Neuroimmunology of autism

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Autism is a complex neurodevelopment disorder characterized by impairment in social skills, verbal communication, behavior and cognitive function. Abnormalities in language development, mental retardation and epilepsy are also found frequently in patients with autism. The role of the immune system in autism is unconfirmed. But studies revealed the immune effect in the nervous system, indicating a novel approach for the study of this disease. In this review, we specifically discuss the neuroimmunologic aspects of the disease at the cellular and molecular levels.

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Review article

Introduction

Autism is a complex, behaviorally defined, developmental brain disorder with an estimated prevalence of 1 in 1000.[1] With the increasing prevalence in recent years, autism has been recognized as a public health problem. Epidemiological studies have shown that the prevalence of autism syndrome has increased to 2-6 per 1000 children, with a male to female ratio of 3-4:1.[2] Autism is now recognized as a syndrome with a strong genetic component, associated with such factors as fetal infection and autoimmunity reaction and so on.[3,4]

Immunological studies of autism

Immunological challenge is one possible point of convergence between genetic and environmental causal factors in autism. The role of the immune system in the development of autism is still unconfirmed.

Two main immune dysfunctions in autism are immune regulation involving pro-inflammatory cytokines and autoimmunity.[5] Mercury and an infectious agent like the measles virus are currently two main candidate environmental triggers for immune dysfunction in autism.[6] Studies showing elevated brain specific antibodies in autism support an autoimmune mechanism. Viruses may initiate the process but the subsequent activation of cytokines is the damaging factor associated with autism. Virus specific antibodies associated with measles virus have been demonstrated in autistic subjects.[7] Environmental exposure to mercury is believed to harm human health possibly through modulation of immune homeostasis. Inflammatory mediators in autism usually involve the activation of astrocytes and microglial cells.[8] Pro-inflammatory chemokines (MCP-1 and TARC) and an anti-inflammatory and modulatory cytokine, transforming growth factor beta1 (TGF-beta1), are consistently elevated in autistic brains.[9] Cytokine alteration of tumor necrosis factor (TNF-alpha) is increased in autistic populations. Toll-like-receptors are also involved in autistic development. High NO levels are associated with autism.[10] Maternal antibodies may trigger autism as a mechanism of autoimmunity. Measles, mumps and rubella (MMR) vaccination may increase risk for autism via an autoimmune mechanism in autism.[11] MMR antibodies are significantly higher in autistic children than in normal children, indicating a role of MMR in autism. Auto-antibodies (IgG isotype) to neuron-axon filament protein (NAFP) and glial fibrillary acidic protein (GFAP) are significantly increased in autistic patients.[12] Further investigations at immunological, cellular, molecular, and genetic levels will allow researchers to continue to unravel the immunopathogenic mechanisms associated with autistic processes in the developing brain.

Recent studies have shown that normal neurons in developing and adult brains express proteins of the major histocompatibility complex (MHC) class I, known for their role in the immune system.[13,14] Furthermore, these immune proteins are required for specific forms of developmental and functional plasticity,

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demonstrating that changes in MHC expression can lead to neurodevelopmental defects. Decreased expression of MHC class I impairs the pruning of inappropriate synaptic connections,[14] an effect that may explain the early developmental increase in brain volume in patients with autism and the symptomatic overlap with fragile X syndrome (FXS). A possibility currently being investigated is that specifically timed changes in neuronal MHC class I expression contribute to the development and/or expression of autism. Moreover, immunogenetic studies have shown an increased frequency of HLA-DR4 in children with autism and their mothers. This finding is consistent with clinical observations of increased frequencies of autoimmune disorders of the family with autism.

The elevation of serotonin levels in platelets is frequently found in autistic patients.[15] It has been suggested that the elevation of serotonin levels in autistic patients may be heterogeneous, with a subgroup with an increase in 5-hydroxy tryptamine (5-HT) uptake and another subgroup with a decrease in 5-HT2 receptor binding. Only recently, possible relations between serotonin, neurodevelopment and autism have been explored.[16] On the other hand, sustained high levels of serotonin indicate a deficit in synaptic release in brains of autistic individuals and may contribute to the increased number of cortical minicolumns.

