A Study of Epigenetic Alterations, Hormonal and Behavioral Disturbances In Relation To Recurrent Childhood Adversities

Thesis
Submitted for Fulfillment of Ph.D. Degree in Childhood Studies
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2017

Acknowledgment

*First and foremost I thank **Allah** the most merciful, for his helping and guiding me throughout this work.*

I would like to express my sincere gratitude to Professor Dr Ehab Mohamed Eid, *Professor of Public Health, Medical Studies Department, Institute of Postgraduate Childhood Studies for his great support, eminent guidance, generous help and precious advice throughout this work.*

My sincere thanks are due to Professor Dr Howida Hosny El Gebali, *Professor of pediatrics Institute of Postgraduate Childhood Studies, for her great effort and faithful encouragement throughout this work.*

A special tribute to Professor Dr Ebtissam Mohamed Salah El-Din, *Researcher Professor of child health, Child Health Department, National Research Center , for her great effort, continuous support, active persistence guidance, faithful advice and overwhelming kindness throughout this work.*

My deep gratitude is awarded to Professor Dr Amany Salah El-Din Elwakkad, *Researcher Professor of Clinical Pathology, Medical Physiology Department, National Research Center for giving me the chance to work under her supervision, and for her great effort, meticulous supervision and valuable advice throughout the work.*

A special appreciation to Professor Dr Somia Mohamed Ismail, *Researcher Professor of Medical Molecular Genetics, Genome Research and Human Genetic Division, National Research Center for her expert participation, valuable time and great effort throughout this work.*

I would like to extend my deep thanks to Dr Manal Abd Elkader, *Researcher of Child Health, National Research Center for her great effort throughout this work.*

Dedication

*To my parents

* To my husband & girls

*To my senior staff in NRC

&

*To all my students

Thank you

Abstract

Background: early childhood Adverse experiences in life and common precipitants of toxic stress such as poverty, abuse or neglect, parental substance abuse or mental illness, and exposure to violence can have a cumulative toll on an individual's physical and mental health.

Objective: to assess the association of exposure to early childhood adversities with epigenetic alterations of glucocorticoid receptor gene, hair cortisol level, cognitive and behavioral status in a sample of Egyptian primary school children.

Subjects and methods: The study included 114 students aged between 7.5 - 11 years, divided into 2 groups according to the Adverse Childhood Experiences International Questionnaire, Group A: (55 student) the exposed group who were exposed frequently to one or two adverse experiences, Group B: (56 student) the highly exposed group with frequent or multiple exposure to three or more adverse experiences. Behavior and IQ assessment were achieved using Pediatric Symptom Checklist (PSCL) and Wechsler Intelligence Scale respectively. Measurement of hair cortisol level and assessment of DNA methylation of glucocorticoid receptor gene were performed in a subsample.

Results: Children exposed to multiple adverse experiences were more likely to have psychosocial disorders, attention deficit, externalizing behavior and low performance IQ. The hair cortisol levels of the two groups were highly above the normal reference ranges of this age regardless the multiplicity of exposure. DNA methylation was detected in 63% of the genetically studied children irrespective to the number of adversities.

Conclusion: exposure to adverse childhood experiences increases the child susceptibility to attention deficit and externalizing behavior with negative impact on IQ scores especially performance IQ. The recorded high hair cortisol level in the studied children promotes its use as a biomarker of chronic stress. Though DNA methylation was detected in some students, large scale studies are still needed.

Key Words: Childhood Adversity – hypothalamic pituitary adrenal axis - Hair Cortisol – DNA methylation.

