

**Steady-State Serum Levels of Vascular Cell
Adhesion Molecule-1 in Children with Sickle
Cell Disease: Relevance to Stroke Risk and
Disease Severity**

Thesis

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Pediatrics**

By

Ahmed Ibrahim Amin Ibrahim
(M.B.B.Ch., MSC)

Supervised by

Prof. Dr. Mona Hassan El-Tagui

Professor of Pediatrics
Faculty of medicine
Cairo University

Dr. Mona Kamal El-Ghamrawy

Assistant Professor of Pediatrics
Faculty of medicine
Cairo University

Dr. Foad Abdelmonem Abd Allah

Assistant Professor of Neurology
Faculty of medicine
Cairo University

Dr. Fadwa Saied Abdel Azzim

Lecturer of Clinical and Chemical Pathology
Faculty of medicine
Cairo University

Faculty of Medicine

Cairo University

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

(قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ أَنْتَ

الْعَلِيمُ الْحَكِيمُ)

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Abstract:

Our study conducted on **85** patients with SCD aged 2-18years, **8.4%** of patients showed high risk study and **12.0%** were conditional. One high risk patient had the qualifying velocity in ACA only. Regression analysis showed transfusion & HU dose are protective against stroke. Mean VCAM level was **1438.12 ± 848.2 ng/ml** for cases enrolled & significantly higher than of normal population. Levels also was higher in patient with normal TCD (**P.038**). However, correlation of VCAM level with TAMMvel using showed +ve correlation with (**P.041**). Levels were higher in HbSβ subgroup, with positive correlation with bilirubin level and frequency of blood transfusion. In SS subgroup, VCAM level was significantly correlated with severity frequency (**P≤.001**) and duration (**P ≤ .001**) of VOCs. Level was lower with HU treatment (**P.041**).

Keywords:

Sickle cell anaemia – Stroke –VCAM-1 – Transcranial Doppler – TCD – SCD

TABLE OF CONTENTS

Lists	Pages
Abstract	I
List of Tables	III
List of figures	V
Abbreviation	VII
Introduction	1
Aim of the work	4
Review of Literature	5
Chapter I :Sickle Cell Anemia	6
Chapter II:Stroke in Children	43
Chapter III: Transcranial Doppler	61
Chapter IV: Vascular cell adhesion molecule-1	72
Subjects and methods	77
Results	82
Discussion	119
Summary and Conclusion	130
Recommendations	135
References	137
Arabic Summary	155

LIST OF TABLES

NO	Title	Page
1	Pharmacological management of pain using the World Health Organization three-step ladder	19
2	Outline of management of acute pain in opioid-naive children	20
3	Bacteria and Viruses That Most Frequently Cause Serious Infection in Patients with Sickle Cell Disease	23
4	Organ-Related Infection in Sickle Cell Disease	24
5	Cytologic Features of Peripheral Blood Smears in Sickle Cell Disease	34
6	Typical schedule of routine clinical laboratory evaluations.	35
7	Causes of Stroke in Children	45
8	Neuroimaging of brain vessels	52
9	Accepted Guidelines for mean flow velocity (MFV) for a Normal TCD Study	63
10	Effects of Different Physiological States on TCD Flow Velocity	63
11	Risk stratification of stroke by TCD according to TAMMvel	67
12	Demographic distribution among the involved subjects	83
13	Clinical Data of the involved subjects	84
14	Morbidity & Mortality among involved subjects (n=85)	85
15	Laboratory parameters of the involved cases (n=85)	85
16	Mean VCAM level of the involved subjects (n=85)	86
17	Classification of subjects according normal VCAM level	86
18	Normal Mean, Range and Standard Deviation for VCAM levels in the used kit	86
19	Descriptive clinical data of sickle cell and sickle beta thalassemia patients	87
20	Laboratory parameters of sickle cell and sickle beta thalassemia patients	88
21	Mean VCAM levels for Sickle cell and sickle beta thalassemia subgroups	88
22	Distribution of transcranial Doppler results among the involved subjects (n=85)	89

