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Impact of Sickle Cell Anemia on children growth and clinical parameters in Al-Ahsa region of Saudi Arabia

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Abstract

Background: Sickle cell disease (SCD) is an autosomal recessive disease caused by a single gene mutation, leading to sickle-shaped red blood cells, causing many clinical complications. Resulting complications may affect the growth of the SCD patients that is a strong measure of severity of disease and helps in disease management strategies in any area. Eastern province of Saudi Arabia has one of the highest SCD incidences. Nevertheless, no studies have been previously carried out of about clinical outcome of SCD in Al-Ahsa area of eastern province. Therefore, this study was conducted to find out the impact of SCD children at king Abdulaziz Hospital Al-Ahsa.

Methods: All pediatric SCD patients were included in the study. Patient data was taken from hospital information system and analyzed using SPSS version 27.

Results: A total of 53 patients were studied. The male to female ratio was 1.4:1 and mean age was 3.3 years (range: 1-9). Eighteen (34%) did not present with sickle cell crisis possibly due to ameliorating effects of high HbF and G6PD deficiency. Although growth parameters of SCD patients were not statistically different from international standards, there was significant difference between weight of SCD patients in recurrent sickle cell crisis group and non-crisis sickle cell (NC-SC) group at diagnosis and after clinical interventions (p= 0.04 and 0.03, respectively) that included hydroxyurea. The corrected reticulocyte (at diagnosis and after clinical intervention) and WBC counts were statistically significant between hydroxyurea and non-hydroxyurea groups (p-value < 0.05).

Conclusions: Overall, one-third of SCD patients in Al-Ahsa region have mild disease and hydroxyurea can minimize the SCD severity through lowering corrected reticulocyte and WBC counts. Exact mechanisms of mild SCD and hydroxyurea in minimizing disease severity are needed to be elucidated.

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Introduction

Sickle cell anemia is an inherited disease with the production of sickled red blood cells and hemoglobin S instead of hemoglobin A [1]. Consequently, hemoglobin's ability of transferring oxygen all over the body decreases. Moreover, normal red blood cells' life span is 120 days, but in sickle cell anemia, red blood cells last for 10-20 days [2,3] The diagnosis of sickle cell anemia is performed by a hemoglobin electrophoresis to check for hemoglobin S and this blood test is part of the routine newborn screening in Saudi Arabia.

Sickle cell anemia patients experience many symptoms that vary from person to person which include fatigue, episodes of pain, painful swelling of limbs, frequent infections, delayed growth, and vision problems [4]. Sickle cell anemia affects a lot of body functions and causes some serious complications. The most common complications among sickle cell anemia patients are the retention of blood in limbs due to blood vessels obstruction, and this is known as hand-foot syndrome [5]. The sickled cells stick to wall of blood vessels and block the blood flow to the different body organs. When blood vessels are blocked, oxygen and nutrients will not be able to reach organs, and that will lead to organ dysfunction and death. A cure for sickle cell anemia is unavailable, so medication is usually taken to help with complications. For instance, hydroxyurea is administered to prevent pain [6]. In case the patient is having a pain episode, medication is given based on the severity of the crisis like aspirin for mild to moderate pain and opioid (morphine) for severe pain. Blood transfusions are effective to compensate the function of the sickled cells [6].

Sickle cell disease can severely affect growth of the children, in addition to other clinical manifestations [2, 4]. There are different reports about impact of sickle cell disease on children growth. A study carried in India in 2004 reported that children with sickle cell anemia had lower weight and height [7, 8]. In another study conducted in US on children and adolescents aged 6 to 18 years, no significant changes in height or weight of SCD children were noted as compared to healthy population [9]. A study conducted in Philadelphia showed that children with sickle cell anemia had low bone mineral density maturation [10]. Studies have shown that sickle cell disease can have varying effects on growth and other health parameters in different ethnic groups that may be due to different SCD phenotypes in different geographic regions of the world [11]. Moreover, various clinical complications resulting due to SCD may affect the growth of the SCD patients that is a strong measure of severity of disease and helps in disease management strategies in any area.