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List of Abbreviations

Abb.	Full term
ACEs	: Adverse childhood experiences.
ACEs - IQ	: Adverse childhood experiences international questionnaire.
ACF/OPRE	: Administration for Children and Families, Office of Planning, Research and Evaluation.
ACTH	: Adrenocorticotropic hormone.
ADHD	: Attention-deficit/hyperactivity disorder.
BMI	: Body mass index.
CDC	: Center for Disease Control and Prevention.
CNS	: Central nervous systems.
COPD	: Chronic obstructive pulmonary disease.
CRH	: Corticotropin releasing hormone.
CRP	: C-reactive protein.
CVD	: Cardiovascular diseases.
DM	: Diabetes mellitus.
DTI	: Diffusion tensor imaging.
EBD	: Echobiodevelopmental.
ELISA	: Enzyme Linked Immunosorbent assay.
fMRI	: Functional magnetic resonance imaging.
GABA	: Gamma amino butyric acid
HCC	: Hair Cortisol Concentration.
HPA	: Hypothalamic Pituitary Adrenal.
IPV	: Intimate partner violence.

List of Abbreviations (Cont…)

Abb.	Full term
IQ	: Intelligence quotient.
LD	: Learning disabilities.
LDL	: Low density lipoprotein.
MR	: Mental retardation
NICU	: Neonatal Intensive Care Unit.
NSCAW	: National Survey of Child and Adolescent Well-Being.
PCR	: Polymerase chain reaction.
PET	: Positron emission tomography.
PFC	: Prefrontal cortex.
PSCL	: Pediatric Symptom Checklist.
PTSD	: Post traumatic stress disorder.
SCN	: Suprachiasmatic nucleus.
SE	: Socioeconomic
SES	: Socioeconomic status.
sMRI	: Structural magnetic resonance imaging.
TL	: Telomere length.
U.K	: United Kingdom.
U.S	: United States.
WBC	: White blood cell.
WHO	: World Health Organization.
WISC	: Wechsler Intelligence Scale.

INTRODUCTION

The experience of trauma, loss and bereavement during childhood have both immediate and long-term consequences for health and general wellbeing ***(Freeman et al., 1993; Cerel et al., 2006).***

Children who have experienced the death of a parent or witnessed violent and/or traumatic events or exposed to physical and sexual abuse and maltreatment during childhood have consistently been linked to an increased likelihood of depression ***(Molnar et al., 2001; Chapman et al., 2004),*** low self-esteem ***(Mullen et al., 1996),*** alcohol and drug abuse during adolescence and adulthood ***(Molnar et al., 2001; Diaz et al., 2002).***

Adverse life events or stressors that occur to a child's parent or within their familial context have also been connected to health, behavioural and social difficulties during childhood, and poorer outcomes later in life. For example, lower educational attainment has been found among adults who grew up with parents who experienced mental health problems ***(Ensminger et al., 2003)***.

Moreover, cumulative and/or concurrent exposure to a number of these adversities (i.e. multiple adversities) has been linked to exponentially poorer outcomes for children compared to their exposure to single adversity ***(Turner & Lloyd, 1995;***

Felitti et al., 1998; Chapman et al., 2004; Zubrick et al., 2005; Jaffee et al., 2007).

The most widely discussed biological basis for these effects is the glucocorticoid cascade hypothesis, where chronic stress evokes persistent hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis ***(Coplan et al., 1996; Ladd et al., 1996)*** leading to hypercortisolemia and associated atrophy of the hippocampus; an important neural substrate for learning and memory ***(Heim et al., 2000; Heim et al., 2001).***

Chronic alterations of HPA axis activity have been shown in rodents and non-human primates exposed to disruptions of parental care such as maternal separation ***(Sanchez et al., 2001; Pryce et al., 2005)*** and maternal neglect ***(Rice et al., 2008),*** and in humans with childhood parental loss, and neglect or other forms of childhood maltreatment ***(Carpenter et al., 2009).***

Elevated glucocorticoids impair neuronal growth and survival ***(Duman, 2009)***, diminish neutrophils and modify immune functions ***(Epel, 2009)***, and accelerate cellular aging ***(Ceccatelli et al., 2007; Epel, 2009).***

Other hormones such as epinephrine, and norepinephrine are released, which over time with repeated exposures, accumulate to contribute to the pathogenic processes that drive cardiovascular diseases (CVD), systemic inflammation, high