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

Thesis

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Degree in Pediatrics

By

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## Tist of Abbreviations

Abb.	Full term
	Attention deficit hyperactivity disorder
	Apnea hypopnea index
	American Society of Hematology
	Adenotonsillar hypertrophy
BMI	Body mass index
CBFV	Cerebral blood flow velocity
Cm	Centimeter
	Central nervous system
CPAP	Continuous positive airway pressure
CVAs	Cerebrovascular accidents
DLCO	Diffusing capacity of carbon monoxide
ECHO	Echocardiogram
EEG	Electroencephalography
EMG	Electromyography
	Grams per decileter
HbS	
IQR	Interquartile range
IU/L	International unit per liter
Kg	
	Kilograms per meter squared
	Middle cerebral artery
	Milligram per deciliter
	Magnetic resonant imaging
N	
NET	Neutrophil extracellular trap
	Nocturnal hypoxia
NO	
NREM	Non-rapid eye movement
	Obstructive sleep apnea
	Partial pressure of oxygen
	Patent foramen ovale
PSG	
RBC	· ·

# Tist of Abbreviations cont...

Abb.	Full term
	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
	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), 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 intermediaterisk. 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 = 0.013) 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 vasoocclusive 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<sup>th</sup> 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 vasoocclusive 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.