Serum level of Nerve Growth Factor in Autistic Children: Relation to Autoimmunity and Serum Serotonin level

Thesis

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Mahmoud Maher Mahmoud

List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
5HT	*Hydroxy tryptamine*
5HTT	*Serotonin receptor*
AAT	*Animal assisted therapy*
ACTH	*Adrenocorticotrophic hormone*
ADHD	*Attention deficit hyperactivity disorder*
ADOS	*Autism diagnostic observation schedule*
ALA	*Alpha linoleic acid*
APA	*American psychiatric association*
ASD	*Autism spectrum disorder*
BALF	*Bronchoalveolar lavage fluid*
CAMP	*Cyclic adenosine monophosphate*
CARS	*Childhood autism rating scale*
CMV	*Cytomegalovirus*
CNS	*Central nervous system*
CSF	*Cerebrospinal fluid*
DHA	*Docosahexaenoic acid*
DNA	*Deoxyribonucleic acid*
DPT	*Diphtheria, tetanus, pertussis vaccine*
DSM	*Diagnostic and statistical manual of mental disorders*
DT	*Diphtheria, tetanus vaccine*
E14	*Embryonic day 14*
EEG	*Electroencephalogram*
EPA	*Eisosapentaenoic acid*
GABA	*Gamma amino butyric acid*
GFCF	*Gluten free casein free*
GIT	*Gastrointestinal tract*
GM-CSF	*Granulocyte monocyte colony stimulating factor*
HBOT	*Hyperbaric oxygen therapy*
HLA	*Human leucocyte antigen*

List of Abbreviations cont...

Abb.	Full term
IFN	*Interferon*
IG	*Immunoglobulin*
IL	*Interleukin*
MBP	*Myelin basic protein*
MHC	*Major histocompatibility complex*
MIA	*Maternal immune activation*
MMR	*Measles, mumps, rubella vaccine*
NGF	*Nerve growth factor*
NK	*Natural killer*
PDD-NOS	*Pervasive developmental disorders not otherwise specified*
POLY(I:C)	*Polyinosinic: Polycytidylic acid*
PUFA	*Polyunsaturated fatty acids*
RNA	*Ribonucleic acid*
RRB	*Restrictive repetitive behaviour*
SCD	*Specific carbohydrate diet*
SCI	*Social communication & interaction*
SLE	*Systemic lupus erythrematosis*
SRS	*Social responsive scale*
SSRI	*Selective serotonin reuptake inhibitors*
TD	*Typically developping*
Th	*T helper*
TNF	*Tumor necrosis factor*
TPH	*Tryptophan hydroxylase*
VDRE	*Vitamin D response element*
VPA	*Valproic acid*

INTRODUCTION

An imbalance between pro- and anti-inflammatory pathways has been proposed to play an important role in the pathogenesis of autism ***(Ahmad et al., 2017).*** Autoimmunity to CNS may have a pathogenic role in autism ***(Cohly and Panja, 2005).*** This may be indicated by the presence of brain-specific auto-antibodies in some autistic children and the increase of autoimmune disorders among autistic families ***(Mostafa et al., 2010; Mostafa et al., 2016).*** Autism is a cognitive disorder ***(Benitez-Burraco, 2008)*** and demyelination may be responsible for this cognitive dysfunction (memory, attention, language, concept formation, problem solving, executive and visuospatial dysfunctions) ***(Fields, 2005).*** Myelin basic protein (MBP) is a protein that is important in the process of myelination of nerves in CNS. Several studies revealed increased frequency of anti-myelin basic protein (anti-MBP) autoantibodies in some autistic children ***(Mostafa and Al-Ayadhi, 2011; Mostafa and Al-Ayadhi, 2015).***

Serotonin is formed by hydroxylation and decarboxylation of tryptophan. Serotonin is known to play a role in brain development prior to the time it assumes its role as a neurotransmitter. Disruption of serotonergic development can leave permanent alterations in brain function and behavior. This may be the case in autism ***(Whitaker-Azmitia, 2001; Narita et***

al., 2002; Geir et al., 2018). Elevated blood serotonin levels were reported in many autistic children ***(Janusonis, 2008; Hranilović et al., 2009; Mostafa and Al-Ayadhi, 2011).*** In CNS, serotonin, an important neurotransmitter and trophic factor, is synthesized by both mast cells and neurons ***(Nautiyal et al., 2012).*** Blood serotonin might serve as analogue marker for serotonergic function ***(Moffitt et al., 1998).***

