Prevalence of glucose-6-phosphate dehydrogenase deficiency and α-thalassemia in children with sickle cell trait

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Abstract

The present study aimed to evaluate the prevalence of alpha-thalassemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency in sickle cell trait (SCT) patients to determine its effect on red blood cells (RBC) parameters. This cross-sectional study was conducted on 102 blood samples obtained from children and teenagers with SCT aged between 5 and 18 years old who were referred to Shahid Beqaei Hematology and Oncology Hospital and Abuzar Children's Hospital in Ahvaz city (Iran) from October 2021 to November 2022. About 5 mL of blood was collected via venipuncture from each patient and used to run G6PD, complete blood count, and hemoglobin (Hb) electrophoresis tests. The data were analyzed using SPSS version 22, and the significance level in all tests was considered less than 0.05. Results showed that the prevalence of heterozygous and homozygous alpha-thalassemia and iron deficiency anemia (IDA) in the examined sample was 18.63%, 18.63%, and 10.78%, respectively. Also, 13.72% of patients suffered from G6PD deficiency. The results imply that G6PD deficiency may increase the severity of anemia in SCT patients. Therefore, it is necessary to screen all SCT patients for G6PD deficiency to ensure that their condition is not exacerbated during unexpected events such as diseases or stress.

Introduction

Sickle cell disease (SCD) is a ubiquitous and life-threatening hematological condition affecting millions of people worldwide. An estimation showed that 300,000 infants were born with sickle cell anemia (SCA) each year.[1,2] During this disease, abnormal sickle-shaped erythrocytes disrupt blood flow in small vessels.[3] This vaso-occlusion leads to distal tissue ischemia and inflammation, with symptoms defining the acute painful sickle-cell crisis.[4] Repeated sickling and ongoing hemolytic anemia, even when subclinical, lead to parenchymal injury and chronic organ damage, causing substantial morbidity and early mortality. SCD is the most common monogenic disorder[2] and includes a variety of genotypes. In the homozygous (HbSS) both betaglobin alleles have an S mutation; in some heterozygous forms, there is one betaglobin allele with an S mutation, and the second allele can include other mutations such as beta thalassemia, HbC, HbD, HbO. In other heterozygous form, the second allele can be a normal allele of beta-globin which results in sickle cell trait (HbSA) and rarely has any clinical symptoms.[5]

Limited studies suggest that the coexistence of hematologic

genetic disorders such as alpha thalassemia and G6PD deficiency may influence the severity of SCA. Most of these studies are on homozygous inheritance (HbSS) and alpha thalassemia or G6PD deficiency. Some studies showed improvement of hematological parameters in co-inherited alpha thalassemia and HbSS and this may explain the high percentage of alpha thalassemia in SCA patients.[6,7]

The prevalence of G6PD deficiency in SCA patients has been different in separate studies. In some studies, there was no significant association between G6PD deficiency and SCA.[8] However, some studies showed that the simultaneous inheritance accelerates hemolysis and they have a statistically significant relationship.[9]

Most studies have been conducted in SCD patients with homozygous genotype (HbSS), and there are limited studies in patients with heterozygous genotype (HbSA). According to the statistics provided by the National Statistical Center of the Islamic Republic of Iran, Khuzestan province ranks first in the prevalence of thalassemia and second in the prevalence of SCD in this country. In Khuzestan province, due to the high prevalence of consanguineous marriages, especially among the Arab people, the prevalence of SCD and, consequently, SCT is high. Therefore, the present study was conducted to determine the simultaneous prevalence of G6PD deficiency and alpha thalassemia in SCT patients, and we sought to answer the question of whether simultaneous inheritance of alpha thalassemia and G6PD deficiency with asymptomatic heterozygous SCD (SCT) will result in symptoms similar to the homozygous form of SCD (SCA).

Materials and Methods

Ethics approval and consent to participate

The Ethics and Protocol Review Committee of Jundishapur University of Medical Sciences School of Medicine granted ethical approval for this study (Ethic Committee Code: IR.AJUMS.HGOLESTAN.REC.1400.077). After the purpose of the study was thoroughly explained to the parents/guardians, informed consent was obtained from them, and assent was obtained from the children. The parents/guardians were advised that their data would be kept private and that they could revoke their consent at any moment to stop taking part in the study.