The incidence of SCD and its phenotypes vary in different parts of Saudi Arabia [8, 12]. The prevalence of SCD trait varies from 2-27% in different parts of Saudi Arabia while disease has a severe and a mild phenotype [8, 12]. Although many studies have been conducted in Saudi Arabia about sickle cell disease, no study has been carried out in Al-Ahsa region about impact of sickle cell anemia on growth parameters (height, weight) of sickle cell patients. Therefore, objective of this study is to find the effect of sickle cell anemia on height, weight and of children at King Abdulaziz Hospital in Al-Ahsa region.

Methods

This study was carried out retrospectively, and it was approved from institutional research committee and ethical review board. Clinically diagnosed SCD patients in children age groups (1-15 years) were included in the study. Adult SCD patients as well as patients with hemoglobinopathies other than SCD were excluded. Patient data was retrieved from the medical records at Division of Hematology/Oncology, Department of Pediatrics, King Abdulaziz Hospital, Al-Ahsa, Eastern region, Saudi Arabia. The data was analyzed using SPSS version 27. The growth parameters were compared between these different patient groups. The paired t-test was used to compare groups. P-values of 0.05 were considered to be significant.

Results

This study included 53 children diagnosed with sickle cell disease (SCD) in King Abdulaziz Hospital Al-Ahsa from 2013-2018. The age group for the selected sample size is from 0-12 years. The numbers of males were 31 (53%) and females were 22 (37%). The male to female ratio was 1.4:1. Moreover, most of the children diagnosed with SCD belonged to age group 0-4 (58.6%) and lowest to age group 5-9 years (32.8%). (Table 1a). Glucose-6-phosphate dehydrogenase deficiency (G6PD) was found in 5 (9.4%) patients while mean HbF was 21.45% ± 9.33 (Table 1b). Out of 53 patients, 18 (34%) did not present with sickle cell crisis (non-crisis sickle cell group). All patients without sickle cell crisis had either high HbF level or G6PD deficiency. Therefore, high HbF levels and G6PD deficiency may have ameliorating effects on sickle cell patients.

Variable		Frequency	Percentage	Mean	SD
Gender	Male	31	53 %	1.5	0.4
	Female	22	37 %		
Age at diagnosis	0-4	34	58.6%	3.3	2.4
	5-9	19	32.8%		
Current age	0-6	21	36.2%	7.1	2.7
	7-12	32	55.2%		

Table 1a: Gender and age groups of all patients included in the study.

Patients included in this study had a variety of moderate to severe complications caused by the disease. One patient (1.8%) was observed with leg ulcer. Bone X-ray images showed that 8.6% of patient bad bone

abnormalities. Splenectomy is a therapeutic procedure that can be done in some severe sickle cell cases. Overall, 8.6% of patients with sickle cell disease had their spleen surgically removed (Figure 1 & Figure 2).

Variable	Value	Frequency	Percentage
RDW at Diagnosis	High	47	88.7%
	Normal	5	9.4%
	Low	0	0
RDW after clinical intervention	High	44	83%
	Normal	6	11.3%
	Low	1	1.9%
LDH	High	45	84.9%
	Normal	1	1.9%
	Low	0	0
Total bilirubin	High	49	92.5%
	Normal	2	3.8%
	Low	0	0
G6PD	Positive	8	15.1%
	Negative	45	84.9%
Mean HbF		21.45% ± 9.33	

Table 1b. Laboratory parameters of Sickle Cell Patients (* RDW=Red cell distribution width, LDH= Lactate dehydrogenase, G6PD=Glucose-6-phosphate dehydrogenase, HbF=Hemoglobin F) and farm wise.

