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EDITORIAL

IMPACT OF IMMUNITY IN AUTISM SPECTRUM DISORDERS

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Autism spectrum disorders (ASDs) are childhood psychopathologies characterized by having difficulties in social interaction, verbal and non-verbal communication as well as sensor motor movements. Evidence suggests that in ASDs environmental toxicant exposure, genetic and mitochondrial dysfunction are involved associated with abnormal immune response with allergic problems and elevated serum IgE. ASDs present the major cytokine and chemokine dysfunction in CNS and is mediated by an increase of pro-inflammatory cytokine levels in the brain, such as TNF, IL-1, IFN-γ, IL-6, IL-8 and others. Mast cells, which are also implicated in ASDs, are worsened by stress and produce proinflammatory cytokines and can be stimulated by neurotensin in the brain and gut, contributing also to the inflammatory response. However, the exact etiology of ASDs remains largely unknown.

Covering the literature from 2003 to the present in PubMed, this editorial summarizes the interrelationship between immunology and autistic subjects. Autism spectrum disorders (ASD) are characterized by having difficulties in social interaction, verbal and non-verbal communication, repetitive behavior, and sensory motor movements (1-3). The prevalence of ASD is about 1% in the US and the number of children with a diagnosis of an ASD has been on the rise for over two decades.

These disorders involve hormonal perturbations in pregnancy or early childhood in the context of genetic control and have become recognized as common childhood psychopathologies. These early molecular events, at a time of rapid development, are intimately linked to concurrent development in the brain and immune system. Autism usually occurs in the first three years of childhood and in spite of increasing diagnosis in recent years, the exact etiology of autism remains largely unknown. Findings also

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support the view that neuro-immune abnormalities occur in the brain of autistic patients and may contribute to the diversity of the autistic phenotypes, although several lines of research support the view that this is a result of a complex combination of neurological, environmental, immunological, and genetic factors. Most proposed perinatal factors seem to converge into the activation of the immune system, suggesting that an early inflammatory response could be a unifying factor in the etiology of autism spectrum disorders. The inflammation could be caused by a defective placenta, immature blood-brain barrier, the immune response of the mother to infection while pregnant, a premature birth, encephalitis in the child after birth, or a toxic environment. However, evidence suggests that in autism genetic, environmental toxicant exposures, oxidative stress and mitochondrial dysfunction are involved (4-7). Therefore, we are convinced that autism spectrum disorder is also associated with altered neuro-inflammatory processes and abnormal immune responses in adulthood. How these immune alterations can affect developmental programming of adult behavior or directly affect behavior later in life is unclear. Therefore the etiological base of autism is still not understood.

It has been reported that ASD children may present a type of allergic problem but in the absence of elevated serum IgE. These findings suggest non-allergic mast cell activation, probably in response to environmental and stress triggers that could contribute to inflammation.

Several authors have reported that elevated cytokines in the cerebral spinal fluid of living autistic children play an important role in the neuro-inflammatory process linked to this disease(s). Many authors reported that cytokine imbalances in autism have pathological roles and have important interaction with the nervous system, contributing to the dysfunction in autism spectrum disorders (8-12).

Although many cytokines and their receptors remain unstudied, the major cytokines interleukin-1 (IL-1)-α, IL1-β, IL-4, IL-6, IL-10, IL-11, IL-13, IL-18, TNF-α, IL1-RA, TGF-β, and CCL2 are all expressed in the healthy CNS (13-16). Many of these cytokines and their receptors have differential expression patterns across the CNS. Interleukin-1, Interleukin-6 (IL-1, IL-6) and tumor necrosis factor alpha (TNF-alpha) are pro-inflammatory cytokines, which represent the key mediators of neuroimmune interactions, leading to severe neurological and mental diseases. IL-6 mRNA and its receptor (IL-6R) are developmentally regulated in the rat brain (17-19) and the adult hippocampus has the highest detectable levels of both transcripts; while IFN-γ is found at neuronal synapses (20-23) suggesting that it may act at the level of the synapse to influence brain function.