Data collection, transportation, and storage

This cross-sectional study was conducted on 102 blood samples obtained from children and teenagers with SCT who were referred to Shahid Beqaei Hematology and Oncology Hospital and Abuzar Children's Hospital in Ahvaz city (Iran) from October 2021 to November 2022. The patients aged between 5 and 18 years with a median age of 13 years old. Blood samples of patients with SCT were collected in ethylene diamine tetraacetic acid (EDTA) tubes, kept at 2-6°C, and processed within 24 hours after collection. Hematological analyses were performed by electronic cell counter. The quantitative and qualitative profile of hemoglobin (Hb) was determined by HPLC. Biochemical parameters were also checked by immunochemistry method and spectrophotometric analysis. High-performance liquid chromatography (HPLC) was used to diagnose SCT. A sickling test was also done using the Sodium metabisulphite method. Determination of hemoglobin type (HbAS or non-HbAS) for SCT was done by cellulose acetate electrophoresis and PCR. To identify the alpha thalassemia genotype (homozygous or heterozygous), 8 mL of blood was collected from the patient's brachial vein in tubes containing 200 µL of EDTA, and the genomic DNA of leukocytes was separated by salt saturation method. The isolated genomic DNA samples were analyzed for common alpha thalassemia mutations (α3.7, α4.2, MED, and αααanti-3.7 triplication) by gap-polymerase chain reaction (gap-PCR) method.[10]

The diagnosis of iron deficiency anemia (IDA) was established following a response to oral iron. Patients were eligible for a therapeutic trial of iron if they met one of the following laboratory criteria: i) transferrin saturation <16%; ii) serum ferritin <15 ng/mL; iii) low mean cell volume (MCV) for age: 0.5 to 2 years <70 fL, 2 to 4 years <73 fL, 5 to 7 years <75 fL, 8 to 11 years <76 fL, 12 to 14 years <77 fL and 15 to 18 years <78 fL.[10]

Statistical analysis

All statistical analyses were performed at a confidence level of 0.05 using the statistical software SPSS version 22 (Armonk, NY: IBM Corp; 2013). Kolmogorov–Smirnov test was used to test the Normal distribution of data. The Kruskal-Wallis test was implemented to compare the laboratory parameters between the different groups of Alpha-thalassemia status and the Mann-Whitney U test was used to compare the two groups of G6PD deficiency and sufficiency children.

Results

The analysis of this study showed that 18.63% (19/102) of the examined patients had heterozygous alpha-thalassemia, 18.63% (19/102) had homozygous alpha-thalassemia, and 10.78% (11/102) suffered from anemia. The remaining people under investigation (51.96% = 53/102) did not have alpha-thalassemia. Of the examined people, 14 cases (13.72%) had G6PD enzyme deficiency (Table 1).

Furthermore, we examined the average blood indices of people with alpha-thalassemia (Table 2). The results showed that the average hemoglobin A1 in people with homozygous alpha-thalassemia was higher (60.37%) than in other groups and people with IDA where we recorded the lowest amount (55.24 %). Non-thalassemia people showed the highest (3.30%) average hemoglobin A2, followed by people with iron deficiency, homozygous alpha disorder, and alpha thalassemia (2.71, 2.49 and 2.46%, respectively). People with IDA by an average of 2.93% recorded the highest fetal hemoglobin and alpha thalassemia was seen with the lowest (0.45%) fetal hemoglobin. The average number of RBCs in people with non-thalassemia was seen the highest by 5.29 million/mm^3, after that people with homozygous alpha disorder (5.15 million/mm^3), alpha thalassemia (4.97 million/mm^3) and IDA (4.37 million/mm^3) was found with the least RBC, respectively. The highest amount of white blood cells (WBC) was seen in people with iron deficiency with 7370 per

Table 1. Relative and absolute frequency distribution of α-thalassemia and G6PD enzyme deficiency in the studied sample.

