



Prevalence of Nocturnal Enuresis in Pediatric Sickle Cell Disease & its Relation to the Disease Morbidity

Thesis

Submitted for Fulfillment of the Master Degree in
Pediatrics

By

Nahla Ahmed Abdel Wahed
M.B., B.Ch

Supervised By

Prof. Dr. Rukaya Mohammed EL Sayed
Professor of Pediatrics
Faculty of Medicine, Cairo University

Prof. Dr. Mona Hassan Abu El Ela
Professor of Pediatrics
Faculty of Medicine, Cairo University

Dr. Mona Kamal El Ghamrawy
Assistant Professor of pediatrics
Faculty of Medicine, Cairo University

Faculty of Medicine
Cairo University
2012

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

بسم الله الرحمن الرحيم

بناء على موافقة الأستاذ الدكتور/نائب رئيس الجامعة بتاريخ 2012/3/4

اجتمعت اللجنة المشكلة من الاساتذة:

عن المشرفين

الأستاذ الدكتور /رقية محمد السيد

ممتحن داخلي

الأستاذ الدكتور/ منى حسن التاجي

ممتحن خارجي

الأستاذ الدكتور /نيرة محمود العقاد

بقاعة الدور (التاسع بمستشفى الاطفال الجامعي بالمنيرة- ابو الريش) لمناقشة رسالة ماجستير طب
الاطفال المقدمة من :

الطبيبة /نهلة احمد عبد الواحد ابراهيم

الموافق 2012/6/3

يوم الاحد

وذلك في تمام الساعة (العاشرة صباحا)

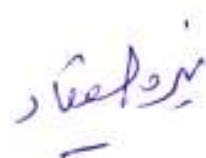
عنوان الرسالة:

مدى انتشار التبول الليلي اللا ارادي لدى اطفال انيميا الخلايا المنجلية وعلاقته بشدة المرض

الملخص:

اجريت هذه الدراسة على 78 من الاطفال المترددين على العيادة الخارجية لامراض الدم بمستشفى
الاطفال الجامعي الجديد- المنيرة-جامعة القاهرة وتهدف للتعرف على مدى انتشار عرض التبول
الليلي اللا ارادي بين الحالات المصابة بانيميا الخلايا المنجلية . وجدنا ان عدد الذكور ممن خضعوا
للداسة (40) والانات (38) حالة بمتوسط اعمار ما بين 5.25 الى 20 عاما. اظهرت النتائج ان
(39.7%) من المرضى يعانون من التبول الليلي اللا ارادي كانوا بالفعل يعانون من كثرة التبول اكثر
من غير المصابين بهذا العرض وكانت نسبة زواج الاقارب بينهم اعلى . في حين لم تكن الفروق
ذات دلالة احصائية فيما يخص القراءات المعملية والمضاعفات المرضية الاخرى المتصلة بمرض
انيميا الخلايا المنجلية (كالاصابة بالجلطة الدماغية والمضاعفات الكبدية والقلبية والصدرية) .

وترى اللجنة قبول البحث



List of Contents

	<i>Page</i>
Abstract	II
Acknowledgement	III
List of Abbreviations	IV
List of Tables	VII
List of Figures	IX
INTRODUCTION	1
AIME OF THE WORK	3
REVIEW OF LITERATURE:	
▪ CHAPTER I: Sickle Cell disease	4
▪ CHAPTER II: Sickle cell Nephropathy	57
▪ CHAPTER III: Nocturnal Enuresis	70
SUBJECTS & METHODS	82
RESULTS	87
DISCUSSION	115
CONCLUSION	124
RECOMMENDATION	125
SUMMARY	126
REFERENCES	129
ARABIC SUMMARY	

Abstract

Nocturnal enuresis is common among children and adolescents with sickle cell disease.

Subjects and methods: This is a cross-sectional study that included 78 steady state sickle cell diseased patients attending at Pediatric Hematology Clinic, New Children Hospital, Cairo University. All patients were subjected to full history taking, clinical and laboratory examinations.

Results: The prevalence of nocturnal enuresis was 39.7%. The genetic predisposition for nocturnal enuresis was suggested by the significant prevalence of nocturnal enuresis among consanguineous families. Enuretic patients showed higher frequency of polyuria. No association was found between nocturnal enuresis and vasoocclusive crisis or other disease-related morbidity.

Conclusion: Further studies are needed to elucidate carefully the underlying pathogenesis of nocturnal enuresis in SCD and to evaluate the role of SCA-related factors in its development. Lack of association of nocturnal enuresis with clinical and laboratory variables in our cohort might indicate that additional psychosocial factors may contribute to the development of nocturnal enuresis.

