

A Study of Silent Cerebral Infarcts in Pediatric Patients with Sickle Cell Disease by Magnetic Resonance Imaging

Eglal Hussein S. S. Al Gohary¹; Muneer Al Bagshi²; Qasem Al Alwan³; Ashwak Safi El Din M.⁴; Waleed H. AlbuAli¹ and Fulton S.D'souza¹

¹Pediatric Department, College of Medicine, King Faisal University

² Pediatric Department, Maternity and Children Hospital- Al Ahsa

³ Radiology Department; King Fahd Hospital- Al Ahsa.

⁴Department of FAMCO Medicine, college of Medicine King Abdel Aziez University
eglal_hussein2007@yahoo.com

Abstract: Sickle cell disease (SCD) is a common hereditary disease in Saudi Arabia, with a high prevalence in the Eastern and Southern regions. Among the genitive basis of the disease, the homozygous form (Hb-SS) is the most serious one. Silent cerebral infarcts (SCI) are the most common form of neurologic injury in those children and are defined as an abnormal magnetic resonance image (MRI) of the brain accompanied by undetectable neurocognitive deficits on examination. **OBJECTIVES:** To detect the relative frequency of SCI using MRI among children with SCD as general and especially homozygous form (Hb-SS). To evaluate associated cognitive impairment on basis of occurrence SCI in one hand and in relation to other risk factors associated with this chronic disease without SCI finding in the other hand. **METHODOLOGY:** A hospital based cross-sectional study was conducted on a total of 90 patients with SCD of both sexes, who had been followed since birth. They were consecutively seen and chosen neither have previous seizure or other neurological abnormality nor having history of cerebrovascular accident. From these patients, 59 were submitted to undergo MRI scanning and to evaluate their IQ level. Relations between MRI finding, IQ levels and laboratory results are conducted. **RESULTS:** Age distribution of the studied SCD patients was ranged from 3 to 12 years and 8 months; with a mean equals 8.08 ± 2.58 yrs. Male to female ratio was 3 to 2. SCI findings are detected in **two patients; homozygous Hb-SS** [A female and male patients, their ages 9.17 and 7.75 years old respectively, have MRI of the brain with increased signal intensity in multiple T2-weighted images] **out of 53 homozygous Hb-SS** (the relative frequency **3.77%**), and out of total 59 sickling patients subjected to MRI study (the relative frequency **3.39%**). Statistical analysis revealed strong significant correlations of IQ values decline in **homozygous Hb-SS** patients having SCI findings with all studied parameters ($P < 0.01$). Moreover, IQ values significantly inversely correlated with both age ($P=0.01$) and percentage of Hb.S ($P=0.04$); where it significantly directly correlated with both total Hb. Concentration ($P=0.05$) and percentage of Hb.F ($P=0.013$) in sickling patients without evidence of SCI. In spite of IQ values in patients with HbS β 0-thalassemia showed the lowest subnormal values, they did not reach to statistical level. Percentage of Hb.A2, serum ferritin level, total leukocyte count, and platelets count are forming also risk factors that should be considered in the follow up of patients with SCD. **CONCLUSION:** SCD-SS is associated with an increased risk of silent infarction in diseased patients in a percentage of **3.77%** in Al Ahsa, eastern area of KSA. A decline in the IQ values of those patients was significantly related to their age, Hemoglobin concentration, and percentage of Hb.S, Hb.F, and Hb.A2. Patients with HbS β 0-thalassemia are emerging to prone to risk of silent infarction & hazard of decline IQ as patient with homozygous Hb.SS. **RECOMMENDATIONS:** Regional newborn screening programs for SCD using hematological genetic phenotypic analysis should be considered in eastern area of KSA. Meticulous follow up of SCD-SS children, specially preteen age, by routine brain MRI scan will yield better prognosis and preserve their cognitive achievements. A Strategy for preventive therapy must be designed.

[Eglal Hussein S. S. Al Gohary; Muneer Al Bagshi; Qasem Al Alwan; Ashwak Safi El-Din M; Waleed H. AlbuAli and Fulton S.D'souza **A Study of Silent Cerebral Infarcts in Pediatric Patients with Sickle Cell Disease by Magnetic Resonance Imaging**] J Am Sci 2012;8(10):629-640]. (ISSN: 1545-1003).
<http://www.americanscience.org>.86

Key words: Sickle cell disease; Silent cerebral infarcts; Magnetic resonance image; Cognitive impairment; IQ; Pediatrics

1. Introduction

Sickle cell disease (SCD) is a group of recessively inherited hemoglobinopathies common among people of Equatorial African, Saudi Arabian and Mediterranean ancestry, and now widespread in

the Americas and Europe (**Steinberg¹**). The causative mutation is the substitution of valine for glutamic acid at the sixth position of the β globin chain (Glu6Val). Sickle cell hemoglobin (HbS) behaves like normal hemoglobin when fully

oxygenated, but at low oxygen tension the hydrophobic valine residues cause the HbS to polymerize, resulting in gel formation and increasing red cell density. The rigid and deformed sickle cell is damaged by mechanical stress during passage through the vasculature, resulting in a chronic hemolytic anemia with red cell destruction, the rate of which is influenced by factors such as infection and drugs (**Kirkham, 2**).

The homozygous state (HbSS) is known as sickle cell anemia; compound heterozygotes with HbS β 0-thalassemia, who also have a severe reduction in the synthesis of β globin chains, have a similar prevalence of complications, including stroke, although variations in phenotype in these conditions are not fully understood (**Buchanan et al., 3**).

In Hofuf area (Located in Al-Hassa region: Eastern province of Saudi Arabia) there is a high prevalence of sickle cell gene; alpha, beta thalassaemia and Glucose 6 phosphate dehydrogenase (G6PD) deficiency; coexistence of these diseases is not uncommon. The frequency of sickle cell gene in Hofuf area ranges from 0.15-0.25. Homozygous SCD prevalence ranges from 1.0-1.5% (**Jastaniah, 4**). It is believed that SCD patients in Hofuf and other areas in Eastern province of Saudi Arabia are having milder disease with less frequent complications and good outcome, due to the interaction between thalassaemia and SCD and for having Asian haplotype (**Alabdulaali, 5**).

Children with SCD can develop acute neurological symptoms and signs consistent with cerebrovascular accident (CVA), either spontaneously or in the context of an acute illness such as infection. There is a high risk of CVA recurrence—particularly for patients presenting spontaneously—that is reduced but not eliminated by regular blood transfusion (**Roach et al., 6**). In patients with SCD, cerebral infarction has been reported to be the most common cause of stroke in the first two decades of life and from the fourth decade onwards, whereas hemorrhagic stroke occurs more commonly in the third decade (**Wellems et al., 7**).

Silent infarction is defined as an abnormal magnetic resonance image (MRI) of the brain with increased signal intensity in multiple T2-weighted images accompanied by undetectable neurologic deficits on examination. SCI is relatively common in children with sickle cell disease and is associated with impaired cognitive function. However, new findings suggest that cognitive impairment can also be present in patients with sickle cell disease who are free of focal brain damage (**Pegelow et al., 8**).

