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ORIGINAL ARTICLE

Fetal hemoglobin and clinical parameters in patients of sickle cell disease.

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ABSTRACT… Objective: To correlate the Hb F levels with clinical parameters of patients with sickle cell disease and sickle beta thalassemia. **Study Design:** Cross Sectional study. **Setting:** Chughtai Institute of Pathology. **Period:** June 2020 to December 2021. **Material & Methods:** A total of 150 diagnosed cases of sickle cell disease and sickle beta thalassemia were included in the study. Hemoglobin electrophoresis was performed and Hb F levels were noted. Detailed history of patients regarding their complications was taken. Data analysis was done using SPSS 23.0. Correlation of Hb F with Hb levels, splenomegaly, other symptoms and number of transfusions required was observed using Pearson test taking P value <0.05 as significant. **Results:** A significant correlation was observed between Hb F levels and Hb levels, splenomegaly, joint pains, jaundice, acute chest syndrome and number of transfusions required by the patient. **Conclusion:** We observed that high levels of Hb F in patients of sickle cell disease have fewer complications and have less need for repeated blood transfusions. Therefore, we recommend that Hb F levels must be noted at the time of diagnosis so that early treatment with hydroxyurea can be started to increase Hb F levels.

Key words: Fetal Hemoglobin, Sickle Cell Disease, Sickle Beta Thalassemia.

INTRODUCTION

Sickle cell disease (SCD) and thalassemia are prevalent throughout the world and constitute the major bulk of inherited hemoglobin disorders. These hemoglobinopathies are estimated to have 7 % carrier rate in the world population.[1] SCD is commonly seen in sub–Saharan Africa, Saudi Arabia and India.[2] In Pakistan, it is estimated that around 4% of the population has sickle cell anemia.[3] In developing countries like Pakistan, the prevalence of sickle cell disease and sickle beta thalassemia remains one of the biggest challenge due to high rate of consanguineous marriages, lack of testing facilities and premarital screening programs. Like the rest of the world Pakistan also faces the economic burden of dealing with complications of sickle cell disease.

SCD is a broad term used to describe all the conditions associated with sickling of red blood cells. SCD is caused by the inheritance of a defective gene which leads to the formation of Sickle hemoglobin (Hb S). Hb S is formed as a result of mutation which leads to a single nucleotide change at position 6 of beta globin chain of hemoglobin by substituting valine for glutamic acid.[1] Sickle beta thalassemia is coinheritance of Hb S and beta thalassemia.[4] Sickling is a process in which red blood cells attain the shape of a sickle as a result of intracellular polymerization of Hb S due to changes in oxygen saturation, intracellular pH and DPG concentration. As a result, the red blood cells lose their elasticity and cause obstruction in microvasculature thereby leading to anemia.[5] The symptoms and complications of sickle cell disease include anemia, pain crisis (sickle crisis), acute chest syndrome, stroke, jaundice, splenic sequestration and priapism.[6]

Fetal hemoglobin (Hb F) constitutes 60-90% of the total hemoglobin in a fetus and its level drops to less than 2% at the age of 6-12 months. The body continues to make Hb F even after this transition. Most normal individuals have Hb F less

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than 0.6%. Only a few rare cases of hereditary persistence of fetal hemoglobin have been found to have Hb F up to 25%.[7] It has been found out that raised levels of Hb F found in patients with SCD (Hb F > 10%) have milder disease, less complications and longer life expectancy as compared to those with lower levels of Hb F. This is because Hb F interferes with polymerization of Hb S thus preventing sickling of red blood cells.8 The aim of this study is to correlate the Hb F levels with clinical parameters of patients with sickle cell disease and sickle beta thalassemia. As per our knowledge no such study has been conducted in Pakistan that has studied the association of Hb F levels with disease severity in our population. So, this study will help clinicians in counselling of patient follow-up, prognosis and consideration for treatment with hydroxyurea which is a disease modifying agent that acts by increasing Hb F levels.

