



# **Neurocognitive deficits in Egyptian sickle cell diseased children**

*Thesis For M.Sc Degree in Pediatrics*

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## **Abstract**

### **Key words:**

Sickle cell disease, cognition, IQ test.

Sickle cell disease (SCD) is a blood disorder characterized by veno-occlusive crises which affect cognition. We studied 40 Children with SCD aged from 6 to 22 years old. We assessed the neurological complications by history, examination & radiological tests using TCD, MRI & MRA. Cognitive ability was assessed using WISC and subtests of IQ.

Impaired cognition increases with cases not receiving Hydroxyurea drug, SCD children with frequent crises, older children has SCD, SCD patients with lower hemoglobin & patients not receiving frequent blood transfusion.

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## List of abbreviations

<b>AAP</b>	American academy of pediatrics
<b>ACA</b>	Anterior cerebral artery
<b>ACS</b>	Acute Chest Syndrome
<b>ADC</b>	Apparent diffusion coefficient
<b>AIS</b>	Arterial Ischemic stroke
<b>AVMs</b>	Arterio-venous malformations
<b>AVN</b>	A vascular necrosis
<b>BA</b>	Basilar artery
<b>BIF</b>	Bifurcation
<b>BMT</b>	Bone marrow transplantation
<b>CBC</b>	Complete blood count
<b>CBF</b>	Cerebral blood flow
<b>CDC</b>	Centers for disease control& prevention
<b>CE-MRA</b>	Contrast enhanced-MRA
<b>cMRI</b>	Conventional MRI
<b>CNS</b>	Central nervous system
<b>CSSD</b>	Cooperative Study of SCD
<b>CTA</b>	Computed Tomography angiography
<b>CVA</b>	Cerebrovascular accident
<b>CVEs</b>	Cerebrovascular events
<b>DCS</b>	Diffuse correlation spectroscopy
<b>dICA</b>	Distal internal cerebral artery
<b>DSST</b>	Digit symbol substitution test
<b>DWI</b>	Diffusion weighted MRI
<b>ED</b>	Emergency department
<b>EDV</b>	End diastolic velocity
<b>FDA</b>	Food and Drug Administration
<b>FLAIR</b>	Fluid Attenuated Inversion Recovery
<b>FSIQ</b>	Full scale score test
<b>Hb</b>	Hemoglobin
<b>HbA</b>	Adult hemoglobin
<b>HbC</b>	Hemoglobin C
<b>HbF</b>	Fetal Hemoglobin
<b>HbS</b>	Hemoglobin S
<b>HbS</b>	Hemoglobin S

<b>HLA</b>	Human leukocyte antigen
<b>HPLC</b>	High performance Liquid Chromatography
<b>HU</b>	Hydroxyurea
<b>ICA</b>	Internal cerebral artery
<b>IQ</b>	Intelligent Quotient
<b>LDH</b>	Lactate dehydrogenase
<b>MCA</b>	Middle cerebral artery
<b>Mg/kg</b>	Milligram per kilogram
<b>MR</b>	Mental Retardation
<b>MRA</b>	Magnetic resonance angiography
<b>MRI</b>	Magnetic resonance imaging
<b>NBS</b>	Newborn screening
<b>NIRS</b>	Near-infrared spectroscopy
<b>OA</b>	Ophthalmic artery maximum velocity
<b>PAH</b>	Pulmonary Artery Hypertension
<b>PC</b>	Prothrombin concentration
<b>PI</b>	Pulsatility Index
<b>PIGF</b>	Protein Insulin Growth Factor
<b>PIQ</b>	Performance Intelligent Quotient
<b>POI</b>	Perceptual organization index
<b>PRES</b>	Posterior reversible encephalopathy syndrome
<b>PRI</b>	Perceptual reasoning index
<b>PSI</b>	Processing speed index
<b>PSV</b>	Peak systolic velocity
<b>PT</b>	Prothrombin Time
<b>PTT</b>	Partial Thromboplastin Time
<b>QoL</b>	Quality of life
<b>RBCs</b>	Red blood cells
<b>RI</b>	Resistive index
<b>SCA</b>	Sickle cell anemia
<b>SCD</b>	Sickle cell disease
<b>SCI</b>	Silent cerebral infarcts
<b>SD</b>	Standard Deviation
<b>SPECT</b>	Single-photon emission computed tomography
<b>SS</b>	Homozygous Sickle Cell Disease
<b>STOP</b>	Stroke Prevention Trial
<b>S<math>\beta</math></b>	Heterozygous sickle cell disease
<b>TAMMV</b>	Time average maximum mean velocity