Categories	Number	Percentage
α-thalassemia status		
α trait thalassemia (-α/αα)	19	18.63
Iron deficiency	11	10.78
Non-thalassemia people	53	51.96
Homozygous α trait disorder (-α/-α)	19	18.63
G6PD enzyme deficiency		
No	88	86.28
Yes	14	13.72

Table 2. Average of different blood indices by separating the status of α-thalassemia

Blood indicators	α status	Mean SD	Reference range	P value[#]
HBA1 %	α trait thalassemia (-α/αα)	60.37±4.79	4.0 to 5.6	0.001*
	Iron deficiency	55.24±9.98		
	Non-thalassemia people	58.78±7.38		
	Homozygous α trait disorder (-α/-α)	65.81±5.90		
HBA2 %	α trait thalassemia (-α/αα)	2.46±0.68	2.5 to 3.5	0.540
	Iron deficiency	2.71±0.67		
	Non-thalassemia people	3.30±4.19		
	Homozygous α trait disorder (-α/-α)	2.49±0.93		
HBF %	α trait thalassemia (-α/αα)	0.45±0.44	0.8 to 2.0	0.095
	Iron deficiency	2.93±7.09		
	Non-thalassemia people	1.41±2.59		
	Homozygous α trait disorder (-α/-α)	1.30±1.48		
Protein S u/mL	α trait thalassemia (-α/αα)	36.63±4.68	60.0 to 140.0	0.004*
	Iron deficiency	37.79±5.54		
	Non-thalassemia people	36.73±5.10		
	Homozygous α trait disorder (-α/-α)	31.37±11.97		
WBC/μL	α trait thalassemia (-α/αα)	6667.5±1886.31	4500 to 10500	0.965
	Iron deficiency	7370.00±3309.50		
	Non-thalassemia people	6924.25±1596.93		
	Homozygous α trait disorder (-α/-α)	6794.44±1852.70		
RBC million/mm^3	α trait thalassemia (-α/αα)	4.97±0.50	4.2 to 5.4	0.016*
	Iron deficiency	4.37±0.65		
	Non-thalassemia people	5.29±3.89		
	Homozygous α trait disorder (-α/-α)	5.15±0.73		
Hemoglobin %	α trait thalassemia (-α/αα)	12.25±1.09	12.0 to 16.0	0.001*
	Iron deficiency	10.20±1.67		
	Non-thalassemia people	12.56±2.64		
	Homozygous α trait disorder (-α/-α)	11.44±1.73		
HCT g/dL	α trait thalassemia (-α/αα)	36.59±2.65	37.0 to 48.0	0.004*
	Iron deficiency	31.51±5.16		
	Non-thalassemia people	37.65±6.74		
	Homozygous α trait disorder (-α/-α)	35.15±5.03		
MCV fL	α trait thalassemia (-α/αα)	74.52±5.23	80.0 to 100.0	0.001*
	Iron deficiency	73.08±8.91		
	Non-thalassemia people	84.87±6.20		
	Homozygous α trait disorder (-α/-α)	66.63±3.52		
MCH pg	α trait thalassemia (-α/αα)	24.55±1.93	28.0 to 33.0	0.001*
	Iron deficiency	23.53±3.12		
	Non-thalassemia people	28.12±2.33		
	Homozygous α trait disorder (-α/-α)	22.04±2.47		
MCHC g/dL	α trait thalassemia (-α/αα)	33.25±1.14	32.0 to 36.0	0.510
	Iron deficiency	32.31±1.92		
	Non-thalassemia people	33.03±1.18		
	Homozygous α trait disorder (-α/-α)	32.21±2.12		
RDW1 %	α trait thalassemia (-α/αα)	21.37±10.75	11.5 to 14.0	0.076
	Iron deficiency	22.22±11.42		
	Non-thalassemia people	20.09±15.36		
	Homozygous α trait disorder (-α/-α)	15.20±1.83		
RDW2 %	α trait thalassemia (-α/αα)	21.18±15.24	11.8 to 16.1	0.020*
	Iron deficiency	15.95±11.43		
	Non-thalassemia people	26.98±18.64		
	Homozygous α trait disorder (-α/-α)	32.98±10.06		
Serum ferritin ng/mL	α trait thalassemia (-α/αα)	78.74±61.29	24.0 to 336.0	0.001*
	Iron deficiency	17.78±7.09		
	Non-thalassemia people	178.50±630.12		
	Homozygous α trait disorder (-α/-α)	65.04±65.39		

