Institute of Postgraduate Childhood Studies
Medical Studies Department

Adrenomedullin and Substance P in Hemodialyzed Children: Relationship to Cognitive Development

Thesis

Submitted for the fulfillment of PhD in *Child Health and Nutrition*
Medical Studies Department

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2010

Abstract

Background. The mortality and morbidity associated with chronic hemodialysis in children have been decreasing. Neurocognitive impairment has been suggested in these patients and would influence their life. **Aim**. to assess neurocognitive function in these patients and to explore its association with various patient parameters. **Design.** Case control study. **Patients & Methods.** Forty-one patients with end stage renal disease (ESRD) on regular hemodialysis (HD) (age 6-15 years) and 40 healthy controls were studied. Assessment of their cognitive performance was done using: Arabic version of the Revised Wechsler Intelligence Scale for Children, Auditory Vigilance test and the figural Memory test. Psychosocial Assessments was done using Pediatric Symptom Check List. Serum Adrenomedullin (AM), Substance p (SP) and Zinc (Zn) were also measured (before and after dialysis). **Results.** Patients had lower IQ, attention and memory scores and worse psycosocial behaviour scores than controls. Patients had lower Zn concentrations which were reduced further after the dialysis session. Low Zn levels were significantly associated with inattention parameters . AM and SP were both higher in patients but were not significantly correlated to psychological parameters. **Conclusions.** Hemodialyzed children have neurocognitive impairment which may need further research to explore causes and support clinicians to help patients cope with their disease.

Key words: End stage renal disease- Hemodialysis- Adrenomedullin- Substance p- Zinc- Cognition

Acknowledgement

First and above all, great endless thanks to **ALLAH**, our creator and our guide, He makes science a way of his worshiping. The more knowledge we earn in His world, the more loving we get His majesty.

I would like to express my sincere gratitude and appreciation to **Professor Dr.Ehab Mohamed Eid,** Professor of Public Health, Institute of Postgraduate Childhood Studies(Medical Department),Ain-Shams University for his unlimited support, keen supervision, and continuous guidance throughout the preparation of this work.

I am greatly indebted to **Professor Dr. Abla Galal Khalifa** , Professor of Child Health and Head of Chlid Health Department, National Research Center, for her sincere effort, valuable remarks, and constant support which have contributed a lot to the delivery of this work.

I'm also deeply grateful to **Professor Dr. Hanaa Hamdy Ahmed,** Prof. Of Hormones, Hormone Research Department, National Research Center, for her great help, support and continuous contribution and guidance.

No words can describe the enormous efforts and generous help of **Dr. Samar Mohammed Sabry**, Assistant Prof. of pediatrics, Cairo University. Her enthusiasm and honest assistance made the achievement of this work possible.

I would like to thank **Dr.Sawsan Tawfiq** assistant professor of child health, National Research Centre for her kind help and sincere encouragement.

Many thanks and heartfelt appreciation to **Professor Dr. Fatina Fadel,** Prof. of pediatrics, Cairo University and **Professor Dr. Gamal Saadi** Prof. of internal medicine, Cairo University for their valuable support.

I am very grateful to **Dr. Hafez M. Bazaraa,** Assistant Prof. of pediatrics, Cairo University for his great help and support.

Many thanks to all members of **nephrology department** of Pediatric hospital, Cairo University, for great help I found.

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List of abbreviations

ADHD	Attention deficit hyperactivity disorder
AM	Adrenomedullin
ARNA	Afferent renal nerve activity
AV	Arteriovenous
AVF	Arteriovenous fistula
BP	Blood pressure
BUN	Blood urea nitrogen
CGRP	Calcitonin gene related peptide
CKD	Chronic kidney disease
CNS	Central nervous system
COX2	Cyclooxygenase 2
Crcl	Creatinin clearance
CRF	Chronic renal failure
CRI	Chronic renal insufficiency
Cu	Cuprophane
CVS	Cardiovascular system
DSM- III	Diagnostic and statistical manual
EBV	Effective blood volume
ESRD	End stage renal disease
Fe	Iron
FSGS	Focal segmental glomerulosclerosis
GABA	g-aminobutyric acid
GFR	Glomerular filtration rate
GH	Growth hormone
HB	Hemoglobin
HD	Hemodialysis
5-HT	Serotonin
IL12	Interleukin 12

IL18	Interleukin 18
IQ	Intelligent Quotient
IVCD	Inferior vena cava diameter
K/DOQI	Kidney disease outcomes quality initiation
NAPRTCS	North American Pediatric Renal Trials and Collaborative Studies
NK1R	Neurokinin1 receptor
NKA	Neurokinin A
NO	Nitric Oxide
nPCR	Normalized protein catabolic rate
NPK	Neuropeptide K
PBMC	Peripheral blood mononuclear cells
PD	peritoneal dialysis
PGE2	Prostaglandin E 2
PSCL	Pediatric Symptom Checklist
PTH	Parathyroid hormone
PVN	Paraventricular nucleus
Qol	Quality of life
RES	Reticuloendothelial system
rHuGH	Recombinant human growth hormone
RRT	Renal replacement therapy
SON	Supraoptic nucleus
SP	Substance p
TAC	Preprotachykinin
TSAT	Transferrin saturation percentage
UF	Ultrafiltration
Zn	Zinc
ZPP	Zinc protoporphyrin

Introduction and Aim of the Study

Introduction

The incidence of chronic renal failure (CRF) showed an increasing trend year after year **(Yang & Yaho (2004)**).The prevalence of both acute renal failure(ARF) and CRF are high in Arab world. Data available on the exact prevalence of various renal diseases are very limited. Nevertheless, the reported prevalence of CRF is 80 to120 per million populations in the Kingdom of Saudi Arabia and 225 per million populations in Egypt (**Shaheen & Alkhder, 2005)**.**The Egyptian Society of Nephrology(2000),** reported that among children aged 5-18 years the incidence of chronic kidney disease (CKD) in Egypt was 1.7%.