Much progress has been made during the past several decades in gaining understanding about the natural history of sickle cell disease and management

approaches aimed at treating or even preventing certain disease complications (**NIH, 9**). In addition to the inhibition of hemoglobin S polymerization, newer targets have been defined during the past one to two decades. (**Scothorn et al., 10**).

Aim of the Work:

This study is designed to address the conundrum of why some patients with sickle cell disease (SCD) do well whereas others fare poorly. Our targets are to evaluate the results of standardized magnetic resonance imaging (MRI) of the brain in children with SCD to determine the frequency of occurrence of Silent cerebral infarcts (SCI) in those patients; to clarify relationship between SCI and the occurrence of other patterns of brain injury as cognitive impairment & to identify the correlation between those neurodiagnostic tests and other risk factors associated with sickle cell disease.

2. Patients and Methods:

A hospital based cross-sectional study was conducted on a total of 90 SCD patients of both sexes (36 *females* and 54 *males*) who had been followed since birth in pediatric outpatient clinic of Hematology and pediatrics inpatient department in the Maternity and Children Hospital in Al Ahsa.

Data were analyzed from 90 children who was diagnosed already to have sickle cell disease-SS; [6 of them were sickle-thalassemia (SCD- **SB**^o)] with age range 2 years to 12 yrs and with a mean equals 8.08 yrs. \pm 2.58 yrs SD. Patients who had experienced an overt stroke, even history of SCI or any neurological disorders were excluded. Patients who participated in this study were subjected to thorough clinical examination; laboratory investigations and MRI. These lab investigations include CBC (HB conc., TLC, and Platelets count), determination of serum ferritin level and determination of hemoglobin S, F, and A2 percentage by hemoglobin electrophoresis. Hemoglobin electrophoresis helps also to detect patients with sickle cell disease-thalassemia (SCD-**SB**^o).

Only, 59 patients could attend to do MRI where 1.5 Tesla MRI Siemens Symphony was used. Patients underwent MR imaging of the brain at 1.5 T (Siemens Medical Systems, Iselin, NJ) with a standard quadrature head coil. A conventional T1-weighted image set was acquired in the transverse plane with parameters as follows: 266/6 (TR/TE), 23-cm field of view, 90-degree flip angle, 256 \times 256 matrix, and three acquisitions in an imaging time of 4 min 35 s. A conventional T2-weighted image set was acquired in the same orientation with parameters as follows: 3.5/19, 93; 23-cm field of view; 256 \times 256

matrix; and one acquisition in an imaging time of 5-7 minutes (Pegelow *et al.*, 11).

Our protocol, Axial T1,T2, Flair; & sagittal T2; and diffusion & MRA, was done for all patients. MRI findings were scored as normal or abnormal, relying on a combination of T1-weighted, T2-weighted, and fluid-attenuated inversion recovery images when available (Wang *et al.*, 12). Small unifocal lesions (<1 cm) or large multifocal lesions were sufficient to classify MR imaging findings, with lesions broadly defined to include lacunar infarction, encephalomalacia, or leukoencephalopathy (Shah and Laude, 13). Leukoencephalopathy was defined as degeneration or demyelination of white matter, usually seen as high signal intensity on T2-weighted MRI (PediatricAtlas, 14; and Vendt *et al.*,15)

Within our patients, there diffuse cortical and subcortical high T2 signal intensities in keeping with multiple infarcts with normal brain stem & cerebellum and normal MRA are noted in 2 cases out of 59.

MRI findings classified the patients as sickling patients with normal MRI [either Hb-SS(51 patients) or Hb- SB^o (6 patients)], and patients with "silent infarct" in their MRI, (They are Hb-SS, 2 cases).

Those 59 patients of total 90 included in this study were subjected to cognitive ability assessment. Results of calculated IQ were classified as **superior** (above average; high IQ), **normal** (normal average range IQ), **subnormal** (below average; low IQ). We have evaluated the patient by three methods:

1- Stanford-Binet Intelligence Scales, Fifth Edition (SB5, 16). According to the publisher's website, it measures the IQ= mental age/actual age X100.

Type: Cognitive ability assessment. Purpose: Individually administered assessment of intelligence & cognitive abilities. Measures: Fluid Reasoning, Knowledge, Quantitative Reasoning, Visual-Spatial Processing, and Working Memory. Ages: 2 to 85+ years.

IQ Scale: Over 140 - Genius or almost genius; 120 - 140 - Very superior intelligence; 110 - 119 - Superior intelligence; 90 - 109 - Average or normal intelligence; 80 - 89 - Dullness; 70 - 79 - Borderline deficiency in intelligence; Under 70 - Feeble-mindedness (SB5, 17)

2- Seguin Form Board Test is used to assess visual discrimination and matching and eye-hand coordination. Previous analysis has shown the factor loadings for the same scale to differ among age levels, so the test may be measuring different abilities at different age levels (Lindstrom *et al.*, 18).

3- Social maturation evaluation (McAnarney, 19).

Normal Distribution of IQ Scores

50% of IQ scores fall between 90 and 110

70% of IQ scores fall between 85 and 115

95% of IQ scores fall between 70 and 130

99.5% of IQ scores fall between 60 and 140

Low IQ & Mental Retardation

An IQ under 70 is considered as "mental retardation" or limited mental ability.

High IQ & Genius IQ

Genius or near-genius IQ is considered to start around 140 to 145.

Statistics studies are applied to evaluate the results, find statistical relations and calculate correlations between different risk factors which having a print on the course of the disease and prognosis of cases.

Statistical Analysis:

All the collected data were reviewed, coded, entered and analyzed using a Statistical Package of Social Science (SPSS) software; version 17.0. Continuous variables were presented as mean values \pm standard deviation, while qualitative variables were presented as absolute frequencies and relative frequencies (percentages).

Contingency tables with calculation of chi-square test will be used to evaluate association between categorical variables to assess the significance in the differences between proportions. On the other hand, the significance in the differences between means was assessed using independent Samples student *t* test for di-chotomous nominal variables and one-way ANOVA test for multi-chotomous nominal variables.

The Pearson Correlation Coefficients will be applied to measure association between the continuous variables. All presented P-values were two-tailed and taken at a significance level of 0.05 and 95% Confidence Interval.

3. Results:

The results of this work are represented in the following tables and figures.

First: patients are classified into patients(Hb-SS) with normal MRI finding (Gr.I), patients(Hb-SS) with silent infarct MRI (Gr.II) and patients(Hb- SB^o) without silent infarct MRI (Gr.III).

In our study, there is 2 cases (3.39%) out of total 59 Sickling patients showed Silent Infarction evidence in their MRI reading.

The 1st case: [A 9 years & 2 months old female patient with small infarct left parietal and subcortical areas] and the 2nd case: [A 7 years & 9 months old male patient with small infarct right parietal and temporal areas] – Figures -1 to 6.

