THE CLINICAL, HEMATOLOGICAL AND BIOCHEMICAL EXPRESSION OF HEMOGLOBIN S (HbS) IN THE EASTERN SAUDI ARABIA

MOHSEN A. F. EL-HAZMI*
ARJUMAND S. WARSY*

SUMMARY: The hematological and biochemical parameters were studied in sickle cell heterozygotes and homozygotes from different provinces of Saudi Arabia and the percentile ranges were calculated. This paper is the first in the series reporting percentile ranges for biochemical and hematological parameters in different hemoglobin S genotypes in the eastern province of Saudi Arabia and presents the percentile ranges in sickle cell anemia patients and sickle cell heterozygotes in comparison with the values encountered in the normal (Hb AA) individuals.

Key Word: Hemoglobin S.

INTRODUCTION

Hemoglobin S (HbS) is the most common variant of β-globin gene, resulting from the replacement of glutamic acid by valine at position 6 in the β-chain. In the deoxygenated state, the solubility of HbS is lower than HbA and, therefore, precipitates as bundles of long fibers which cause sickling of the red cell. During oxygenation de-sickling occurs, but some cells become Irreversibly Sickled Cells (ISC) and do not regain the normal red cell shape. The cell membrane becomes fragile due to the constant reversal of sickling and de-sickling phenomenon and is eventually lysed, thus resulting in a chronic hemolytic state. Under the action of certain factors such as cold, fever, dehydration and infections, sickle cell crisis may be precipitated. The crisis predisposes to aggregation of sickle cells, which may produce vasocclusion of the capillaries, resulting in pain, swelling and infarction (1, 2).

The pathology of sickle cell hemoglobin is considerably variable. In the heterozygous state, the presence of HbS in low concentration in red cells does not result in the sickling phenomenon under normal conditions and so the carriers of HbS are generally asymptomatic with normal hematological parameters values. The homozygous state has been defined as an incapacitating disease in which the hematological and several biochemical parameter values are abnormal. The clinical expression of HbS is reported to be variable even within the same population (2,3). It ranges from a severe disease with painful crisis and life threatening complications to a disease with mild symptoms. The effect on hematological and biochemical parameter values is also variable and is influenced by the severity of the disease and the occurrence of the crisis (2, 4).

In Saudi Arabia, HbS gene has been reported to occur at a high frequency in several regions of the country (5, 6), and the sickle cell disease is reported to be mild (3, 7, 8). Leg ulceration and hand and foot syndrome, which are a common finding in African and Jamaican sickle cell anemia patients are not seen in the Saudi population (7-9). We conducted these cross-sectional studies on Saudi HbS homozygous and heterozygous individuals from different provinces to determine the influence of these hemoglobin genotypes on the hematological, biochemical and clinical expression of HbS in this population. A group of males and females with normal hemoglobin were used as controls.

This is the first in a series of papers reporting percentile values for biochemical and hematological parameters in the AS and SS groups compared to the normal AA group from the eastern province of Saudi Arabia. The results are discussed in the light of the findings reported for other population.

*From Department of Biochemistry College of Science, King Saud University Center for Sciences and Medical Studies for Girls, Riyadh, Saudi Arabia.

MATERIALS AND METHODS

The subjects investigated in this study included 718 adult Saudi males and females visiting the various health clinics in Al-Hafouf, Al-Qateef and neighboring villages in the eastern province of Saudi Arabia. Physical examination was carried out, history was taken and retrospective analysis of the clinical files was carried out to determine the extent of hospitalization and number of blood transfusions received. All data was filled on standard forms. Five to ten milliliters of blood was drawn into heparinized tubes. Blood smears were prepared, air dried and the red cell morphology was studied after staining. The whole blood was used for the estimation of hematological parameters on Coulter Counter ZF6 with a hemoglobinometer attachment. The red cell indices were obtained from the Coulter Counter or calculated (10). The plasma was separated by centrifugation and was used to determine the values of biochemical parameters using Technicon SMAC and SMA-12 auto-analyzers according to methods reported previously (11). Both internal (Technicon Multi-System Control) and external quality control (Middle East External Quality control Scheme) procedures were used to control the methodological error of the procedure in application in the laboratory.