Neurobiology of autism

According to the effects of age on brain volume and head circumference in autism, there are several developmental neurobiological implications of accelerated brain growth in children with autism.

Brain size has been defined by head circumference, a reliable indicator of volume especially during early childhood. A recent study[17] demonstrated that brain volume was significantly larger in autistic children aged 12 years or younger than in normally developing children. Brain volume in individuals older than 12 years was similar between the autism and control groups. The data indicate that there is a brain growth phenotype in autistic spectrum disorders (ASD). The early increase of brain volume may reflect increased numbers of neurons and glia or premature and accelerated proliferation of synapses, axonal and dendritic arbors, axons, and increased myelination. Recent findings shed some light on the cerebellar role in attention deficits in autism and suggest that developmental cerebellar abnormality has functional implications for cognitive and motor systems.[18]

The earliest fMRI study focused on social perception, such as person recognition through the face.[19] A recent study examined the perception of facial expression, joint attention, empathy, and social cognition.[20] These studies indicate that the skill deficits of ASD are accompanied by reduced neural activity in regions that normally govern the specific functional domain. These abnormalities in the specific regions of the brain include the cerebellum, mesial temporal structures, brainstem, basal ganglia and corpus callosum.[21-28]

Investigations revealed a low number of Purkinje cells in the cerebellums of autistic patients,[29,30] especially in the posterolateral neocerebellum and in the adjacent archicerebellar cortex (posterior and inferior portions of the cerebellum). The inferior olivary nucleus in the investigated brains did not show expected retrograde neuronal loss (secondary to the loss of Purkinje cells). This suggests the abnormalities of the brains of autistic individuals at 30 weeks' gestation, before the establishment of the connection between olive and Purkinje cells.

The cells of the limbic system (hippocampus, amygdala, mamillary bodies, cingulate gyrus and septal nuclei) are small, but a large number per unit of volume (increased cell density) compared to the controls. This led to the hypothesis of a delay in the maturational development of the limbic system circuits. Several investigators have recently proposed that autism might be caused by an imbalance between excitation and inhibition in key neural systems including the cortex.[31]

Neuroimmunology of autism

There have been no immune findings in the central nervous system (CNS) until recent studies found peripheral immune abnormality that could support immune hypotheses. The role of neuroglial activation and neuroinflammation could be of importance in maintaining the abnormalities of the CNS in autistic patients. Abnormalities have been found in peripheral blood, including dysfunction of T-cells, B-cells and NK-cells. Researchers have also found that autoimmunity against brain antigens may contribute to the neuropathology of autism. Decrease in immunoglobulin subsets and complements, the presence of auto-antibodies against CNS antigens and the effect of maternal antibodies have also been proposed as pathogenic factors.

Circulating auto-antibodies against CNS antigens have been detected in autistic patients, reacting to myelin basic protein, frontal cortex, cerebral endothelial cells and neurofilament protein. Besides, studies of maternal serum have shown that mother's serum may cause antibodies binding to fetus Purkinje cells when they were injected into pregnant mice.[32] Maternal antibodies may therefore contribute to prenatal brain development by

interfering with cell signaling in the developing brain as well as disturbing the patterns of CNS organization.

A recent study of neruoglia's response[33] showed that innate immunity could mediate the neuroglia activation and neuroimmunity response in the neuropathology of autism. An assessment of the magnitude of astrogliosis using immunocytochemistry for glial fibrillary acidic protein (GFAP) in the midfrontal (MFG) and anterior cingulated gyrus (ACG) and cerebellum (CBL) of autistic brain revealed increased astroglial reactions characterized by a large volume of perikarya and glial processes.[33]

In conclusion, the neuroimmunology of autism is still unclear, even though antibodies in autism patients' serum have been demonstrated to react against human brain tissue. As part of the immunopathogenic mechanism of the disease, innate neuroimmunal response is responsible for the generation of autism syndrome. Also, neuroglial activation and neuroinflammation are vital factors for CNS abnormalities present in this disorder.

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