



Autism Spectrum Disorder with the Perspective of Etiopathogenesis; Environmental, Genetic, and Epigenetic Factors

Etiyo-Patogenez Perspektifi ile Otizm Spektrum Bozukluğu; Çevresel, Genetik ve Epigenetik Faktörler

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Dear Editor,

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder that is characterized with deficits in social skills (communication and interaction), language skills and presence of stereotypical repetitive behaviours, and interests or activities that can persist throughout life.^[1] ASD prevalence was recently reported with an increase at 1 in 59 children by Center for Disease Control and Prevention (CDC) USA.^[2]

Although definite etiology of the ASD is still unclear; different evidences were determined from many conclusions of the studies suggesting and supporting etiologic and causative association of three factors (environmental, genetic and epigenetic factors) with ASD. Each factor has two or three sided interaction with each other. Intestinal microbiota homeostasis is one of the most important element of environmental factors.^[3,4]

Human gut microbiota consisting of more than three thousand of different bacterial species belonging to six different phyla and ten fold higher than cell numbers of human body. Human gut microbiota has bidirectional communication (cross-talk) with the human brain called as microbiota gut brain axis (MGBA) via determined four different pathways; 1. Metabolic pathway 2. Neural (neuronal) pathway 3. Neuro-endocrin pathway 4. Immunologic pathway.^[4] Perinatal maternal microbiota composition changes (density and diversity) resulting

with maternal dysbiosis altering expression of the genes related with autism etiology (*CC2D1A*, *SHANK1-3*, *CASPR2*, *CNTNAP2*, *BRSK2*) and also epigenetic mechanisms. Maternal dysbiosis also results in regression of fetal neurodevelopment and maturation of neuronal and brain cell of the fetus at intrauterine period. Maternal dysbiosis at perinatal period may also triggers maternal immun activation that may also have a negative affect on fetal neural development. Neuronal connectivity and signal transmission impaired as a result of the explained neuro-immuno pathologies triggered with perinatal maternal dysbiosis. Accession of toxic and harmful molecules to brain is blocked by two major barriers: Bowel Brain Barrier (BBB) and Blood Brain Barrier (BBB).^[5] Integrity of the two barriers are maintained by functions of tight junction proteins. Barrier functions are obtained and protected by eubiosis of intestinal microbiota. Dysbiosis leads to impairment of barrier functions and results in increased intestinal permeability. Short chain fatty acids (propionate, acetate, butyrate) are components of the cellular membrane of especially two anaerobic species (*Bacteroides spp.*, and *Clostridium spp.*) and they can also be derived from fermentation of complex carbohydrate molecules such as inulin in the intestine. Propionic acid (PPA) is a potent activator of pro inflammatory cytokines (IL1 β , TNF α , IL6) synthesis, and can reach to the brain and initiates neuroinflammation. Overgrowth of Bacteroides



and Clostridium strains in the intestinal microbiota results in excessive production of PPA and initiates the neuroimmunopathologic changes that is one of the known mechanisms of autistic brain.^[4,5]

Etio-pathogenesis of the neuro-immunopathologic changes in the autistic fetal brain can be explained with perinatal maternal dysbiosis, which causes alterations in maternal and fetal gen expressions, epigenetic mechanisms, maturation of neuronal cells and fetal neurodevelopment, concluding with abnormal neural signal transmissison, and maternal immune activation.

ETHICAL DECLARATIONS

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