Genetic analysis revealed that both cases with manifestations SCI are homozygous (Hb-SS), giving a frequency rate of 3.77% out of homozygous Hb-SS (53) patients and frequency rate of 3.39% out of all

patients either homozygous or heterozygous **Hb- SB^o** (59) patients.

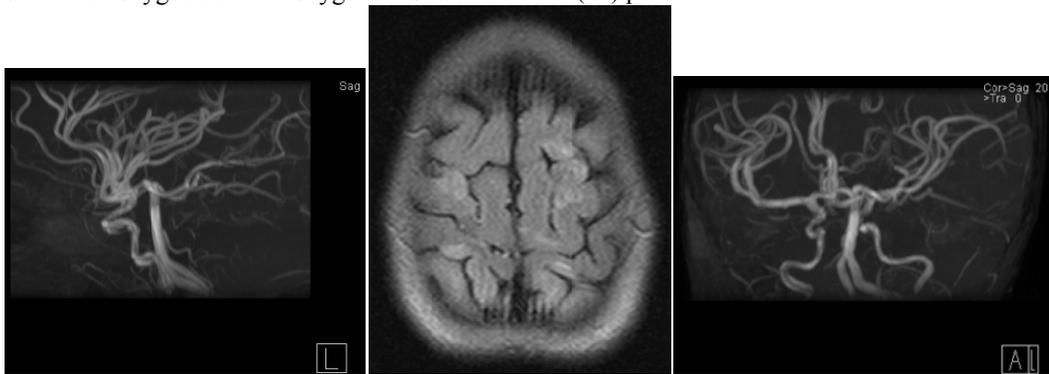


Figure 1

Figure 2

Figure 3

[MRI angiography shows Grade 1 turbulence in an asymptomatic child with SCD. The left posterior communicating artery shows less signal intensity compared with the right.]

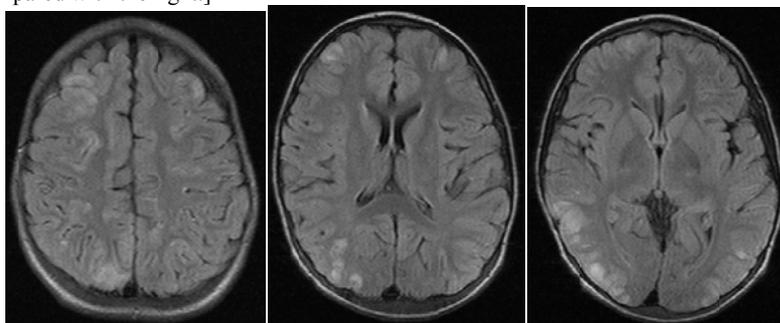


Figure 4

Figure 5

Figure 6

[T2-weighted MRI scan of the brain shows areas of increased signal intensity involving the white matter of the left parietal lobe, reversible posterior leukoencephalopathy.]

Table 1: Descriptive &Comparative data for all variables among patients with Hb-SS, either with normal MRI(86.4%) or have infarct MRI(3.39%), and patients with Hb-SB^o(10.2%) who are with normal MRI:

Variables	Groups	N	%	Mean	± SD	±Std. Error	Range	M. Square	F	Sig.
AGE (years)	Normal-MRI/HbSS	51	86.4%	7.4	2.7	0.30	2.00-12.00	2.183	.298	.743
	Infarcts-MRI/HbSS	2	3.4%	8.4	0.9	0.63	7.75-9.00	7.334		
	Normal-MRI/Hb- SB ^o	6	10.2%	8.2	3.7	1.51	3.00-11.25			
IQ%	Normal-MRI/HbSS	51	86.4%	92.8	18.02	2.50	35.00-122.0	303.913	.956	.391
	Infarcts-MRI/HbSS	2	3.4%	90.7	7.07	5.00	86.00-96.00	317.921		
	Normal-MRI/Hb- SB ^o	6	10.2%	82.2	17.44	7.12	59.0-100.0			
S. Ferritin (ng/dl)	Normal-MRI/HbSS	51	86.4%	219.7	231.91	30.19	51.2-1769.0	20228.843	.412	.664
	Infarcts-MRI/HbSS	2	3.4%	202.5	74.25	52.5	150.0-255.0	49041.357		
	Normal-MRI/Hb- SB ^o	6	10.2%	133.7	52.29	21.35	91.2-212.0			
Hb.Conc. g/dl	Normal-MRI/HbSS	51	86.4%	8.94	1.31	0.15	6.8-12.0	2.339	1.471	.236
	Infarcts-MRI/HbSS	2	3.4%	7.75	0.21	0.15	7.6-7.9	1.590		
	Normal-MRI/Hb- SB ^o	6	10.2%	8.32	0.57	0.23	7.4-9.0			
WBC Cell/mm ³	Normal-MRI/HbSS	51	86.4%	9.08	3.59	0.41	3.30-18.90	19.337	1.393	.254
	Infarcts-MRI/Hb-SS	2	3.4%	5.05	1.34	0.95	4.10-6.00	13.88		
	Normal-MRI/Hb- SB ^o	6	10.2%	10.10	5.59	2.28	4.30-18.80			
Platelets Count Cell/mm ³	Normal-MRI/HbSS	51	86.4%	339.7	101.79	11.60	124.0-528.0	7498.99	.696	.501
	Infarcts-MRI/HbSS	2	3.4%	411.0	125.87	89.00	322.0-500.0	10767.3		
	Normal-MRI/Hb- SB ^o	6	10.2%	371.7	126.15	51.50	234.0-536.0			
MCV	Normal-MRI/HbSS	51	86.4%	75.22	9.69	1.104	54.00-99.00	215.59	2.232	.114
	Infarcts-MRI/HbSS	2	3.4%	77.00	15.56	11.00	66.00-88.00	96.57		
	Normal-MRI/Hb- SB ^o	6	10.2%	66.53	10.36	4.23	53.00-83.00			
Hb-S%	Normal-MRI/HbSS	51	86.4%	65.58	7.44	0.87	45.80-81.90	33.61	.545	.582
	Infarcts-MRI/HbSS	2	3.4%	65.39	2.69	1.90	60.00-63.80	61.72		

