بسم الله الرحمن الرحيم

∞∞∞∞

تم رفع هذه الرسالة بواسطة / سلوي محمود عقل

بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات:
.....
.....
.....
.....
.....

Sleep Disordered Breathing and its Relation to Stroke and Pulmonary Hypertension in Patients with Sickle Cell Disease

Thesis

Submitted for Partial Fulfillment of MD Degree in Pediatrics

By

Noura Bahaa El-Dien Mohammed Hassan

Master's Degree in Pediatric, 2016, Faculty of Medicine, Ain Shams University

Under Supervision of

Prof. Dr. Azza Abdel Gawad Tantawy

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Prof. Dr. Fatma Soliman Elsayed Ebeid

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Prof. Dr. Nayera Hazza Khalil Abdelhafez El-Sherif

Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Prof. Dr. Nahed Salah Eldin Ahmed Saleh

Professor of Neurology

Faculty of Medicine, Ain Shams University

Prof. Dr. Sara Mostafa Mohammad Makkeyah

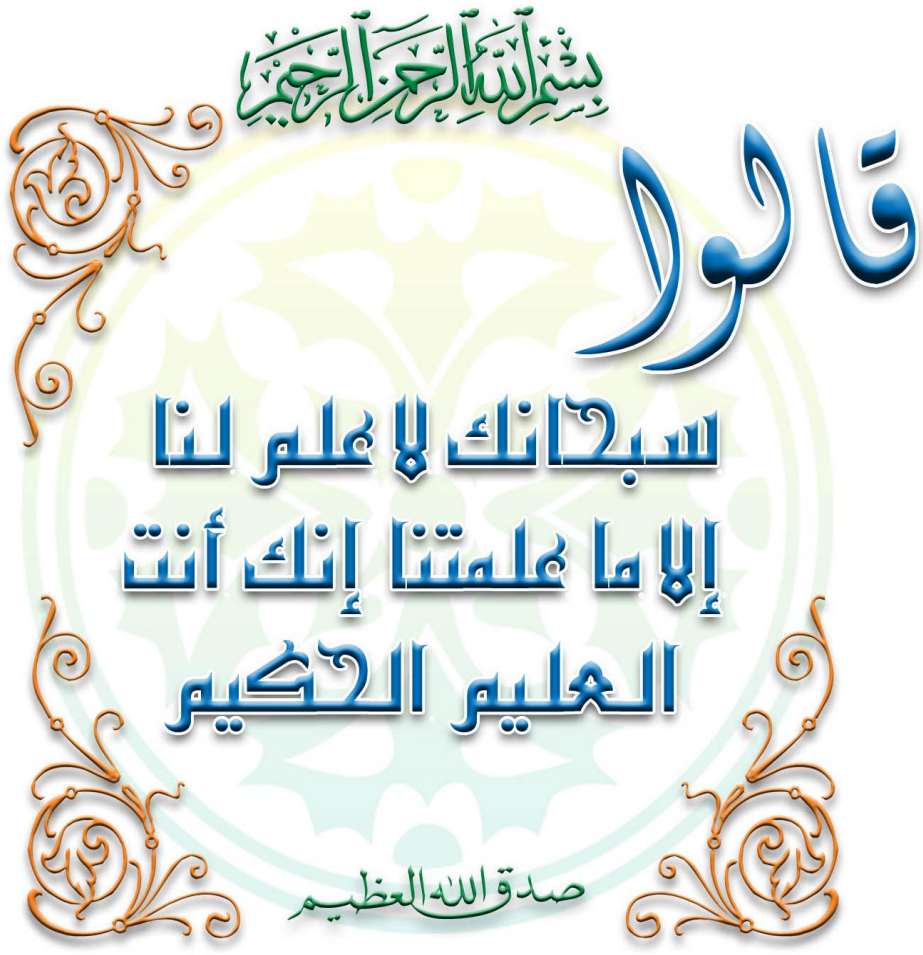
Assistant Professor of Pediatrics

Faculty of Medicine, Ain Shams University

Faculty of Medicine

Ain Shams University

2022



سورة البقرة الآية: ٣٢

Acknowledgments

First and foremost, I feel always indebted to ***Allah*** *the Most Beneficent and Merciful.*

I would like to express my sincere appreciation and gratitude to ***Prof. Dr. Azza Abdel-Gawad Tnatawy,*** *Professor of Pediatrics, Faculty of Medicine, Ain Shams University for her kind supervision and valuable instructions.*

I wish to express my deepest thanks, gratitude and appreciation to ***Prof. Dr. Fatma Soliman Elsayed Ebeid,*** *Professor of Pediatrics, for her outstanding support, kind guidance, valuable instructions sincere efforts, fruitful encouragement and generous help. No words would ever pay our debt for what you have done.*

I am deeply thankful to ***Prof. Dr. Nayera Hazza Khalil Abdelhafez El-Sherif,*** *Assistant Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her great help, outstanding support, active participation and guidance.*