It has been reported that many cytokines, such as IL-1-beta, IL-6, IL-4, IFN-γ, and TGF-beta, are implicated in the nervous system and therefore in autism. Other authors reported that increased pro-inflammatory cytokine levels in the brain (TNF-α, IFN-γ, IL-1β and IL-8); and NF-kappaB, may also contribute to autism spectrum disorders (24-27). In addition, other authors confirmed that several cytokines and chemokines, including IL-1β, IL-6, IL-8 and IL-12p40, are elevated in the ASD plasma of very young children (ages 2–5 years old), and that these increases are associated with more impaired communication and aberrant behaviors (28-31).

It has been reported that mast cells express leptin and leptin receptors, a finding implicating paracrine or autocrine immunomodulatory effects of leptin on mast cells (32-35). Leptin may play a role in ASD. In fact, leptin is higher in obese subjects (36-42) and elevated plasma leptin levels during pregnancy are indicative of placental dysfunction (43-46) and plasma levels of leptin are significantly higher in patients with autistic disorder.

Stress also may have a role in this disease(s). Acute stress leads to high serum IL-6 that is mast cell-dependent (47-49). Mast cells have been implicated in inflammatory conditions that are worsened by stress (50-52). Mast cell-derived cytokines, such as IL-6, can increase blood–brain-barrier (BBB) permeability (47, 53-56). Corticotropin-releasing hormone (CRH) may have an immunomodulatory role and has been associated with intestinal inflammation. In addition, CRH can also be secreted from immune cells (57-60), mast cells (61-63), skin (64-69) and post-ganglionic nerve endings (70-72), leading to pro-inflammatory effects (73-75). When mast cells are activated with CRH they release several pro-inflammatory cytokines (76-78). Patients with stress, result in secretion

of CRH from the hypothalamus and regulates the hypothalamic-pituitary-adrenal (HPA) axis (79-81). Increased plasma levels of CRH have been linked to preterm labor (82-85) and in mothers with anxiety during that period of pregnancy (86). A number of cytokines, including IL-1 and IL-6, can trigger secretion of CRH *in vitro* (87-89). Moreover, CRH stimulates IL-6 release from human peripheral blood mononuclear cells that infiltrate the fetal membranes and the placenta during intrauterine infection (90-91).

Other cytokines may also be implicated in ASD. For instance, TNF increases about 50-fold in the cerebrospinal fluid and IL-6 gene expression also increases in the brain of ADS patients. Since mast cells are surely involved in this disease, macrophage chemoattractant-protein-1 (MCP-1), a potent chemo-attractant for mast cells, is also important. Acting on mast cells, TGF-β1 along with IL-9 may also have a role in worsening ASD symptoms. Recently, it has been reported that IL-9 induces mast cell release of vascular endothelial growth factor (VEGF) (92-94) which also inhibits gut mast cell function (95-96). In addition to cytokines, essential components of the complement cascade, including C1q and C3, are also expressed in the CNS.

Neurotensin (NT) is a brain and gut peptide that contributes to gut inflammation due to acute stress (97-98). This is an important molecule, augmented and secreted in serum of children with autism (99-100), which can stimulate mast cell and mediate ASD. A common link among the neurobehavioral disorders associated with intrauterine inflammation appears to be the evidence for immune disregulation in the developing brain. Other immune parameters, including maternal infection and disregulated cytokine signaling, have been found to be associated with ASD. However, the role of the cytokines in the pathogenesis of ADS remain to be determined.

While detailed pathogenic mechanisms remain unclear, the hypothesis that some cases of ASD may be influenced, or even caused, by maternal fetal brain-reactive antibodies or other *in utero* immune-related exposures is an important area of investigation.

It has been observed that extremely high gamma-aminobutyric acid (GABA) levels in the urine and blood and high plasma ammonia (NH_3) were found in a child with autism. This concept is very important since GABA is considered a major inhibitory neurotransmitter of the mammalian brain and in particular the corpus callosum, located in the center of the brain, involved in intelligence, language and speech. Moreover, Cohen has also demonstrated that elevated levels of NH_3 in the plasma result in a decrease in the efficiency of the enzyme GABA-transaminase, which is responsible for the catabolism of GABA.