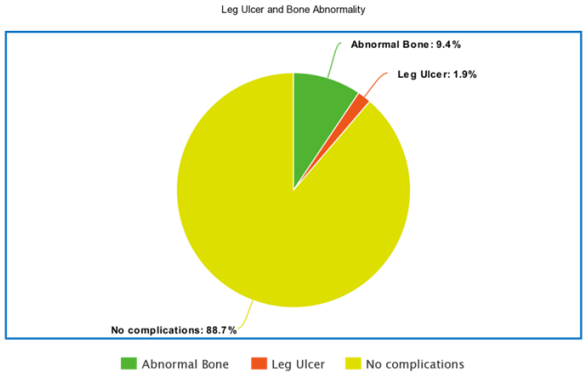

Figure 1: Frequency of SCD patients with bone abnormalities and leg ulcer.

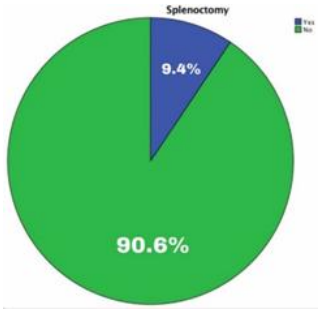

Figure 2: Frequency of SCD patients with splenectomy.

Overall, most of the male and female SCD patients had normal height and weight when compared with the international height and weight standards for healthy children (Table 2 and Table 3).

Furthermore, the patients were divided into two groups, the patients suffering from recurrent sickle cell crisis (RC-SC) group (35/53=66%) and patients with non-crisis sickle (NC-SC) cell group (18/53=34%). Chi-square test results showed that there was significant difference in weight of the patients in two groups at diagnosis and after clinical intervention (p-values: 0.04 and 0.03, respectively) (Table 4). Moreover, there was no statistically significant difference in height of both patient groups and body-mass index (BMI) at diagnosis (Table 4). Nevertheless, significant difference in BMI of both groups was noted after clinical intervention (p=0.05).

Crisis and non-crisis sickle cell patients

Not all patients agree to hydroxyurea treatment. Treatment with hydroxyurea had on impact on sickle cell crisis management. Among group I patients (RC-SC) patients, 71.1% were taking hydroxyurea while 37.5% group 2 patients (NC-SC) provided consent for hydroxyurea urea. (P-value: 0.06). It necessitates needs to counsel all SCD patients and their families to take hydroxyurea.

It was also found that hydroxyurea significantly affected corrected reticulocytes and WBC count in SCD patients. Corrected reticulocytes count in both at diagnosis and current was higher in non-hydroxyurea group (50%) as compared to hydroxyurea group (7.1%). WBCs count was low in 27.9% of patients taking hydroxyurea as compared to 12.5% of non-hydroxyurea group patients. The hematological parameters like corrected reticulocyte count (diagnosis and current) and WBC were statistically significant between hydroxyurea and non-hydroxyurea groups (p-value: 0.03, 0.005 and 0.05) (Table 5) (Figures 3-5). It shows that hydroxyurea lowers reticulocytes and WBC count in sickle cell patients that can help in reducing severity of disease. Exact mechanisms involved in these beneficial effects of hydroxyurea for sickle cell patients through lowering down reticulocyte and WBC counts are needed to be investigated.

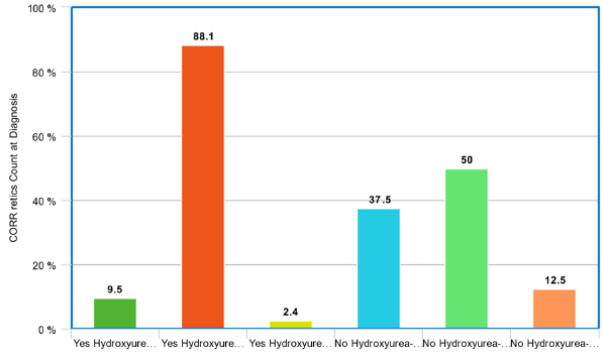

Figure 3: Corrected reticulocytes count at diagnosis in hydroxyurea and non-hydroxyurea groups.

