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Correlation of haemoglobin-f levels with biochemical parameters in pediatric patients with sickle cell anemia from Jazan, Saudi Arabia.

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Abstract

Objectives: To determine the Hb F levels and to correlate with Biochemical parameters such as Liver Function Test (LFT), Complete Blood Count (CBC) and disease severity in diagnosed cases of Sickle Cell Anemia (SCA) aged 1-16 years from Jazan Region of Saudi Arabia.

Methods: 5 ml blood was collected in Ethylene Diamine Tetraacetic Acid (EDTA) in vacutainers for automated complete blood count for determination of Hb F levels. 3 ml of blood was taken in plain tubes for analyses of biochemical parameters.

Results: Significant variations in CBC parameters were observed. There was a significant increase in White Bood Cells counts (WBC), platelets levels and Red Blood Cell Distribution Width (RDW) compared to controls while other indices were significant decreased compared to controls. More importantly, significant variations in Liver Function Test (LFT) parameters were observed and all LFT parameters were increased compared with controls. Hb S levels remained highly elevated to 77.74 ± 9.86% (mean ± SD) in all patients compared to controls in which HbS could not be detected. Interestingly, the levels of Hb F were significantly elevated 13.19 ± 9.85% (mean ± SD) in patients compared to controls 1.4 ± 0.6% (mean ± SD). Increases in all parameters were seen in both male and female patients compared to controls.

Conclusion: The clinical phenotype of SCA in Saudi Arabia undergoes regional variations with the Western province reporting more severe phenotype compared to the Eastern province which has many mild features. This indicates a need for long-term comprehensive studies with special attention and timely screening of SCA complications in each region.

Keywords: Hemoglobinopathies, Hereditary hematological disorder, Homozygous, β-Thalassaemia.

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Introduction

Hemoglobinopathies are a family of genetic disorders encompassing structural abnormalities of the haemoglobin molecule. The two commonest inherited disorders of haemoglobin that influence global well-being are β-thalassemia and Sickle Cell Disease (SCD). Both illnesses arise from alterations in the β-globin gene locus [1,2]. An estimated 300,000 new-borns with these disorders are born globally, every year. Sickle cell disease (SCD) results from a hereditary haematological disorder comprising defects in normal haemoglobin [3]. In the United States, roughly 80,000 Americans are suffering with the disease [4]. The occurrence of SCD is 1 in every 400-500 live births for the African-American population where the disease is the most prevalent [5]. SCD also occurs in descendants of settlers from Greece, Italy, India, Asia Minor and countries neighbouring the Mediterranean and Caribbean Seas [5]. The typical life expectancy for individuals with SCD is projected to be amongst 42 and 48 years of age, with about 85% living to be at least 20 years of age [6]. The sickle cell trait is the most found in individuals from Africa, South America, Central America, Caribbean islands, Mediterranean, India, and Saudi Arabia. Due to developments in clinical recognition, new-born screening, and therapeutic and preventative interventions, the death rates of children with SCD have reduced by roughly 53% over the past four decades [7].

SCD is triggered by a point mutation in the 6th codon of the β-globin gene in which 'T' is switched for 'A', altering a glutamic acid residue into a valine residue [8], and causing an altered β-globin chain, denoted to as sickle globin (βS). Two βS chains associate with two β-globin chains and become a variant haemoglobin molecule called sickle haemoglobin (HbS). This HbS is less soluble in its deoxygenated state and polymerizes, producing a distorted, sickle like shape of the red blood cells. The sickle cells get trapped in the circulation causing ischemic organ damage and pain crises. Sickled cells are extremely fragile with a reduced lifespan, leading to haemolytic anaemia [9]. Sickle cell anaemia mutation changes

the chemical properties of haemoglobin, the iron and protein complex that carries oxygen within red blood cells [10]. Individuals with two normal A alleles (AA) have normal haemoglobin, but subjects with two mutant S alleles (SS) develop sickle cell anaemia. Subjects who are heterozygous for the sickle cell allele (AS) have both normal and abnormal haemoglobin. Heterozygous (AS) subjects are carriers of the sickle cell trait with both A and S alleles being codominant [11].

