



A proposed mechanism for autism: an aberrant neuroimmune response manifested as a psychiatric disorder

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ABSTRACT

Autism, an incurable neurodevelopmental brain disorder, is a complex psychopathology in which the affected individual cannot effectively self-regulate their sensory inputs toward coherent and focused motor outputs. There have been many hypotheses as to the etiology of autism – genetics, neurotransmitter imbalances, early childhood immunizations, xenobiotic and teratogenic agents, and maternal infection; the disorder can perhaps be studied best under the field of “Psychoneuroimmunology”, which analyzes systemic and psychopathologies from an integrated approach through the combined effects of the nervous, immune, and endocrine systems. Using principles of psychoneuroimmunology along with previously established but yet un-linked scientific principles and observations, this paper proposes a neuroimmune-based mechanistic hypothesis for the etiology of autism that connects elevated levels of maternal pro-inflammatory cytokines to autistic symptoms in her offspring through a logical sequence of events. While both researchers and clinicians often note correlations between pro-inflammatory cytokine levels and autistic symptoms in affected individuals, no specific mechanism has been documented that logically and directly connects the two. I propose that pro-inflammatory cytokines arising from maternal inflammation, infection, and, possibly, autoimmunity, pass through the placenta; enter the fetal circulation; cross the fetal blood–brain barrier (BBB); and cause aberrant neuronal growth and plasticity within the fetal brain via a “cytokine-storm”. Microglia and astrocyte stimulation lead to a positive-feedback loop that also facilitates the development of a chronic inflammatory environment within the fetus, pre-disposing it to lifelong comorbid psychiatric and systemic pathologies. Such a mechanism could account for many of the observed symptoms and behaviors of autistic individuals such as hyper-sensitivity to environmental stimuli, object fixation, echolalia, repetitive physical behaviors, chronic enterocolitis, autoimmune disease, and, at the extreme, savantism. The thiazolidinedione pioglitazone (and possibly rosiglitazone), a non-steroidal anti-inflammatory drug (NSAID), which is commonly used to lower blood glucose levels and associated inflammatory markers in patients with diabetes, and histamine receptor blockers, as well as monitoring and limiting sucrose-containing foods, might prove to be effective preventative therapies for the development of autism in the fetus for pregnant women displaying either a cytokine-induced depression or other elevated systemic inflammatory state conditions.

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Introduction

Autism is an incurable neurodevelopmental brain disorder in which the affected individual cannot effectively self-regulate sensory inputs toward coherent and focused motor outputs. It is a failure of central nervous system (CNS) integration at the level of the pre-frontal cortex, amygdala, hippocampus, and cerebellum [1–3]. An autistic individual's inability to self-regulate behavior is particularly evident when observing autistic individuals interacting in a decision-making environment. These individuals often get lost in the small details of planning, and cannot maintain a more global

perspective toward processing the information and making and implementing final decisions.

Autism is defined by the *Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revision (DSM-IV-TR)* as having three categories of observable deficits within the individual – social interaction skills, communication skills and repetitive or ritualistic behaviors. A formal diagnosis of autism is made when an individual displays at least two social interaction deficits, one communication deficit, and one repetitive or stereotypic behavior [4]. Several clinical tools such as the *Autism Diagnostic Observation Schedule (ADOS)*, *Checklist for Autism in Toddlers (CHAT)*, and *Modified-CHAT (M-CHAT)* currently exist for evaluating behaviors within the context of test-specific criteria by using developmentally-targeted modules [5,6].

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