Age	Male height	Male weight	Female height	Female weight
0-4	49.8-102.3 cm	3.3-16.3 kg	49.2-100 cm	3.3-15.4 kg
5-9	109.2-133.3 cm	18.4-28.6 kg	107.9- 133.3 cm	17.9-28.1 kg
0-6	49.8-115.5 cm	3.3-20.6 kg	49.2-115.5 cm	3.3-19.9 kg
7-12	121.9-149.1 cm	22.9-39.9 kg	121.1-149.8 cm	22.4-41.5 kg

Table 2: International normal ranges of height and weight in males and female children.

Variables	Female		Male		P-value
	Normal	Low	Normal	Low	
Height at diagnosis	68.2%	31.8%	60%	40%	0.54
Weight at diagnosis	59.1%	40.9%	56.7%	43.3%	0.86
Current height	61.9%	38.1%	70%	29%	0.49
Current weight	47.6%	52.4%	58.1%	41.9%	0.45

Table 3: Height, weight and BMI before and after diagnosis compared between the groups.

Variable	Non-crisis Sickle cell crisis (18) Group 2		SC crisis group(35) Group 1		P-value
Growth parameters	Low	Normal	Low	Normal	
Weight at diagnosis	71.4%	28.6%	29.4%	70.6%	0.04
Current weight	64.7%	35.5%	33.3%	66.7%	0.03
Height at diagnosis	68.6%	31.4%	52.9%	47.1%	0.27
Current height	70.6%	29.4%	61.1%	38.9%	0.48
BMI at diagnosis	5.7%	94.3%	82.4%	17.6%	0.17
Current BMI	11.8%	88.2%	100%	0%	0.05

Table 4: Comparison of Height, weight and BMI before and after diagnosis with sickle cell crisis and non-crisis sickle cell patients.

Variable	Hydroxyurea			No hydroxyurea			P-value
	HIGH	Low	Normal	High	Low		
Corr. Retics at diagnosis	9.5%	2.4%	88.1%	37.5%	12.5%	50%	0.03
Current corr. Retics	7.1%	7.1%	85.8%	50%	0%	50%	0.005
Current WBCs	0%	27.9%	72.1%	12.5%	12.5%	75%	0.05

Table 5: Comparison of hematological variables between hydroxyurea and non-hydroxyurea patients.

Variable	Hydroxyurea		No hydroxyurea		P-value
	Normal	Low	Normal	Low	
Current height	66.7%	33.3%	71.4%	28.6%	0.8

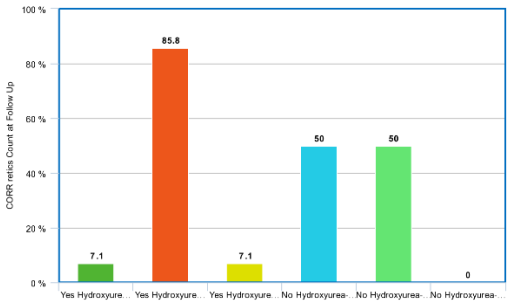

Figure 4: Effect of hydroxyurea on current reticulocytes count.

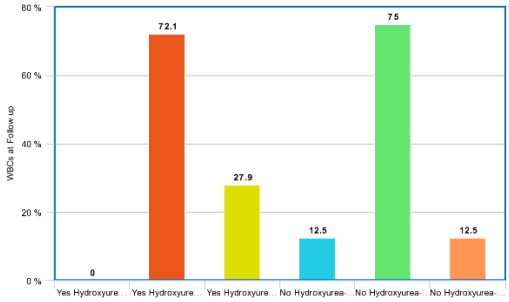

Figure 5: Comparison of white blood cell count between hydroxyurea and non-hydroxyurea groups.

Among all growth parameters the current weight, height and BMI were lower in SCD patients not taking hydroxyurea as compared to hydroxyurea group. However, the p-value is more than 0.05 which is statistically not significant (Table 6). Studies with higher number of patients may explain the exact correlation of these growth parameters with hydroxyurea treatment.

Overall, one third of SCD patients in Al-Ahsa region have mild disease and hydroxyurea can minimize the SCD severity through lowering corrected reticulocyte and WBC counts. Exact mechanisms of mild SCD and hydroxyurea in minimizing disease severity are needed to be elucidated.