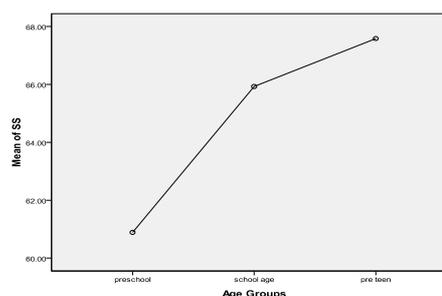
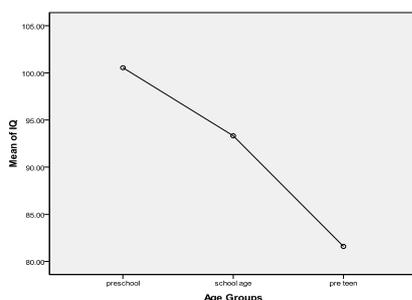
	Normal-MRI/Hb- SB ^o	6	10.2%	62.77	12.86	5.25	48.90-81.59			
Hb-F%	Normal-MRI/HbSS	51	86.4%	32.6	7.37	0.86	16.20-51.90	14.85	.238	.788
	Infarcts-MRI/HbSS	2	3.4%	32.0	2.83	2.00	34.00-38.00	62.29		
	Normal-MRI/Hb- SB ^o	6	10.2%	33.8	13.76	5.62	13.10-49.00			
Hb-A2%	NormalMRI/HbSS	51	86.4%	1.88	0.83	0.10	0.50-3.50	6.67	8.99	0.00
	Infarcts-MRI/HbSS	2	3.4%	2.30	0.14	0.10	2.00-2.20	0.74		
	Normal-MRI/Hb- SB ^o	6	10.2%	3.43	1.30	0.53	2.00-5.30			

Another classification is conducted between the patients according their age group; preschool age group; school age group age; and preteen age group, One Way ANOVA of Age Groups and All Variables is conducted.

Table 2: Comparative study of all variables in relation to different age groups (Preschool, School, Preteen Age Group)

Variables	Age Group	N	%	Mean	±S.D Deviation	±SE	Range	M. Square	F	Sig.
IQ%	preschool	11	18.6%	100.55	12.36	3.73	77.00-122.00			
	school age	31	52.5%	93.323	19.47	3.50	35.00-120.00	1335.24	4.31	0.018
	preteen	17	28.9%	81.588	16.67	4.04	46.00-111.00	309.850		
Hb.Conc. g/dl	preschool	23	25.6%	8.752	1.15	0.24	6.90-11.10			
	school age	41	45.5%	8.668	1.32	0.21	6.80-12.00	3.046	1.92	0.152
	preteen	26	28.9%	9.3032	1.25	0.27	7.60-11.80	1.583		
Hb.S%	preschool	23	25.6%	60.912	9.36	1.95	40.00-77.00			
	school age	41	45.5%	66.027	6.89	1.10	52.80-81.90	281.378	4.46	0.015
	preteen	26	28.9%	67.688	8.14	1.87	51.00 - 81.59	63.081		
Hb.F%	preschool	23	25.6%	37.102	8.85	1.85	21.00 - 58.0			
	school age	41	45.5%	31.977	6.87	1.10	16.80-46.0	282.577	4.59	0.013
	preteen	26	28.9%	30.311	8.46	1.94	13.10-46.0	61.610		
Hb.A2%	preschool	23	25.6%	2.0087	1.15	0.24	0.60-5.50			
	school age	41	45.5%	2.0949	0.89	0.14	0.50-4.00	0.067	.061	0.941
	preteen	26	28.9%	2.1053	1.20	0.27	0.60-5.30	1.095		
WBC C/mm3	preschool	23	25.6%	9.2563	3.78	0.77	3.90-17.60			
	school age	41	45.5%	8.6171	3.28	0.51	3.70-16.30	3.229	.250	0.780
	preteen	26	28.9%	8.9818	3.95	0.84	3.30-18.80	12.925		
Platelet Count C/mm3	preschool	23	25.6%	343.63	110.53	22.56	169.0 - 528.0			
	school age	41	45.5%	350.88	92.58	14.46	178.0-635.0	1761.96	.151	0.860
	preteen	26	28.9%	335.32	129.73	27.66	124.0-536.0	11633.8		
MCV	preschool	23	25.6%	70.721	8.68	1.77	56.0-85.0			
	school age	41	45.5%	74.702	9.81	1.53	54.0-90.0	195.741	2.05	0.134
	preteen	26	28.9%	76.268	10.73	2.29	53.0-99.0	95.231		
S. Ferritin (ng/dl)	preschool	23	25.6%	118.35	76.71	24.26	51.20-308.30			
	school age	41	45.5%	257.04	280.74	47.45	69.7 - 1769.0	83466.2	1.74	0.185
	preteen	26	28.9%	190.87	114.76	25.66	82.40-483.10	48112.2		

By Using One Way ANOVA of Age Groups and All Variables, the mean of IQ, mean of Hb-S level, mean of Hb-F level, mean of Hb-A2 level in relation to age group which represent in the following figures.



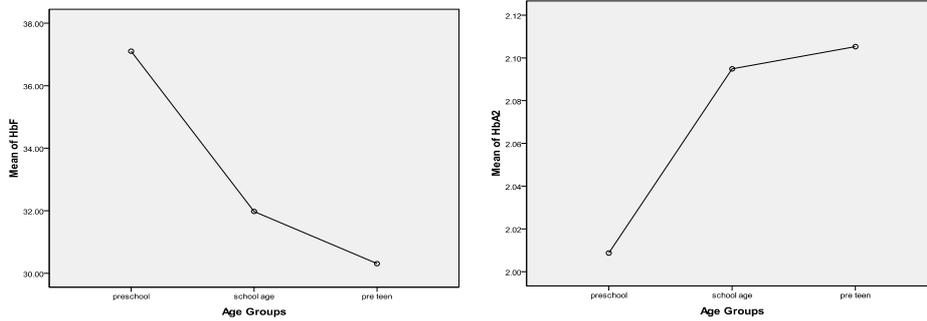


Figure 8: Presentation of some variables levels in relation to age groups (Preschool, School, and preteen age)
 It is noticed that patients in the preteen age (8-12) achieve the lowest score in IQ values & % of Hb.F. In addition they have highest values of % of Hb.S& Hb.A2.

Table 3: Correlation of Hb-SS within all patients in relation to age, sex, Hb-F%, Hb-A2%

variable	All Patients' Hb-SS	
	Pearson correlation	Sign.(2-tailed test)
Age controlled Sex	0.256	≤ 0.02*
Age uncontrolled Se	0.260	0.017*
Hb-F	-0.992	≤ 0.000**
Hb-A2	-0.079	0.475

Table 4: Comparative study (One Way ANOVA) of the all variables readings in all patients classified according to their Intelligent Quotient:

Variable	Group	N	%	Mean	±S. D.	S. E	Range	M. Sq	F	Sig.
Age	Below Average	21	35.6%	9.31	2.21	0.495	3.25-12.0			
	Normal Average	28	47.5%	7.31	2.37	0.418	3.00-12.0	27.59	5.032	0.010*
	Above Average	10	16.9%	7.163	2.56	0.905	3.00-11.0	5.48		
Hb. Conc.	Below Average	21	35.6%	8.99	1.44	0.338	6.90-11.8			
	Normal Average	28	47.5%	8.73	1.26	0.222	6.80-12.0	.526	0.299	0.743
	Above Average	10	16.9%	8.63	1.35	0.511	7.50-11.4	1.757		
Hb. S%	Below Average	21	35.6%	68.02	9.11	2.145	51.00-81.6			
	Normal Average	28	47.5%	64.32	7.64	1.351	45.80-81.9	327.98	6.041	0.045*
	Above Average	10	16.9%	62.09	4.31	1.524	53.80-66.7	54.29		
Hb.F%	Below Average	21	35.6%	29.71	9.45	2.228	13.10-46.0			
	Normal Average	28	47.5%	33.71	7.44	1.32	16.80-51.9	157.19	2.539	0.074
	Above Average	10	16.9%	36.6	4.91	1.74	31.0-45.4	61.908		
Hb.A2%	Below Average	21	35.6%	2.33	1.17	.276	0.90-5.30			
	Normal Average	28	47.5%	2.00	0.77	.135	0.50-4.30	2.997	3.496	0.037*
	Above Average	10	16.9%	1.28	0.91	0.32	0.50-3.00	0.857		
WBC C/mm3	Below Average	21	35.6%	9.63	3.37	0.80	4.80-16.70			
	Normal Average	28	47.5%	7.57	3.44	0.61	3.30-18.80	29.349	2.432	0.097
	Above Average	10	16.9%	9.49	3.85	1.36	4.30-13.90	12.069		
Platelets	Below Average	21	35.6%	317.5	117.96	27.80	124-536			

Count C/mm3	Normal Average	28	47.5%	354.7	101.32	17.91	172-522	11910.8	1.100	0.340
	Above Average	10	16.9%	375.1	76.52	27.05	275-511	10832.		
MCV	Below Average	21	35.6%	73.58	8.28	1.95	53.0-86.0			
	Normal Average	28	47.5%	75.03	9.65	1.71	58.0-90.0	450.95	2.792	0.004*
S. Ferritin (ng/dl)	Below Average	21	35.6%	193.6	97.23	22.31	82.4-433.0			
	Normal Average	28	47.5%	175.5	101.2	18.48	55.0-483.1	7113.5	.725	0.489
	Above Average	10	16.9%	138.4	92.77	37.87	64.3-321.0	9814.		

Presentation of some variables regarding different patients groups with below average (<70 - 90),

normal average(91 -110), superior average (111 - >130) IQ will be showed in the following figures.

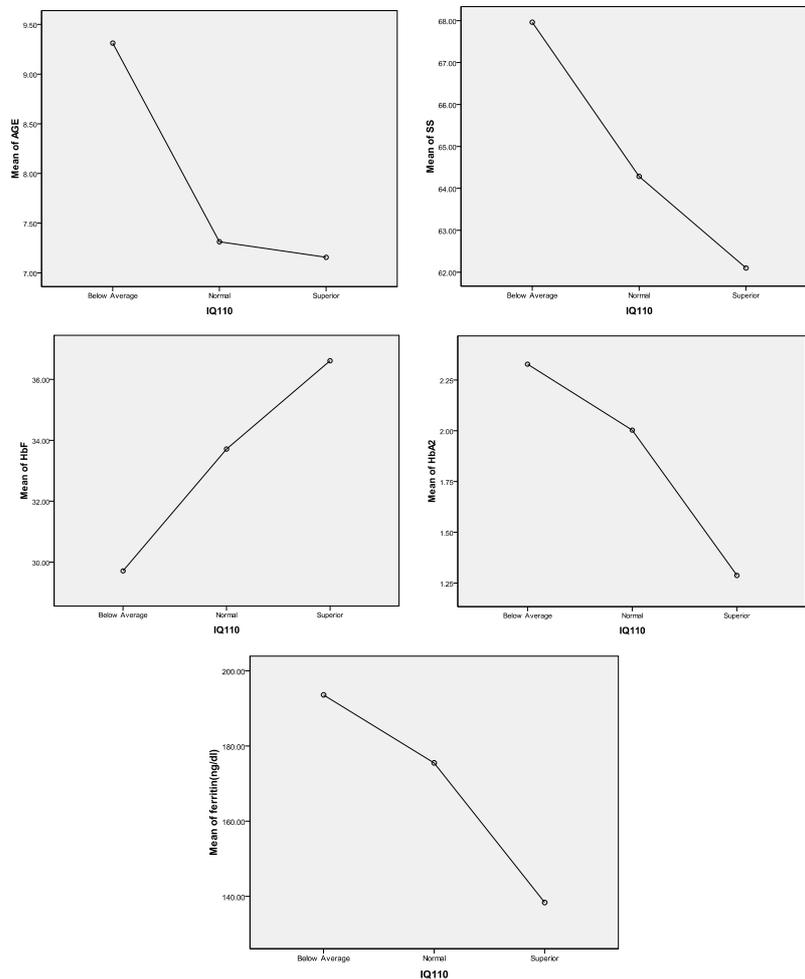


Figure9: Presentation of the mean of age, Hb.S, Hb.F, Hb.A2 levels and serum Ferritin level in relation to distribution of IQ level within all patients.

It is noticed that patient with IQ below the average are the oldest patients and achieved the highest values of Hb. S% & A2% and s. ferritin level. Where the same group scores the lowest value of Hb.F%.

Depending on IQ levels, Correlation Studies are conducted within all patients between the level of IQ and all variables (Age in years, S. Ferritin, Hb.Conc, MCV, WBC, Platelets count, Hb-SS%, Hb-F% & Hb-A2%) are represented in the following table.

Table 5: Correlation of IQ with all variables among all patients with or without infarction:

Variable	Hb-SS With Infarction IQ Correlation		Hb-SS Without infarction IQ Correlation		Hb-SB ⁰ Without infarction IQ Correlation	
	Pearson correlation	Sign. 2-tailed test	Pearson correlation	Sign. 2-tailed test	Pearson correlation	Sign. 2-tailed test
Age	- 1.0	≤ 0.01*	-.375	.003**	-.749	.076
S. Ferritin	- 1.0	≤ 0.01*	-.181	.185	-.677	.139
HbConc	1.0	≤ 0.01*	-.127	.345	.241	.645
MCV	1.0	≤ 0.01*	-.052	.699	.341	.509
WBC	- 1.0	≤ 0.01*	-.128	.338	-.346	.502
Platelets	- 1.0	≤ 0.01*	.129	.333	-.112	.832
Hb-SS	- 1.0	≤ 0.01*	-.236	.056	-.456	.364
Hb-F	1.0	≤ 0.01*	.261	.048*	.473	.343
Hb-A2	1.0	≤ 0.01*	-.260	.049*	-.496	.317

4. Discussion:

Silent infarction is defined as an ischemic change in brain tissue that is visible on MR images of patients with no clinical history of stroke (Steen *et al.*, 20). Despite evidence that Silent cerebral infarcts (SCI) are prominent in Sickle cell anemia (SCA), associated with significant morbidity and a significant risk factor for progressive neurologic disease, the optimal evaluation and treatment remain vague (Kwiatkowski *et al.*, 21). In our study SCI is diagnosed on the basis of an abnormal MRI finding of the brain and a normal neurological examination, without a history or physical findings associated with an overt stroke. Within our patients, there are 2 patients showed SCI (mean age 8.4± 0.9yr SD; having Hb-SS) out of 59 (all sickling patients submitted to MRI with age range 2 to 12 yrs and mean 8.1±2.6yrs SD) giving frequency rate equal 3.39%. Within the sickling group having homozygous Hb.SS (53 patients having Hb-SS with mean age 7.4±2.7), frequency rate of SCI occurrence is 3.77%. So, SCI is expected in older age within our patients.

