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EDITORIAL

AUTISM AND IMMUNITY: REVISITED STUDY

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Autism spectrum disorder is of interest neurochemically because it represents a relatively homogeneous disorder with regard to disease development, abnormal cognitive development and intellectual development disturbance. A consistent finding in autistic children is a high number of mast cells and a high level of serotonin which is also found at elevated concentrations in the urine of autistic patients. In addition, a dysfunction of clinical conditions, such as gastrointestinal and immunological symptoms, is frequently noted in autistic children, however, IgE does not appear to be prevalent in these children but probably an increase of cytokines/chemokines produced by mast cells at an early age may play an important role. Therefore an immune hypothesis, involving also autoimmunity, is one possible pathogenetic mechanism in autism. In conclusion, mast cell activation could contribute to immune and neuroinflammatory abnormalities that are evident in patients with autism spectrum disorders.

Autism and autism spectrum disorders are complex neuro-developmental disorders characterized by disturbance and impairments in social skills and interaction, verbal communication, often accompanied by repetitive and stereotyped behavior, deviant imaginative play, and motor stereotypes (1-2). These disorders have become recognized as common childhood psychopathologies

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(3). Autism usually occurs in the first three years of childhood and in spite of increasing diagnosis over the last years, the exact etiology of autism remains largely unknown. Findings also support the view that neuro-immune abnormalities occur in the brain of autistic patients and may contribute to the diversity of the autistic phenotypes (4). Although several lines of research support the view that this is a result of a complex combination of neurological, environmental, immunological, and genetic factors, it is widely reported that several white blood cells are important in the pathogenesis of neurological diseases (5-8), and it is established in animal and human diseases such as autoimmunity, inflammation and cancer (9-14). In addition, proinflammatory cytokines secreted by different types of cells contribute to the pathogenesis of neuro-inflammation (12, 15).

For instance, Cohen BI, observed that extremely high gamma-aminobutyric acid (GABA) levels in the urine and blood and high plasma ammonia (NH3) were found in a child with autism (16). 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 (17). Moreover, Cohen has also demonstrated that elevated levels of NH3 in the plasma result in a decrease in the efficiency for the enzyme GABA-transaminase, which is responsible for the catabolism of GABA (18).

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 (19-21). 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 (22-25). 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 pathology in autism has been reported (26-27); however, other studies also reported no association between autism and gastrointestinal diseases (28).

Another important parameter in autism is the augmented whole blood serotonin (5-HT) levels found in about 1/3 of cases (29-31). Serotonin and other biogenic amines have been shown to facilitate formation and maintenance of synapses in the central nervous system (32-34). Neurons in the cerebral cortex express serotonin 5-HT2A receptor which has been shown to mediate the function of serotonin (35). Immune dysfunctions in autism are related to hyperserotoninemia, autoantibodies to 5-HT receptors, and 5-HT's role in autoimmunity (36).

C4 components of a classical complement pathway have 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 (37). 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: cigarette smoking, pollution, infection and possibly stress (38). 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 neuroglial activation by cytokines leading to neuroinflammation. Inflammatory mediators in autism usually involve activation of astrocytes and microglial cells. In addition, pro-inflammatory chemokines such as MCP-1 and TARC, and an anti-inflammatory and modulatory cytokine, TGF-beta1, are consistently elevated in autistic brains (39-41). 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 (42). 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. So, 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 aged 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 of or a contributor to autism.

We have contacted many organizations for support and funding. We have also applied for funding to the National Institute of Health, and the National Autism Foundation. We believe that a better understanding of this mechanism/s in the pathogenesis of autism may have important clinical and therapeutic implications.

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