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REVIEW ARTICLE

Red cell glucose-6-phosphate dehydrogenase deficiency in Turkey

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common erythrocyte enzyme deficiency in the world. The epidemiological, biochemical and molecular studies on G6PD enzyme deficiency performed over the past 50 years are summarized herein, with special emphasis on the findings of studies related to the enzyme deficiency in Turkey.

Key words: Glucose-6-phosphate dehydrogenase (G6PD) deficiency

ÖZET

Türkiye'de eritrosit glukoz-6-fosfat dehidrogenaz (G6PD) enzim eksikliği

Eritrosit glukoz-6-fosfat dehidrogenaz (G6PD) enzim eksikliği dünyada en sık görülen eritrosit enzim eksikliğidir. Eritrosit glukoz-6-fosfat dehidrogenaz enzim eksikliğinin epidemiyolojisi, biyokimyasal ve molekuler analizleri ile ilgili dünyada ve ülkemizde son 50 yılda yapılan çalışmalar özetlenmiştir.

Anahtar kelimeler: Glukoz-6-fosfat dehidrogenaz eksikliği

INTRODUCTION

The anti-oxidative mechanism is very important for survival of cells from damages resulting from oxidative stress. In the mature red blood cell, the anti-oxidative mechanism depends solely on the generation of NADPH from NADP through hexose mono phosphate shunt in the glycolytic pathway by mediation of glucose-6-phosphate dehydrogenase (G6PD) enzyme. Reduction in NADPH level due to G6PD deficiency results in impairment in GSSG-GSH formation, which is the critical substrate of the anti-oxidative mechanism. Therefore, in G6PD deficiency, during oxidative stresses, destruction of hemoglobin and other stromal proteins leading to cell death becomes inevitable. The importance of red cell G6PD deficiency and its relation with the X-chromosome were published for the first time in the literature by Carson *et al.* [1] and Childs *et al.* [2], respectively. Examination of the enzyme by electrophoresis and by several biochemical methods revealed the presence of several silent and deficient variants of the enzyme [3,4]. Red cell G6PD deficiency was found to be associated with favism, chronic congenital hemolytic anemia, drug- or infection-caused acute hemolytic anemia episodes and increased risk of neonatal hyperbilirubinemia [4,5]. Association of G6PD deficiency with cancer, cataract formation and some other disorders has also been reported with controversial results [5-10]. G6PD compound heterozygous females affected with malignancies served as very good models in some studies searching for clonal origin of several malignancies [11]. Complete deficiency of the enzyme in leukocytes was reported to be associated with chronic granulomatous disease due to neutrophil dysfunction [12,13].

The G6PD variants have been divided into five classes according to the level of enzyme activity as follows: Class 1 - complete deficiency or very severe reduction in the enzyme level causing mild-severe chronic congenital nonspherocytic hemolytic anemia; Class 2 - severe enzyme deficiency (less than 10%); Class 3 - moderate to mild enzyme deficiency (10-60%); Class 4 - very mild or no enzyme deficiency; and Class 5 - increased enzyme activity. It was shown that the mutations causing chronic nonspherocytic hemolytic anemia are clustered near the carboxy end of the enzyme, in the region between amino acids 362-446, while most of the clinically mild mutations are located at the amino end of the molecule. It was stated that the majority of the Class 1 G6PD variants have the mutations surrounding either the substrate or NADP binding site [14].

Prevalence studies of the enzyme deficiency worldwide have shown that geographical distributions of frequency patterns of common G6PD deficiency alleles are highly correlated with the prevalence of malaria, suggesting that these mutations provided selective advantages against malaria falciparum infection [15-17].

Before DNA studies became available, more than 440 variants were identified worldwide as characterized by biochemical methods [18,19]. In 1986, Martini *et al.* [18] disclosed that the human G6PD gene is 18 kb long, with 13 exons. Later, molecular studies of the enzyme showed that many variants that were thought to be unique were identical on sequence analysis [20]. Vulliamy *et al.* [21] (1993) tabulated 58 different mutations in the G6PD gene that account for 97 named G6PD variants. Beutler and Vulliamy [22] (2002) reported the presence of 140 enzyme variants, including the silent polymorphic ones, by DNA studies. The G6PD mutations were exclusively missense mutations, causing single amino acid substitutions, except for G6PD Nara with 24bp deletion [23]. The absence of large deletion, frame shift and nonsense mutations suggests that a total lack of the enzyme activity would be lethal.