The red cells were washed twice with cold saline and hemolysates were prepared. The hemoglobin electrophoresis was carried out at alkaline pH using 0.2 M Tris-EDTA borate buffer, pH 8.9 using cellulose acetate strips (12), the samples with Hb phenotype AA, AS and SS were separated. The confirmation of presence of HbS was carried out by electrophoresis at acid pH using 0.05 M sodium citrate buffer pH 6.0 on agar plates (13). Hemoglobins A_2 and F were estimated using an elution technique following cellulose acetate electrophoresis (12) and alkali denaturation procedure (14), respectively.

The thalassaemic cases were identified using the results of red cell morphological study, and by applying one or more of the discriminant factors (Pearson's threshold (15); Shine and Lal (16) and England and Fraser (17)) to each sample. The male and female samples were divided into the Hb AA, AS and SS groups on the basis of the results of electrophoresis. The total number of individuals in each group are given in Table 1. Cases with associated α- or β-thalassaemia diagnosed on the basis of discriminant factors, HbA_2, HbS level, α/β-chain ratio and gene studies, wherever possible were excluded from this study. The value of hematological and biochemical parameters in each group were fed on computers at the Computer Center, King Saud University and using the Statistical Analysis System (SAS) the value for mean, median, mode, standard deviation, quantiles and percentile ranges were obtained. Histograms and normal probability plots were plotted by the computer. The normal range in the Hb AA group was calculated using mean$\pm$2SD and from the percentile values.

RESULTS

The mean, median (50th percentile), mode, standard deviation and 2.5th-97.5th percentile values for the hematological parameters are presented in Table 2. The statistical significance of the difference in the mean of any two groups was determined using the students 't' test. P less than 0.05 was considered statistically significant. These results show that the mean, median, mode and percentile ranges in the Hb AS group are similar to the Hb AA group, but the SS group shows statistically significant differences for total Hb, packed cell volume (PCV), red cell count and HbF levels when compared with the values obtained for the Hb AS and Hb AA group. The values for MCV, MCH, and MCHC were similar to those in the Hb AA and Hb AS group.

The biochemical parameters analyzed were grouped into profiles of specific tissue function, as liver function tests, renal function tests, bone function tests, and electrolytes. Glucose and uric acid were also analyzed. The mean, median, mode and percentile values for liver function tests are presented in Table 3. The total and direct

Table 1: The total number of individuals with the different hemoglobin genotypes.

Hemoglobin Types	Sex	Number of samples investigated
AA	Male Female	174 277
AS	Male Female	73 38
SS	Male Female	38 18
Total	Male Female	285 433

bilirubin, Serum glutamate oxaloacetate transaminase (SGOT), total protein and albumin were slightly elevated in the Hb SS while triglycerides (TAG) and cholesterol values were lower compared to the Hb AA and Hb AS groups. The Serum glutamate pyruvate transaminase (SGPT) level and Albumin/ Globulin (A/G) ratio did not show any significant differences.

Renal function tests are given in Table 4. A significantly lower level of plasma creatinine and urea are found in the Hb SS group compared to the Hb AS group, who have lower values than the values obtained for the Hb AA group.

The values of electrolyte in the three groups are presented in Table 5. No obviously significant difference was found in the three hemoglobin genotypes. Values for glucose and uric acid are presented in Table 6.

The HbS heterozygotes (Hb AS) were asymptomatic and showed no clinical abnormalities. The clinical mani-

Table 2: 'Percentile Range' for hematological parameters in Saudi HbS homozygous, heterozygous and in normal individuals.

