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Influence of Alpha Thalassemia and Hemoglobin F Co-inheritance on Sickle Cell Disease Outcomes

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ABSTRACT

The presence of alpha thalassemia and levels of hemoglobin F (HbF) significantly influence the clinical presentation of sickle cell disease (SCD) across different populations. This study was conducted to investigate the effects of these two factors on SCD patients in northern Iraq. A total of 74 patients with sickle/β0 thalassemia or sickle cell anemia, with a mean age of 16 years, participated in the study, of which 56.8% were male. Comprehensive clinical evaluations and lab tests were performed, including blood and reticulocyte counts, HbF levels, and analysis of serum lactic dehydrogenase and bilirubin. Screening for alpha-thalassemia mutations was performed using multiplex PCR and reverse hybridization. The results showed a positive correlation between HbF levels and hemoglobin, as well as negative correlations with reticulocyte count, HbA2, and the frequency of blood transfusions (P = 0.033, 0.041, 0.037, and 0.02, respectively). However, HbF was not correlated with other clinical symptoms. Nine patients had alpha-thalassemia (eight with –α3.7/αα and one with –α4.2/αα), but no significant hematological or clinical effects were observed in these patients. This study showed that HbF, rather than alpha-thalassemia, primarily modulates the disease phenotype in SCD patients from northern Iraq, which is different from findings in populations from Africa, the Arabian Peninsula, and Iraq, where alpha-thalassemia often plays a more influential role, sometimes more than HbF.

Keywords: HbF, Sickle cell disease, Alpha thalassemia, Phenotype, Iraq

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Introduction

Sickle cell disease (SCD) is an inherited blood disorder caused by a mutation in the β-globin gene at codon 6, resulting in the production of hemoglobin S (HbS, α2βS2). This variant of hemoglobin tends to polymerize when deoxygenated, leading to red blood cells adopting a sickle shape [1]. This sickling reduces cell lifespan (hemolysis), impairs deformability, and causes difficulty navigating narrow blood vessels, which results in blockages and multi-organ damage [2]. SCD is most common among individuals of African descent, but it also affects populations in India, the Arabian Peninsula, and the Mediterranean [1]. In Iraq, SCD shows a distinct geographic distribution, being more frequent in the southern Basrah and northern Duhok provinces, while it is rare in other regions of the country [3]. The disease presents in various genetic forms, with the most common being sickle cell anemia (homozygosity for the sickle cell gene), followed by compound heterozygosity with β-thalassemia or other structural hemoglobinopathies, such as Hb SC or Hb SD [4]. The clinical progression of SCD

varies widely, making its course difficult to predict. Extensive research has been conducted to identify genetic modifiers that might help predict disease severity and offer potential therapeutic targets. Key factors influencing SCD include increased fetal hemoglobin (Hb F) production and the co-inheritance of α-thalassemia [5]. These factors' effects differ across populations, and this study aims to evaluate how they impact hematological and clinical outcomes in SCD patients from Northern Iraq.

Materials and Methods

Patients

Seventy-four patients diagnosed with sickle cell disease were enrolled in the study from the Inherited Blood Disorders Center in Duhok, Iraq. The study focused on confirmed cases of sickle cell anemia (SCA) and sickle/β0 thalassemia, excluding individuals with sickle/β+ thalassemia. Inclusion criteria required patients to be aged 2 years or older, have a confirmed SCD diagnosis, and be in a stable condition, defined as no sickle cell crises for at least four weeks. Patients who were on hydroxyurea treatment were not included. The study received approval from the ethics committee of the Health Directorate in Duhok, Iraq, and informed consent was obtained from all participants or their guardians.

Each participant underwent a comprehensive medical history review and physical examination, with a thorough assessment of their medical records. This included documenting demographic information and evaluating clinical events such as the occurrence of sickle cell crises, the number of blood transfusions, pain episodes, hospitalizations due to vaso-occlusive crises, and any other sickle cell-related admissions over the past year.

Upon enrollment, various tests were performed, including complete blood counts (Swelab, BouleMedical AB, Spånga, Sweden), reticulocyte counts, and high-performance liquid chromatography (HPLC) to measure HbF and HbA2 (D10, BioRad Laboratories, Hercules, CA, USA). Biochemical testing involved measuring serum bilirubin, ferritin, and lactate dehydrogenase (LDH) levels using an automated biochemistry analyzer (Cobas c501, Roche Diagnostics, HITACHI, Tokyo, Japan).