Among the most common G6PD variants, G6PD B+, G6PD A+, and G6PD A- were analyzed in a group of African Americans to understand the evolution of the G6PD gene [24]. Among these three, G6PD B+ was concluded to be the most ancient genotype. G6PD A+ mutation occurred in G6PD B gene as substitution of Guanine for Adenine (376G). The G6PD A- (202A/376G) occurred in an individual with A+ (376G) as substitution of Adenine for Guanine at position 202 (202A). Statistical modeling indicated that A- allele arose within the past 3840 to 11760 years and the B- Med allele (563T) within the past 1600 to 6640 years [25].

G6PD STUDIES IN TURKEY

Early studies

Prevalence studies of the red cell G6PD deficiency in Turkey began in 1965 and have continued up to 2006 [26-46]. The frequency of the enzyme deficiency was reported to vary from 0.5 to 20% depending upon geographical areas and/or the different ethnic groups studied (Table 1). The overall frequency of the enzyme deficiency representing the randomly selected normal males and male newborns was reported to be 0.5% [35]. The frequency was high in the costal region of the Mediterranean Sea and the highest rate was obtained in Çukurova, where there is a high prevalence of Hb S (Table 1). In one study, the deficient enzyme was studied by electrophoretic methods in 50 subjects and only G6PD Med was reported to be present [35]. Several articles were published about possible new mutations, such as G6PD Adana, Samandağ, Tarsus and Ankara in Turkish patients with acute hemolytic episodes, as studied by biochemical methods [37,38].

The first patient with severe chronic hemolytic anemia associated with G6PD enzyme deficiency was reported in 1989. Biochemical methods suggested the presence of a novel variant, named G6PD Çorum, after the patient's city (Table 2) [47,48]. Several studies have been conducted in an effort to understand the relation of red cell G6PD deficiency and neonatal hyperbilirubinemia [35]. These studies have indicated a higher rate of G6PD deficiency in newborn hyperbilirubinemia as compared to the normal population. The frequency of G6PD deficiency was determined as a risk factor in cataract formation [9]. In one subject, increased G6PD variant was reported to be present [28].

Molecular studies

Unfortunately, the Turkish patients previously reported as having new variants as mentioned above were not available for DNA study except for the patient with G6PD Çorum [47,48]. Molecular study of this patient revealed that the patient was indeed affected with a novel mutation (820GAG-AAG or 274 Glu-Lys) (Table 2) [48].

Table 1. Distribution of glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency in Turkey and Northern Cyprus

Region	Newborn	Newborn*	Student	GP**	Incidence%	Author and Reference Number
Diyarbakır	-	+	-	-	18	Katar *et al.* [45]
Balıkesir	-	-	-	+	6.9 (M/F, 7.24/6.51)	Turan *et al.* [34]
İstanbul	-	+	-	-	3.8	Atay *et al.* [33]
Erzurum	-	-	-	+	0.25	Ozmen *et al.* [46]
Denizli	-	-	+	-	1.23	Keskin *et al.* [32]
Gaziantep	-	-	-	+	2.3	Erbağcı *et al.* [41]
Cyprus	-	-	-	+	6.7 (Cypriot male) 1.6 (Turkish male)	Sozuoz *et al.* [44]
Çukurova	-	-	-	+	5 (males)	Akoglu *et al.* [29]
Çukurova	-	-	-	+	6.5 (males)	Altay *et al.* [26]
Çukurova	-	-	-	+	10 (males)	Ozsoylu *et al.* [40]
Çukurova	-	-	-	+	8.2	Yalın S *et al.* [28]
Thrace	-	-	-	+	5	Aksoy *et al.* [31]
Cyprus	-	-	-	+	12.4	Cin *et al.* [39]
Antalya	-	-	-	+	5.4	Aksoy *et al.* [30]
Antalya	-	-	-	+	M/F, 7.4/1.8	Aksu *et al.* [43]
Ankara	+	-	-	-	0.007 (males)	Altay [35]
Ankara	+	-	-	-	0.5 (males)	Say *et al.* [27]
Ankara	-	+	-	-	M/F, 3.5/0.7	Altay *et al.* [35]
Eastern Anatolia	-	-	-	+	1.0	Aksu *et al.* [42]

* Newborn with neonatal jaundice
**General population screening
M: Males. F: Females.