Parameter	Hb Genotype	Sex	Mean	Median	Mode	SD	Percentile				
							2.5 th	25 th	50 th	75 th	97.5 th
RBC ($x10^{12}$/l)	SS	M F	4.4 3.9	4.4 3.6	3.4 3.2	0.68 0.74	3.0 2.8	3.7 3.5	4.4 3.6	4.8 4.4	5.4 5.0
	AS	M F	5.6 4.8	5.6 4.9	5.6 4.2	0.45 0.50	4.6 3.8	5.4 4.2	5.6 4.9	5.7 5.0	6.2 5.3
	AA	M F	5.4 4.8	5.4 4.9	5.4 4.9	0.35 0.45	4.4 4.0	5.2 4.3	5.4 4.9	5.6 5.2	6.1 5.7
Hb (g/dl)	SS	M F	12.9 11.6	13.2 11.7	11.8 11.0	0.91 1.35	11.0 9.8	12.5 10.8	13.2 11.7	13.6 12.5	14.2 13.0
	AS	M F	15.6 13.5	15.7 13.7	15.7 13.6	1.23 1.50	13.1 10.5	15.4 11.8	15.7 13.7	15.9 14.6	18.0 15.0
	AA	M F	15.6 13.6	16.0 14.0	16.0 14.0	1.25 1.40	13.8 11.2	14.8 12.7	16.0 14.0	16.4 14.6	18.2 16.4
PCV (l/l)	SS	M F	0.32 0.33	0.34 0.33	0.34 0.33	0.09 0.06	0.30 0.30	0.32 0.32	0.34 0.33	0.35 0.34	0.48 0.39
	AS	M F	0.47 0.40	0.47 0.41	0.47 0.35	0.03 0.03	0.40 0.34	0.43 0.35	0.47 0.41	0.48 0.42	0.53 0.43
	AA	M F	0.47 0.41	0.48 0.41	0.48 0.42	0.04 0.05	0.41 0.30	0.45 0.36	0.48 0.41	0.52 0.43	0.53 0.49
WBC ($x10^{9}$/l)	SS	M F	9.4 10.7	10.1 8.9	9.9 8.9	3.3 4.0	4.4 4.3	7.9 8.2	9.9 8.9	11.0 12.2	13.1 13.0
	AS	M F	5.9 6.8	5.7 5.6	5.7 5.0	1.05 3.3	4.3 4.1	5.3 4.5	5.7 5.0	6.0 6.1	7.9 11.6
	AA	M F	6.5 6.1	5.7 5.8	6.8 5.8	1.4 1.5	4.2 4.3	5.1 5.2	6.7 5.7	7.6 6.5	9.2 9.0

(Cont.) Table 2: 'Percentile Range' for hematological parameters in Saudi HbS homozygous, heterozygous and in normal individuals.