DNA was extracted using a modified salted-out technique that ensures high-quality and pure DNA yield [6]. Screening for alpha-thalassemia was carried out using multiplex polymerase chain reaction (PCR) and reverse hybridization with allele-specific oligonucleotide probes (ViennaLab Diagnostics GmbH, Vienna, Austria). This method detects 21 different α-globin mutations, including deletions such as −α3.7, −α4.2, −−MED, −−SEA, −−THAI, −−FIL, and −(α)20.5, along with the ααααanti-3.7 gene triplication. It also identifies non-deletional α-thalassemias, such as mutations in the α1 gene (codon 14 (G > A) and Hb Adana (codon 59 (G > A)), and 11 point mutations on the α2 gene, including the initiation codon mutation ATG > ACG, codon 19 (−G), IVS-I, −5 nucleotides (−TGAGG), Hb Adana [codon 59 (G > A)], Hb Quong Sze [codon 125 (T > C)], Hb Constant Spring [codon 142 (T > C)], Hb Icaria [codon 142 (T > A)], Hb Paksé [codon 142 (A > T)], Hb Koya Dora [codon 142 (A > C)], and variations in polyadenylation signal sites (poly A1 [Saudi type] and poly A2 [Turkish type]).

Statistical Methods

Data analysis was conducted using SPSS software (Version 22, SPSS Corporation, Chicago, IL, USA). Descriptive statistics for continuous variables were expressed as median values with interquartile ranges (IQR). To compare groups, the Mann-Whitney test, the Kruskal-Wallis test, and Spearman correlation were applied as appropriate. A P-value < 0.05 was considered statistically significant.

Results and Discussion

The median age of the patients included in the study was 16.0 years (with a range of 2 to 47 years), comprising 42 males and 32 females. Among them, 59 had sickle cell anemia (SCA), and 15 had sickle/β0 thalassemia. **Table 1** presents the key clinical and laboratory characteristics of the enrolled patients.

Table 1. Key clinical and laboratory characteristics of 74 patients with sickle cell disease

Parameter	Median	IQR
Age (years)	16.0	10–23
Sex (Male: Female)	42: 32	
Hb (g/L)	88	79–98
Reticulocyte (%)	12.5	8–15

MCV (fL)	84.2	75.8–91.7
MCH (pg)	28.4	25.1–32.0
WBC (x10^9/L)	12.9	9.6–16.9
Platelets (x10^9/L)	440.0	251–616
Bilirubin (µmol/L)	58.1	41.9–94.6
HbF (%)	11.4	6.7–20.1
HbA2 (%)	3.15	2.78–3.85
LDH (IU/L)	555.0	304–934
Ferritin (ng/mL)	155.1	92–382
Overall hospitalization per year	1.0	0–3
Hospitalization for VOC per year	1.0	0–2
Pain episodes per year	2.0	0–6
Blood transfusions per year	0	0–1.25

History of Conditions

- Acute Chest Syndrome: 13 (17.6%)
- Splenectomy: 13 (17.6%)
- Avascular necrosis of femoral head: 7 (9.5%)
- Aplastic Crisis: 4 (5.4%)
- Splenic Sequestration: 4 (5.4%)
- Leg ulcers: 1 (1.4%)

IQR: Interquartile range

Correlation of Hemoglobin F (%) with Clinical and Laboratory Variables

The relationship between hemoglobin F (%) and various clinical and laboratory parameters was examined, with the results outlined in **Table 2**. The main findings revealed a positive correlation between Hemoglobin F and hemoglobin levels (**Figure 1**) as well as RBC counts (P = 0.033 and 0.009, respectively). On the other hand, negative correlations were observed with reticulocyte count (**Figure 2**), Hb A2 (%), frequency of blood transfusions, and platelet count (P = 0.041, 0.037, 0.020, and 0.030, respectively). Additionally, no significant association was found between Hemoglobin F and the yearly incidence of pain episodes or hospitalizations. It also showed no significant differences between patients with or without a history of sickle cell crises.

Table 2. Non-parametric correlations and associations between hb f (%) and various hematological and clinical variables in 74 patients with sickle cell disease

Parameter	HbF	Spearman coefficient	P-value	Mann-Whitney test (P Value)
Age	-0.131	0.265		
Hb	0.248	0.033*		
RBC count	0.303	0.009*		
MCV	-0.108	0.360		
MCH	-0.177	0.131		
Reticulocyte count	-0.238	0.041*		
WBC count	-0.109	0.354		
Platelet count	-0.253	0.030*		
Hb A2	-0.242	0.037*		
LDH	0.016	0.894		
S. Ferritin	-0.003	0.980		
S. Bilirubin	-0.142	0.227		
Frequency of blood transfusions per year	-0.270	0.020*		
Overall hospitalization per year	0.051	0.615		
Hospitalization for VOC per year	0.124	0.294		
Pain episodes per year	0.125	0.289		
Sex				0.639
Acute chest syndrome				0.972
Splenectomy				0.842
Avascular necrosis of the femoral head				0.305
Splenic sequestration				0.311
Aplastic crisis				0.990

Note: Asterisks indicate statistically significant correlations.