Key Words: Prevalence -Nocturnal Enuresis -Sickle cell disease

Acknowledgement

*First and foremost thanks to **ALLAH** to whom I relate my success in achieving any work in my life.*

*No words can fulfill the feeling of gratitude and respect I carry to Prof Dr. **Rukaya Mohsen**, Professor of Pediatrics for giving me the honor of working under her supervision for her valuable help constructive suggestion continuous guiding and indispensable direction.*

*Sincere gratitude and respect to Prof. Dr. **Mona Abo Ela**, Professor of Pediatrics for her great support and kind co-operation she generously offered through whole the work.*

*I am deeply indebted to Dr. **Mona Kamal El Ghamrawi**, Assistant professor of pediatrics who devoted me a lot of effort, care and close supervision for her precious advice and great help she offered to me.*

My deepest thanks to all staff members and very kind patients of the Hematology Outpatient Clinic, Pediatric hospital, Cairo University

Finally, I would like to express my appreciation and gratitude to my lovely parents, my family and special respect to the youth of the revolution of 25th January for I have been deeply inspired by their soul of dignity and persistence

Nahla Ahmed Abdelwahed

2012

List of Abbreviations

ACE	: Angiotensin converting Enzyme.
ADH	: Anti- Diuretic Hormon.
ADHA	: Attention Deficit Hyper Kinetic Disorder.
AHRQ	: Agency for Healthcare Research and Quality
AMOFS	: Acute Multiple Organs Failure Syndrome.
ASC	: Acute Chest Syndronme>
ATPase	: Adenosine triphosphatase).
AVN	Avascular Necrosis
BCAM/Lu	: Basal cell adhesion molecule/Lu .
CAR	: Central African Republic.
CBC	: Complete Blood Picture.
CD64	: Cluster Determinant no 64.
CERHR	: Center for the Evaluation of Risks to Human Reproduction.
DE	: Diurnal Enuresis
DI	: Diabetes Insipidus
DM	: Diabetes Mellitus.
DSM IV	: Diagnostic & Statistical Manual of Mental Disorders (4 th edition. Washington DC, American Psychiatric Association, 1994)
EN	: Enuresis
ESR	: Erythrocytic Sedimentation Rate
ESRD	: End Stage Renal Disease
FSGS	: Focal Segmental Glomerulo_sclerosis
GFR	: Glomerular Filtration Rate.
GVHD	: Graft-versus-host disease.
HCT	: Human Cell Transplant
HDAC	: Histone deacetylase.
HLA	: Human Leucocyte Antigen.
HPLC	: High Performance Liquid Chromatography
HSCT	: Hematopoietic stem cell transplantation
ICA	: Internal Carotid Artery
	:

(ICAM-4)	: Intercellular adhesion molecule-4.
IL-1	: Interleukin-1
ISCs	: Irreversibly sickled cells
L-NMMA	: ^N -monomethyl-L-arginine
MCA	: Middle Cerebral Artery
MCHC	: Mean corpuscular hemoglobin concentration
MCV	: Mean Corpuscular Volume
MRA	: Magnetic resonance angiography
NE	: Nocturnal Enuresis.
NF-κB	: Nuclear Factor kappa-light-chain-enhancer of activated B cells
NOSII	: nitric oxide synthase II
NSAIDs	: Non- steroidal Anti-inflammatory Drugs.
OSA	: Obstructive Sleep Apnea Syndrome
PAF	: Platelet activating factor)
PAH	: Pulmonary Artery Hypertention
PCR	: Polymerase Chain Reaction
PGs	: Prostaglandins
PHT	: Pulmonary Hypertension.
PIGF	: Placental growth factor
PNE	: Primary Nocturnal Enuresis
RPN	: Renal papillary Necrosis>
RTA	: Renal Tubular Acidosis.
SCD	: Sickle Cell Disease
SFE	: Systemic Fat Embolisation
sFLT-1	: Soluble Fms-like tyrosine kinase-1
SNE	: Secondary Nocturnal Enuresis
TAMBF	: Trans arterial minimal Blood Flow velocity
TCD	: Transcranial Doppler.
TIA	: Transient Ischemic Attacks.
TNF-α	: Tumor Necrosis Factor
UTI	: Urinary Tract Infection.
VCAM-1	: Vascular adhesion molecule-1.
VEGFR	: The vascular endothelial growth factor receptor.
VLA-4	: Very late activation antigen 4 on reticulocytes;

VOCs : Vaso- occlusive crises.
WBCs : White Blood Corpuscles.