This results are similar to a study of Adekile *et al.* (22), in Kuwait who mentioned that the prevalence of silent brain infarcts before 17 years of age was 3.3%, whereas the prevalence was 20% at a median age of 31.8 years (Marouf *et al.*, 23). They explained these results to the presence of appropriate percentage of Hb.F reaching approximately 30% in young patients, but with increasing age and decline in hemoglobin F level, clinical complications start occurring (Adekile *et al.*, 24). Coexistence with this explanation, cases having SCI are associated with the lowest values of Hb.F% which scored (32%±2.8) in Gr.II (SCD Hb-SS) the affected group (Table1). Moreover, Adams (25), suggested that silent brain infarcts in the Arab-Indian (Asian) haplotype occur with a similar prevalence to that reported in the African haplotype but in an older (30 years) age group.

However, the prevalence of SCI (3.39%) in between our sickling patients is low in comparison to prevalence in other areas in the world. But this result

is expected in eastern area of Saudi Arabia (S.A.), as it is believed that SCD patients in Hofuf and other areas in Eastern province of SA are having milder disease with less frequent complications and good outcome, due to the interaction between thalassemia and SCD and for having Arab-Indian (Asian) haplotype. Moreover, a study was done by Alabdulaali (26), who mention that Acute chest syndrome in SCD patients in Eastern province of SA is relatively uncommon, its prevalence and recurrence is low if compared to that of patients with African haplotypes (Al-Qurashi *et al.*, 27 and Akinyoola *et al.*, 28).

The pathophysiology of SCD is essentially similar in these different areas although the frequency and severity of complications may vary between areas (Al-Suleiman *et al.*, 29).

So, the clinical manifestations of SCD are unpredictable and variable which could be explained by the presence of two clinical phenotypes of SCD; the hemolysis-associated phenotype and the vaso-occlusion-related phenotype

Silent stroke is a stroke that causes no immediate symptoms but is associated with damage to the brain (Adams, 25). Despite the terminology, it is becoming increasingly apparent that silent infarcts are clinically significant given their association with subsequent overt stroke (Miller *et al.*, 30) and neurocognitive deficits in school-aged children (Bernaudin *et al.*, 31). Kwiatkowski *et al.* (21), reported that SCI occur most commonly in school-aged children with homozygous sickle cell disease (SCD-SS) and are associated with neurocognitive deficits.

As a marker for disease severity in the brain, evaluation of the association of cognitive dysfunction in relation to laboratory finding in those patients is recommended. New understanding of risk factors, associated laboratory findings, and imaging technology are impacting substantially on treatment options.

Buchanan *et al.* (3), study demonstrated that 80% of children with SCA and SCI were found to

have clinically significant impairments in at least one neurocognitive domain, when compared to 30% of the children with SCA and a normal MRI of the brain.

Because this hypothesis has been controversial, we try to find a relationship between cognitive achievement by (IQ), MRI finding for SCI detection, and level of anemia by (Hb Conc.) in a cohort of patients with sickle cell disease (Hb.S%). Powerful relationships are detected within our patients between the level of IQ, in one hand, and the presence of SCI, in the other hand.

Recorded IQ scores are 92, 90, 82 in patients with Hb-SS having normal MRI(GrI); patients with Hb-SS having abnormal(with SCI) MRI (GrII); and patients with Hb-SB⁰ having normal MRI(GrIII), respectively(table-1). It is noticed that IQ value recorded low limits of normal average of intelligence within all the patients. Children with SCI have significant cognitive deficits that are intermediate in magnitude compared to children with overt strokes and those with normal MRI. Children with SCI have IQs in the low 80s, whereas children with overt strokes or normal MRI have IQs in the 70s and 90s, respectively (Schatz *et al.*, 32). Steen *et al* (20), added that patients with imaging abnormalities had more cognitive impairment than did patients with normal imaging findings in verbal intelligence quotient ($P < .02$) and verbal comprehension ($P < .01$).

Moreover patients with Hb- S/B⁰ (Gr.III) have the lowest IQ level while they all have normal MRI finding. In spite of the group of mixed phenotype (Hb-S/B⁰) did not show SCI in MRI finding(Gr.III), they showed affection in other domains as IQ value, and Hb. Conc.(Table 1). In comparison to non infarct Hb.S patients group (Gr.I), patients in Gr.III, are scoring lower percentage of IQ (82.2±17.4%; 92.8±18%), as well as Hb conc. showed lower concentration in comparison to Gr. I (8.3±0.57; 8.9 ±1.3g/dl respectively). So, we could conclude that the presence of Hb. S/B⁰ gives both effects as sickle cell anemia associated with thalassemic anemia.

The explanations for the phenotypic heterogeneity of SS remain incomplete, but the answers will likely be found among the multitude of genes that are co-inherited with the sickle (β^S) mutation (Memish *et al.*, 33). That is, to understand a monogenic disease like SS, one must consider the molecular genetic context of the causative mutation in each individual. Until newer, comprehensive methods are available, we must continue to rely upon simple tools that include individual clinical features, laboratory values, and a small number of genetic polymorphisms (Kirkham, 2).

Regarding evaluation of risk factors associated with low values of IQ, Hb Concentration, showing the lowest level (7.75±0.2g/dl) in GrII (Hb-SS with

abnormal MRI), even it is not show significant difference but showing significant correlation with the percentage of Hb-S conc. and indirectly significant correlation with IQ level. The other two groups without SCI showed reading (8.9±1.3g/dl) in Gr.I and Gr.III reading (8.3±0.57g/dl). The same results are detected in the study of (Schatz *et al.*, 32), where mean of Hemoglobin conc. in sickling patients with SCI was 7.7 ± 0.8(g/dl) to 8.3 ± 1.1(g/dl) in non infarct children($P = 0.05$).

Also correlation study is conducted in between IQ level and different studied parameters in patients of each group. In the presence of SCI, strong highly significant correlations are detected between IQ level and all studied parameters (Age, Hb. Conc., platelets count, WBC) (Table 5) within patients with Hb-SS having SCI in MRI. In addition in the absence of SCI, significant correlations are detected between IQ level and Age, Hb-S%, Hb-F%, & Hb-A2% parameters in patients with Hb-SS having normal MRI. Where, significant correlations are detected between IQ level and Age only in patients with Hb-S/B⁰ having normal MRI.

Chen *et al.* (34), found in their study on children with sickle cell disease, a linear association between IQ and regional gray matter volume. This finding suggests that some variance in intellectual ability in children with sickle cell disease is accounted for by regional variability of gray matter volume, which is independent of neuroradiological evidence of infarct. In the current study, this point could be accessed through providing significant correlations in between IQ levels and all studied risk factors in patients with SCI, where in patients without evidence of SCI, there are significant correlations in between IQ value with age and levels of Hb.S, F, A2 percentage (Table 5).