[#]Kruskal–Wallis test; *P<0.05; HBA1, hemoglobin A1; HBA2, hemoglobin A2; HBF, Fetal hemoglobin; WBC, white blood cell; RBC, red blood cell; HCT, Hematocrit; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, Red Cell Distribution Width.

microliter and the lowest amount was found in alpha thalassemia people with 6667.5 per microliter. Regarding the average hematocrit (HCT), after non-thalassemia people, alpha-thalassemia (36.59 g/dL), homozygous alpha-thalassemia (35.15 g/dL), and IDA (31.51 g/dL) people were recorded with the lowest HCT, respectively. Serum ferritin in non-thalassemia people was found at 178.50 ng/mL, followed by alpha thalassemia, homozygous alpha-thalassemia, and IDA, respectively.

Finally, we analyzed the average of different blood indices according to G6PD deficiency status. The mean hemoglobin A1, A2, and F in people suffering from G6PD enzyme deficiency were 56.00 ± 12.10%, 2.55 ± 0.63%, and 2.35 ± 4.75%, respectively. The mean of hemoglobin A1, A2, and F was not significantly different between those with G6PD enzyme deficiency and those without (P >0.05). The average number of WBC in people with G6PD enzyme deficiency was considerably higher than in people who did not have G6PD enzyme deficiency (the average WBC in people with G6PD enzyme deficiency was 7534.62 per microliter, and in people who did not have G6PD enzyme deficiency was 6784.51 per microliter (P =0.017). The average number of RBCs in people with G6PD deficiency was 4.37 million/mm^3; in people without G6PD deficiency was 5.22 million/mm^3. The average serum ferritin in people with G6PD enzyme deficiency was equal to 398.08 ng/mL; in people without this deficiency it was 73.27 ng/mL. Table 3 shows more details about the mean and standard deviation of blood indices according to the status of G6PD enzyme deficiency.

Discussion

In the current study, 102 patients (children and teenagers) with heterozygote forms of SCD (SCT) were examined. According to the findings of this study, the prevalence of heterozygous and homozygous alpha-thalassemia and IDA in the examined sample was 18.63%, 18.63%, and 10.78%, respectively. Furthermore, 13.72% of those tested revealed a G6PD enzyme deficiency. Although our study was on the SCT group, the results were consistent with some studies on the sickle cell anemia (SCA) group. For example, in a study in Burkina Faso, the prevalence of G6PD enzyme deficiency in students at primary schools with severe SCA was 27.03% (20 out of 74 patients), and in people with SCT, it was 18.57% (26 cases out of 114 patients).[11] According to Chan, G6PD deficiency in Nigerian men with SCD ranged from 2 to 25%, in Kenyan men from 2 to 25%, and in Ghanaian men it was 24%.[12] In another study, the prevalence of G6PD enzyme deficiency in men with SCA in Ibadan, Nigeria, was 16%. This value was 25%, 24%, and 19% in sickle-shaped patients in Chicago, New York, and Los Angeles, respectively.[13] In another study, 44 patients with SCA were examined for G6PD enzyme deficiency; the research showed that 22% suffered from G6PD enzyme deficiency.[14] In a separate study by Antwi-Baffour et al. in Ghana, the prevalence of partial and complete deficiency of the G6PD enzyme was 14.17% and 8.33%, respectively.[15]

When we examined the blood indicators, the results were as follows: the average Hb A1, A2, RBCs, and HCT in people with G6PD

Table 3. Average of different blood indices according to the status of G6PD enzyme deficiency.

Blood indicators	G6PD Enzyme deficiency	Mean SD	P value[#]
HBA1 %	No	60.63±6.59	0.253
	Yes	56.00±12.10	
HBA2 %	No	2.97±3.24	0.590
	Yes	2.55±0.63	
HBF %	No	1.23±2.77	0.625
	Yes	2.35±4.75	
Protein S u/mL	No	35.58±7.37	0.431
	Yes	37.37±5.45	
WBC/µL	No	6784.51±1933.09	0.017*
	Yes	7534.62±1942.90	
RBC million/mm^3	No	5.22±3.00	0.073
	Yes	4.37±0.87	
Hemoglobin %	No	12.14±2.27	0.135
	Yes	11.37±2.22	
HCT g/dL	No	36.56±5.85	0.095
	Yes	33.99±6.18	
MCV fL	No	77.90±9.25	0.446
	Yes	80.13±10.54	
MCH pg	No	25.77±3.41	0.648
	Yes	26.01±3.80	
MCHC g/dL	No	32.87±1.57	0.290
	Yes	32.55±1.19	
RDW1 %	No	19.10±10.87	0.974
	Yes	22.63±19.90	
RDW2 %	No	25.94±14.97	0.793
	Yes	25.32±22.71	
Serum ferritin ng/mL	No	73.27±65.65	0.963
	Yes	398.08±1198.56	