MATERIAL & METHODS

This is a cross sectional study that was conducted at Chughtai Institute of Pathology, Lahore after getting approval from the ethical and research committee of the institute (CIP/IRB/1047). The duration of the study was from June 2020 to December 2021. A total of 150 diagnosed cases of sickle cell disease and sickle beta thalassemia were included in the study. The sample size was calculated using Openepi calculator, version 3. Both males and female between the age of 1 to 74- years were included in this study. Patients on treatment with hydroxyurea, pregnant females and those who had undergone blood transfusion in the last two months were excluded from the study. After obtaining informed consent from the patients/guardians 4 ml of venous blood was drawn in two Ethylenediamine tetra acetic acid (EDTA) vials. One EDTA sample was run on automated hematology analyzer Sysmex XN 1000 to obtain hemoglobin levels. The other sample was used to perform hemoglobin electrophoresis on SEBIA Capillary 2 Flex piercing using capillary electrophoresis and Hb F levels were noted. Detailed history of patients was taken from either the patient or their guardians related to their age of onset of symptoms, blood transfusion requirements, splenomegaly, pain crisis, jaundice or any other complications like ulcers, dactylitis or joint pains was taken.

STATISTICAL ANALYSIS

Data analysis was done using SPSS 23.0. Frequencies were calculated and expressed as percentages. Correlation of Hb F with Hb levels, splenomegaly, other symptoms and number of transfusions required was observed using Pearson test and Pearson Chi-Square. P value <0.05 was taken as significant.

RESULTS

A total of 150 patients (n = 150) with SCD were included in this study with mean age 11.2±8.2 years (Range: 1year-74 years) with 70.7% affected male population and 29.3% female population (Table-I). Mean Hemoglobin (Hb) 8.9±1.9 g/dl (Range: 4.7g/dl - 14.0 g/dl) and mean Hb F 25.8±13.2% (Table-II). Out of 150 patients, 15 (16.7%) patients had enlarged spleen. 39 (26%) patients had jaundice, 23 (15.3%) had joint pains, 13 (8.7%) had acute chest syndrome (ACS), 5 (3.3%) had ACS with joint pains, 2 (14%) had ACS with ulcers. Dactylitis, infection and kidney problems constitute (2%) of the total patients. 72(48%) patients required transfusions whereas 78(52%) patients did not require any transfusion. A significant correlation was observed between Hb F levels and Hb levels, splenomegaly, other symptoms and number of transfusions using Pearson Test taking P value <0.05 as significant. (Table-III to VI). Patients with Hb F <10% showed that they needed more transfusions than the patients having Hb F >10%. Hb F levels have significant inverse relationship with the requirement of transfusions as calculated by Pearson Chi-Square showing P value of 0.000 which is <0.05(significant value).

Characteristics	Values
Mean age (years)	11.2±8.2
Male	106 (70.7%)
Female	44 (29.3%)

Table-I. Mean age and gender frequency of patients

	Hb (g/dl)	Hb F (%)
Mean	8.9±1.9	25.8±13.2

Table-II. Mean Hb (g/dl) and Hb F (%).

Correlations			
		HbF %	Hb g/dl
HbF %	Pearson Correlation	1	.481**
	Sig. (2-tailed)		.000
	N	150	150
Hb g/dl	Pearson Correlation	.481**	1
	Sig. (2-tailed)	.000	
	N	150	150

Table-III. Correlation of HB F (%) with HB (g/dl).
****. Correlation is significant at the 0.01 level (2-tailed).**

Correlations			
		Hb F %	Number of Tranfusions
HbF %	Pearson Correlation	1	.402**
	Sig. (2-tailed)		.000
	N	150	150
Number of tranfusions	Pearson Correlation	.402**	1
	Sig. (2-tailed)	.000	
	N	150	150

Table-IV. Correlation of HB F (%) with number of transfusions.

		HB F %	spleen
HbF %	Pearson Correlation	1	-.173*
	Sig. (2-tailed)		.034
	N	150	150
spleen	Pearson Correlation	-.173*	1
	Sig. (2-tailed)	.034	
	N	150	150

Table-V. Correlation of Hb F (%) with splenomegaly.

		HB F %	Any Other Symptoms
HbF %	Pearson Correlation	1	.427**
	Sig. (2-tailed)		.000
	N	150	150
Any other symptoms	Pearson Correlation	.427**	1
	Sig. (2-tailed)	.000	
	N	150	150

Table-VI. Correlation of Hb F (%) with other symptoms.

DISCUSSION

The greatest burden of SCD is present in Africa and Asia. The Asian countries with prevalence of SCD include Saudi Arabia, India, Pakistan, Turkey, Oman, Yemen and Lebanon.[9] A study conducted at University of Alabama in Birmingham found out that patients with SCD live 22 years less than those without the disease. Along with reduced life expectancy these patients have poor quality of life and have large constraint on their annual income as huge amounts are spent in management of their disease's complications.[10] As par our knowledge no study has been conducted that gives us the exact data about mortality rate, quality of life of patients or the economic burden of SCD in Pakistan thereby we have tried to establish the correlation of Hb F with different complications that may help in overcoming the challenges faced by the health sector of the country.

