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Review

Immunological and autoimmune considerations of Autism Spectrum Disorders

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ABSTRACT

Autism Spectrum Disorders (ASD) are a group of heterogeneous neurodevelopmental conditions presenting in early childhood with a prevalence ranging from 0.7% to 2.64%. Social interaction and communication skills are impaired and children often present with unusual repetitive behavior. The condition persists for life with major implications for the individual, the family and the entire health care system. While the etiology of ASD remains unknown, various clues suggest a possible association with altered immune responses and ASD. Inflammation in the brain and CNS has been reported by several groups with notable microglia activation and increased cytokine production in postmortem brain specimens of young and old individuals with ASD. Moreover several laboratories have isolated distinctive brain and CNS reactive antibodies from individuals with ASD. Large population based epidemiological studies have established a correlation between ASD and a family history of autoimmune diseases, associations with MHC complex haplotypes, and abnormal levels of various inflammatory cytokines and immunological markers in the blood. In addition, there is evidence that antibodies that are only present in some mothers of children with ASD bind to fetal brain proteins and may be a marker or risk factor for ASD. Studies involving the injection of these ASD specific maternal serum antibodies into pregnant mice

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during gestation, or gestational exposure of Rhesus monkeys to IgG subclass of these antibodies, have consistently elicited behavioral changes in offspring that have relevance to ASD. We will summarize the various types of studies associating ASD with the immune system, critically evaluate the quality of these studies, and attempt to integrate them in a way that clarifies the areas of immune and autoimmune phenomena in ASD research that will be important indicators for future research.

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1. Introduction

The underlying causes of Autism Spectrum Disorders (ASD) are still unknown. This limits the current treatment of ASD to intensive behavioral therapy for the core symptoms. There is an urgent need to improve our understanding of the underlying pathology of ASD in order to explore new therapeutic approaches for this severe lifelong condition. We will review studies that investigated various immunological aspects associated with ASD, and attempt to evaluate the quality of these studies, in an effort to direct future research towards the possible underlying mechanisms of ASD.

2. Autism spectrum disorder (ASD)

2.1. General background

In 1943 Leo Kanner [1894–1981] first described autism as a highly variable neuro-developmental disorder. In 1979, Wing and Gould characterized autism clinically by the triad of: a) Impaired social interaction, b) restricted communications skills, and c) unusual repetitive behavior. These categories have over time expanded to include

- *Impaired social interaction*- Infants show reduced attention to social stimuli, smile less, and manifest reduced eye contact and facial/emotional expression, significant impairment in initiating and maintaining peer relationship; poor shared enjoyment and joint attention skills; lack of empathy and poor understanding of social rules
- *Restricted communication skills*- with delayed babbling, diminished responsiveness, no integration of gestures with words, less/no sentence construction, often repeating someone else's words (echolalia), poor conversation skills; immediate and delayed echolalia; poor symbolic and make believe play
- *Unusual repetitive behavior*- including stereotypic repetitive movements, compulsive behavior, ritualistic behavior and self-injury, unusual sensory interests and unusual repetitive patterns of interests

Due to the often broad, heterogeneous clinical presentation of autism, the term Autism Spectrum Disorders (ASD) was coined, which includes Asperger's syndrome, Rett's syndrome, Childhood Disintegrative Disorder, Pervasive Developmental Disorders Not Otherwise Specified (PDD-NOS). In May 2013, the APA (American Psychological Association) plans to release the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) which will likely merge several previously separate diagnoses. A variety of additional symptoms are associated with ASD including: epilepsy and/or subclinical increase in epileptic waveforms; anxiety disorders; insomnia and nocturnal awakening; mental retardation; sensory abnormalities with poor muscle tone and motor skills; and gastrointestinal dysfunction. Some children with ASD experience developmental regression previously described in the literature as "*autism with regression*", "*autistic regression*", "*setback-type autism*", or "*acquired autistic syndrome*," characterized by a loss of previously-acquired skills, primarily in the areas of language, social interest, adaptive functioning and motor skills. It remains debatable whether or not this represents a distinct subset of autism. Although the numbers of individuals with ASD that have one or more of these additional features are substantial, the exact frequencies that appear in the ASD are not firmly established.

Prevalence estimates for ASD range from 0.7% to 2.64% and represent a dramatic increase since the 1980s. Diagnosis occurs early in childhood but symptoms typically remain stable throughout adulthood. Most individuals have severe disabilities requiring intense care throughout their lifespan including medical care, educational support and many are unable to live independently. The etiology for ASD is likely multi-factorial. Many theories evoking different or inter-related pathways have been suggested:

- A genetic component is likely to exist in some cases, since siblings—in particular twins—are often affected. While various known genetic abnormalities are associated with approximately 10% of individuals with ASD, the critical loci remain unknown [1]. While in the past genetic screening was suggested primarily for children with dysmorphic features, more recently, some geneticists recommend the use of microarray CGH in any child with ASD due to the high rate of copy-number variants (CNVs) found.
- Association of ASD with prenatal risk factors [2] has been suggested including advanced age of both parents, use of psychiatric drugs, bleeding disorders of the mother, teratogenic factors, and familial autoimmune diseases or immune conditions including diabetes, maternal celiac disease, maternal allergies/asthma with onset during pregnancy.
- Recent post-mortem transcriptomic analysis of brain specimens from individuals with ASD and controls revealed the existence of two "modules" of gene co-expression networks; a neuronal module and an immune module. In the neuronal module, known autism susceptibility gene variants are enriched and under expressed while in the immune module immune/inflammatory genes are enriched and up regulated [3].
- Theories blaming vaccine components as a cause for ASD were suggested in the past, but these controversial theories have been largely rejected due to a current lack of scientific evidence.
- Epidemiological studies indicate that ASD might be associated with endocrine dysregulation and in particular steroid function [4].

The pathology of ASD also remains enigmatic with various neurobiological theories suggested [5] and alterations in many brain systems implicated including cortex, limbic system, cerebellum, corpus callosum, basal ganglia and brainstem. However, altered early brain development might be more relevant for ASD than documented pathological findings in adults. Aspects of the early developmental processes that cannot be documented as pathology include: neuronal migration [6], connectivity or plasticity [7], neuronal organization of the white matter [8], reduced synaptic maturation [9], reduced dendritic maturation [5], and abnormal serotonin metabolism/transport [10]. For instance, disrupted synaptic development might be associated with epilepsy in 20% of ASD [11]. However, the linkage between the pathology and the clinical neuro-psychological manifestation is not fully understood [8]. So

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