

# **Study of TGF $\beta$ 1 in a sample of Egyptian Children with Autism Spectrum Disorder**

*Thesis*

*Submitted for Partial Fulfillment of MSc. Degree in  
Pediatrics*

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**2017**



" قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا  
إِلَّا مَا عَلَّمْتَنَا  
إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ "



## **ACKNOWLEDGMENT**

*First and foremost, thanks and praise to **ALLAH**, Most gracious, Most merciful.*

*I would like to express my deep gratitude, thanks and respect to our eminent **Prof. Eman Amin Abdel-Aziz**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University for granting me the privilege of working under her supervision and for her great encouragement and unfailing tender advice throughout this work and throughout my career. She is a great model for the ideal psychiatrist.*

*No words can be sufficient to express my deep gratitude, admire and appreciation to **Dr. Walaa Youssef Youssef**, Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University for her great support, valuable advice and continuous encouragement. Her sincere effort and help will never be forgotten.*

*I am greatly thankful to **Dr. Marwa Matboly Sayed**, Lecturer of Medical Biochemistry & Molecular Biology, Faculty of Medicine, Ain Shams University for her great effort, kind help, great support, careful supervision, continuous advice and guidance.*

*I would like to thank my patients and their parents for their cooperation and trust. I wish them all the best of health.*

*Last but not by any means least, I would like to express my warm gratitude to all the members of my family for their kindness, trust, unfailing support and much needed encouragement.*

***Mohammed Khairy***

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## List of Abbreviations

| <i>Abb.</i>     | <i>Full Term</i>                                    |
|-----------------|---|
| <b>3di</b>      | Developmental, Dimensional and Diagnostic Interview |
| <b>AAI</b>      | Animal-Assisted Therapy                             |
| <b>ABA</b>      | Applied Behavior Analysis                           |
| <b>ADHD</b>     | Attention deficit hyperactivity disorder            |
| <b>ADOS</b>     | Autism Diagnostic Observation Schedule              |
| <b>AEDs</b>     | Antiepileptic drugs                                 |
| <b>ALA</b>      | Alpha-linoleic acid                                 |
| <b>APA</b>      | American Psychiatric Association                    |
| <b>APLS</b>     | Antiphospholipid Syndrome                           |
| <b>ASDs</b>     | Autistic spectrum disorders                         |
| <b>ATEC</b>     | Autism treatment evaluation checklist               |
| <b>ATX</b>      | Atomoxetine   |
| <b>BBB</b>      | Blood brain barrier                                 |
| <b>BMP</b>      | Bone morphogenetic proteins                         |
| <b>CAM</b>      | Complementary and Alternative Medicine              |
| <b>cAMP</b>     | Cyclic adenosine monophosphate                      |
| <b>CARS</b>     | Childhood autism rating scale                       |
| <b>CARS2-HF</b> | CARS2-High Functioning Version                      |
| <b>CARS2-ST</b> | CARS2-Standard Version                              |
| <b>CBMNC</b>    | Cord blood mononuclear cell                         |
| <b>CBT</b>      | Cognitive Behavioral Therapy                        |
| <b>CC</b>       | Corpus Callosum                                     |
| <b>CDC</b>      | Center for Disease Control and prevention           |
| <b>CKIs</b>     | Cyclin-dependent kinase inhibitors                  |
| <b>CMV</b>      | Cytomegalovirus                                     |
| <b>CNS</b>      | Central nervous system                              |

|            |                                 |
|------------|---------------------------------|
| <b>CSF</b> | Cerebrospinal fluid             |
| <b>DAT</b> | Dopamine active transporter     |
| <b>DC</b>  | Dendritic cell                  |
| <b>DDT</b> | Dichlorodiphenyltrichloroethane |