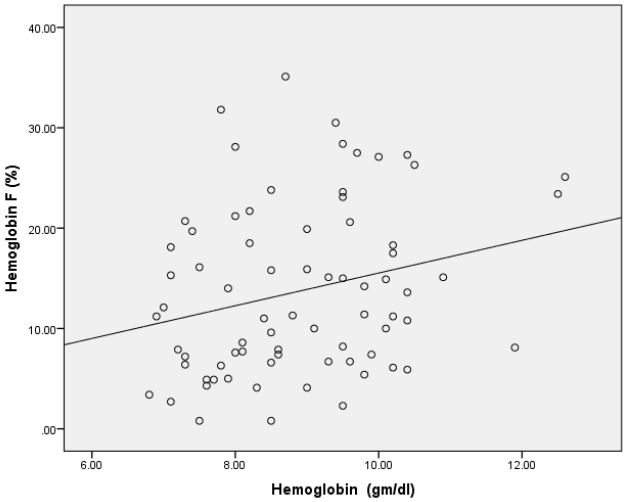

Figure 1. A scatterplot showing the positive correlation between HbF and hemoglobin concentration (Spearman coefficient = 0.248; P = 0.033)

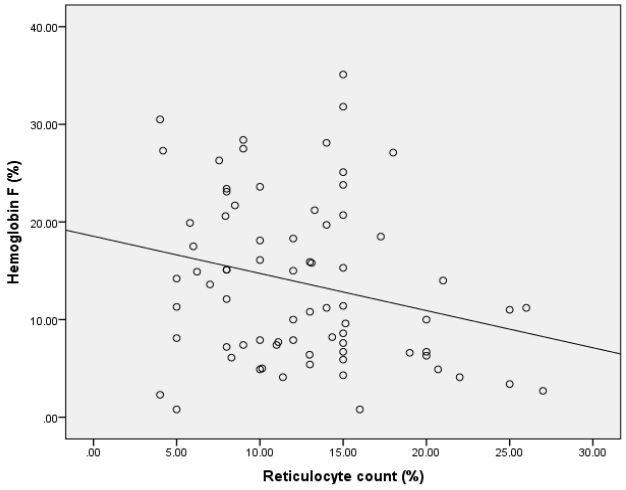

Figure 2. A scatterplot showing the negative correlation between HbF and the reticulocyte count (Spearman coefficient -0.238, P = 0.041)

Alpha Thalassemia and Clinical Characteristics

Out of the patients studied, nine were diagnosed with alpha thalassemia, including eight with the (-α3.7/αα) mutation and one with (-α4.2/αα). No cases of double α-gene deletions or non-deletional α-thalassemia were detected. When comparing those with and without α-thalassemia, no significant differences in clinical or laboratory parameters were found (**Table 3**). Interestingly, none of the nine α-thalassemia carriers had a history of avascular necrosis of the femoral head, splenic sequestration, aplastic crisis, or leg ulcers, and only one individual had a history of acute chest syndrome (all P > 0.05).

Further analysis categorized patients into SCA, sickle/β0-thalassemia, and HbSS/α-thalassemia groups (**Table 4**). The results showed that Hemoglobin F levels were significantly higher in sickle/β0-thalassemia, followed by SCA, and then HbSS/α-thalassemia (P = 0.032). Hb A2 levels were highest in sickle/β0-thalassemia, then HbSS/α-thalassemia, and lowest in SCA (P = 0.001). In terms of MCV and MCH, sickle/β0-thalassemia exhibited the lowest values, followed by HbSS/α-thalassemia, with SCA showing the highest (P < 0.001 for both). Additionally, the frequency of blood transfusions was most frequent in SCA, followed by HbSS/α-thalassemia, and least in sickle/β0-thalassemia (P = 0.039).