23A	Distribution of TCD results according to the arteries affected (numbers)	89
23B	Distribution of TCD results according to the arteries affected (percentage)	90
24	Distribution of arteries among affected patients (n=17)	90
25	Sensitivity of different arteries in detecting the abnormal subjects	91
26	Value of performing TCD study on arteries other than MCA in detecting abnormal subjects	91
27	Time averaged mean of the maximum velocity among selected cases (n=85)	92
28A	TAMMvel of SS and SB patients.	92
28B	TCD results of SS and SB patients	92
29	Correlation between TCD results and VCAM level	93
30	Correlation between MCA time-averaged mean of the maximum velocity (TAMMvel) and VCAM level	93
31	Correlation of VCAM level with clinical data of the all subjects involved (n=85)	94
32	Relation of transfusion and HU treatment and their effect on VCAM level among the whole population (n=85)	96
33	Correlation of VCAM level with laboratory data of the all subjects involved (n=85)	97
34	Correlation of VCAM level with clinical data of the SS subjects (n=57)	99
35	Correlation of VCAM level and TCD results with laboratory data of SS subjects (n=57)	101
36	Correlation of VCAM level with clinical data of the SB subjects (n=28)	103
37	Correlation of VCAM level with laboratory data of the Sb subjects (n=28)	105
38	Correlation of TCD results with clinical data of the all subjects involved (n=83)	107
39	Correlation of TCD result with laboratory data of the all subjects involved (n=83)	111
40	Correlation of TCD results with clinical data of the SS subjects (n=56)	113
41	Correlation of VCAM level and TCD results with laboratory data of SS subjects (n=56)	116
42	Logistic regression analysis for risk factors of abnormal TCD	118

LIST OF FIGURES

No	Title	Page
1	The polymerization of deoxy-HbS	7
2	Smear represents circulating irreversibly sickled cells	8
3	NO bioactivity in sickle cell disease	10
4	The pathophysiology of sickle cell disease	11
5	Distribution of Sickle cell gene and its relation to malaria	12
6	Pathogenesis of manifestation of SCD	14
7	Diffusion weighted imaging showing a cytotoxic odema due to an acute cerebral infarct in the left middle cerebral artery.	50
8	Axial T1 weighted MRI showing established left middle cerebral infarct with cystic encephalomalacia and gliosis in	50
9	Axial MRI image showing subcortical right middle cerebral artery stroke secondary to post varicella angiopathy	50
10	Multidop T brand of TCD device	61
11	TCD probe positions over different acoustic windows of the skull	62
12	Algorithm for TCD Screening for Stroke	69
13	Major systems involved in sickle red blood cells adhesion to the endothelium	75
14	TCD of right MCA of involved case showing normal velocity.	80
15	TCD of right MCA of involved case showing high risk velocity	80
16	Demographic distribution of sex, consanguinity and diagnosis among the involved subjects	83
17	Mean age of involved subjects (n=85)	83
18	Mean VCAM level of the involved subjects (n=85)	86

19	Distribution of transcranial Doppler results among the involved subjects (n=83)	89
20	Distribution of TCD results according to the arteries affected (Percentage)	90
21	Distribution of arteries among affected patients (n=17)	91
22	Distribution of TCD results according to treatment with HU among the all subjects	108
23	Distribution of TCD results according to state of spleen among the all subjects	108
24	Effect of splenectomy on TCD results	109
25	Mean age of Normal & Abnormal groups (all patients)	109
26	Distribution of TCD results according to sex of subjects involved	109
27	Distribution of TCD results according to diagnosis	110
28	Distribution of TCD results according to severity of VOCs	110
29	Influence of treatment with HU and compliance on TCD results among the SS group (n=57)	114
30	Influence spleen status on TCD results among the SS group (n=57)	114
31	Mean age of Normal & Abnormal groups (SS group)	115
32	Distribution of TCD results according to sex of the involved subjects among SS group (n=57)	115
33	Distribution of TCD results according to severity of VOCs among SS group (n=57)	115
34	Normal P-P plot of logistic regression test	118
35A	Regression correlation of HU with TCD result	118
35B	Regression correlation of Blood transfusion with TCD result	118

