Neurocognitive deficits in Egyptian sickle cell diseased children

Thesis For M.Sc Degree ***in Pediatrics***

By

Mahmoud Mahrous Rashad

(M.B.B.Ch, Cairo University)

Supervised By

Prof. Dr. Ilham Youssry Ibrahim

Professor of Pediatric Hematology
Faculty of Medicine- Cairo University

Prof. Dr. Mona Kamal Ali El Ghamrawy

Professor of Pediatric Hematology
Faculty of Medicine- Cairo University

Dr. Hadeel Mohemed Seif

Assistant Professor of Radiology
Faculty of Medicine-Cairo University

Faculty of Medicine
Cairo University
2016

Acknowledgement

To Allah "the most Merciful, the most Graceful"

To my respective professors:

Prof. Dr. **Ilham Youssry Ibrahim**, Prof. Dr. **Mona Kamal Ali El Ghamrawey** and assistant Prof. Dr. **Hadeel Mohemed Seif** who supervised this study for the sake of medical research and Egyptian children .

To the pioneer hematology staff in Abo El Reish hospital for her noticed support and cooperation in my assessment of sickle cell disease children and her continued patience in supervising all the stages in this study. The team of psycho socialist and behavioral therapist in Abo El Reish preventive hospital who offered big efforts in psychiatric and I.Q. tests for all participants.

To my Psychaitric Senior supervisor who supported me substantially with best regards.

All my thanks to dear innocent Egyptian children sickle cell diseased from different governorates for their participation in this study under the supervision and coordination of Pediatric Hematology Department of Cairo university hospital.

I would like to thank my family members for supporting and encouraging me to pursue this degree.

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 assesed 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.

Index

List of Figures

List of tables

Tables in the review

Tables of the results

List of abbreviations

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

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

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

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 (α 2 β S2), results from point mutation in hemoglobin gene that substitutes Thymine for Adenine (GAG to GTG) in the sixth codon of β 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 βS genes, five other major sickle genotypes are linked to the disease; including double heterozygous states HbS/B° thalassaemia, HbS/β+ thalassaemia and HbSC disease **(**the most common double heterozygous state). Other rare types are HbS/hereditary persistence of fetal Hb (S/HPHP) HbS/HbE syndrome **(Stuart & Nagel, 2004).**

Sickle cell trait:

It is a heterozygous state without serious clinical subsequences; only one of two β 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.