Table 3. Comparison between various continuous variables in sickle cell disease with or without α-thalassemia using Mann-Whitney U test

Parameter	Median (IQR)		P-value
	SCD without α-thal	SCD with α-thal	
Age (years)	16 (10-23)	15 (10.5-25.5)	0.993
Hb (g/L)	88 (79.5-98)	86 (76-100)	0.766
RBC ($x10^{12}$/L)	3.04 (2.5-3.7)	3.05 (2.9-3.3)	0.960
Reticulocyte count (%)	12 (8.0-15.0)	13.0 (10.1-15.0)	0.476
MCV (fL)	84.3 (75.6-94)	79.2 (74.9-88.2)	0.350
MCH (pg)	28.4 (24.9-33.1)	26.4 (25.5-29.9)	0.376
HbF (%)	13.6 (7.3-20.95)	7.4 (5.213.1)	0.077
HbA2 (%)	3.1 (2.65-4.0)	3.5 (3-3.75)	0.466
LDH (IU/L)	540 (297-917)	570 (422-1204)	0.602
Ferritin (ng/ml)	152 (83-363)	162 (103-538)	0.710
Overall hospitalization annual	1 (0-3)	0 (0-2)	0.311
Hospitalization for VOC (Annual)	1 (0-2)	0 (0-1)	0.182
Pain episodes annual	2 (0-6)	0 (0-2)	0.092
Blood transfusion annual	0 (0-1.5)	0 (0-1.5)	0.837
Bilirubin (umol/L)	56.4 (39.3-95.1)	59.9 (47-93.2)	0.882
WBC ($x10^9$/L)	12.6 (9.1-17.0)	14.1 (11.8-17.2)	0.350
Platelets ($x10^9$/L)	438 (248-618)	489 (269-581)	0.862

*VOC: Vaso-occlusive crisis.

Table 4. Comparison between various continuous variables in sickle cell anemia (SCA), sickle/β^0-thalassemia, and Hb SS/α-thalassemia using the Kruskal-Wallis test

Parameter	Median (IQR)			P-value
	SS/α-thal	Sickle/β^0 thal	SCA	
Age (years)	15 (10.5-25.5)	16 (10-25)	16.5 (9.8-23)	0.896
Hb (g/L)	86 (76-100)	95 (80-99)	86 (77-97)	0.445
RBC ($x10^{12}$/L)	3.05 (2.9-3.3)	4.0 (3.7-4.3)	2.86(2.40-3.45)	< 0.001
Reticulocyte count (%)	13.0 (10.1-15.0)	14.0 (9-15)	11.7 (8-15)	0.587
MCV (fL)	79.2 (74.9-88.2)	71.8 (68.7-73.4)	86.4 (83-95.9)	< 0.001
MCH (pg)	26.4 (25.5-29.9)	23.5 (22.7-24.2)	30.0 (27.4-33.6)	< 0.001
HbF (%)	7.4 (5.213.1)	21.2 (8.2-28.1)	12.9 (6.7-18.8)	0.032
HbA2 (%)	3.5 (3-3.75)	4.8 (3.1-5.4)	3.0 (2.5-3.4)	0.001
LDH (IU/L)	570 (422-1204)	700 (446-1107)	521 (278-880)	0.140
Ferritin (ng/ml)	162 (103-538)	181 (102-350)	146 (71-382)	0.661
Overall hospitalization annual	0 (0-2)	1 (0-2)	1 (0-4.25)	0.369
Hospitalization for VOC (Annual)	0 (0-1)	0 (0-2)	1 (0-2.25)	0.283
Pain episodes annual	0 (0-2)	4 (2-7)	2 (0-6)	0.115
Blood transfusion annual	0 (0-1.5)	0 (0-0)	0 (0-2.25)	0.039
Bilirubin (umol/L)	59.9 (47-93.2)	44.5 (34.2-56.4)	63.3 (46.2-99.2)	0.043
WBC ($x10^9$/L)	14.1 (11.8-17.2)	12.6 (9.1-17.0)	12.7 (9.1-16.9)	0.645
Platelets ($x10^9$/L)	489 (269-581)	438 (181-580)	438 (251-638)	0.895

*VOC: Vaso-occlusive crisis

Red Cell Indices and Their Correlations with Laboratory and Clinical Parameters

The relationships between various red cell indices, laboratory measurements, and clinical variables were explored, with some significant correlations summarized in Table 5. Notable findings include: a negative correlation between hemoglobin levels and both reticulocyte count and LDH (P = 0.001 and 0.022, respectively); LDH showing a positive correlation with reticulocyte count, pain episode frequency, and transfusion frequency (P = 0.007, 0.030, and 0.006, respectively); and both MCV and MCH being positively correlated with transfusion frequency (P = 0.034 and 0.020, respectively). Further correlations are provided in **Table 5**.