Parameter	Hb Geno-type	Sex	Mean	Median	Mode	SD	Percentile				
							2.5 th	25 th	50 th	75 th	97.5 th
MCV (fl)	SS	M F	88.0 86.0	87.0 84.0	80.0 84.0	3.7 3.7	78.0 79.0	81.0 81.0	80.0 84.0	87.0 90.0	101.0 93.0
	AS	M F	84.0 82.0	84.0 83.0	87.0 83.0	4.0 2.1	78.0 78.0	80.0 80.0	84.0 82.0	87.0 83.0	92.0 85.0
	AA	M F	84.7 84.0	84.0 84.0	85.0 87.0	4.6 3.8	78.0 77.0	81.0 81.0	84.0 84.0	87.0 87.0	94.0 92.0
MCH (pg)	SS	M F	30.0 29.0	29.0 28.0	29.0 32.0	3.3 3.3	25.0 25.0	28.0 26.0	29.0 28.0	30.0 30.0	35.0 32.0
	AS	M F	34.0 28.0	34.0 28.0	33.0 27.0	0.75 1.3	32.5 26.0	33.5 -	34.0 28.0	35.0 -	35.5 32.0
	AA	M F	28.5 28.6	29.0 28.0	29.0 28.0	1.6 1.4	25.0 26.0	27.0 27.0	28.0 28.0	29.0 30.0	31.0 31.0
Hb A_2 (%)	SS	M F	3.0 2.8	3.0 2.9	2.9 2.9	0.3 0.22	2.5 2.5	2.7 2.7	2.9 2.8	3.0 3.0	3.5 3.1
	AS	M F	3.0 3.0	3.0 3.0	3.0 3.0	0.30 0.30	2.5 2.5	2.9 2.9	3.0 3.0	3.0 3.1	3.5 3.5
	AA	M F	3.0 3.0	3.0 3.0	3.0 3.0	0.25 0.30	2.5 2.5	2.8 2.8	3.2 3.0	3.4 3.2	3.5 3.4
HbF (%)	SS	M F	7.7 7.7	7.1 7.2	7.4 7.3	4.9 5.0	3.2 3.3	6.7 6.5	7.1 7.2	10.5 13.0	17.7 17.1
	AS	M F	1.0 1.0	1.0 1.0	1.0 0.6	0.4 0.6	0.5 0.6	0.7 1.0	1.0 1.0	1.2 1.0	1.3 1.2
	AA	M F	0.70 0.64	0.60 0.60	0.60 0.60	0.44 0.28	0.2 0.2	0.4 0.4	0.6 0.6	0.9 0.9	1.2 1.2

festation encountered in the HbS homozygotes are presented in Table 7. The clinical severity was evaluated for each patient by determining the presence or absence of the common symptom reported in association with sickle cell anemia. These included: severity of anemia, jaundice, joint pain, bone pain, hepatomegaly, splenomegaly, splenectomy, crisis, hand and foot syndrome, osteomyelitis, aseptic necrosis of bone, numbers of blood transfusion and hospitalization. For each patient presence of each symptom was given a score of 1. For anemia the scoring was based on the level of hemoglobin. Patients with hemoglobin above 12.0 g/dl were assigned a score of 0, between 11.9-10.0 g/dl were scored as 1, between 9.9-8.0 g/dl were scored as 2, between 7.9-6.0 g/dl were scored as 3 and less than 6.0 g/dl were given the score of 4. For each patient the total score were added and the mean and standard deviation were obtained for the scores of all patients. Extent of

Table 3: 'Percentile Range' for Liver Function Tests in Saudi HbS homozygous, heterozygous and in normal individuals.

Parameter	Hb Geno-type	Sex	Mean	Median	Mode	SD	Percentile				
							2.5 th	25 th	50 th	75 th	97.5 th
Total protein (g/l)	SS	M F	76.5 76.0	76.5 78.0	70.0 78.0	4.0 4.5	68.0 68.0	75.0 74.0	76.0 78.0	77.0 79.0	83.0 82.0
	AS	M F	74.0 75.0	74.0 76.0	73.0 70.0	3.0 4.3	68.0 67.0	73.0 72.0	74.0 76.0	76.0 77.0	83.0 82.0
	AA	M F	72.0 74.0	73.0 73.0	74.0 73.0	4.4 6.7	64.0 57.0	69.0 67.0	73.0 74.0	75.0 78.0	81.0 83.0
Albumin (g/l)	SS	M F	45.0 44.6	46.0 45.0	46.0 45.0	3.8 2.3	36.0 37.0	43.0 44.0	46.0 45.0	47.0 46.0	49.0 49.0
	AS	M F	44.0 44.0	43.0 43.0	43.0 41.0	2.5 2.5	37.0 36.0	42.0 41.0	43.0 43.0	45.0 44.0	49.0 47.0
	AA	M F	42.0 41.0	42.0 41.0	42.0 41.0	3.2 3.5	35.0 32.0	41.0 38.0	42.0 41.0	45.0 43.0	48.0 47.0
Total Bilirubin (μmol/l))	SS	M F	5.8 4.5	5.8 4.5	5.7 4.4	2.0 2.0	1.0 0.9	3.8 3.6	5.80 4.50	6.5 5.4	9.8 8.5
	AS	M F	5.4 4.3	5.4 4.3	5.4 4.3	2.0 2.0	1.0 0.6	3.3 2.4	5.4 4.3	6.8 4.6	8.5 6.1
	AA	M F	4.9 3.9	5.1 3.4	5.1 5.1	2.0 1.76	0.6 0.6	3.4 2.0	5.1 3.4	6.0 4.3	8.5 6.8
Triglyceride (mmol/l)	SS	M F	1.2 1.04	1.1 1.04	0.9 1.04	0.5 0.4	0.3 0.2	- 0.8	1.1 1.04	- -	1.7 1.3
	AS	M F	1.05 1.07	0.9 0.7	0.9 0.4	0.71 0.50	0.86 0.50	- -	0.9 0.7	0.94 -	1.8 1.2
	AA	M F	1.7 1.5	1.6 1.3	1.4 1.2	0.51 0.71	0.51 0.3	1.12 1.02	1.55 1.28	1.91 1.80	3.07 3.9