ABBREVIATIONS

ACA	ANTERIOR CEREBRAL ARTERY
ACS	ACUTE CHEST SYNDROME
AIS	ACUTE ISCHEMIC STROKE
ALT	ALANINE TRANSIFRASE
APCs	ANTIGEN PRESENTING CELLS
AVN	AVASCULAR NECROSIS
BIF	BIFURCATIONAL ARTERY
BUN	BLOOD UREA NITROGEN
CBC	COMPLETE BLOOD COUNT
CT	COMPUTED TOMOGRAPHY
ELISA	ENZYME LINKED IMMUNOSORBENT ASSAY
ESRD	END-STAGE RENAL DISEASES
FV	FLOW VELOCITY
GFR	GLUMERULAR FILTRATION RATE
HB	HEMOGLOBIN
HU	HYDROXYUREA
ICA	INTERNAL CAROTID ARTERY
ICH	INTRACRANIAL HEMORRHAGE
IL	INTERLEUKIN
KFTs	KIDNEY FUNCTION TESTS
LDH	LACTATE DEHYDROGENASE
LFTs	LIVER FUNCTION TESTS
MCA	MIDDLE CEREBRAL ARTERY
MRI	MAGNETIC RESONANCE IMAGING
NO	NITRIC OXIDE
NSAIDs	NON-STEROIDAL ANTI-INFLAMMATORY DRUGS
PCA	POSTERIOR CEREBRAL ARTERY
PT	PROTHROMBIN TIME
PTT	PARTIAL THROMBOPLASITN TIME
RBCs	RED BLOOD CORPUSCLES
SCD	SICKLE CELL DISEASE
STOP	STROKE PREVENTION TRIAL IN SICKLE CELL ANEMIA
TAMMVEL	TIME-AVERAGED MEAN OF THE MAXIMUM VELOCITY
TCD	Transcranial Doppler
TIA	TRANSIENT ISCHEMIC ATTACK
TNF	TUMOR NECROTIC FACTOR
VCAM-1	VASCULAR CELL ADHESION MOLECULE-1
VLA-4	VERY LATE ANTIGEN-4
VOC	VASO-OCCLUSIVE CRISIS

Introduction

Sickle cell disease (SCD) is one of the commonest genetic disorders world-wide and is the most common inherited hematological disease affecting humans (**Steinberg, 2001**).

SCD has its cardinal features of chronic hemolytic anemia and recurrent painful episodes. These and all other elements of the disease are the result of mutant sickle cell hemoglobin (Hb S) within the red blood cells (**Yogen et al, 2005**).

This mutant Hb S is produced as a result of a mutation in the β -globin gene that changes the sixth amino acid from glutamic acid to valine (**Benz, 2010**).

Substitution of valine for glutamic acid on the outer surface of the Hb S molecule reduces solubility and polymerization of Hb S when deoxygenated, which leads to sickling and poor deformability of polymer-containing erythrocytes that results in occlusion by this sickle red cells of the microvasculature. (**Yogen et al, 2005**).

Approximately half the individuals with homozygous HbS disease experience vaso-occlusive crises (VOC). The frequency of crises is extremely variable. Some individuals have as many as 6 or more episodes annually, whereas others may have episodes only at great intervals or none at all (**Maakaron, 2011**).

These VOCs, which are considered the key feature of SCD, are the end result of a series of red cell, endothelial, monocyte and platelet interactions (**Corrina, 2006**).

The red cell adheres to the endothelium through a series of mechanisms, either directly via exposed red cell membrane phosphatidylserine or sulfated glycans, or by using soluble adhesion molecules (e.g., integrins, thrombospondin, high-

molecular-weight von Willebrand factor and/or vascular cell adhesive molecule-1 (VCAM-1) as a bridge (**Corrina2006**).

VCAM-1 which plays a very important role in the pathophysiology of VOC and stroke is an immunoglobulin-like adhesion molecule expressed on activated endothelial cells and participates in neointima formation after vascular wall injury, because it facilitates monocyte infiltration into injured arteries or/and directly enhances smooth muscle cell proliferation (**Klaus & Yuqing2001**).

Moreover, a study conducted at 2011 concluded that levels of VCAM-1 were significantly higher in subjects with severe SCD (**Dworkis et al., 2011**).

As stroke -which has devastating consequences on children- affects approximately 11% of SCD patients younger than 20 years of age (**Dworkis et al., 2011**), detection of high risk patients and those liable for strokes is very critical in management of those patients (**Adams, 2001**).

Careful screening with trans-cranial Doppler (TCD) ultrasonography and treatment with chronic blood transfusion will likely reduce the number of strokes in children with sickle cell anemia (**Bruce, 2007**).

TCD is a well-established predictor of future cerebrovascular symptoms, it can measure flow velocities in the large intracranial arteries. The narrowing of these arteries, which leads to cerebral infarction, is characterized by an increased velocity of flow therefore, estimating the flow velocity across intracranial arteries helps identifying children at risk of stroke due to increased cerebral velocities (**Colombatti et al., 2009**).

AIM OF WORK

Our aim is to estimate serum levels of VCAM-1 and correlate it with findings of trans-cranial Doppler and clinical condition in children with sickle cell anemia To determine its value as a predictive marker for stroke in sickle cell disease and to identify any association, if present, between serum VCAM-1 levels and disease severity, transfusion therapy and treatment given is also our objective.