A Study of the Role of Methylenetetrahydrofolate Reductase (MTHFR) Gene Polymorphisms in Children with Attention Deficit Hyperactivity Disorder

THESIS

Submitted for fulfillment of Ph.D. degree in childhood studies

Faculty of Postgraduate Childhood Studies

SUBMITTED BY

Khaled Ismail Abd El-Shakoor Mohamed

MBBCh., 1990, M.SC Pediatrics1995

Faculty of medicine, Ain Shams University

SUPERVISED BY

Prof. Dr. / Howida Hosny El Gebaly

Professor of Pediatrics

Faculty of Postgraduate Childhood Studies

Ain Shams University

Prof. Dr. /Eman Ahmed Zaky

Professor of Pediatrics

Faculty of Medicine

Ain Shams University

Dr. Tarek Mostafa Kamal

Consultant of Human Genetics

Faculty of Medicine - Ain Shams University

Ain Shams University

2018

DEDICATION

I dedicate this work:

To the memory of my father,

To my mother,

To my beloved wife for her wonderful and unlimited support and to my lovely kids Mohamed & Nour.

Acknowledgment

I would like to express my deep appreciation and gratitude to ***Prof. Dr. Howida El Gebali,*** Professor of Pediatrics, Faculty of Graduate Studies for Childhood, Ain Shams University, for her motivating guidance and continuous help which have influenced greatly the accomplishment of this work.

I wish to express my sincere gratitude to ***Prof. Dr. Eman Ahmed Zaky*** Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her continuous encouragement, unlimited cooperation and support during conducting this work.

I am also deeply grateful to ***Dr. Tarek Mostafa Kamal*** Consultant of Human Genetics, Faculty of Medicine, Ain Shams University, for his considerable help and valuable leading comments.

Finally, I’m greatly thankful for all enrolled children and their caregivers, without their participation, this work would not been completed.

Contents

hyperkinetic disorder

2.7.2.1 – Demonstrates abnormality at home

2.7.2.2 – Demonstrates abnormality at school

2.7.2.3 – Directly observed abnormality

2.7.2.4 – Doesn't meet criteria of others

2.7.2.5 - Onset

2.7.2.6 – Duration

2.7.3 – Physical Neurological Examination

2.7.4 – EEG indications for ADHD

2.7.5 – MRI or CT scan indications for ADHD

2.7.6 – Blood tests

2.8 Methods of Management of ADHD

2.8.1- Pharmaceutical treatment

2.8.1.A - Psychostimulants

2.8.1.A. 1 – Mechanism of action

2.8.1.A. 2 – Dose and response

2.8.1.A. 3 – Side effects

2.8.1.B – Alternative Medication to stimulant

2.8.1.B. 1 – The none stimulant atomoxtine

2.8.1 B. 2 – Alpha 2- adrenergic agonist

2.8.1 B. 3 – Other medications

2.8.2- Psychosocial intervention

2.8.2.A – Psycho-education

2.8.2.B – Behavior modification

2.8.2.C – Social intervention

2.8.2.D – Educational intervention

List of Figures

List of Tables

A Contribution of Methylenetetrahydrofolate Reductase (MTHFR) Gene Polymorphisms in Children with Attention Deficit Hyperactivity Disorder.

ABSTRACT

Background: Attention deficit hyper-activity disorder (ADHD) is a neuro-behavioral, complex disorder influenced by many genes. The MTHFR gene C677T and A1298C polymorphisms affect both nucleotide synthesis and DNA methylation. This study aimed to assess the relationship between Methylenetetrahydrofolate Reductase (MTHFR) gene polymorphisms and ADHD in a sample of Egyptian children.

Methods: MTHFR gene polymorphisms were evaluated in 60 participants, 30 ADHD patients and 30 controls of healthy children with normal developmental and psychiatric evaluation with comparable age and sex. The patients were recruited from Psychiatric clinic, Faculty of Postgraduate Studies for Childhood - Ain Shams University, Cairo, Egypt during the period from January to August 2015 with age ranged from 6 to 12years. MTHFR C677T and A1298C alleles distribution was investigated via polymerase chain reaction (PCR) and reverse hybridization.

Results: The recorded genetic results showed heterozygous advantage (Heterosis) regarding studied C677T allele genotype with statistically significant association reported in controls compared to ADHD cases (p=0.0159). Genotype distributions of A1298C allele showed statistically high significant association with ADHD cases compared to controls (p=0.0002). A significant association was found between males of ADHD cases and hetero- homozygous A1298C allele compared to controls (p=0.0079). Meanwhile, ADHD females showed statistically significant higher distribution of the hetero- homozygous genotypes compared to controls (p=0.0072).

Conclusions: There was an evident association between ADHD phenotype and MTHFR A1298C gene polymorphism, and there was a heterozygous advantage (Heterosis) regarding C677T allele genotype and ADHD cases leading to absence of association between MTHFR C677T gene polymorphism and ADHD

1 - Introduction

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric disorder of the neurodevelopmental type (Caroline and Clauss-Ehlers, 2014). It is defined by symptoms of developmentally inappropriate inattention, hyperactivity, and or acting impulsively that are not appropriate for a person's age (Childress and Berry, 2012). The symptoms must begin by the age of six to twelve years old and continue to be present for more than six months (Dulcan and Beth, 2014).

A recent meta-analysis estimated the world-wide prevalence of ADHD to be about 7.2% (Thomas et al., 2015) and diagnosed in about 2 to 16% in school aged children. It is a chronic condition that affects millions of children and often persists into adulthood; the social and economic costs of childhood ADHD are considerable (Leibson et al., 2001).

Family twin and adoption studies suggested a 70 % heritability rate for the disorder (Faraone et al., 2005). Evidence from animal and human studies implicates degranulation of the fronto-striatal and fronto-cerebellar catecholaminergic circuits in children and adolescents with ADHD (Biederman and Faraone, 2005).

Hypoactivity of the dorsolateral prefrontal cortex, caudate nucleus and thalamus was also demonstrated in ADHD probands (Dickstein et al., 2006). Although the exact cause of ADHD is unknown, heredity prenatal or perinatal factors, exposure to toxins and heavy metals, socio-psychological stress, diet, structural and functional abnormalities of the brain were reported to contribute to its etiology (Gokcon et al., 2011).