A study conducted by Oner *et al.* [49] in 50 unrelated deficient males showed that 80% of the patients had Mediterranean type of G6PD B- (563T) deficiency, two patients (4%) had A- (376G/202A) and one patient (2%) had G6PD Chatham (1003A); in the remaining seven patients (14%), molecular pathology could not be detected (Table 2). The two patients with G6PD A- were living in middle Anatolia (Ankara), and the patient with G6PD Chatham was from Southern Anatolia (Isparta). It was reported that none of the five patients from Çukurova region where Hb S is prevalent had other than B- variant. It was speculated that G6PD mutations had occurred sometime after the introduction of HbS into this population [49]. According to Oner *et al.* [49], presence of isolated G6PD A- mutation in Central Anatolia indicates that in Turkey, the African G6PD gene was introduced by slavery and not by large population movements. A similar assumption has been reported for some other Mediterranean countries [5]. The G6PD Chatham was reported first in Asian Indians, then in Syria and in patients of some Mediterranean countries [50]. Recent studies from Iran indicated that this mutation is second to G6PD Med mutation in various ethnic groups in that country [51,52]. Oner *et al.* [53] examined a patient from Eastern Anatolia (Van) with severe congenital chronic hemolytic anemia associated with neonatal hyperbilirubinemia leading to kernicterus. The patient was the only child and the mother had died after giving birth. DNA sequencing revealed that this patient had G6PD- Guadalajara 1159 C → T (387 Arg → Cys). To date, G6PD Çorum and G6PD Guadalajara are the two G6PD enzyme deficiencies associating with chronic hemolytic anemia reported from Turkey [48,53]. Unavailability of the mothers and other maternal family members of the two patients with chronic hemolytic anemia make it impossible to draw any conclusion about whether or not these mutations are de nova.

A recent molecular study conducted in a western Anatolian city (Denizli) disclosed no pathology other than G6PD Mediterranean type [32]. The number of the sample studied was too small to draw any definite conclusions. It was interesting that in both of the molecular studies conducted by Oner *et al.* [49] and Keskin *et al.* [32], the molecular make-up in quite a high number of patients could not be solved. These results may be indicative of some laboratory difficulties in conducting molecular study of the G6PD enzyme in this country.

CONCLUSION

From the studies conducted in Turkey, the following assumptions can be made: 1) G6PD deficiency is not rare in Turkey. 2) Since there is positive correlation between G6PD deficiency and hyperbilirubinemia, newborns with hyperbilirubinemia should be searched routinely for the enzyme deficiency. 3) The number of deficient samples examined by DNA methods was quite small and far from representative of all of the deficiency states in the country; therefore, the number of studies concerning molecular pathology of G6PD should be increased and expanded to cover all of the patients belonging to various geographical areas of the

Table 2. Results of molecular studies in glucose-6-phosphate dehydrogenase (G6PD)-deficient subjects associated with acute hemolytic episodes (I) and chronic hemolytic anemia (II)

Genotype	Changes in amino acid	Affected chromosomes		City
		Number	Percent	
I-				
G6PD B- (563T)	188 Ser→Phe	40	80	Throughout Turkey
G6PD A-(376G/202A)	126 Asn→Asp,	2	4	Ankara
	68 ValÆMet			
G6PD Chatam (1003A)	335 Ala→Thr	1	2	Isparta
Unknown		7	14	
Total		50	100	
II-				
G6PD Guadalajara (1159T)	387 Arg→Cys	1	-	Van
G6PD Çorum (820A)	274 Glu→Lys	1	-	Çorum

country. 4) The necessary efforts should be made to solve the problems associated with laboratory or other insufficiencies leading to inefficiency in studying molecular pathologies of the G6PD enzyme. 5) Presence of African A- type of G6PD deficiency may suggest that African type A+ should also be present in this population. Therefore, future screening analysis of molecular pathology of the enzyme should cover not only deficient males but males without any history of hemolytic anemia and/or females to determine the prevalence for A+ and other silent variants.

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