Assessment of Serum Glutamate in Autism Spectrum Disorders

Thesis

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بسم الله الرحمن الرحيم

رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ
الَّتِي أَنْعَمْتَ عَلَيَّ وَعَلَى وَالِدَيَّ
وَأَنْ أَعْمَلَ صَالِحًا تَرْضَاهُ وَأَدْخِلْنِي
بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ

صدق الله العظيم

الاية ١٩من سورة النمل

Abstract

The autism spectrum disorders (ASD) or the pervasive developmental disorders (PDD) are two synonyms of the same group of disorders. They comprise a group of neuropsychiatric disorders characterized by specific delays and deviation in social, communicative, and cognitive development, with an onset starting before 3 years. despite the great array of observations being made at the cellular and molecular dysfunctions associated with autism spectrum disorders, the basic central mechanism of these disorders hasn‘t been proposed in major scientific literature. Multiple etiological factors were discussed including genetic, biochemical, immunological, perinatal, neuroanatomical and psychosocial factors .

Glutamate is the principal excitatory neurotransmitters in the mammalian brain. The brain contains abundant glutamate receptors and that destruction of different brain structures could result from excessive stimulation of these receptors leading to many neurodevelopmental or neurodegenerative disorders through a process known by immunoexcitotoxicity. In autism spectrum disorders, immunoexcitotoxicity is accused to be the cause behind the neurodevelopmental changes that occur in autistic patients .

Key Words :

Antigen presenting cells - Dimethyl glycine – Methylphenidate .

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Dedication

This work is dedicated to my family: my ever sacrifying parents, my exceedingly kind sister, my extremely helpful brother, and my highly supportive husband.

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List of Abbreviations

ABC	Autism Behavior Checklist
ACPD	Agonist 1-amino-1, 3-cyclopentonedi carboxylic acid
ADIR	Autism Diagnostic Interview–Revised
ADOS	Autism Diagnostic Observation Schedule
AED	Antiepileptic drugs
AMPA	ὰ-amino-3-hydroxy-5-methyl-4-isoxazoleproprionate
APC	Antigen presenting cells
ASD	Autism spectrum disorders
BBB	Blood brain barrier
CaMK	Calcium modulin Kinase
CARS	Childhood autism rating scale
CDD	Childhood disintegrative disorder
CHAT	Checklist for Autism in Toddlers
DA	Dopamine
DMG	Dimethyl glycine
DZ	Dizygotic
EAA	Excitatory amino acids
GABA	Gamma-amino-butyric acid
GARS	Gilliam Autism Rating Scale
GLAST	Glial glutamate and aspartate transporter

GluR	Glutamate receptors
HBOT	Hyperbaric Oxygen Therapy
IgG,M	Immunoglobulin G,M
LPP	Lipid peroxidation products
LTP	Long term potentiation
MCHAT	Modified checklist for autism in toddlers
MGluR	Metabotropic glutamate receptors
MHC	Major histocompatability
MIF	Macrophage inhibitory factor
MPH	Methylphenidate
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MSG	Monosodium glutamate
MZ	Monozygotic
NMDA	NMDA (N- methyl-D-aspartate)
NO	Nitric Oxide
NR1	NMDA receptor 1
PCP	Phencyclidine
PDD	Pervasive developmental disorders
PECS	Picture exchange cards
PGE	Prostaglandins
PPI	Prepulse inhibition
ROS	Reactive oxygen species
SES	Socioeconomic standard

STAT	Screening Tool for Autism in Two-Year-Olds
TNF	Tissue necrosis factor
TGF	Transforming Growth factor B

Glossary

Gulf war syndrome: A chronic multisymptom disorder affecting veterans and civilians after the 1991 Gulf War .It includes a wide range of acute and chronic symptoms such as fatigue, musculoskeletal pain, cognitive problems, skin rashes and diarrhea.

Human fetal alcohol syndrome: A pattern of mental and physical defects that can develop in a fetus in association with high levels of alcohol consumption during pregnancy.

Ubiquitin: A small regulatory protein that has been found in almost all tissues of eukaryotic organisms. Ubiquitin can be attached to proteins and label them for destruction.

Angelman syndrome: Neuro-genetic disorder characterized by intellectual and developmental disability, sleep disturbance, seizures, jerky movements (especially hand-flapping), frequent laughter or smiling.

Growth cone: dynamic, actin-supported extension of a developing axon seeking its synaptic target.

Dendritic arborization: branched projections of a neuron that act to conduct the electrochemical stimulation received from other neural cells to the cell body, or soma, of the neuron from which the dendrites project. Electrical stimulation is transmitted onto dendrites by upstream neurons via synapses which are located at various points throughout the dendritic arbor.

Introduction

The autism spectrum disorders (ASD) or the pervasive developmental disorders (PDD) are two synonyms of the same group of disorders. They comprise a group of neuropsychiatric disorders characterized by specific delays and deviation in social, communicative, and cognitive development. Despite the common association with mental retardation, these disorders differ from other developmental disorders in that their behavioral features are distinctive and do not simply reflect developmental delay **(Rutter et al., 1978)**. Although better definitions of the syndrome continue to be needed, the validity of autism as a well defined disorder is now established. In addition to autism, various other disorders are included with the PDD class in DSM-IV. These include Asperger's disorder, Rett's disorder, childhood disintegrative disorder (CDD), and pervasive developmental disorder not otherwise specified (PDD-NOS) **(American Psychiatric association, 2000).**

The DSM-IV definition of autism was developed on the basis of a very large, international, multisite field trial. Previous definitions of autism were put into consideration but adding to it that age of onset (before age 3 years) is included as a necessary diagnostic feature and criteria are more well framed **(Lewis, 2000)**.

The social and communicative deficits are obvious in patients with ASD relative to their developmental level. Social difficulties are characteristic in autism and considered as key diagnostic features. Complexities for definitions of autism have included the broad range of syndrome presentation, changes in syndrome expression with age, and differentiation from other psychiatric and developmental disorders **(Klin et al., 1995)**.

However, despite the great array of observations being made at the cellular and molecular dysfunctions associated with autism spectrum disorders, the basic central mechanism of these disorders hasn‘t been proposed in major scientific literature. One of the proposed theories was the biological theory and the role of neurotransmitters in the pathophysiology of autism **(Geschwind et al., 2011)**.

There are many neurotransmitters in the central nervous system while there are only two in the peripheral nervous system which are acetylcholine and norepinephrine. There are excitatory and inhibitory neurotransmitters. Glutamate is considered the main excitatory neurotransmitter while GABA is considered the main inhibitory one. In many cases (such as dopamine), it is the receptor which determines whether the neurotransmitter will act as inhibitory or excitatory one. It also determines if the neurotransmitter will act directly through ion channels or indirectly through second messenger **(Best, 1995)**.