CONTRIBUTION OF SOME ENVIRONMENTAL AND GENETIC FACTORS IN THE ETIOLOGY OF AUTISM

By

Rasha Rashad Mohamed

B.Sc.Med. and Surg., Ain Shams University , 1996

Master in Clinical Pathology , Ain Shams University, 2000

A Thesis Submitted in Partial Fulfillment
of
The Requirement for the Doctor of Philosophy Degree
In
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APPROVAL SHEET

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مساهمات بعض العوامل البيئية والجينية كمسببات لمرض التوحد

رسالة مقدمة من الطالبة

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أجيزت الرسالة بتاريخ / /2010

موافقة مجلس المعهد **موافقة الجامعة**

/ /2010 **/ /2010**

2010م

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List of Abbreviation

5-Ht	Serotonin Transporter
5-HIAA	Hydroxyindole Acetic Acid
AGA IgG	Antigliadin Immunoglobulin G
ASD	Autistic Spectrum Disorders
CARS	Childhood Autism Rating Scale
CD	Coeliac Disease
CGG	Cytosine Guanine Guanine
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
DC	Dendritic Cell
DNA	Deoxyribonucleic acid
DSM -IV	Diagnostic and Statistical Manual of Mental Disorders
EEG	Elector encephalography
ELISA	Elisa linked immunosorbent assay
FXS	Fragile X Syndrome
GABA	Gamma aminobutyric acid
GFCF	Gluten casein free diet
GIT	Gastro Intestinal system
GS	Gluten sensitivity
HLA	Human leukocyte antigen
IL-1	Interlukin 1
IQ	Intelligance Quotient
MMR	Measles Mumps Rubella

NTD	Neural Tube Defects
PDD	Pervasive Developmental Disorders
PDD-NOS	Pervasive Developmental Disorders Not Otherwise Specified
PKU	Phenylketonuria
RNA	Ribonucleic acid
SNPs	Single Nucleotide Genetic Polymorphisms
TNF	Tumour Necrotising Factor
t-TG	Tissue Transglutaminase

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ENVIRONMENTAL AND GENETIC INFLUENCES IN AUTISTIC CHILDREN

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ABSTRACT

Autism is a neurodevelopmental disorder of unknown cause Both Genetic and environmental influences are claimed to contribute to the etiology of Autism. Several studies were done to determine the factors that contribute to the expression of the symptoms.

We studied genetic, epigenetic and environmental factors that may influence the neurodevelopmental alteration that can cause vulnerability to autism.

We did a controlled study on 44 patients who volunteered to participate at two Egyptian health clinics over 10 month duration, full clinical evaluation, Cytogenetic analysis, Biocard celiac test to detect anti-t TG Ig A antibodies for gluten sensitivity test and Quantase Neonatal phenylalanine screening to detect the phenylalanine level in blood using ELISA.

A part of significant positive family history, no significant association was found between Autism and the studied parameters.

This study points to the important role of genetic susceptibility compared to the environmental factors and the role of family studies to determine the susceptible individuals to autism.

Key words: autism, genetics and environmental interaction.

INTRODUCTION

Autistic Disorder:

Autism is a neurodevelopmental disorder and is considered one of the most disabling syndromes for the neurological, emotional and intellectual development of the affected child.

Our perceptions of autism have evolved considerably in the last 60 years since the initial descriptions of this disorder by Leo Kanner and Hans Asperger ***(Kanner, 1943; Asperger, 1944)***, A wide spectrum of autism-like disorders and traits is now recognized and diagnosed. Almost 80% of affected children develop signs and symptoms of autism during the first year of life (Infantile autism), while the rest develop the full – blown disease by the time they reach the third year of life (Regressive autism) Compelling data have emerged to support the view of autism spectrum disorders (ASD) as a group of biologically based brain disorders with a strong genetic basis ***(Muhle et at., 2004).*** The considerable expansion of autism research efforts in the past decade have been driven largely by this premise, with numerous efforts to identity genetically determined substrates for ASD.***(Folstein& Rosen-Sheidly 2001).***

Regression in Autistic Disorder:

A major unanswered question, and one that has considerable importance for discerning environmental contributions to autism, is whether regressive autism reflects a distinct etiology from non-regressive autism. There has been significant concern that environmental exposures during the early postnatal period trigger autism. The parent who notes a loss of language and other skills

shortly after a discrete event (illness, vaccination) understandably questions whether a causal relationship exists. The occurrence of regression per se does not implicate environmental causation, however, as other disorders that are known to be linked to a single gene can feature a period of relatively normal development followed by regression (e.g., Rett syndrome), this can give us a lead to follow in autism.***(Lawler et al.,2004)***

If regressive autism is an etiologically distinct disorder, then studies that fail to distinguish regressive and non-regressive cases may fail to discern environmental factors that contribute to only one form of autism. The possibility that regressive autism may be triggered by an environmental exposure suggests the 'need to examine carefully a variety of postnatal exposures in addition to exposures that may have occurred in utero. It should be noted, however, that regressive autism does not necessarily imply that the relevant exposures are coincident with the emergence of regression, Instead, regressive autism may reflect a latent effect of much earlier exposures***.(Caronna et al.,2008)***

Environmental Influences:

Against this background of strong support for genetic influences, there has been a growing interest in the potential contribution of chemical, biological, and infectious environmental agents to ASD. A number of factors have contributed to this heightened interest. Foremost is the large apparent increase in ASD prevalence. Although there is general agreement that greater awareness by health professionals and a broadening of diagnostic criteria have contributed to an increase in prevalence, it is difficult to determine