Hb F has 2 α-globin polypeptide chains and 2 γ-globin chains. The γ-globin chains are encoded by the genes (HBG2 and HBG1) present in the β-globin gene-like cluster (Chr 11p) that differ by the presence of glycine/alanine at position γ136 [12]. The pathophysiology of SCD is based on polymerization of deoxy sickle Hb. Increased levels of Hb F retard this process because Hb F reduces Hb S concentration [13]. Because of the importance of HbF in this biochemical process, it is important to evaluate patients with SCD for HbF regularly. The current study was thus designed to evaluate the Hb F concentrations and correlate with chemical markers such as Liver Function Test (LFT), Complete Blood Count (CBC) and disease severity in subjects from Jazan Region of Saudi Arabia.

Materials and Methods

Study design

Identification and screening of 1 to 16 years old patients was carried out at Samtah General Hospital, Jazan, Saudi Arabia. Information on age at onset of symptoms, number of transfusions, hospitalizations, and severe pain episodes in the past year; cerebrovascular complications, and avascular necrosis; and findings on physical examination were recorded. A cross sectional study was conducted over a four month period after confirmation of homozygous SS disease by Hb electrophoresis. All patients who were severely anaemic (Hb<5 g/dl) were excluded. Patients along with their parents provided signed informed consent. The study was approved from ethical committee of College of Applied Medical Sciences (CAMS, KSU).

Sample collection

About 5 ml of peripheral venous blood samples each were collected in anti-coagulant vials for assessments of complete blood count and fetal haemoglobin levels. Blood was also collected without anti-coagulant for analyses of biochemistry markers.

Complete blood count (CBC)

Hematological values were measured on fully Automatic blood cell counter hematology analyzer (Coulter LH 780). The following parameters were subjected into analysis: erythrocyte parameters - red blood cell count (RBC), hemoglobin concentration (HGB), hematocrit (HCT) or packed cell volume (PCV), MCH, MCHC and RDW. Information related to the size, shape, and relative maturity of blood cells; leukocyte parameters and platelet parameters were collected. All the hematological values were compared to the reference values.

Sickle cell screening

Screening of blood for the detection haemoglobin S was carried out. Erythrocytes were lysed by saponin and the released haemoglobin is reduced by dithionite in a phosphate buffer. Reduced HbS is characterized by its very low solubility and formation of nematic liquid crystals called tactoids. The system becomes turbid in the presence of HbS or non-S sickling haemoglobin's. This was further confirmed by electrophoresis.

Liver function tests

Enzyme activity was measured for Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) using the Dimension® Xpand® Plus clinical chemistry system based on the conversion of NADH to NAD involved in the reactions catalyzed by the enzymes. The change in absorbance with time due to this conversion product is directly proportional to the AST activity and is measured using a bichromatic rate technique with measurements at 340, 700 nm. Alkaline phosphatase (ALP) activity was also measured where p-nitrophenol (p-NP) was produced by the catalytic activity of ALP. The change in absorbance at 405 nm due to the formation of p-NP which is proportional to the ALP activity, since other reactants are present in non-rate limiting quantities and is measured using a bichromatic (405, 510 nm) rate technique.

Total bilirubin (TBI)

Bilirubin in the sample was solubilized by dilution in a mixture of caffeine/benzoate/acetate/EDTA. Following addition of diazotized sulfanilic acid, diazo-bilirubin, a red chromophore is formed representing the total bilirubin which is measured using wavelengths 540nm and 700 nm. Direct bilirubin (DBI) test was also performed by which the direct bilirubin conjugated by the liver and set ready for excretion could be found.

Hemoglobin electrophoresis

The fully automated VARIANT™ II Hemoglobin Testing System was used for the estimation of hemoglobin's A2 and F. The presumptive identification of hemoglobin variants was done based on chromatographic separation of the analytes by high performance liquid chromatography (HPLC). Lipemia up to a level of 5680 mg/dL of triglycerides and icterus up to a level of 20 mg/dL do not interfere. Hemolysis of the sample is not relevant, as whole blood is hemolyzed in the course of the analysis.

Statistical analysis

Data was analysed using SPSS software. Normally distributed continuous variables were summarized as mean and compared using the student's t test. In all cases, $p < 0.05$ was considered significant.