hospitalization, transfusion and crisis were assessed on the basis of the number per year. One transfusion / year was given a score 1 and two transfusions/year were given a score 2. In the same way the extent of hospitalization/year and crisis/year were assessed.

In the 46 patients investigated the minimal clinical severity score was 2/14 and the maximum was 10/14, and the mean was 7.65.

DISCUSSION

The presence of HbS in homozygous state influences the red cell stability and rate of survival. Since the cell are steadily hemolyzed a state of chronic anemia exists. The increase in the rate of breakdown of hemoglobin may result in increased levels of serum bilirubin. In addition, hepatic dysfunctions may occur due to sequestration of the liver by the sickled cells. Bone infarction due to

(Cont.) Table 3: 'Percentile Range' for Liver Function Tests in Saudi HbS homozygous, heterozygous and in normal individuals.

Parameter	Hb Geno-type	Sex	Mean	Median	Mode	SD	Percentile				
							2.5 th	25 th	50 th	75 th	97.5 th
Cholesterol (mmol//l)	SS	M F	3.0 3.0	2.6 3.3	2.5 3.3	0.9 0.9	1.2 1.0	- 2.8	2.5 3.3	- 3.5	3.6 4.0
	AS	M F	4.4 4.5	4.5 4.3	4.5 4.0	1.0 0.7	2.1 2.6	4.5 -	4.5 3.7	4.7 3.9	5.4 4.1
	AA	M F	4.9 4.2	4.9 4.9	4.9 4.2	1.2 1.4	2.8 3.3	3.9 4.1	4.9 4.9	5.7 5.9	7.3 8.6
SGOT (U/l)	SS	M F	41.5 38.0	35.0 36.0	28.0 36.0	12.4 16.4	25.0 20.0	- 23.0	35.0 36.0	- 53.0	60.0 56.0
	AS	M F	34.0 20.0	25.0 21.0	23.0 20.0	14.4 11.5	22.0 10.0	23.0 23.0	25.0 25.0	41.0 35.0	56.0 42.0
	AA	M F	30.0 23.0	27.0 21.0	24.0 20.0	11.5 6.5	9.0 10.0	23.0 18.0	27.0 21.0	35.0 25.0	54.0 39.0
SGPT (U/l)	SS	M F	13.0 13.0	11.0 14.0	8.0 14.0	6.0 4.5	1.0 4.0	- 8.0	11.0 14.0	- 15.0	23.0 18.0
	AS	M F	13.0 13.0	12.0 13.0	12.0 -	6.8 7.1	3.0 1.0	- 3.0	12.0 13.0	13.0 17.0	35.0 19.0
	AA	M F	13.0 8.6	12.0 6.0	9.0 -	9.6 6.7	3.0 2.0	7.0 4.0	12.0 6.0	18.0 10.0	36.0 27.0
ALP (U/l)	SS	M F	116.0 96.0	94.0 33.0	- 73.0	40.0 43.0	36.0 10.0	- 67.0	94.0 73.0	- 104.0	178.0 125.0
	AS	M F	92.0 75.0	88.0 73.0	63.0 54.0	20.2 20.3	63.0 35.0	70.0 59.0	88.0 73.0	- 82.0	157.0 100.0
	AA	M F	92.0 73.0	93.0 63.0	105.0 68.0	30.0 29.0	49.0 34.0	66.0 52.0	83.0 63.0	104.0 88.0	200.0 120.0