In our study we found that high levels of Hb F were associated with a smaller number of blood transfusions and fewer complications. These findings are consistent with those of a study conducted in Kampala, Uganda.[8]

The mean Hb F level of our study group was found out to be 25.8 ± 13.2 % whereas the mean Hb F level in Kuwait's population is ~20%. Like our population, high Hb F with fewer complications was also observed in Kuwaiti, Indian and Saudi population.[11]

In our study group 52% patients never received any blood transfusion which is less as compared to Senegalese patients. A study conducted in Dakar, Senegal 69.3% patients with sickle cell anemia never received any blood transfusion.[12] A study conducted at Al-Sadaqa Teaching Hospital, Yemen found out that 21.1% of pediatric patients with SCD were not transfused whereas 77.9% of their study population required transfusion during their 12-month study duration.[13] This rate of transfusion is much higher as compared to our population. Variations in transfusion requirement may be attributed to different genetic and environmental factors among these populations.

In our study population 16.7% of patients had splenomegaly whereas a study conducted in Nigeria had 21% SCD patients with splenomegaly.[14] In Senegal a study conducted found out 17.5% patients with splenomegaly.[15] These findings are quite similar to our observation. Spleen is the most common organ effected in SCD. Most often splenomegaly occurs during the first decade of life and later atrophies due to vaso-occlusion and infractions leading to auto splenectomy. The splenic complications play a major role in

morbidity and mortality of SCD.[16]

Our study population included more males (70.7%) as compared to females (29.3%). SCD is autosomal recessive disorder and its incidence is not gender biased but it has been found out that males have greater morbidity and mortality as compared to females.[17]

Acute chest syndrome (ACS) is the second most common cause of hospitalization and mortality in SCD. It presents most often with symptoms similar to that of pneumonia and can lead to lung injury.[18] According to Cooperative Study of SCD, the largest natural history study of SCD that includes both adults and children suggested incidence rate of ACS in SCD is 1.95 per 100 patient-years and 3.27 per 100 patient-years in Sickle beta thalassemia.[19] In our study also 8.7% patients had an episode of ACS in their lifetime.

The complications seen in our study group are quite consistent with findings seen elsewhere in the world and it can be concluded that patients with SCD are more likely to suffer and have poor quality of life as compared to a normal individual thus drastic measures must be taken by the health sector of the country to provide patient with SCD with a better chance of survival.

CONCLUSION

High levels of Hb F have beneficial effects in patients of sickle cell disease as these patients mostly remain asymptomatic, develop fewer complications and require blood transfusions less frequently. Therefore, we recommend that Hb F levels must be checked and noted at the time of diagnosis so that treatment with disease modifying drugs like hydroxyurea can be initiated. This will not only help patients to improve their quality of life but also increase their life expectancy. The further benefit would be reduced economic burden on the health sector of the country as fewer complications would require less money being spent on an individual patient.

LIMITATIONS

Our sample size is not an accurate depiction of the population of Pakistan with SCD. Only a limited number of patients who presented to us were included in the study. Hemoglobin electrophoresis is an expensive test that is not readily available everywhere in the country thereby most of the patients remain undiagnosed. There is also a possibility that many patients with low Hb F levels did not present to us because they died early in infancy due to complications of SCD and were never diagnosed. Thus, we recommend that hemoglobin electrophoresis test should be made available even in remote and rural areas of Pakistan so that no child with SCD remain undiagnosed and must have an equal and just chance of living a healthy and prosperous life.

REFERENCES

1. Hoffbrand A, Higgs D, Keeling D, Mehta A. **Postgraduate haematology.** Chichester, West Sussex: John Wiley and Sons, Inc; 2016.

2. Aygun B, Odame I. **A global perspective on sickle cell disease.** Pediatric Blood & Cancer. 2012; 59(2):386-390.

3. **Sickle Cell Anemia - World Sickle Cell Day [Internet].** Shifa4u.com. 2022 [cited 4 July 2022]. Available from: https://www.shifa4u.com/blog/sickle-cell-anemia-world-sickle-cell-day/18

4. Vincent O, Oluwaseyi B, James B, Saidat L. **Coinheritance of B-Thalassemia and Sickle Cell Anaemia in Southwestern Nigeria.** Ethiopian Journal of Health Sciences. 2016; 26(6):517.