Results

Comparison between results of ALL patients and control in Complete Blood Count

The mean of WBC in the patients was significantly elevated to 15.0 ± 6.9 × 10^9/L (P<0.0001) compared to that of controls (7.25 ± 3.75 × 10^9/L). This significance was also seen in platelets (P<0.0004), with Platelet mean for patients being 383.66 ± 175.75 while in controls it was 300 ± 150. While all other parameters observed in CBC (RBC, Hb, Hct, MCV, MCH, and RDW) were significantly higher (P<0.0001) and in MCHC (P<0.0038) compared to controls (Table 1).

Table 1. Complete blood count of clinical finding in all patients and controls.

Parameter	Patients		Controls		Two tailed P- Value
	Mean	SD	Mean	SD	
WBC	15.01	6.90	7.25	3.75	<0.0001
RBC	3.02	0.78	5	1.5	<0.0001
Hb	7.41	1.18	15.5	2.5	<0.0001
HCT	23.24	3.78	47	7	<0.0001
MCV	78.96	9.62	86	10	<0.0001
MCH	25.25	3.72	29.5	2.5	<0.0001
MCHC	31.94	1.97	33	3	0.0038
RDW	21.55	3.91	12.75	1.75	<0.0001
PLT	383.66	175.75	300	150	0.0004

Comparison between results of ALL patients and control in liver function tests

Statistically significant variations (P<0.0001) were observed in the levels of liver function test parameters in patients with mean being AST (53.5 U/L ± 26.41), ALT (29.8 U/L ± 21.15), ALP (172.7 U/L ± 65.32), total bilirubin (48.7 µmol/L ± 51.28) and direct bilirubin (12.4 µmol/L ± 26.52) compared to controls and values of 23.5 ± 13.5, 25 ± 15, 78 ± 39, 8.5 ± 8.5, 2.25 ± 2.25 respectively were reported (Table 2).

Table 2. Liver function test of clinical finding in all patients and controls.

Parameter	Patients		Controls		Two tailed P- Value
	Mean	SD	Mean	SD	
AST	53.53	26.41	23.5	13.5	<0.0001
ALT	29.88	21.45	25	15	0.0599
ALP	172.75	65.32	78	39	<0.0001
TBI	48.79	51.28	8.5	8.5	<0.0001
DBI	12.48	26.52	2.25	2.25	0.0002

Comparison between results of ALL patients and control in hemoglobin sub-types

HbS levels remained highly elevated with mean 77.74 ± 9.86 in patients compared to controls who did not show HbS in their blood. In healthy subjects, the mean of HbA were approximately 96.5 ± 1.5 compared to mean of patients 5.22 ± 9.46 (P<0.0001). In addition, the mean of HbF were significantly elevated to up to 13.19 ± 9.85 in patients compared to only 1.4 ± 0.6 in controls (Table 3).

Comparison between results of male patients and controls in complete blood count

The male patients who comprised 61% of the studied population are presented in (Table 5). The mean of WBC in the patients was 14.7 ± 6.68 × 10^9/L while in controls it was 7.25 ± 3.75 × 109/L that was highly significant (P<0.0001). Similar observations (P<0.0023) were seen in platelets of the patients with 392.24 ± 175.61 while in controls, the mean of platelet was 300 ± 150. All other CBC incidences (RBC, Hb, Hct,

MCV, MCH, and RDW) were considered significant (P<0.0001) and in MCHC (P<0.0856) (Table 4).

Table 3. Hemoglobin electrophoreses of clinical finding in all patients and controls.

Parameter	Patients		Controls		Two tailed P- Value
	Mean	SD	Mean	SD	
Hb A	5.22	9.46	96.5	1.5	<0.0001
Hb A2	3.84	1.22	2.5	0.5	<0.0001
Hb F	13.19	9.85	1.4	0.6	<0.0001
Hb S	77.74	9.86	--	--	--

Table 4. Complete blood count of clinical finds in male patients and controls.