List of Figures

<i>Fig. No.</i>	<i>Title</i>	<i>Page No.</i>
1.	Inheritance of SCD.	5
2.	Role of (NO) in Mechanism of Vasculopathy in SCD	13
3.	Peripheral blood smear of a patient with hemoglobin SS.	29
4.	Pathogenesis SCD nephropathy, Scheinmann, 2007, modified	65
5.	Sex distribution of the studied population (n=78).	88
6.	Genotypes of the studied populations (n=78)	89
7.	Family history of consanguinity among studied population (n=78).	89
8.	Family History of other affected siblings among studies populations (n=78).	90
9.	Frequency of Patients affected with different SCD associated morbidity among studied populations (n=78).	91
10.	Frequency of Renal manifestations among studied populations (n=78).	92
11.	Frequency of patients received blood transfusion therapy over the last year among studied populations (n=78).	94
12.	Abnormalities detected in Urine analysis of studied populations (n=78).	96
13.	Drug therapy of studied Population (n=78).	96
14.	Prevalence of Nocturnal Enuresis (n=31) among our studied population (n=78).	98
15.	Sex Distribution of the Enuretic patients (n=31).	98
16.	Age distribution of the studied enuretic patients (n=31).	99
17.	Age distribution of the enuretic patients according to age stratification of whole studied population (n=78).	100
18.	NE as reported (as a present or past complaint) by the studied enuretic patients (n=31).	101
19.	Stratification of enuretic patients (n=31) according to the different frequencies of episodes/month.	102
20.	Distribution of the studied enuretic patients (n=31) according to increased frequency of NE during acute exacerbations of VOC	103
21.	Causes of resolution of NE in the previously enuretic patients (n=9).	103

<i>Fig. No.</i>	<i>Title</i>	<i>Page No.</i>
22.	Different therapeutic modalities used by some of the studied enuretic patients (n=23) & their outcome	104
23.	Comparison between the two studied groups as regards sex and genotype distribution.	106
24.	Comparison between Enuretic (n=31) & Non –xcxfdEnuretic (n=47) patients as regards risk factors of statistical significance	108
25.	Comparison between enuretic & non-enuretic patients as regards Hydroxyurea & chelation therapy	112
26.	Drug therapy in the enuretic & non enuretic patients	113

List of Table

<i>Table No.</i>	<i>Title</i>	<i>Page No.</i>
1.	Causes of ACS.	19
2.	Clinical Presentation of ACS	19
3.	Potential laboratory and clinical indications for hydroxyurea treatment in patients with SCD	36
4.	Baseline work-up required by the consulting hematologist before hydroxyurea treatment initiation:	39
5.	Indications for Episodic Blood Transfusion in Patients with Sick cell Disease	44
6.	Values of albumin /creatinine ratio	85
7.	(7-IA) Demographic data of studied population (n=78).	88
	(7-IB) Clinical data of studied population(n=78)	91
	(7-IC) Renal manifestations among the included patients (no=78)	94
	(7-ID): Laboratory findings of studied patients n=78	95
8.	(8IIIA)_Comparison between the demographic data of the enuretic (n=31) & the non-enuretic groups of patients	105
	(8-IIIB) Comparison between enuretic & non-enuretic groups as regards Clinical criteria	107
	(8-IIIC) Comparison of renal manifestation among enuretics & non- enuretic patients	110
	(8-IIID)comparison between.enuretic & non-enuretic patients as regarding laboratory findings	111
	(8-IIIE): Comparison of the drug therapy between the enuretic & non-enuretic	113



Introduction And Aim of Work

INTRODUCTION

Enuresis and nocturnal enuresis are acknowledged to be more common in children with sickle cell disease. Prevalence estimates range from 20% to 69% for enuresis, whereas nocturia has been described in up to 68% of children with SCA in USA (**Field et al., 2008**).

Among general population, the prevalence of enuresis at age 5 yr is 7% in males and 3% in females .At age 10 yr, it is 3% in males and 2% in females, and at age 18 yr, it is 1% in males and extremely rare in females. Evidence suggests different rates of bed-wetting by ethnicity and culture (**Boris. and Dalton, 2007**)

However, **Barakat et al (2001)** estimated the prevalence of enuresis at age 5 years to be 15% among the general pediatric population, and that of nocturia to be 40% in children ages 6 to 11 years.

There is evidence of genetic predisposition to primary nocturnal enuresis (**Van Hoeck et al, 2008**).

The literature examining the etiology for increased rates of nocturnal enuresis in SCD children is equivocal (**Jordan et al,2005**), with some studies finding support for the disease related etiologies, (**Suster & Oski,1967, Noll et al ,1967,)** and others failing to do so(**Redeatt et al 1990, Field et al ,2008**) (b))

The association between nocturnal enuresis and sickle cell disease has been attributed to poor urinary concentrating abilities and obligatory high urinary volumes (**Suster & Oski, 1967, Noll et al 1967, Kawak et**

al 1969, Statius et al 1970, Serjeant et al,1986, Akinyanju et al, 1989), although no experimental evidence to support this hypothesis **(Readett,1990 (b))**

Vaso-occlusion due to rigid sickle erythrocytes causes many of the complications associated with SCD **(Noll et al 1967, Kwak et al, 1969, Barakat et al 2001 Babela et al, 2004),** .However the relation between enuresis and nocturia and vaso-occlusive complications such as pain and Acute Chest Syndrome is not well defined. **(Field et al,2008).**