vasocclusion of the capillaries is a common finding (18) and is associated with bone pains. The damage is repaired constantly by osteoblasts, thus showing increase in alkaline phosphatase level. Renal functions are also affected in sickle cell anemia patients and the common findings is an inability to concentrate urine. Some of the changes are more pronounced during the painful crisis (19,20).

The results of this study on Saudis shows that the HbS in heterozygous state is asymptomatic and the hematological and biochemical parameters do not show marked changes between the Hb AA and Hb AS group. However, HbS in homozygous state influences the values of some of the hematological and biochemical parameters, show quite a significant variation. Some individuals have severe anemia while others have hemato-

Table 4: 'Percentile Range' for Renal Function Tests in Saudi HbS homozygous, heterozygous and in normal individuals.

Parameter	Hb Genotype	Sex	Mean	Median	Mode	SD	Percentile				
							2.5 th	25 th	50 th	75 th	97.5 th
Creatinine (μmol//l)	SS	M F	68.0 53.0	70.0 53.0	70.0 53.0	13.5 13.9	40.0 27.0	- 44.0	70.0 53.0	- 62.0	80.0 70.0
	AS	M F	76.7 68.0	88.0 70.0	88.0 62.0	14.9 4.9	53.0 58.0	62.0 -	88.0 70.0	- -	88.0 71.0
	AA	M F	88.0 61.0	88.0 62.0	88.0 53.0	17.7 14.8	53.0 28.0	75.0 53.0	88.0 62.0	100.0 75.0	115.0 85.0
Urea (mmol/l)	SS	M F	4.0 3.2	4.0 3.2	4.0 3.2	1.3 0.78	1.4 1.6	- 2.9	4.0 3.2	- 3.6	6.1 4.3
	AS	M F	4.7 4.2	4.7 4.5	4.7 2.9	1.2 0.9	3.2 2.3	3.6 2.9	4.7 4.3	5.0 4.7	6.5 5.0
	AA	M F	5.5 3.4	5.4 4.0	5.4 4.3	1.6 1.6	2.9 1.98	4.2 2.9	5.2 4.0	7.0 4.7	8.1 6.2

logical parameters values not significantly different from those in the control group. Similar variations are found in the values of biochemical parameters. The mean for direct bilirubin, SGOT, total protein and albumin show deviation from the normal and the values are elevated. While for triglycerides, cholesterol, creatinine and urea the mean in HbS homozygotes is lower than the normal mean.

Comparison of the results of the hematological and biochemical parameters in Saudi sickle cell anemia patients with the values reported in literature for Jamaicans shows that the expression of HbS in Saudis is remarkably mild (2). Jaundica is considered as a regular feature in sickle cell anemia cases (2) but it is seen in only 20% of patients investigated in this study. This confirms further the mildness of sickle cell anemia in the eastern province as previously shown in a case control study on Saudi sickler (21). Reduction in cholesterol and triglyceride has been reported in Sudanese population (22) and hypolipoproteinemia is known to occur in sickle cell anemia cases. Hypoproteinemia and hypoalbuminemia have been reported in other studies (20) but were not seen in the Saudi patients. The Saudi cases show reduction in plasma cholesterol, and triglycerides but not as marked as those reported for other populations (23). These results confirm the results of a previous case control study on Saudi sicklers (24). The significant change is a reduction in the serum creatinine and urea level. The reduction in serum urea may be a consequence of liver dysfunction while the reduction in serum creatinine could be due to reduced muscle mass in the sickle cell anemia patients. In addition, increase in plasma volume reported in sickle cell anemia patients could also result in an overall decrease in urea and creatinine. These results and those of a previous investigation (25) stress the need for detailed investigations on the renal functions on Saudi sicklers including clearance studies'. In literature there are reports of hyperuricaemia in patients with Hb SS disease (26), however, the results of this study show that the uric acid level is only slightly elevated in the Saudi sicklers.