So, we could suggest that SCD is associated with cognitive effects even in the absence of SCI. To support this suggestion some statistical analysis within our results are done. According to IQ grads, our patients are classified into 3 stages. First stage contain sickling patients with IQ below average (IQ <70%-90% comprises 35.6% of all patients), 2ndstage containing patients = 47.5% with normal average intelligence (IQ 91—110), and 3rd stage containing 16.9% of the patients with superior intelligence (IQ range ≥ 111). Within these groups of patients, IQ values showed significant difference with age ($P < 0.01$), Hb-S% ($P < 0.045$), Hb-A2% ($P < 0.037$) and to a lesser extent Hb-F% ($P < 0.08$) and MCV ($P < 0.004$) are detected (Table 4). So, all these factors could be considered as risk factors associated with SCD affecting cognitive attainment in those patients.

Steen *et al.* (20), mentioned that the incidence of mild mental deficiency was elevated at least 11-fold in a small sample of patients with sickle cell disease

with no clinical history of stroke, and the full-scale intelligence quotient (IQ) of these patients correlated with hematocrit. **Schatz et al. (34)**, explained that the causes of this cognitive decrement may include direct effects of SCD on brain function or indirect effects of chronic illness. This supports the hypothesis that cognitive impairment and lowered intellectual function in children with sickle cell disease is partly explained by function of chronic hypoxia of the brain (**Steen et al., 35**)

Moreover, in other reports from the Cooperative Study of Sickle Cell Disease (CSSCD) serial cognitive testing suggested children with SCD and normal brain magnetic resonance imaging (MRI) exams showed declines in verbal IQ scores over the course of a 5-year period (**Wang et al., 12**). In addition, there were age-related declines on a test of psychomotor speed and focused attention (coding subtest of the Wechsler scales) and mathematics achievement (**Schatz et al., 32**). This point of view is consistent with our results. All patients are classified into 3 stages of age group (preschool, school, and preteen age group) to study the parameters used in the study in relation to age in sickling patients (Table 2). There are highly significant difference in the reading of IQ score ($P=0.018$), Hb.S% ($P=0.015$), Hb.F% ($P=0.013$), in relation to age group. On the other hand the percentage of Hb.S concentration in homozygous Hb-SS group is strongly correlated with and dependent on age ($P=0.017$), sex ($P\leq 0.02$), and Hb.F% ($P\leq 0.000$) (Table 3).

Added more, in **Brown et al., (36)** study who found progressive decrease of IQ score (94% \rightarrow 84%) with increase of age (9 \rightarrow 13yr.), in children with SCD. Within our patients; there is progressive decrease in IQ score (93.3% \rightarrow 81.5%) in our sickling patients group (6 \rightarrow 12.7yr.) (Table 2).

In addition, strong significant correlations are detected between decrease IQ %, in one side, with increased age ($P=0.01$); increased Hb-S% ($P=0.045$) and positive relationship with decrease Hb-F% ($P=0.08$), in the other side (Table 4).

From all of the above significant relations and differences detected in between different factors included in the study, cognitive impairment is age dependent, and concentration dependent of Hb.S %, Hb.F% and Hb.A2% in patient with SCD. The percentage of hemoglobin S, F and A2 concentration are considered as risk factors associate with cognitive impairment in SCD. Cognitive impairment is considered in children with SCD either showing evidence if SCI or not. The appreciable cognitive dysfunction of SCD with or without SCI demand more effective treatments and ultimate prevention. This results could be explained by **Brown et al. (37)**, study who mentioned that the pathophysiology

characteristic of SCD can interfere with brain function and constrain intellectual development, even in absence of an infarct.

Regarding a study conducted by **Day and Chismark (38)**, they concluded that, central nervous system complications are widespread among students with SCD and include stroke, silent cerebral infarction, and cognitive impairment. The effects of these complications may lead to academic failure, limited career options, and for some, total disability.

The phase 3 National Heart, Lung and Blood Institute-sponsored Multicenter Study of Hydroxyurea trial proved clinical efficacy for preventing acute vaso-occlusive events in severely affected adults. Management approaches include the erythrocyte membrane, changes in the red cell intracellular content (especially loss of water), endothelial injury, and free radical production (**Heeney and, Ware, 39**). Based on this cumulative experience, hydroxyurea has emerged as an important therapeutic option for children and adolescents with recurrent vaso-occlusive events; recent evidence documents sustained long-term benefits with prevention or reversal of chronic organ damage (**Ware, 40**).

Recommendations:

1. **Silent cerebral infarcts are known to confer additional disease burden**, this information is important for further evaluation of patients and the efficacy of preventive strategy.
2. Considering MRI test for meticulous follow up for patients with sickle cell disease
3. Sickle/ thalassemic patients need more attention

Corresponding authors

Eglal Hussein S. S. Al Gohary

Pediatric Department, College of Medicine, King Faisal University

eglal_hussein2007@yahoo.com

References:

1. **Steinberg MH.** Management of sickle cell disease. *N Engl J Med.* **1999**;340:1021–1030.
2. **Kirkham FJ.** Therapy insight: stroke risk and its management in patients with sickle cell disease. *Nat ClinPract Neurol.* **2007**;3(5):264–78.
3. **Buchanan GR, DeBaun MR, Quinn CT, Steinberg MH.** Sickle cell disease. *Br J Haematol.* **2004**;35–47. *Author manuscript; available in PMC 2010 August Hematology Am Soc Hematol Educ Program.*
4. **Jastaniah W.** Epidemiology of sickle cell disease in Saudi Arabia. *Ann Saudi Med.* **2011**; 31(3): 289–293.