5. Sundd P, Gladwin MT, Novelli EM. **Pathophysiology of sickle cell disease.** Annu Rev Pathol. 2019 Jan 24; 14:263-292. doi: 10.1146/annurev-pathmechdis-012418-012838. Epub 2018 Oct 17. PMID: 30332562; PMCID: PMC7053558.

6. Tanabe P, Spratling R, Smith D, Grissom P, Hulihan M. **CE: Understanding the complications of sickle cell disease.** AJN, American Journal of Nursing. 2019; 119(6):26-35.

7. Olaniyi J, Olaniyi O, Arinola A. **Foetal haemoglobin (HbF) status in adult sickle cell anaemia patients in Ibadan, Nigeria.** Annals of Ibadan Postgraduate Medicine. 2011; 8(1):30-33.

8. Mpalampa L, Ndugwa C, Ddungu H, Idro R. **Foetal haemoglobin and disease severity in sickle cell anaemia patients in Kampala Uganda.** BMC Blood Disorders. 2012; 12(11):1-7.

9. Kuikel S, Rauniyar R, Kharel S, Bist A, Giri S, Thapaliya S et al. **Prevalence of stroke in Asian patients with sickle cell anemia: A systematic review and meta-analysis.** Neurology Research International. 2021; 2021:1-7.

10. Lubeck D, Agodoa I, Bhakta N, Danese M, Pappu K, Howard R et al. **Estimated life expectancy and income of patients with sickle cell disease compared with those without sickle cell disease.** JAMA Network Open. 2019; 2(11):e1915374.

11. Adekile A. **The genetic and clinical significance of fetal hemoglobin expression in sickle cell disease.** Med Princ Pract. 2021; 30(3):201-211. doi: 10.1159/000511342. Epub 2020 Sep 4. PMID: 32892201; PMCID: PMC8280415.

12. Diop S, Thiam D, Cisse M, Toure-Fall A, Fall K, Diakhate L. **New results in clinical severity of homozygous sickle cell anemia in Dakar, Senegal.** Hematology and Cell Therapy. 1999; 41(5):217-221.

13. Al-Saqladi A, Maddi D, Al-Sadeeq A. **Blood Transfusion frequency and indications in yemeni children with sickle cell disease.** Anemia. 2020; 2020:1-7.

14. Olaniyi J, Abjah U. **Frequency of hepatomegaly and splenomegaly in Nigerian patients with sickle cell disease.** West African Journal of Medicine. 2007 Oct-Dec; 26(4):274-7.

15. Diagne I, Coly JI, Deme-Ly I, et al. **Prevalence and evolution of splenomegaly in children and adolescents with sickle cell disease in Senegal.** Archives of Disease in Childhood 2008; 93:pw297.

16. Al-Salem A. **Splenic complications of sickle cell anemia and the role of splenectomy.** ISRN Hematology. 2011; 2011:1-7.

17. Ceglie G, Di Mauro M, Tarissi De Jacobis I, de Gennaro F, Quaranta M, Baronci C et al. **Gender-Related differences in sickle cell disease in a pediatric cohort: A single-center retrospective study.** Frontiers in Molecular Biosciences. 2019;6(140):1-5.

18. Jain S, Bakshi N, Krishnamurti L. **Acute chest syndrome in children with sickle cell disease.** Pediatr Allergy Immunol Pulmonol. 2017 Dec 1; 30(4):191-201. doi: 10.1089/ped.2017.0814. PMID: 29279787; PMCID: PMC5733742.

19. Castro O, Brambilla D, Thorington B, Reindorf C, Scott R, Gillette P et al. **The acute chest syndrome in sickle cell disease: Incidence and risk factors.** The Cooperative Study of Sickle Cell Disease. Blood. 1994; 84(2):643-649.

AUTHORSHIP AND CONTRIBUTION DECLARATION

No.	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Iqra Rasool	Data collection and Literature search.	
2	Aiman Mahmood Minhas	Article writing and literature search.	
3	Mavra Fatima	Statistical analysis and Proof reading.	
4	Murad Mehmood	Data collection.	
5	Ayisha Imran	Drafted the study design.	
6	N.A. Malik	Overall supervision of the study.	