hemolytic disorders, especially in men, affecting around 10% of the world population [2]. The prevalence of G6PD deficiency can vary considerably between different geographic locations and ethnicity and is more common in Asians, Africans, and Mediterranean people [4]. Despite the high prevalence of this disorder, most people are asymptomatic, and symptoms may appear in cases such as internal and external oxidative stresses, microbial agents, diabetic acidosis, and the consumption of certain foods and drugs [5]. These symptoms include acute hemolytic anemia, neonatal jaundice, and congenital non-spherocytic hemolytic anemia, and the onset and severity of these symptoms can vary depending on the amount of stress and the amount of enzyme activity [5-7]. Among these symptoms, neonatal jaundice has been reported more in Asian and Mediterranean patients [4]. There are various methods for diagnosing G6PD enzyme deficiency: the Heinz body test, brilliant crystal blue, hemoglobin reduction, dichlorophenol indophenol, phenazine methosulfate screening, and spot fluorescence [7]. Although G6PD deficiency is present worldwide, many studies have focused on malaria-endemic areas due to the correlation between malaria and the prevalence of G6PD deficiency [1,4]. The prevalence of deficiency of this vital enzyme plays a crucial role in the choice of antimalarial drugs. Primaquine is one of the most important antimalarial drugs widely used in malaria-endemic regions to treat and prevent malaria [8]. However, primaquine can cause mild to severe hemolytic anemia in people with G6PD deficiency through oxidative stresses. This disorder in people with *Plasmodium vivax* is more than in other species of *Plasmodium* due to receiving higher doses of primaquine [1]. Numerous studies have investigated the prevalence of G6PD deficiency in Iran and other countries [9-11]. The city of Kerman in southern Iran is one of the areas of particular importance in malaria, especially *Plasmodium vivax* [12]. However, a lack of knowledge about the prevalence of this enzyme deficiency can increase the risk of hemolytic anemia and its complications in patients with malaria. This study investigated the prevalence of G6PD deficiency in patients with clinically suspicious favism in Kerman.

Materials and Methods

In this descriptive cross-sectional study, patients with favism symptoms like paleness, jaundice, and hemoglobinuria were investigated. Blood samples were taken from all suspected favism

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patients referred to a general hospital in Kerman in southern Iran from 2016 to 2021. Participants were divided into groups of neonates (≤ 1 month), children (> 1 month -≤ 18 years), and adults (≥ 18 years). Evaluation of G6PD activity was performed qualitatively using Kimia Pajohan Company Kit (Kimia Pajouhan, Iran, Lot: 98605) by spot fluorescence method. According to the kit brochure, 5 ml of tampon solution was added to the substrate reagent's vial and shaken slowly until completely dissolved. One hundred microliters of the prepared reagent and ten microliters of whole blood were dispensed into small plastic tubes and shaken slightly. After 15 minutes, one drop of this mixture was dispensed on the filter paper of the kit and allowed to dry completely. All filter papers were examined under a fluorescent light lamp in the next step. In samples with strong fluorescence, enzyme activity was sufficient. In samples with low fluorescence, enzyme activity was partially deficient; in samples with no fluorescence, enzyme activity was severely deficient. Ethics Committee of Jiroft University of Medical Sciences has approved this study. (Ethics Code: IR.JMU.REC.1400.027).

Statistical analysis

The collected data were statistically analyzed by SPSS version 24 software using descriptive statistics, binomial, and Chi-square tests. In the present study, p-value of less than 0.05 was considered statistically significant.

Results

A total of 6369 patients (3479 males and 2890 females) were included in this study. The Binomial Test revealed that the number of males was significantly higher than a number of females ($p < 0.001$). Normal activity of G6PD was seen in 5945 (93.3%) participants (Table 1). G6PD deficiency was seen in 424 (6.7%) subjects. Out of 424 patients, 359 (84.7%) patients were found to be severely G6PD deficient, and 65 (15.3%) patients exhibited partial deficiency. The present study, G6PD deficiency was seen in 324 (9.3%) males and 100 (3.4%) females. The chi-square test revealed a significant relationship between sex and activity of G6PD ($p < 0.001$). In this study, 5582(87.6%) participants were neonates. Of the neonates, 3065 (54.9%) were male and 2517 (45.1%) were female. Normal activity of G6PD was seen in 5245 (94%) neonates. G6PD deficiency was seen in 337 (6%) neonates. Out of 337 neonates, 285 (84.6%) were found to be severe G6PD deficient, and 52 (15.4%) exhibited partial deficiency.