Discussion

The aim of the study was to investigate the impact of sickle cell disease on children from Al-Ahsa region, Eastern Province, Saudi Arabia. Our study shows that 34% patients had no sickle cell crisis or other severe clinical manifestations. This is in accordance with previous studies reporting milder SCD in Eastern Province of Saudi Arabia and other regions [8, 12]. All of the SCD patients with milder disease had either high HbF (fetal hemoglobin) level or G6PD deficiency. Several other studies have reported protective effects of high HbF levels and G6PD deficiency in SCD [13, 14]. Level of HgF is controlled by multiple genetic loci likeHBB cluster, BCL11A, and HMIP-2 (HBS1L-MYB) and expression of these genes is under tight genetic control as manifested by involvement of many gene repressors,

enhancers and other factors. Silencing of repressors of HgF-inducing genes, for example, BCL11A repressor, is being investigated as innovative therapeutic strategy to develop novel medications for inducing high protective levels of HgF in SCD with initial promising results [15]. Several HgF-inducing drugs like hydroxyurea are already in clinical use [13, 15].

There are ethnic and phenotypic variations in impact of SCD on growth parameters of patients in different parts of the world [9-11]. In our studies, overall male and female SCD patients had normal height and weight in comparison to international height and weight standards for healthy children. This is in accordance with a study published from USA, that reported no significant changes in height or weight of SCD on children and adolescents aged 6 to 18 years as compared to healthy population [9]. Nevertheless, weight was significantly lower in sickle cell crisis group as compared to non-crisis SCD group at diagnosis (p=0.03) as well as after clinical interventions (0.04) in our studies. It could be Furthermore, non-crisis SCD group had more improvement in weight, height and BMI as compared to sickle-cell crisis group but it was not significant. It is understood as vaso-occlusive crisis is the major reason of major complications in SCD [16].

Hydroxyurea is the drug of choice for SCD patients, specifically for patients with vaso-occlusive crisis, but not all patients provided consent to take this medication. It is utilized as inducer of HgF expression that has protective effects for SCD patients [13, 14]. Our studies showed that SCD patients receiving hydroxyurea treatment had more improvement in body-mass index as compared to patients not receiving hydroxyurea. Similar results have been reported from investigators [17]. Our studies further showed decreased in WBC and corrected reticulocytes count in SCD patients receiving hydroxyurea, which is in accordance with other reports [17,18]. Although there is correlation between SCD, hydroxyurea treatment, lowering of WBC/reticulocytes and clinical improvement of SCD complications, exact mechanism of action of hydroxyurea still remains to be elusive [17-19]. Further studies by employing state-of-the-art multi-omics technologies are required to find out factors associated with milder SCD in Al-Ahsa region of Saudi Arabia and to unravel cellular molecular mechanism of action in of hydroxyurea in SCD patients.

Our study shows 18 (34%) did not present with sickle cell crisis possibly due to ameliorating effects high HbF levels and G6PD deficiency. Although growth parameters of SCD patients were not statistically different from international standards, there was significant difference between weight of SCD patients in recurrent sickle cell crisis group and non-crisis sickle (NC-SC) cell group at diagnosis and after clinical intervention (p-values: 0.04 and 0.03, respectively) that included hydroxyurea in eligible patients. The corrected reticulocyte (at diagnosis and after clinical intervention) and WBC counts were statistically significant between hydroxyurea and non-hydroxyurea groups (p-value < 0.05). Overall, one third of SCD patients in Al-Ahsa region have mild disease and hydroxyurea can minimize the SCD severity through lowering corrected reticulocyte and WBC counts. Exact mechanisms of mild SCD and hydroxyurea in minimizing disease severity are needed to be elucidated.

Conflict of interest

The authors declare that they have no competing interests.

Author Contributions

All authors have contributed to the article per international requirements of the authorship. The manuscript has been read and approved by all the authors, and the requirements for authorship have been met, and that each author believes that the manuscript represents original and honest work.

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