Articles showing peripheral immune abnormalities support immune hypotheses, but until recently there have been no immune findings. However, several immune abnormalities have been noted in autistic subjects. For example, the question of a connection between vaccination and autism is surrounded by controversy. In addition, several studies showing elevated brain specific antibodies in autism support an autoimmune mechanism. However, recently it has been reported that vaccines as well as autoimmunity do not seem to be the cause of autism. In addition, an involvement of gastrointestinal pathophysiology in autism has been reported; however, other studies also reported no association between autism and gastrointestinal diseases.

Another important parameter in autism is the augmented whole blood serotonin (5-HT) levels found in about 1/3 of cases. Serotonin and other biogenic amines have been shown to facilitate formation and maintenance of synapses in the central nervous system. Neurons in the cerebral cortex express serotonin 5-HT2A receptor which has been shown to mediate the function of serotonin. Immune dysfunctions in autism are related to hyperserotoninemia, autoantibodies to 5-HT receptors, and 5-HT's role in autoimmunity.

C4 component of a classical complement pathway has been associated with several diseases. C4 has been identified in developing brain neurons. C4 allotype deficiency may be important in disease pathogenesis and is related to C4B deficiency and autoimmune-associated diseases, such as autism.

Interleukins (IL) are inflammatory proteins that modulate the immune system. Inflammation leads to the tissue damage and release of pro-inflammatory cytokines, which augment the above process. The tissue damage causes exposure of nerve endings, which can lead to the activation of axon reflexes. Environmental factors that may trigger the expression

and secretion of cytokines in inflammatory diseases include: alcohol, cigarette smoking, pollution, infection and possibly stress.

These factors, may initiate the process of immune activation but the subsequent release of cytokines is the damaging factor associated with autism. In fact, our hypothesis is related to the neuroglia activation by cytokines leading to neuro-inflammation. Inflammatory mediators in autism usually involve activation of astrocytes and microglial cells. In addition, pro-inflammatory chemokines such as MCP-1 and modulatory cytokine, such as TGF-beta-1, are consistently elevated in autistic brains. However, the role of the immune system in the development of autism is controversial.

We recently reported a discovery which may have uncovered an important clue to causes of the development of Autism. A strong connection is believed to be the disease mastocytosis in which the skin and the intestines contain more mast cells than average. These mast cells are very sensitive to various allergenic triggers. In the past, mast cells were thought to be reactive in allergic conditions such as pollens and various animal hairs. We were the first to show in our report published in the journal, "Trends in Pharmacological Sciences", that stress and viruses can also be accomplices in the activation of mast cells. In our findings, only about 10-12% of patients had allergic reactions. Thus, our goal was to determine what the mast cell does in people who do not have allergies.

We learned that many mastocytosis patients had at least one family member with both mastocytosis and autism. We were excited to have found a relationship between autism and mastocytosis. This discovery would allow researchers to study the role of mast cells and provide insight into the connection with autism. Researchers are trying to understand the role of the mast cell in the brain because they are aware of patients with mast cell disorders who also manifest central nervous system symptoms.

We are in the process of requesting funding for additional studies investigating this relationship between mast cell and autism.

We suggest that the previous thought that was connected to "leaky gut" theory in children does not stand, as several studies of this nature have been disproved. Instead, we are searching for other causes which stimulate mast cells both in the intestines and the brain of young children ages 1-4. We feel that some food, stress or viruses could activate mast cells in the intestine. It is believed that these would cause the cells to release cytokines which disrupt the lining of the intestines and of the brain. When the protective layer of the brain is disrupted, noxious substances are allowed entry. These substances could cause an inflammation of the brain which is believed to be a cause or a contributor to autism.

Together, these reports suggest that autism may in fact be a systemic disorder with connections to abnormal immune responses. Therefore, we believe that a better understanding of this mechanism/s in the pathogenesis of autism and the involvement of the immune response, may have important clinical and therapeutic implications and may represent novel targets for treatment.

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