Clinically, the mild nature of the sickle cell anemia was also apparent. Almost 41% of the patients had hemoglobin level above 12.0 g/dl and in those who were anemic 12 had hemoglobin level less than 10.0 g/dl. No cases with hand and foot syndrome, and aseptic necrosis of the bone were encountered. Five of the patients showed signs of osteomyelitis and 3 had complained of ulcers on the legs. The most common finding was pain in bones and joints, which was the presenting complaint of 35/46. The extent of hospitalization was also high (35/46), and in most cases this was due to pain in bones and joints, dehydration, high fever, weakness and anemia. Blood transfusion once in the life time was received by 50% of the patients, twice by 7.7% of them and thrice by 3.8% of these patients.

Table 5: 'Percentile Range' for Electrolytes in Saudi Hb homozygous, heterozygous and in normal individuals.

Parameter	Hb Genotype	Sex	Mean	Median	Mode	SD	Percentile				
							2.5 th	25 th	50 th	75 th	97.5 th
Sodium (mmol/l)	SS	M F	138.0 140.0	138.0 140.0	187.0 140.0	1.2 1.09	135.0 136.0	- -	138.0 140.0	- -	140.0 148.0
	AS	M F	139.0 140.0	139.0 140.0	139.0 139.0	1.0 1.5	137.0 137.0	138.0 -	139.0 139.0	- 141.0	140.0 142.0
	AA	M F	139.5 136.0	139.0 137.0	139.0 136.0	6.9 6.5	128.0 118.0	136.0 135.0	139.0 137.0	- 139.0	157.0 141.0
Potassium (mmol/l)	SS	M F	4.7 4.4	4.7 4.2	4.6 4.2	0.63 0.46	3.5 3.4	- -	4.6 4.2	- 4.3	5.8 5.2
	AS	M F	4.4 3.9	4.3 3.9	4.0 3.8	0.37 0.2	4.0 3.5	4.2 -	4.3 3.8	4.5 4.1	5.0 4.2
	AA	M F	4.3 4.1	4.2 4.1	4.2 4.0	0.65 0.52	3.0 2.7	3.9 3.9	4.2 4.1	4.5 4.4	5.8 5.4
Chloride (mmol/l)	SS	M F	102.0 103.0	103.0 103.0	103.0 103.0	1.8 1.0	98.0 101.0	- -	- 103.0	- -	104.0 105.0
	AS	M F	102.0 104.0	102.0 104.0	102.0 102.0	3.0 2.1	98.0 100.0	100.0 102.0	102.0 104.0	104.0 105.0	107.0 107.0
	AA	M F	97.8 101.0	101.0 102.0	100.0 102.0	10.6 6.3	60.0 75.0	98.0 100.0	101.0 102.0	103.0 104.0	106.0 109.0
Carbon Dioxide (mmol/l)	SS	M F	21.5 23.0	21.5 23.0	21.0 23.0	0.5 3.1	20.5 17.0	- 21.0	21.0 23.0	- 25.0	22.0 27.0
	AS	M F	22.0 21.5	23.0 22.0	23.0 22.0	2.6 1.0	16.0 19.0	21.0 20.0	22.0 22.0	- -	23.0 24.0
	AA	M F	20.0 20.0	20.0 20.0	18.0 20.0	3.2 3.7	14.0 12.0	18.0 17.0	20.0 20.0	23.0 23.0	26.0 27.0