Table 1. Distribution of G6PD activity values in patients with clinically suspicious favism in Kerman city in southern Iran

Age category	Sufficiency N (%)		Severe deficiency N (%)		Partially deficiency N(%)		Total
	Male	Female	Male	Female	Male	Female	
Neonates	2803 (50.2%)	2442 (43.8%)	222 (4.0%)	63 (1.1%)	40 (0.7%)	12 (0.2%)	5582(100%)
Children	309 (48.7%)	250 (39.4%)	51 (8 %)	15 (2.3%)	5 (0.8%)	5 (0.8%)	635(100%)
Adults	42 (27.6%)	99 (65.1%)	4 (2.7%)	4 (2.7%)	2 (1.3%)	1 (0.6%)	152(100%)

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In the present study, 787 children and adults (413 males and 374 females) participated. The mean age of the participants was 8.1 years (SD = 14.2; range = 0.08–86) and 12.5 years (SD = 16.2; range = 0.08–82) in males and females, respectively. Normal activity of G6PD was seen in 700 (88.9%) children and adults. G6PD deficiency was seen in 87 (11.1%) subjects. Out of 87 patients, 74 (85.1%) were found to be severely G6PD deficient, and 13 (14.9%) exhibited partial deficiency.

Discussion

Malaria is a severe and sometimes fatal disease caused by *Plasmodium* species [13]. Today, one-third of malaria-endemic countries have programs to eradicate the disease. These programs are quite different from routine malaria control and, in addition to reducing clinical symptoms, require a complete reduction of the parasite reservoir by attacking the gametocytes responsible for transmission and killing the hypnosis to prevent the recurrence of the infection [14]. Primaquine and 8-aminoquinoline are the only effective drugs to achieve this goal [8]. However, the development of hemolytic anemia in patients with G6PD deficiency can limit the use of these drugs [8]. Therefore, before taking these drugs, it is necessary to have accurate information about the prevalence of G6PD deficiency in malaria-endemic areas. The present study determined the prevalence of G6PD deficiency to help treat and prevent malaria in Kerman city. The current study, G6PD deficiency was seen in 6.7% of patients. In our two previous studies in Jiroft and Qaleh Ganj cities, G6PD deficiency was seen in 24.7% and 10% of subjects, respectively [1, 15]. Qaleh Ganj and Jiroft cities are located near the city of Kerman. The current study's finding was lower than that done in Bam city (9.09%), near Kerman city [10]. This suggests that G6PD deficiency in adjacent cities may not have the same geographical distribution. However, the result of our study was similar to a meta-analysis that reported an enzyme deficiency of 6.7% in Iran [16]. This result of our study was similar to the study of Kotepui et al. [17] in Thailand (6.9%) and was higher than the studies conducted by Castro et al. [18] in Brazil (1.4%) and Alabdulaali et al. [19] in Riyadh (0.78%). The differences in the results of mentioned studies may be due to the selection of patients, sample size, geographical location, individual genetics, differences in enzyme measurement methods, and technician's skill in measuring enzyme activity. In the present study, the prevalence of enzyme deficiency was significantly higher in men than in women. This is similar to the findings of other studies [1,10,17]. This may be because G6PD deficiency is an inherited disease associated with the X chromosome, with the male tending to be at higher risk than the female as the male has only one X-chromosome [17]. So, male hemizygotes and female homozygotes are most often affected [18]. Heterozygous females have mixed G6PD normal and deficient red blood cells, and their total activity of G6PD enzyme and susceptibility to hemolysis depends on the

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balance between the expression of the normal and abnormal X-chromosomes [17].

Furthermore, in this study, the number of male participants was significantly higher than women, which may be effective in achieving this result. Contrary to our study, the number of women with enzyme deficiency in some studies was higher than men [15, 19]. This result may be related to the number of participants, patient selection, and the Lyon hypothesis [15]. In the current study, partial deficiency of G6PD was seen in 1% of patients. This result of the study was higher than our previous studies in Jiroft City (0.6%) [1] and was lower than our previous studies done in Qaleh Ganj City (8.5%). There are fewer people with partial G6PD deficiency than people with severe G6PD deficiency because people with partial G6PD deficiency are usually asymptomatic and, therefore, less recognized [15]. In some studies, using qualitative methods also causes the lack of identification of people with partial G6PD deficiency [20, 21]. Failure to identify these people can cause hemolytic anemia and serious injuries following the consumption of food and oxidative drugs [21]. In the present study, most patients were in the newborn group. Deficiency of this enzyme is associated with increased bilirubin, neurological complications, and death in newborns [22]. Some biochemical changes and depletion in the antioxidant defense system, can occur in the storage of G6PD-deficient blood, which can cause an increase in hemolytic complications in blood recipients [15]. Therefore, 6.7% of the people we studied could not suitably donate blood in the future. G6PD deficiency is significantly associated with an increased risk of cardiovascular diseases up to 70% [1]. Therefore, many people in our study need attention and care to prevent these diseases.

Conclusion

Our study's results confirmed that many people in Kerman are exposed to hemolytic complications if they use antimalarial drugs for treatment or prevention. In addition, our study showed that the deficiency of this enzyme could be very different in cities close to each other. Considering the fact that this region is prone to malaria, a screening program, especially in infants, is recommended to determine the actual prevalence of this enzyme deficiency. In addition to determining the prevalence of G6PD deficiency, this program can be valuable for future planning and monitoring of jaundice to prevent acute encephalopathy caused by hyperbilirubinemia encephalopathy and cardiovascular disease.

Conflict of Interest

The authors declare that there is no conflict of interest.

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