5. **Alabdulaali** MK. Sickle cell disease patients in eastern province of Saudi Arabia suffer less severe acute chest syndrome than patients with African haplotypes. *Ann Thorac Med.* **2007**;2:158–62.
6. **Roach**, E.S.; Golomb, M. R.; Robert Adams, R.; Biller, J.; Daniels, S.; Gabrielle deVeber, G.; et al. Management of Stroke in Infants and Children. *Stroke.* **2008**;39:2644-2691.
7. **Wellems** TE, Hayton K, Fairhurst RM : "The impact of malaria parasitism: from corpuscles to communities". *J. Clin. Invest.*(**2009**) 119 (9): 2496–505.
8. **Pegelow** CH, Wang W, Granger S, et al. Silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity. *Arch Neurol.* **2001**;58:2017–2021.
9. **National Institute of Health**. Department of Health and Human Services. The Management of Sickle Cell Disease. **2002**. <http://www.nhlbi.nih.gov/health/prof/blood/sickle>.
10. **Scothorn** DJ, Price C, Schwartz D, et al. Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. *J Pediatr.* **2002**;140:348–354.
11. **Pegelow** CH, Macklin EA, Moser FG, Wang WC, Bello JA, Miller ST, et al. Longitudinal changes in brain magnetic resonance imaging findings in children with sickle cell disease. *Blood.* **2002**;99:3014–8.
12. **Wang** WC, Gallagher DM, Pegelow CH, Wright EC, Vichinsky EP, Abboud MR, Moser FG, Adams RJ. Multicenter comparison of magnetic resonance imaging and transcranial Doppler ultrasonography in the evaluation of the central nervous system in children with sickle cell disease. *J Pediatr Hematol Oncol.* **2000**; 22(4) :335-9.
13. **Shah** BR, Laude TL: Atlas of Pediatric Clinical Diagnosis. WB Saunders, Philadelphia, **2000**, p. 265.
14. **Pediatric Atlas** > Chapter 11. Hematology > Copyright ©2007 The McGraw-Hill Companies. Privacy Notice. Any use is subject to the Terms of Use and Notice. Additional Credits and Copyright Information.
15. **Vendt** BA, McKinsty RC, Ball WS, Kraut MA, et al.: Silent Cerebral Infarct Transfusion (SIT) trial imaging core: application of novel imaging information technology for rapid and central review of MRI of the brain. *J Digit Imaging.* **2009** Jun;22(3):326-43.
16. **SB5** Assessment Service Bulletin #4 - Special Composite Scores for the **Stanford-Binet Intelligence Scales**, Fifth Edition. Technical Report - Quality of Performance and Change-Sensitive Assessment of Cognitive Ability, Gale H. Roid, **2004**.
17. **SB5** Assessment Service Bulletin #4 - Special Composite Scores for the **Stanford-Binet Intelligence Scales**, Fifth Edition. Technical Brief - Interpretation of SB5/Early SB5 Factor Index Scores, Gale H. Roid, **2005**.
18. **Lindstrom**, David R.; Shipman, Virginia C. Sequin Form Board; Technical Report 20. Disadvantaged Children and Their First School Experiences. ETS-Head Start Longitudinal Study. Technical Report Series. **1997**-12-00.
19. **McAnarney**, E.R. Social maturation: A challenge for handicapped and chronically ill adolescents. *Journal of Adolescent Health Care.* **1985**, Mar. Volume 6, Issue 2, P 90–101.
20. **Steen** R G, Milesb M A, Heltona K J, Strawnc S, et al.: Cognitive Impairment in Children with Hemoglobin SS Sickle Cell Disease: Relationship to MR Imaging Findings and Hematocrit. *AJNR Am J Neuroradiol*, **2003**, 24:382-389.
21. **Kwiatkowski**, JL., Zimmerman R., Pollock AN., Seto W., Smith-Whitley K., Shults J., Blackwood-Chirchir A., and Kwaku-Ohene-Frempong, Silent Infarcts in Young Children with Sickle Cell Disease. *Br J Haematol.* **2009**; 146(3): 300–305.
22. **Adekile** AD, Yacoub F, Gupta R, Sinan T, Haider MZ, Habeeb Y, et al. Silent brain infarcts are rare in Kuwaiti children with sickle cell disease and high Hb F. *Am J Hematol.* **2002**;70:228–31.
23. **Marouf** R, Gupta R, Haider MZ, Adekile AD. Silents infarcts in adult Kuwaiti sickle cell disease patients. *Am J Hematol.* **2003**;73:240–3.
24. **Adekile** A, Al-Kandari M, Haider M, Rajaa M, D'souza M, Sukumaran J. Hemoglobin F concentration as a function of age in Kuwaiti sickle cell disease patients. *Med Princ Pract.* **2007**;16:286–90.
25. **Adams** RJ "Big strokes in small persons". *Arch. Neurol.*, (**2007**). Nov. 64 (11): 1567–74.
26. **Alabdulaali** MK. Sickle cell disease patients in eastern province of Saudi Arabia suffer less severe acute chest syndrome than patients with African haplotypes. *Ann Thorac Med.* **2007**;2:158–62.
27. **Al-Qurashi** MM, El-Mouzan MI, Al-Herbish AS, Al-Salloum AA, Al-Omar AA. The prevalence of sickle cell disease in Saudi children and adolescents. A community-based survey. *Saudi Med J.* **2008**; 29(10):1480-3.
28. **Akinyoola** AL, Adediran IA, Asaley CM. Avascular necrosis of the femoral head in sickle

- cell disease in Nigeria: A retrospective study. Niger Postgrad Med J. **2007**;14:217–20.
29. **Al-Suleiman** A, Aziz G, Bagshia M, El Liathi S, Homrany H. Acute chest syndrome in adult sickle cell disease in eastern Saudi Arabia. Ann Saudi Med **2005**;25:53-5.
 30. **Miller** ST, Macklin EA, Pegelow CH, et al. Silent infarction as a risk factor for overt stroke in children with sickle cell anemia: a report from the Cooperative Study of Sickle Cell Disease. **2001**;139(3):385–390.
 31. **Bernaudin** F, Verlhac S, Freard F, et al. Multicenter prospective study of children with sickle cell disease: radiographic and psychometric correlation. J Child Neurol. **2000**; 15:333–343.
 32. **Schatz** J; Finke R; Kellett J; and Kramer J.: Cognitive Functioning in Children with Sickle Cell Disease: Meta Analysis. Med J Ped Psych **2002**; vol.27,(8);P.739-748.
 33. **Memish** Z. A.; Owaidah T.M.; Saeedi M. Y.: Marked regional variations in the prevalence of sickle cell disease and β -thalassemia in Saudi Arabia: Findings from the premarital screening and genetic counseling program. Journal of Epidemiology and Global Health. **2011**, 1 (1): 61-68.
 34. **Chen** R, Pawlak MA, Flynn TB, Krejza J, Herskovits EH, Melhem ER.: Brain morphometry and intelligence quotient measurements in children with sickle cell disease. J Dev Behav Pediatr. **2009** Dec; 30 (6) :509-17.
 35. **Schatz** J, Brown RT, Pascual JM, Hsu L, DeBaun MR. Poor school and cognitive functioning with silent cerebral infarcts and sickle cell disease. Neurology. **2001**;56:1109–1111.
 36. **Steen** RG, Xiong X, Mulhern RK, Langston JW, Wang WC. Reply to Letter to the Editor. Ann Neurol., **2000**;47:280.
 37. **Brown**, R. T., Davis, P. C., Lambert, R., Hsu, L., Hopkins, K., & Eckman, J. Neurocognitive functioning and magnetic resonance imaging in children with sickle cell disease. Journal of Pediatric Psychology, **2000**, 25, 503 -513.
 38. **Day** S, and Chismark E.: The Cognitive and Academic Impact of Sickle Cell Disease. The Journal of School Nursing **2006** 22(6):330-335.
 39. **Ware** RE. : How I use hydroxyurea to treat young patients with sickle cell anemia. Blood. **2010**, 1;115(26):5300-11.
 40. **Heeney** MM, Ware RE.: Hydroxyurea for children with sickle cell disease. Hematol Oncol Clin North Am. **2010** Feb;24(1):199-214.