Prevalence of β-Thalassemia Trait and Glucose-6-Phosphate Dehydrogenase Deficiency in Iranian Jews

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Background. β-thalassemia is the most common inherited single gene disorder worldwide, and glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzyme deficiency. The goal of this study was to compare the frequency of β-thalassemia trait and G6PD among the Moslem and Jewish populations in Shiraz, southern Iran.

Methods. We examined 201 Moslem and 187 Jewish subjects who were selected by random sampling. For diagnosis of thalassemia, complete blood count and hemoglobin electrophoresis were carried out and for G6PD deficiency, fluorescent spot test methods were used as a screening test.

Results. Among Moslem subjects, 14 cases (7.0%) were diagnosed as carriers of β-thalassemia minor, whereas no carriers were detected among Jewish subjects. Seven Moslems (7%) and eight Jewish subjects (7.5%) were found to have G6PD deficiency. Among both groups the most common mutation was the Mediterranean type (563 C>T). In one Moslem subject, the detected mutation was 1003 (G>A) and in two Jewish subjects the mutations were 1376 (G>T) and G6PD A–.

Conclusions. Whereas the frequency of β-thalassemia minor among Moslems is higher than in the Jews in Shiraz, the frequency of G6PD deficiency was not significantly different in the two populations. These findings suggest that obligatory premarital β-thalassemia screening for Jews in the community is not necessary, whereas neonatal screening for G6PD could be useful for both Jews and Moslems.

Key Words: β-thalassemia minor, G6PD, Moslem, Jews, Iran.

Introduction

Glucose-6-phosphate dehydrogenase deficiency (G6PD) is the most common human enzyme deficiency disorder and is characterized by considerable biochemical and molecular heterogeneity (1). The prevalence of this X-linked erythrocyte enzymopathy in the Middle East varies between 1% in Egypt and 11.55% in Iran (2,3) On the other hand, β-thalassemia is the most common inherited single gene disorder in the world with the highest prevalence in areas where malaria was or still is endemic (4). Fars province in southern Iran is estimated to have about 10% Iranian β-thalassemia patients, whereas only 5% of the total population of Iran lives in this province (4). In the Fars province, 6.9% of the population are β-thalassemia carriers (5).

Moslems constitute the majority of the population in Iran. The Jews constitute a religious and ethnic minority in Iran who live in several cities of Iran including Tehran (north), Isfahan, Yazd (center), and Shiraz (south). During the Achaemenid Empire, Jews settled at Shiraz during an early period (537 BCE). A high frequency of consanguineous marriage in an isolated religious community caused an
increase in the prevalence of many inherited disorders in this subpopulation. Accordingly, we compared the frequency of β-thalassemia and G6PD as well as mutation analysis among the Moslem and Jewish populations in Shiraz, southern Iran.

**Patients and Methods**

This study was performed in 201 Moslem and 187 Jewish subjects who lived in Shiraz in 2005 and who were selected by random sampling method. After obtaining informed written consent, using K2-EDTA tube, blood samples were obtained for complete blood count (CBC) by automatic hematology analyzer (Sysmex KX21; Sysmex, Kobe, Japan). Hemoglobin electrophoresis was performed by HPLC (HbGold Drew Scientific Company, Cumbria, UK), and fluorescent spot test method as screening test for G6PD.

Diagnosis of β-thalassemia trait was established on the basis of the following criteria: mean corpuscular hemoglobin (MCH) <27 pg, mean corpuscular volume (MCV) <80 fl, HbA2 > 3.2% (6).

For screening of G6PD activity, a rapid fluorescent spot test detects the generation of NADPH from NADP (7). Inadequate G6PD activity fails to fluoresce under ultraviolet light.

We also performed molecular analysis of G6PD and β-globin genes. The following polymorphic G6PD molecular variants were tested by polymerase chain reaction based on fragment length polymorphism (PCR-RFLP): G6PD Mediterranean (563 C>T), G6PD A− (202G>A/376 A>G), G6PD Seattle (844C), G6PD Aures (143C), G6PD Santamaria (376G/542T).

Mutations of β-thalassemia were analyzed by using PCR-ARMS methodology. Because of the multi-ethnicity of the studied population we have also included the 290-bp and 619-bp Indian deletions, and the Mediterranean IVS-I-130 and Cd 39 mutations.

Data were analyzed by SPSS Windows 10.0.5 (SPSS, Chicago, IL). Student’s t-test, Mann-Whitney, and χ² tests were used for statistical analysis. Significance level was considered to be <0.05.