Parameter	Patients		Controls		Two tailed P- Value
	Mean	SD	Mean	SD	
WBC	14.7	6.68	7.25	3.75	<0.0001
RBC	3.04	0.76	5	1.5	<0.0001
Hb	7.49	1.08	15.5	2.5	<0.0001
HCT	23.29	3.39	47	7	<0.0001
MCV	78.57	9.84	86	10	<0.0001
MCH	25.32	3.79	29.5	2.5	<0.0001
MCHC	32.19	2.08	33	3	0.0857
RDW	21.60	3.65	12.75	1.75	<0.0001
PLT	392.24	175.61	300	150	0.0023

Comparison between results of MALE patients and control in liver function tests

In male patients, the mean of liver function test parameters were AST (55.9 U/L ± 30.65), ALT (31.8 U/L24.05), ALP (174.7 U/L ± 65.7), total bilirubin (52.2 µmol/L ± 58.47) and direct bilirubin (13.32 µmol/L ± 27.23) were significantly higher (P<0.0001) compared to control subjects where means of 23.5 ± 13.5, 25 ± 15, 78 ± 39, 8.5 ± 8.5, and 2.25 ± 2.25 respectively were reported (Table 5).

Table 5. Liver function test of clinical finds in male patients and controls

Parameter	Patients		Controls		Two tailed P- Value
	Mean	SD	Mean	SD	
AST	55.98	30.65	23.5	13.5	<0.0001
ALT	31.82	24.05	25	15	0.0626
ALP	174.82	65.70	78	39	<0.0001
TBI	52.22	58.47	8.5	8.5	<0.0001
DBI	13.32	27.23	2.25	2.25	0.0020

Comparison between results of male patients and control in hemoglobin sub-types

HbS levels remained highly elevated with mean 80.30 ± 9.08 in males compared to controls. The mean of HbA was 96.5 ± 1.5 in controls, these levels drastically dropped in male subjects with SCA to as low as 3.66 ± 7.56. The mean of HbA2 and HbF were significantly higher (P<0.0001) (4.04 ± 1.13,

11.97 ± 8.93) compared to controls (2.5 ± 0.5, 1.4 ± 0.6) respectively (Table 6).

Table 6. Hemoglobin electrophoreses clinical find in male patients and controls.

Parameter	Patients		Controls		Two tailed P- Value
	Mean	SD	Mean	SD	
Hb A	3.66	7.56	96.5	1.5	<0.0001
Hb A2	4.04	1.13	2.5	0.5	<0.0001
Hb F	11.97	8.93	1.4	0.6	<0.0001
Hb S	80.30	9.08	-	-	--

Comparison between results of female patients and control in complete blood count

The female patients who comprised 39% of the studied population are presented in (Table 7). The mean of WBC in the patients was 15.4 ± 7.3 × 10^9/L while in controls it was 7.25 ± 3.75 × 10^9/L that is considered highly significant (P<0.0001). Similarly, the mean of platelet in the female patients was 370.23 ± 177.38 while in control it was 300 ± 150, considered significant (P<0.0628). All other CBC incidences (RBC, Hb, Hct, MCV, MCH, and RDW) were highly significant (P<0.0001) and in MCHC (P<0.0096).

Table 7. Complete blood count of clinical finds in female patients and controls.

Parameter	Patients		Controls		Two tailed P- Value
	Mean	SD	Mean	SD	
WBC	15.4	7.29	7.25	3.75	<0.0001
RBC	2.97	0.80	5	1.5	<0.0001
Hb	7.27	1.31	15.5	2.5	<0.0001
HCT	23.15	4.36	47	7	<0.0001
MCV	79.56	9.35	86	10	<0.0044
MCH	25.13	3.65	29.5	2.5	<0.0001
MCHC	31.53	1.71	33	3	0.0096
RDW	21.46	4.33	12.75	1.75	<0.0001
PLT	370.23	177.38	300	150	0.0628

WBC: White Blood Cells; RBC: Red Blood Cells; Hb: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; RDW: Red Cell Distribution Width; PLT: Platelets

Comparison between results of female patients and control in liver function tests

In female patients the mean of liver function test parameters were AST (49.6 U/L ± 17.55), ALT (26.8 U/L ± 15.37), ALP (169.8 U/L65.45), total bilirubin (43.4 µmol/L37.46) and direct bilirubin (11.14 µmol/L ± 25.66) highly significant (P<0.0001) compared to control subjects with values of 23.5 ± 13.5, 25 ± 15, 78 ± 39, 8.5 ± 8.5, 2.25 ± 2.25 respectively (Table 8).

Table 8. Liver function test of clinical finds in female patients and controls.