In conclusion, this study shows that, based on the results of clinical, hematological, and biochemical parameters, the SS disease is mild in Saudis from the eastern province compared to the disease reported for other populations and for other regions of Saudi Arabia (El-Hazmi *et al*, in preparation). Within the Saudi sickle cell anemia cases, variation is seen in the values of hematological and biochemical parameters. The exact cause (s) of this variation is/are not clear. It is possible that genetic and environmental factors all play a role in amelioration of the sickle cell disease. In previous studies, the HbF level has been implicated as one of the factors resulting in a mild disease. The HbF level is found to be higher in Saudis, but it is variable and there are several cases with lower HbF levels yet mild clinical manifestations. Other causes may include the interaction with other genetic abnormalities such as enzymopathies and thalassaemias. Recent studies on

Table 6: 'Percentile Range' for Glucose and Uric Acid in Saudi HbS homozygous, heterozygous and in normal individuals.

Parameter	Hb Geno-type	Sex	Mean	Median	Mode	SD	Percentile				
							2.5 th	25 th	50 th	75 th	97.5 th
Glucose (mmol//l)	SS	M F	4.9 4.5	5.0 4.6	3.6 4.6	0.9 0.4	3.0 3.5	- 4.4	4.9 4.6	- 4.7	6.3 5.0
	AS	M F	4.3 5.8	4.2 5.9	5.0 4.9	0.75 0.6	3.2 4.6	3.6 4.9	4.2 5.9	5.0 6.0	5.1 6.4
	AA	M F	4.6 4.4	4.3 4.1	4.3 4.0	1.8 1.2	1.6 1.9	3.6 3.7	4.3 4.1	5.3 5.2	8.0 6.7
Uric Acid (μmol//l)	SS	M F	323.0 260.0	333.0 270.0	260.0 270.0	45.0 44.0	223.0 182.0	318.0 240.0	333.0 270.0	- -	372.0 318.0
	AS	M F	348.0 294.0	360.0 307.0	360.0 -	33.4 163.0	300.0 100.0	312.0 114.0	336.0 200.0	360.0 414.0	390.0 450.0
	AA	M F	316.0 260.0	312.0 246.0	300.0 -	64.0 72.0	180.0 130.0	270.0 198.0	312.0 246.0	360.0 300.0	432.0 400.0

Table 7: Clinical findings in 46 sickle cell anemia patients in the eastern province.

Clinical Finding	No. of sickle cell anemia patients	% of sickle cell anemia patients
Anemia	27	58.7
Jaundice	9	19.6
Joint Pain	35	76.1
Bone Pain	35	76.1
Hepatomegaly	14	30.4
Splenectomy	0	0
Crisis	0	0
Hand and Foot Syndrome	0	0
Osteomyelitis	5	10.9
Aseptic Necrosis of bone	0	0
Leg Ulcers	3	6.5
Hospitalization	35	76.1
Transfusions	23	50.0

Saudis has shown an increase frequency of G-6-PD deficiency in HbS homozygotes and a beneficial effect of presence of G-6-PD deficiency in sickle cell anemia cases, on the hematological parameters and the clinical manifestation of sickle cell anemia in the eastern province (27,28). In addition, α-thalassaemia plays a significant role in amelioration of the sickle cell disease (3,29). Furthermore, the environmental factors including the climate and diet may add to the mildness and variability of the sickle cell disease in the Saudi population. There are extensive studies being conducted in the Saudi population, conducted in the Saudi population, to determine the possible ameliorating factors, both at genetic and cellular level.

ACKNOWLEDGEMENTS

This study was supported partly by a grant from King Abdulaziz City for Science and Technology, Project No. AT-4-074 and partly by King Saud University.

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Correspondence:
Mohsen A.F. El-Hazmi
Dept. of Medical Biochemistry,
College of Medicine,
King Khalid University Hospital,
P. O. Box 2925,
Riyadh 11461,
SAUDI ARABIA.