I would like also to express my sincere appreciation and gratitude to ***Prof. Dr. Nahed Salah Eldin Ahmed Saleh,*** *Professor of Neurology, Faculty of Medicine, Ain Shams University, for her continuous directions and support throughout the whole work.*

I am also deeply thankful to ***Prof. Dr. Sara Mostafa*** Mohammad ***Makkeyah,*** *Assistant Professor of Pediatrics, for her great help, meticulous supervision, active participation and guidance and for her continuous directions and support throughout the whole work. I really appreciate her patience and support.*

I would also like to thank ***Dr. Nanies Salah Eldien*** *, Lecturer of pediatrics cardiology and* ***Dr. Ahmed Okba*** *,Lecturer of Interventional Radiology for their active participation and great help throughout the whole work*

I would like to express my hearty thanks to my dear husband, ***Abdelhay****, and to all my family for their support till this work was completed. Your prayers for me was what sustained me this far.*

Also I would like to thank the entire participants who agreed to contribute to this work and made it possible to be done, thanks for your dedication that helped in generation of new knowledge. They all deserve a thank you. They rightly deserve a much more.

Noura Bahaa El-Dien Mohammed Hassan

List of Contents

List of Tables

List of Tables cont...

List of Figures

List of Abbreviations

Abb.	Full term
ADHD	Attention deficit hyperactivity disorder
AHI	Apnea hypopnea index
ASH	American Society of Hematology
ATH	Adenotonsillar hypertrophy
BMI	Body mass index
CBFV	Cerebral blood flow velocity
Cm	Centimeter
CNS	Central nervous system
CPAP	Continuous positive airway pressure
CVAs	Cerebrovascular accidents
DLCO	Diffusing capacity of carbon monoxide
ECHO	Echocardiogram
EEG	Electroencephalography
EMG	Electromyography
g/dl	Grams per decileter
HbS	Hemoglobin S
IQR	Interquartile range
IU/L	International unit per liter
Kg	Kilograms
Kg/m^2	Kilograms per meter squared
MCA	Middle cerebral artery
mg/dl	Milligram per deciliter
MRI	Magnetic resonant imaging
N	Number
NET	Neutrophil extracellular trap
NH	Nocturnal hypoxia
NO	Nitric oxide
NREM	Non-rapid eye movement
OSA	Obstructive sleep apnea
PaO2	Partial pressure of oxygen
PFO	Patent foramen ovale
PSG	Polysomnography
RBC	Red blood cell

List of Abbreviations cont...

Abb.	Full term
REM	Rapid eye movement
ROS	Reactive oxygen species
SCA	Sickle cell anemia
SCI	Silent cerebral infarcts
SD	Standard deviation
SDB	Sleep disordered breathing
SDS	Standard deviation score
SPSS	Statistical Package for Social Sciences
sRBC	Sickle red blood cell
TAMMV	Time averaged maximum mean velocity
TCD	Transcranial Doppler
TRV	Tricuspid regurgitation velocity
TST	Total sleep time
UARS	Upper airway resistance syndrome
VCAM	Vascular cell adhesion molecule-1
VOC	Vaso-occlusive crisis
VWF	Von Willebrand factor

Abstract

Background: Sleep disordered breathing (SDB), a common underdiagnosed sequela of sickle cell disease (SCD) has been linked to the frequency of vaso-occlusive crises, cardiac abnormalities and central nervous system events. **Objective:** To determine the frequency of SDB in patients with SCD and its association to SCD-related complications. **Methods**: Thirty children and adolescents with SCD were evaluated using overnight polysomnography after completing the modified STOP-Bang questionnaire. Transcranial doppler (TCD) and assessment of tricuspid regurgitation velocity (TRV) were performed. **Results:** The mean age of the studied cohort was 10.2 years, with male: female ratio 1.7:1. Six patients (20%) had high-risk for obstructive sleep apnea (OSA), while nine (30%) were at intermediate-risk. Sleep apnea defined as apnea (AHI) > 1 event/hour was found among 18/30 (60%) subjects (14 males and 4 females). Patients with AHI > 5 (moderate to severe OSA) had significantly higher TRV ($p = 0.007$) and left MCA flow velocity ($p = 0.049$) when compared to those with AHI < 5. Patients with AHI > 5 were at higher risk of OSA according to the modified STOP-Bang questionnaire ($p = 0.02$). AHI positively correlated with TRV ($r = 0.53$, $p = 0.003$), right MCA flow velocity ($r = 0.45$, $p = 0.013$) and left MCA flow velocity ($r = 0.55$, $p = 0.002$), and negatively correlated to BMI-SDS ($r = -0.48$, $p = 0.008$). **Conclusion**: Sleep apnea in patients with SCD is associated with risks of pulmonary hypertension and cerebral blood flow alterations which highlights the need for early diagnosis and management.