Parameter	Patients		Controls		Two tailed P- Value
	Mean	SD	Mean	SD	
AST	49.68	17.55	23.5	13.5	<0.0001
ALT	26.83	15.37	25	15	0.5962

ALP	169.68	65.45	78	39	<0.0001
TBI	43.42	37.46	8.5	8.5	<0.0001
DBI	11.14	25.66	2.25	2.25	0.0343

AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; ALP: Alkaline Phosphatase; TBI: Total Billirubin; DBI: Direct Billirubin

Comparison between results of female patients and control in haemoglobin sub-types

HbS levels remained highly elevated with mean 73.74 ± 9.79 in male patients compared to controls who did not show HbS in their blood. While the mean of HbA was 96.5 ± 1.5 in controls, these mean drastically dropped in the patients with SCA to as low as 7.64 ± 11.51. The mean of HbA2 and HbF were also elevated (3.52 ± 1.29 and 15.09 ± 10.99) considered highly significant (P<0.0001) compared to controls (2.5 ± 0.5 and 1.4 ± 0.6) respectively (Table 9).

Table 9. Hemoglobin electrophoreses clinical find in female patients and controls

Parameter	Patients		Controls		Two tailed P- Value
	Mean	SD	Mean	SD	
Hb A	7.64	11.51	96.5	1.5	<0.0001
Hb A2	3.52	1.29	2.5	0.5	<0.0001
Hb F	15.09	10.99	1.4	0.6	<0.0001
Hb S	73.74	9.79	-	-	--

Discussion

Sickle cell disease (SCD) is a genetic disorder resulting due to the existence of a mutated hemoglobin called hemoglobin S (HbS) [1-2]. Sickle cell trait or the carrier state is the heterozygous form characterized by the presence of around 40% HbS, absence of anemia, isosthenuria and hematuria [4]. Under conditions leading to hypoxia, it may become a pathologic risk factor. Though carriers of sickle cell trait do not suffer from SCD, individuals with one copy of HbS and one copy of a gene that codes for HbC or Hb beta-thalassemia have a less severe form of the disease [12]. SCD is the most severe form. For the first 6 months of life, infants are protected largely by elevated levels of Hb F; soon thereafter, the condition becomes evident.

The prevalence of SCA in Saudi Arabia was found to be a relatively common genetic disorder and varies considerably in different parts of the country [14]. The highest prevalence rate was reported in the Eastern province, followed by the Southern and Western provinces [14]. Clinical and haematological variability was found in SCA pathophysiology in Saudi Arabia with existence of a milder and a severe phenotype [15]. Therefore, the current cross sectional study was conducted in children with Sickle Cell Anaemia and assessments of fetal haemoglobin and other hemoglobin sub-types along with alterations in liver function tests markers and variations in complete blood counts were performed in around 100 patients who attended Samtah General Hospital, Jazan, Saudi Arabia. In addition, close monitoring of disease severity with respect to frequency of admissions and blood transfusions were monitored in all subjects.

The complete blood picture of children with SCA was reported to be changing with age. These changes include mean levels of haemoglobin and its subtypes, increases in percentage of sickle cells and alterations in blood parameters such as Hb, WBCs, RBCs, platelets etc. Quantitative and qualitative changes in RBCs and haemoglobin levels due to the process of sickling have been well reported [16]. This can happen due to haemolysis and the degree of haemolysis is inversely proportional to haemoglobin concentration SCA [17]. In addition, although SCA is primarily a disease of the red blood cell, the WBCs and other parameters are significantly altered in SCA.

In the current study which includes all patients with SCA, there was a significant increase in WBC counts and platelets levels compared to controls while other indices decreased compared to controls (p<0.0001). Similar results were observed in male and female subjects who showed similar significant increases in WBC counts and platelet levels compared to controls while other CBC parameters were significantly altered (P<0.0001). Similar results were observed [17-19]. Anaemia was commonly present in this study but very well tolerated. It has been shown that while patients with Hb levels of 6-7 g/dL can participate in activities of daily life but, their exercise tolerance is very limited. Anaemia may result from augmented RBC turnover and foliate utilization [20].