<b>TAMV</b>	Time average mean velocity
<b>TCD</b>	Trans-cranial Doppler
<b>TIA</b>	Transient ischemic attacks
<b>VCI</b>	Verbal comprehension index
<b>VIQ</b>	Verbal Intelligent Quotient
<b>VOC</b>	Vaso-occlusive crisis
<b>VST</b>	Venous sinus thrombosis
<b>WBCs</b>	White blood cells
<b>WISC</b>	Wechsler Intelligence Scale for Children
<b>WMI</b>	Working memory index

## Introduction

Sickle cell disease (SCD) is a chronic hemolytic anemia characterized by red cells that contain primarily hemoglobin S, which polymerizes when deoxygenated, causing a lot of complications (**Hebbel and Hoffman, 2005**). These complications include bone disease, splenic dysfunction, pulmonary complications, skin ulceration, depression or behavioral disorders, neurologic, cognitive deficits & sensory impairments of vision or hearing (**Swanson et al., 2011**).

Neurologic complications (25% of SCD patients) include transient ischemic attacks, overt & silent cerebral stroke, cerebral hemorrhage, infections, Moya-Moya pattern, posterior reversible encephalopathy syndrome (PRES), dural venous sinus thrombosis, thickness of the diploic space & cerebral atrophy. These complications may have an impact on a child's daily life, cognitive impairment & consequently a lifetime to limited career options or total disability (**Yildirim et al., 2005**).

Estimates of the prevalence of silent brain infarcts, in children with SCD range from 17% to 35% (**Kwiatkowski et al., 2009**). Silent cerebral infarcts (SCI) are often associated with cognitive impairment & an increased risk for further silent or overt stroke (**Dowling et al., 2010**). The cognitive complications in SCD patients include deficits in short-term memory & difficulties in verbal tasks that lead to declining IQ scores & learning difficulties (**Vichinsky et al., 2010**). The number of published reports describing cognitive functioning & potential cognitive deficits in children with SCD has increased greatly, however, incidence of cognitive deficit among SCD patients with neurological complications is still unknown (**Schatz et al., 2002**).

Transcranial Doppler (TCD) & MRI are well established methods for prevention & diagnosis of CNS complications & thereafter control of cognitive deficits. Thus, early TCD screening & intensification therapy allowed the reduction of stroke-risk by age 18 from the previously reported 11% to 1.9% (**Françoise et al., 2012**).

## **Aim of the work**

1. To estimate the prevalence of silent neurologic deficit in SCD.
2. To detect the association between silent neurologic deficit & cognitive deficit in SCD
3. To detect risk factors of cognitive deficits in SCD.

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# Chapter I

## Sickle Cell Disease

### Introduction

Sickle cell disease (SCD) is clinically one of the most important hemoglobinopathies. It is characterized by hemolytic anemia, increased susceptibility to infections and vaso-occlusion that occurs in almost all vascular beds leading to ischemic tissue injury with organ dysfunction and early death (**Schnog et al., 2004**).

In one thousand Egyptian candidates, HbS was detected in 3 cases (0.3%) (**El-Beshlawy et al., 1994**).

Formation of 'sickle hemoglobin', or HbS ( $\alpha 2 \beta S_2$ ), results from point mutation in hemoglobin gene that substitutes Thymine for Adenine (GAG to GTG) in the sixth codon of  $\beta$  globin chain, thereby encoding valine instead of glutamine (**Munker et al 2007**).

These changes lead to HbS polymer formation. This polymer is a rope-like fiber that aligns with each other to form a bundle, distorting the red cell into classic crescent or sickled forms (**Stuart & Nagel 2004**).

### Sickle cell disease genotypes

Sickle-cell disease denotes all genotypes containing at least one sickle gene. In addition to the homozygotic HbSS disease (sickle-cell anemia) due to inheritance of two Hb  $\beta S$  genes, five other major sickle genotypes are linked to the disease; including double heterozygous states HbS/B<sup>0</sup> thalassaemia, HbS/ $\beta^+$  thalassaemia and HbSC disease (the most common double heterozygous state). Other rare types are HbS/hereditary persistence of fetal Hb (S/H<sup>+</sup>HPH) HbS/HbE syndrome (**Stuart & Nagel, 2004**).

### Sickle cell trait:

It is a heterozygous state without serious clinical subsequences; only one of two  $\beta$  globins is affected. Infants with sickle cell trait are generally asymptomatic. Rarely, they exhibit painless hematuria, and occasionally these patients have sickle cells on peripheral blood smear, but hemoglobin electrophoresis provides the definitive diagnosis.