Table 5. Some significant bivariate correlations between various hematological and clinical parameters in 74

SCD disease patients were examined

Parameters	Spearman coefficient	P-value
Hemoglobin and age	+ 0.431	< 0.001
Hemoglobin and RBC count	+ 0.666	< 0.001
Hemoglobin and reticulocyte count	- 0.389	0.001
Hemoglobin and Hb F (%)	+0.284	0.033
Hemoglobin and LDH	-0.266	0.022
Hemoglobin and platelets	+0.318	0.006
Reticulocyte count and RBC count	-0.318	0.006
Reticulocyte count and Hb F(%)	-0.238	0.041
Reticulocyte count and LDH	0.309	0.007
Hb F and RBC count	0.303	0.009
Hb F and transfusion frequency/year	-0.270	0.020
Hb F (%) and Hb A2 (%)	-0.242	0.037
Hb F(%) and platelets	-0.253	0.030
LDH and frequency of pain episodes/year	+0.253	0.030
LDH and frequency of transfusions/year	+0.318	0.006
Frequency of hospitalization and pain episodes /year	+0.688	< 0.001
Frequency of hospitalization and transfusions/year	+0.272	0.019
Leucocytes and frequency of hospitalization/year	+0.219	0.061
Leucocytes and platelet counts	+0.374	0.001

Assessment of Clinical and Laboratory Parameters in Sickle Cell Disease

When evaluating the history of sickle cell crises about other laboratory and clinical parameters, several important associations were observed. Acute chest syndrome was linked with more frequent pain episodes and hospital admissions, though only the association with pain episodes was statistically significant (P = 0.037). Avascular necrosis of the femoral head showed no significant correlations with any tested parameters, although these patients tended to be slightly older (P = 0.102). In contrast, a history of splenectomy was significantly associated with older age, higher hemoglobin, and platelet counts (P = 0.020, 0.048, and 0.043, respectively).

In Iraq, sickle cell disease (SCD) presents with a distinct geographical distribution, with two primary epicenters: one in the north, associated with the Benin haplotype, and another in the south, linked to the Arab Indian haplotype. The Benin haplotype is associated with moderate disease severity, while the Arab Indian haplotype often corresponds with higher levels of HbF and a milder disease course. The current study's findings, including a median HbF of 11.4% and hemoglobin levels of 88 g/L, align with what has been observed in areas with the Benin haplotype, such as Southwest Saudi Arabia, but are lower than those in regions with the Arab Indian haplotype, such as Southern Iraq and the Arabian Peninsula [7-11].

Hemoglobin F (HbF) has been identified as a potent modulator of sickle cell disease phenotypes, as it inhibits the polymerization of deoxygenated HbS and reduces the mean concentration of HbS in red cells. In this study, HbF was positively correlated with hemoglobin concentration and negatively with reticulocyte count and transfusion frequency, which is consistent with its protective role. Similar findings have been reported in studies of Jamaican and American SCD patients [12-14]. Additionally, a negative correlation between HbF and HbA2 was observed, which may reflect a preferential survival of cells with higher HbF levels. Despite these correlations, no significant association between HbF and clinical manifestations like pain episodes or other sickle cell crises was found, aligning with previous research in Jamaican and Saudi Arabian populations. However, other studies have shown that higher HbF levels are linked to a reduced frequency of vaso-occlusive episodes [12, 15, 16].

Alpha thalassemia, which reduces α-chain production and subsequently lowers the intracellular HbS concentration, was found in 12.2% of the studied sample. This is similar to the rate observed in Northern Iraq but lower than in Southern Iraq or the Arabian Peninsula countries. The co-inheritance of α-thalassemia with sickle cell disease has been associated with various clinical outcomes, including higher hemoglobin levels, lower reticulocyte counts, and protection against certain complications like stroke and leg ulcers. However, the current study found no significant differences in hemoglobin or reticulocyte counts between those with or without α-thalassemia. Although fewer pain episodes were noted in patients with HbSS/α-thalassemia, no significant clinical associations were found. This could be due to the predominance of single α-gene deletions in this study, while

previous studies often included cases with double gene deletions, which are believed to have a more substantial ameliorating effect on SCD symptoms [17-33].

The study's limitations include its cross-sectional design, its focus on patients in a steady state, and the exclusion of individuals on hydroxyurea therapy, which may have reduced the pool of eligible participants.

Conclusion

In conclusion, the findings of this study indicate that in SCD patients from Northern Iraq, hemoglobin F (HbF) plays a more significant role in modulating the disease phenotype than α-thalassemia. This contrasts with the findings in many studies from Africa, the Arabian Peninsula, and Southern Iraq, where α-thalassemia is a major modulator of the disease and, in some cases, even has a greater effect than HbF.

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