**Results**

Among the Moslem population, 101 females and 100 males and in the Jewish population 80 females and 107 males participated in this study. The difference between sex distributions of the two groups was not statistically significant. Mean age of the Moslem and Jewish groups was 38.6 and 48.9 years, respectively. The age difference between the two groups was not statistically significant.

β-thalassemia minor was detected in the 14 Moslem individuals (7.0%), whereas no carrier was found among Jewish subjects. The difference between the two groups considering the frequency of β-thalassemia minor was significant (p <0.001).

Mutation analysis of the 14 β-thalassemia trait carriers showed that IVS-II−1 (G>A) mutation was present at the highest rate (26%) followed by IVS-I−5 (G>C), Cd 36−37 (−T), Cd 5 (−CT), IVS I−1 (G>A), and IVS I, 3’ end −25 nt DEL.

Alleles of Cd 39 (C>T) and Cd 44 (−C), which rank in the top 10 or more frequent β-thalassemia mutations in the region, were not detected in these samples.

G6PD activity in the male Moslems and Jews disclosed seven (7%) and eight (7.5%) cases of G6PD deficiency, respectively. The difference between the frequency of G6PD deficiency was not statistically significant.

The G6PD Mediterranean mutation (563 C>T) was detected in 80% of all samples including Jews and Moslems. Among other screened variants, we identified one allele, Chatam (1003G>A), in a Moslem, and alleles of Canton (1376G>T) and G6PD A− in two Jews.

Comparison of the mutation analysis between Moslems and Jews did not show any statistical difference (p <0.05).

**Discussion**

β-thalassemia is a global problem and Iran, like other Middle Eastern countries, has a large number of β-thalassemia major patients (8). This study confirms the results of previous reports (9,10) showing that in Moslems the IVS-II−1 (G>A) is a frequent mutation followed by IVS-I−5 (G>C), which confirm the previous studies (11).

Despite the high frequency of β-thalassemia carriers among the Kurdish Jews (estimated to be 20%) (12) and among Jews from Middle Eastern countries and North Africa (estimated to be 2−4% (13), in this cohort study, we could not detect any cases of β-thalassemia carriers. This difference in the frequency of the carriers between Kurdish Jews and the other Middle Eastern Jewish populations could be originated from a founder effect in the different Jewish communities.

Among the Jews, a case presented with the G6PD A− mutation. This mutation is predominantly an African allele that occurs at low frequency in the north and south shore of the Persian Gulf (15−17). This allele may come through a local mutation or minimal admixture of the Jewish community with a local population during a long history. Further haplotype analysis is required to establish the origin of this allele.

In Iran, especially in its southern areas, malaria was endemic. A selective advantage in a malaria milieu may be an explanation for the high frequency of thalassemia carriers in the native population of this region that later became Moslem. Iranian Jews immigrated later to these regions and, therefore, the frequency of thalassemia remained relatively low because of relative isolation of this group and high frequency of intermarriage.
On the contrary, the frequency of G6PD deficiency was similar in both Jews and Moslems and both frequency and mutation analysis were high and similar among the two ethnic groups. Similar frequency was reported among Kurdish Jews (14) and southern Iranian Moslems (18,19). In addition to the thalassemia and G6PD, many other human genes are known as malaria resistance genes (e.g., Duffy blood group (20), CD40 (21), glycophosphoryls (22), and pyruvate kinase (23)). Malaria selection seems to have occurred for G6PD gene for at least 30 million years in the past (24) and G6PD Mediterranean allele dates back about 6000 years (25), before detection of the β- or α-gene mutations. The Jewish community seems to have acquired their G6PD mutations before immigration in 727 B.C. from Samaria to Persia (Fars). The haplotype linked to the G6PD Mediterranean allele in the Moslem group are the Mediterranean (1311 C > T) and Asian type, whereas among Jews only Mediterranean haplotype was detected (data not shown). This may be a reason supporting the above-described concept.

Finally, the preliminary results can be extended in a larger sample size and in other Moslem and Jewish populations who live in different parts (central, northern, etc.) of Iran or other countries to evaluate the difference between the incidences of these two genetic diseases in these populations.

Beyond the genetic aspect, on the basis of our finding, obligatory premarital thalassemia screening and prenatal diagnosis, which have existed in Iran since 1996, is not obligatory for the Jewish community, but screening for G6PD is recommended for couples who are at risk, in both Moslems and Jews.

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References