Irregularities in LFTs have been reported to be common in SCA. Although the frequency and pathophysiology of liver disease in SCA patients along with the etiological and pathological features are not totally understood, the assessment of liver function is employed routinely [21]. In the current study, statistically significant alterations were also seen in

which the levels of liver function test parameters in all patients were compared to controls ($p<0.0001$). These results were also coherent in male and female patients wherein the levels of liver function test parameters significantly elevated compared to controls ($p<0.0001$). Unlike a previous study which reported no significant alterations in the levels of various liver function enzymes in steady state [22], the current study showed significant increases in LFT parameters similar to the results observed [23] and milder increases as also observed [24]. These findings suggest that a multifactorial etiology can exist for occurrence of liver disease in SCA patients such as blood transfusions, extent of sickling, presence of confounding diseases etc.

SCA is suggested by the characteristic clinical picture of chronic hemolytic anemia and vaso-occlusive crisis. The diagnosis is established when electrophoresis shows the occurrence of homozygous HbS [15]. In addition to HbSS, this test may likewise document other hemoglobinopathies [1]. While hematologic changes symptomatic of the disorder are apparent as early as the age of 10 weeks, clinical features of SCD largely do not appear until the latter half of the first year of life, when fetal Hb levels drop inadequately for abnormalities caused by HbS to manifest. Sickling variants and sickle trait need to be distinguished from HbS disease [4]. HbS occurs in combination with other hemoglobin's in a double heterozygous state.

A homozygous patient will have hemoglobin SS (HbSS, 80-90%), hemoglobin F (HbF, 2-20%), and hemoglobin A2 (HbA2, 2-4%). A carrier will have HbSS (35-40%) and hemoglobin A (HbA, 60-65%). The levels of HbS levels remained highly elevated to approximately 77% in all patients compared to controls in whom HbS could not be detected ($p<0.0001$). Similar increases were also reported in male and female subjects compared to controls. The levels of HbA were predominant as expected in healthy subjects while patients with SCA reported minimal levels. Interestingly, the levels of HbF were significantly elevated in approximately 13% in patients compared to controls. In addition, the HbS and HbA2 levels remained highly elevated in all patients compared to controls. The levels of HbS observed in the current study were far higher than previously reported for a study from the Middle Eastern region who showed the range of HbS levels to be <40% [25]. In addition, the HbF levels reported in this study are slightly greater (13%) than previously reported values of 5-8% in SCA, but in the range for values reported for SCA trait carriers (1.4-14%) [26]. It is interesting to note that in persons with SCA, high levels of HbF in children may decrease the severity of the disease. This could be due to the inhibition of polymerization of HbS by HbF [27].

More importantly, in this study, the assessment for evaluation of disease severity in patients was performed by evaluating the frequency of admissions and blood transfusions and monitoring of the frequency and types of pain indicated that a majority of subjects underwent hospital admissions and blood transfusions. Most subjects also reported pain predominantly in the back, legs and arms. Similar results of blood transfusions and admissions were observed [28,29]. In addition, the pain episodes observed in this study were coherent with the earlier studies [30]. Therefore, pain management is a necessary part of SCA symptomatic relief.

In summary, this study revealed that SCA caused significant variations in CBC along with LFT parameters. In addition, variations were observed in percentages of various haemoglobin's. A significant number of people reported hospital admissions, blood transfusions and pain in arms, leg and back during the course of the study. This study indicates that closer monitoring of these parameters is needed to improve the overall quality of life of subjects with SCA. Since sickle cell patients present with symptoms and signs of various hepatobiliary conditions, careful history and clinical examination and specific laboratory tests are essential to avoid unnecessary complications. Hemolysis, a characteristic of SCA along with liver disease can contribute to the elevation of direct and indirect bilirubin and liver enzymes. The study signifies that more detailed cohort and interventional studies are necessary to assess the role of liver function test parameters in children for efficient management of SCA.

Conclusion

This study has conclusively established the substantial variations in liver function test parameters in SCD in patients and control from Samtah General Hospital, Jazan, and Kingdom of Saudi Arabia. The clinical phenotype of SCA in Saudi Arabia undergoes regional variations with the Western province reporting more severe phenotype compared to the Eastern province which has many mild features. This indicates a need for long-term comprehensive studies with special attention and timely screening of SCA complications in each region. There is a need for methodical, case-control studies that document the occurrence, genetic and clinical epidemiology of SCA in different areas of Saudi Arabia to help forecast disease severity in Saudi Arabia. Further studies on the risk stratification of patients can identify more children with disease and prevent disease complications.

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