Neurotrophic factors comprise a broad family of biomolecules, most of which are peptides or small proteins, that support the growth, survival and differentiation of both developing and mature neurons. The prototypical example and best characterized neurotrophic factor is nerve growth factor (NGF). NGF is also synthesized by non-neuronal cells as cells of the immune-haematopoietic lineage ***(Skaper, 2017).*** Mast cells are capable of producing and responding to NGF. NGF is a mast cell chemoattractant and it increases mast cell-mediator release, including serotonin ***(Skaper et al., 2005).*** In addition, NGF stimulates the proliferation of B and T lymphocytes with production of antibodies ***(Thorpe and Perez-Polo, 1987; Otten et al., 1989; Kimata et al., 1991).*** NGF concentrations are elevated, and may participate in numerous inflammatory and autoimmune states such as multiple sclerosis ***(Bazhenov et al., 2018)*** and systemic lupus erythematosus ***(Kalinowska-Łyszczarz et al., 2017).***

Aim of the Work

This work was the first to investigate the relationship between serum levels of NGF and both hyperserotonemia and the frequency of serum anti-myelin basic protein (anti-MBP) auto-antibodies in autistic children.

Chapter 1

AUTISM SPECTRUM DISORDER (ASD)

Definition:

Autism Spectrum Disorder (ASD) is defined by the Diagnostic Statistical Manual of Mental Disorders 5 (DSM-V) as a neurobehavioral disorder manifested by persistent deficits in social and communication interaction, deficits in developing, understanding and maintaining relationships. In addition, there is abnormal and fixed interests and repetitive behavior. Symptoms must be present at early childhood and interfere with daily function ***(American psychiatric association (APA), 2013).***

Epidemiology:

Prevalence of ASD in 2014 was estimated to affect 1 in 68 which is 30% higher than the previous estimate of 1 in 88 in 2008. It is unclear whether these rates are indicative of a true increase in incidence of the disorders or are due to broader diagnostic criteria or increased awareness. Males are at greater risk for ASD than females by 4–5 times ***(McCarthy, 2014).***

Etiology:

It results from a combination of three factors genetic, environmental and neurological. Also, the immune system has

been implicated in ASD during both the prenatal and postnatal periods ***(Estes and McAllister, 2015).***

A) Genetic:

ASD heritability could be as great as 50 % with many potential transmission modes. Nearly 2000 individual genes have been implicated in ASD,but none are specific to the disorder ***(Xu et al., 2012).***

Genetic syndromes associated with ASD:

1. **Fragile X syndrome:** ASD occurs in 21–50% of males with fragile X syndrome ***(Wadell et al., 2013).***

2. **Rett syndrome:** Rates of ASD in Rett syndrome range from 25 to 40% ***(Moss and Howlin, 2009).***

3. **Klinefelter syndrome:** There is increased susceptibility to ASD in this XYY karyotype ***(Bishop et al., 2011).***

4. **Tuberous sclerosis:** Up to 60% have the diagnosis of ASD ***(Moss and Howlin, 2009).***

5. **Hamartoma Tumor Syndrome:** It is reported in autistic individuals with macrocephaly ***(Leslie and Longy, 2016).***

6. **15q11-13 Deletion or Duplication Maternal/Paternal:**

Mutations in 15q11-13 are associated with either duplication, which is more frequent genetic abnormality in

autism, or gene deletion causing Prader-Willi syndrome or Angelman syndrome according to maternal or paternal origin ***(Lasalle et al., 2015).***

7. **Fetal alcohol syndrome:** Prenatal alcohol exposure is associated with possible high risk of ASD ***(Sayal et al., 2007; Jacobson et al., 2006).***

B) Environmental:

Expression and the impact of many genes is influenced by environmental factors ***(Lee et al., 2012).*** They include:

I. Prenatal factors:

1) Intrauterine infections and inflammation:

An increased rate of ASD was found among children born to mothers that were hospitalized due to infection during pregnancy ***(Zerbo et al., 2013).***

a- Cytomegalovirus (CMV) infection:

CMV DNA was detected among ASD cases in a higher prevalence than in the general population ***(Sakamoto et al., 2015).*** ASD children who are seropositive for CMV tend to be worse in the major severity scales than the seronegative ones ***(Gentile et al., 2014).***

b- Congenital rubella:

Maternal rubella infection in pregnancy is associated with an increased rate of ASD in the offspring ***(Chess et al., 1978).***

c- Influenza:

It seems that fever may be the trigger for the increased ASD rate following maternal influenza infection without direct effect of the virus ***(Zerbo et al., 2013).***

d- Toxoplasma:

The development of autism may be due to the reactivation of latent toxoplasmosis ***(Prandota, 2010).***

2) Maternal and paternal factors:

a- Maternal and paternal age:

Both advanced maternal and paternal age are associated with autism. Maternal age may be due to increased risk of chromosomal abnormalities in ova of increased age or unstable trinucleotide repeats. It is 51% more likely for mothers older than age 40 to give birth to an autistic child, than mothers between the ages of 25 and 29 ***(Shelton et al., 2010).*** Paternal age may be due to imprinted genes or de novo spontaneous mutations that accumulate with advancing age in spermatagonia ***(Reichenberg et al., 2006).***