## List of Abbreviations (Cont...)

| <b>Abb.</b>      | <b>Full Term</b>   |
|------------------|--|
| <b>DHA</b>       | Docosahexaenoic acid   |
| <b>DIR</b>       | Relationship-based model   |
| <b>DISCO</b>     | Diagnostic Interview for Social and Communicative Disorders                            |
| <b>DNA</b>       | Deoxyribonucleic acid  |
| <b>DPT</b>       | Diphtheria, Tetanus, Pertussis Vaccine   |
| <b>DSM</b>       | Diagnostic and statistical manual of mental disorders                                  |
| <b>DSM-III-R</b> | Diagnostic and statistical manual of mental disorders third edition-revised            |
| <b>DSM-IV</b>    | Diagnostic and statistical manual of mental disorders – fourth edition                 |
| <b>DSMIV-TR</b>  | Diagnostic and statistical manual of mental disorders – fourth edition – text revision |
| <b>DSM-V</b>     | Diagnostic and statistical manual of mental disorders – fifth edition                  |
| <b>DT</b>        | Diphtheria and tetanus toxoids Vaccine   |
| <b>DTT</b>       | Discrete Trial Training  |
| <b>DUI</b>       | Daytime urinary incontinence   |
| <b>EAAT</b>      | Equine-assisted activities and therapies   |
| <b>EC</b>        | The endothelial cell   |
| <b>EEG</b>       | Electroencephalography   |
| <b>eg</b>        | For example  |
| <b>EIBI</b>      | Early Intensive Behavioral Intervention  |
| <b>ELISA</b>     | Enzyme-linked immunosorbent assay  |
| <b>EPA</b>       | Eicosapentaenoic acid  |
| <b>EPS</b>       | Extrapyramidal symptoms  |
| <b>ESDM</b>      | Early Start Denver Model   |
| <b>FDA</b>       | Food and Drug Administration   |
| <b>FI</b>        | Fecal incontinence   |
| <b>GABA</b>      | Gamma amino butyric acid   |
| <b>GARS 2</b>    | Gilliam Autism Rating Scale Second Edition   |

## List of Abbreviations (Cont...)

| <i>Abb.</i>     | <i>Full Term</i>                                  |
|-----------------|---|
| <b>GD</b>       | Gestational diabetes                              |
| <b>GDF</b>      | Growth and differentiation factors                |
| <b>GFCF</b>     | Gluten free casein free                           |
| <b>GI</b>       | Gastrointestinal                                  |
| <b>GIT</b>      | Gastrointestinal Tract                            |
| <b>HAH</b>      | Halogenated Aaromatic Hy-drocarbons               |
| <b>HBOT</b>     | Hyperbaric oxygen therapy                         |
| <b>IFN-γ</b>    | Interferon gamma                                  |
| <b>Ig</b>       | Immunoglobulines                                  |
| <b>IGF-1</b>    | Insulin-like growth factor                        |
| <b>IL</b>       | Interleuken                                       |
| <b>IQ</b>       | Intelligent quotient                              |
| <b>ITC</b>      | Infant Toddler Checklist                          |
| <b>IU</b>       | International unit                                |
| <b>ITP</b>      | Idiopathic thrombocytopenic purpura               |
| <b>LAP</b>      | latency associated peptide                        |
| <b>lb</b>       | Pound   |
| <b>LEAP</b>     | Learning Experiences, An Alternative Program      |
| <b>LTBPs</b>    | Latent TGF-β binding proteins                     |
| <b>mcg</b>      | Micrograms  |
| <b>M-CHAT-R</b> | Modified Checklist for Autism in Toddlers-Revised |
| <b>mg</b>       | milligram   |
| <b>miRNA</b>    | Micro RNA   |
| <b>MMR</b>      | Measles, Mmumps,Rrubella Vaccine                  |
| <b>MPH</b>      | Methylphenidate                                   |
| <b>MR</b>       | Mental retardation                                |
| <b>MRI</b>      | Magnetic resonance imaging                        |
| <b>mRNA</b>     | Messenger ribonucleic acid                        |
| <b>NAC</b>      | N-Acetylcysteine                                  |
| <b>nAChR</b>    | Nicotinic acetylcholine receptor                  |
| <b>NE</b>       | Nocturnal enuresis                                |

## List of Abbreviations (Cont...)

| <i>Abb.</i> | <i>Full Term</i> |
|-------------|------------------|
|-------------|------------------|