INTRODUCTION

Sickle cell disease (SCD) is a monogenic, yet highly phenotypically variable disease with multisystem pathology. Morbidities associated with SCD include pain from vaso-occlusion, acute chest syndrome, neurologic and cardiovascular complications (e.g., stroke), hemolytic anemia, and infections ***(Rees et al., 2010)***. It is well recognized that SCD is characterized by a vasculopathy which is thought to result in multiple clinical complications including ischemic stroke, pulmonary hypertension, and chronic kidney disease ***(Ataga et al., 2016)***.

Sleep disordered breathing (SDB) including obstructive sleep apnea (OSA) and tonsillar hypertrophy that leads to intermittent hypoxemia, hypercapnia and fragmented sleep; is a common underdiagnosed sequela of SCD and characterized by daytime sleepiness, behavioral changes, cognitive deficits, growth delays, and cardiovascular complications ***(Marcus et al., 2012)***. The pathophysiologic consequences of SDB, may include endothelial dysfunction with altered nitric oxide bioactivity, altered redox biology, chronic systemic inflammation, and increased expression of cell adhesion molecules ***(Connes, 2015)***. Studies in children and adolescents with SCD have demonstrated associations between nocturnal desaturations and severity of anemia ***(Halphen et al., 2014)***, frequency of vaso-occlusive crises and acute chest syndrome ***(Hargrave et al., 2003),*** cardiac abnormalities including left ventricular hypertrophy and diastolic dysfunction ***(Johnson et al., 2010),*** CNS events ***(Hollocks et al.,***

2012), priapism and nocturnal enuresis ***(Gileles-Hillel et al., 2015).***

SDB is prevalent among patients with SCD. The intermittent apneic episodes in some of these patients with SDB may lead to hypoxemia that could trigger red blood cell sickling and result in the development of vaso-occlusive and hemolytic episodes. There is now increasing evidence to suggest an overlap of the pathophysiologic processes of these two disorders ***(Gileles et al., 2015)***.

SDB among patients with SCD has been evaluated deeply among children and young adults' population. Prevalence of Snoring and sleep apneas was found to be markedly evident in children with SCD compared to those without SCD ***(Downes et al., 2017)*** Many other similar studies of variable sample sizes have also found SDB to be common among children and young adults with SCD ***(Samuels et al., 1992; Mascarenhans et al., 2015).***

The pathophysiologic consequences of SDB, may include endothelial dysfunction with altered nitric oxide bioactivity, altered redox biology, chronic systemic inflammation, and increased expression of cell adhesion molecules ***(Gileles-Hillel et al., 2015).*** Each of these processes could contribute to hemolysis and vaso-occlusion. Studies in children and adolescents with SCD have demonstrated associations between nocturnal desaturations and severity of anemia ***(Halphen et al., 2014),*** frequency of vaso-occlusive crises and acute chest syndrome ***(Hargrave et al., 2003)***

cardiac abnormalities including left ventricular hypertrophy and diastolic dysfunction ***(Johnson et al., 2010),*** CNS events, impaired cognition and executive function ***(Hollocks et al., 2012),*** priapism ***(Gileles-Hillel et al., 2015),*** and nocturnal enuresis ***(Gileles-Hillel et al., 2015).***

Neurological complications are of the many severe consequences of SCD including overt stroke: acute stroke and chronic cerebral ischemia which are among the most disabling ***(Platt, 2005)***, silent cerebral infarcts (SCI) and neurocognitive dysfunction. The incidence of stroke in the population with SCD is approximately 11% ***(Ohene-Frempong et al., 1998)***. SCI is the most commonly recognized cause of neurological injury in SCD ***(Miller et al., 2001)*** and occurs in 37% of pediatric population prior to their 14^{th} birthday ***(Bernaudin et al., 2011)***. Cerebral hemodynamics is often abnormal in SCD increasing the risk of ischemia in the territories of stenosed large vessels and the border zones between them. The risk of tissue injury is also increased by chronic anemia and low daytime and nocturnal oxygen saturation ***(Kawadler et al., 2015).***

Oxygen desaturation and impaired dynamic cerebral autoregulation may predispose patients with SCD to stroke ***(Quinn et al., 2009)***. It has been proposed that SDB plays a pivotal role in precipitating nighttime hypoxemia and the vaso-occlusive episodes associated with SCD. Endothelial dysfunction leading to small vessel disease and insufficient CBF are important

factors proposed in the etiology of SCIs in SCD ***(van der Land et al., 2015)***.

Pulmonary hypertension (PH) is a well-known and often fatal complication of sickle cell disease (SCD) ***(Sedrak et al., 2009).*** About 11–46% of children with SCD have been found to have PH by echocardiogram (ECHO) ***(Pashankar et al., 2008)***. PH in SCD is more likely to be a sequela of increased pulmonary blood flow secondary to chronic anemia, chronic hemolysis, and chronic hypoxemia. Chronic nocturnal hypoxia (NH) is common in children with SCD and may also play a role in the development of PH. Echocardiogram is recommended as the first-line diagnostic investigation when suspecting PH ***(Abman et al., 2015)***. Echocardiograms provide pressure estimates as well as structural assessments, which are essential in the identification and management of PH.