[#]Mann-Whitney U Test; *P<0.05; HBA1, hemoglobin A1; HBA2, hemoglobin A2; HBF, Fetal hemoglobin; WBC, white blood cell; RBC, red blood cell; HCT, Hematocrit; MCV, mean cell volume; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, Red Cell Distribution Width.

deficiency were lower than in people with the normal function of G6PD. On the other hand, the amount of serum ferritin, MCV, mean cell hemoglobin (MCH), WBC, protein S, and hemoglobin F in people with a G6PD enzyme deficiency was higher than in people whose function of this enzyme was normal in their body. However, most of these differences were not statistically significant, which can be attributed to the small sample size in this study. It is possible that if the sample size increases in future studies, these differences would probably become significant. This finding shows the worsening of anemia and the drop in the performance of blood indices in the case of the co-morbidity of SCT and G6PD enzyme deficiency. This finding is not surprising because the defect in G6PD enzyme activity and sickle cell anemia, both genetic disorders related to RBCs, predispose a person to hemolytic anemia. This finding was consistent with the research conducted by Antwi-Baffour *et al.*, which showed that people with SCA have a higher concentration of Hb and a lower concentration of RBCs.[9] In other words, the most common classic manifestation of G6PD enzyme deficiency is acute hemolytic anemia, which is caused by contact with oxidant substances and has symptoms such as weakness and lethargy, irritability or sleepiness in the patient, a relative increase in body temperature, nausea, headache, abdominal pain, diarrhea, and rarely vomiting. Therefore, evaluating the status of the G6PD enzyme in patients with SCA prevents oxidative stress in red blood cells.[9,13]

The findings of this research also showed that in SCT people with alpha-thalassemia, the average Hb A1, WBCs, and distribution range of RBCs were higher than those without alpha-thalassemia. Also, in simultaneous incidence with SCT and alpha-thalassemia, MCV and MCH decreased.[15,16] These findings are consistent with the results of previous studies, which indicate that an alpha/beta-globin gene mutation can modulate the hematological status of SCA patients.[17-20] According to several studies, the simultaneous presence of alpha-thalassemia with SCA causes a decrease in MCV and MCH, which leads to milder anemia. Nevertheless, this condition reduces hemolysis and increases total hemoglobin, which makes patients prone to painful vascular occlusion crises. Therefore, SCT and thalassemia would possibly interact to create particular impacts on hematologic parameters.

Our study had some limitations. First, the sample size of our study was smaller than similar studies. The second limitation was related to the cost of hematologic laboratory tests. In this regard, we had to take all the cases from the medical records archive unit, check them one by one, and find cases under 18 years old with SCT. Then we contacted each of them to help us in doing this study and refer to the hospital to perform newer tests and supplementary tests. For this purpose, it took a lot of energy and time to convince parents to allow their children to participate in this research and visit the hospital. On the other hand, conducting this study in Khuzestan province was one of the main strength points, because family marriage among Arab people is common in this province, so the number of patients with SCT reached the expected level.

Conclusions

Alpha-thalassemia and G6PD are frequent among children and teenagers with SCT. There was a significant difference between the blood indices of normal G6PD and G6PD-deficient participants and between alpha-thalassemia participants and those without thalassemia. G6PD deficiency may increase the severity of anemia in subjects with SCT. SCT patients must be aware of their G6PD condition to refrain from taking medicines and foods that may cause oxidative stress in their RBCs. In addition, we propose checking all units for G6PD deficiency and SCT, and postponing donations from donors with any of these disorders unless they are required for unique blood group compatibility, platelet apheresis, or if they are likely to impair blood bank inventory. Special measures must be taken if such blood is to be utilized to avoid issues in high-risk patients.

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