|                                |   |
|--------------------------------|---|
| <b>NK</b>                      | Natural killer  |
| <b>NO.</b>                     | Number  |
| <b>NTFs</b>                    | Neurotrophic factors                                      |
| <b>NREMS</b>                   | Non-rapid eye movement sleep                              |
| <b>OT</b>                      | Occupational therapy                                      |
| <b>p</b>                       | Probability of variance                                   |
| <b>PCP</b>                     | Primary care pediatrician                                 |
| <b>PDD</b>                     | Pervasive developmental disorders                         |
| <b>PDD-NOS</b>                 | Pervasive developmental disorders not otherwise specified |
| <b>PECS</b>                    | Picture Exchange Communication System                     |
| <b>PET</b>                     | Positron emission tomography                              |
| <b>Pg/ml</b>                   | Picogram per milliliter                                   |
| <b>PGD</b>                     | Pregestational diabetes                                   |
| <b>PIT</b>                     | Parent implemented training                               |
| <b>PM</b>                      | Particulate matter  |
| <b>PPAR<math>\gamma</math></b> | Peroxisome proliferator activated receptor gamma          |
| <b>PRT</b>                     | Pivotal Response Training                                 |
| <b>PT</b>                      | Parent training   |
| <b>PUFAs</b>                   | Polyunsaturated fatty acids                               |
| <b>RDI</b>                     | Relationship Development Intervention                     |
| <b>ROS</b>                     | Relative Oxygen Species                                   |
| <b>RRB</b>                     | Restrictive, Repetitive Behavior                          |
| <b>SCD</b>                     | Specific carbohydrate diet                                |
| <b>SCI</b>                     | Social communication and interaction                      |
| <b>SD</b>                      | Standard deviation  |
| <b>SGAs</b>                    | Second generation antipsychotics                          |
| <b>SI</b>                      | Sensory Integration                                       |
| <b>SIB</b>                     | Self-injurious behaviors                                  |
| <b>SP</b>                      | Streptavidin-Peroxidase                                   |
| <b>SRS</b>                     | Social Responsiveness Scale                               |

## List of Abbreviations (Cont...)

| <b>Abb.</b>                   | <b>Full Term</b>                               |
|-------------------------------|--|
| <b>SSRIs</b>                  | <b>Selective serotonin reuptake inhibitors</b> |
| <b>TGF<math>\beta</math>1</b> | Transforming growth factor beta 1              |
| <b>Th</b>                     | T helper cell                                  |
| <b>TLE</b>                    | Temporal lobe epilepsy                         |

|                                |   |
|--------------------------------|---|
| <b>TMS</b>                     | Transcranial Magnetic Stimulation             |
| <b>TNF-<math>\alpha</math></b> | Tumor necrosis factor alpha                   |
| <b>TPN</b>                     | Total parenteral nutrition                    |
| <b>TPO</b>                     | Thyroid disease with anti-thyroid peroxidase  |
| <b>TZDs</b>                    | Thiazolidinediones                            |
| <b>UCMSC</b>                   | Umbilical cord-derived mesenchymal stem cells |
| <b>US</b>                      | United States                                 |
| <b>USA</b>                     | United States of America                      |
| <b>VBI</b>                     | Verbal Behavior Intervention                  |
| <b>VEGF</b>                    | Vascular endothelial growth factor            |
| <b>VPA</b>                     | Valporic acid                                 |
| <b>WHO</b>                     | World Health Organization                     |

# **Introduction**

Autism spectrum disorders (ASDs) represent a group of neurodevelopmental disorders characterized by impairments in verbal and non-verbal communication, social withdrawal and stereotypical behaviors, which may or may not be associated with cognitive deficits, self-injurious behaviors and other neurological comorbidities (*Salmi et al., 2013*).

A dramatic rise in incidence of ASDs has occurred in the past 25 years. ASD has a current estimated prevalence of about 1 in 68 children aged 8 years; estimated prevalence was significantly higher among boys (23.6 per 1000) than among girls (5.3 per 1000) (*Christensen et al., 2016*). The exact etiology of autism remains unknown, it is likely to result from a complex combination of genetic, immunological and environmental susceptibility (*Cohen et al., 2005*).

There is growing awareness of an immunological involvement in children with ASD. Evidence of immune dysregulation has been observed in some individuals with ASD including increase levels of pro-inflammatory cytokines in brain tissue, CSF and plasma and increased production of pro-inflammatory cytokines by peripheral blood mononuclear cell culture when compared to typically developing control (*Ashwood et al., 2008*).

Also, immunosuppressive cytokines are critical for immune homeostasis and transforming growth factor beta 1 (TGF $\beta$ 1) is one of them and it is the most important immune regulator that can effectively control diverse aspects of the immune response. TGF- $\beta$ 1 is a multifunctional immunosuppressive cytokine and has pivotal neurodevelopmental functions with potential therapeutic effects (*den Haan et al., 2007*).