Studies aimed at investigating neurocognitive impairment in children with CKD have identified a wide range of delays in motor and cognitive development. Most studies have demonstrated lower IQ scores among children with end stage renal disease (ESRD) than in unaffected siblings **(Bakr et al,2007),**or the general population **(Maddan et al.,2003).**and also when pre- and post-transplantation performances are compared **(Mendley & Zelko,1999).** Memory deficits also have been identified in children with mild CKD as well as ESRD; Improved attention performance has also been demonstrated in children with ESRD after transplantation **(Mendley & Zelko,1999)**. Observations of hyperactivity at school also have been noted in a study assessing cognitive outcomes following dialysis during infancy **(Maddan et al.,2003).**

The measures of cognitive performance in each of these studies varied widely but, when viewed collectively, suggest that children with CKD are vulnerable to cognitive deficiencies in IQ, memory and attention. This might reflect the presence of other clinical variables, such

as duration on dialysis, dialysis adequacy, or presence of residual renal function, which could also influence cognitive performance.

(Jennifer et al., 2007).

Complications of CKD such as anemia, hypertension, and malnutrition are likely key factors contributing to the cognitive deficits of children with CKD.Anemia has been shown to slow the cognitive event related potential in adults with CKD (mean hematocrit =23.7) and impaired cognitive function among otherwise healthy children aged 6-11years with hemoglobin levels less than 11.8g/dl. The optimal hemoglobin for cognitive function in children with CKD remains to be determined. Iron is also an essential cofactor in the synthesis of neurotransmitters such as dopamine, nor-epinephrine, and serotonin.

(Halterman et al,2001)

The effects of hypertension on cognition may be related to the degree of blood pressure elevation, brain injury consequent to hypertensive or hypotensive episodes, and side effects of antihypertensive therapy. Hypertension was associated with lower scores in subtests representing memory, attention, and arithmetic **(Lande et al, 2003).**

Furthermore, malnutrition in young infants without kidney or other chronic disease has been linked to impaired brain growth and developmental delay significant effort has been applied to the nutritional support of children with CKD **(Dibbie et al., 2004).**

Zinc deficiency leads to anorexia, growth retardation, disorders of neurodevelopment, and mental lethargy **(Sayed et al., 2006). Esfahani et al. (2006)** found that serum concentration of Zn in children undergoing regular hemodialysis(HD) was significantly lower than that in healthy children. There was an inverse linear relation between the duration of HD

and serum levels of Zn. Consequently, HD may produce a deficiency of Zn in children on a regular HD regimen.

Sustained hypotension in end-stage renal disease patients is characterized, despite an over activation of the sympathetic and renin-angiotensin systems, by decreased vascular resistance and a blunted vascular response to pressor stimuli. An increased production of one or more vasodilator substances might play a role in the reduced vascular resistance and response to pressor stimuli in these patients **(Cases et al., 2000)**. There are many factors that affect blood pressure in children undergoing HD one of them is volume status **(El-Sonbaty MM,2006)** , also increased production of nitric oxide and/or adrenomedullin (AM) has a possible role in the pathophysiology of chronic hypotension in HD patients **(Cases et al.,2000).**

Adrenomedullin (AM) is a novel 52-amino acid-peptide hormone, originally isolated from human phaeocromocytoma. AM acts as a local autocrine and/or paracrine vasoactive hormone and has vasodilator and blood lowering properties, but its exact role is still uncertain. AM is considered to play an important endocrine role in various tissues maintaining the electrolyte and fluid homeostasis. Its normal plasma concentration is low. In hypertension, CRF and congestive heart failure its plasma concentration increases parallel to the seriousness of the disease. It is assumed that this peptide may be important under pathologic conditions compensating the effects of the vasoconstrictor molecules**(Ruzicska et al, 2001).**

Immunohistochemical, electrophysiological, and pharmacological studies suggested that AM in the CNS acts as a neurotransmitter, neuromodulator, or neurohormone, or as a cytoprotective factor in

ischemic/hypoxic conditions, in addition to its vasodilator role **(Serrano et al., 2002).**

The structurally related neuropeptides, substance P (SP), neurokinin A, and neurokinin B, belong to a family of molecules termed tachykinins and are widely distributed in the central and peripheral nervous systems. These peptides mediate their effects through three G protein coupled receptor subtypes, the neurokinin-1, neurokinin-2 and neurokinin-3 receptors, respectively. Disruption of the neurokinin-3 receptor (NK3) leads to cognitive deficits **(Siuciak et al.,2007).**

The neurokinin SP has neurotrophic as well as memory-promoting effects. Direct application of SP into the region of the nucleus basalis magnocellularis is memory-promoting and reinforcing

(Huston et al., 1995).

The Dorsal Raphe nucleus, in human brain, contains serotonin (5-HT) neurons that innervate the cortex and limbic system and through these projections is thought to regulate cognition and behavior. These peptides are positioned to fine-tune the activity of selective groups of serotonergic neurons within the DR and thereby 5-HT release in different terminal fields. SP act independently and interdependently to influence DR-5-HT function **(Valentino & Commons, 2005)**. In the central nervous system (CNS), dopamine is involved in the control of locomotion, cognition, affect and neuroendocrine secretion. SP have been used as monitors of dopaminergic activity in the CNS (**Jaber et al.,1996).**