

LETTER TO THE EDITOR

NEUROIMMUNOLOGY OF AUTISM: A MULTIFACETED HYPOTHESIS

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AUTISM AWARENESS

*They looked at me with compassion
I hadn't a clue why
Then they told me my son was challenged
and I began to cry*

*Your son may be Autistic of
Have some related disease.
I've never heard of it, I said
Explain in to me, please?*

*It occurs one in every one hundred births,
Four times more often in boys.
Families of all racial and ethnic backgrounds
Regardless of stature or poise*

*It's a Lifelong neurological impairment
That affects the ability to speak
Play or socially interact.
I felt my knees grow weak*

*My husband took me in his arms
We held each other tight,
My five-year-old beside me asking,
Mommy, is Stevie alright?*

*We wouldn't have known there was a problem
If not for his speech delay
We thought he was just a little shy,
and preferred solitary play.*

*When we said, they don't know what causes it
I just wanted to die.
My God, this isn't happening,
They can't even tell us why?*

*God is not sleeping, I said to myself
Over and over again
Holding fast to my faith in God
To help me endure the pain*

These 4 little angels are just a few of so many precious children with autism who inspired us to do this research.



*Clearly there needs to be research
It's imperative we find a way
Of getting the programs funded,
If we're ever to gain some headway*

*Our children are so precious
They look to us for care
Let's show them how much we love them
and make everyone aware.*

Linda Demos

NEUROIMMUNE RELATIONS IN AUTISM: AN OVERVIEW

Autism is becoming well known in today's society as more of the population recognizes the syndrome and those who are affected actively seek different treatments. It is consoling that consciousness has been raised internationally (1) and focused within the American population so that there are support groups that provide interpersonal consolation whereas others generously assist by helping in raising funds to support research. There are frequent reports in the media and examples of popular press that treat autism in a sophisticated manner (2-3). At the end of the editorial those known as geniuses will be exposed as possible victims with a form of autism.

Commonly defined, according to the Oxford American Dictionary, "*autism is a form of mental illness that causes a person to withdraw into a private world of fantasy and be unable to communicate with others or respond to the real environment*". Inherent in this broad definition there is the suggestion of behavior difficulties and therefore an implication for the nervous system. However as the lead article will point out, the etiology of the syndrome is complex and there is no single explanation that provides a precise definition as to the causative agents. Publications from the Vojdani laboratory (see the lead article and others) do much to extend existing levels of understanding concerning complexities of autism. Clearly there are important implications for affected children, their progression to adulthood and therefore for society at large (1-4). The link here is more related to the immune system specifically what may be happening to lymphocyte receptors.

This editorial will therefore extend that focus to be broader and will highlight certain linkages between the nervous and immune systems two of the three regulatory systems (endocrine is also a member of the triumvirate but not mentioned in this review) that are responsible for maintaining a balanced milieu. Autism is defined more extensively as a syndrome of early childhood (first diagnosed no later than 30 months) marked by abnormal serotonin metabolism in the brain. This disease is characterized by a systemic array of symptoms that result in organic defect in the brain as well as disorders of the: immune, endocrine, hepatic, musculoskeletal, and renal systems. Several factors have been implicated in the pathogenesis of autism: genetic, environmental, immunological, and neurological.

Vojdani et al. (4) certainly agree that autism is a

developmental disorder with unknown etiology. However, there has been a specific direction toward unraveling one of the assumed factors, the immunological with links to the nervous system. As a result, their several approaches have detected antibodies against nine different, neuron-specific antigens in the sera of children with autism. These antibodies, are bound to different encephalitogenic molecules, e.g. milk butyrophilin, *Chlamydia pneumoniae* and streptococcus M protein with neurological antigens. Specific antibodies against neurological antigens suggest that bacterial enterotoxins, viral antigens and maybe metals (e.g. mercury and lead), might increase adhesion molecules on brain endothelial cells. This supports the environmental component as a crucial factor in the development of autism.

Extending approaches to neuroimmune mechanisms, immunological research has suggested autoimmunity as a pathogenic factor in autism. A possible autoimmune component in autism has been further strengthened. This involves the demonstration of antibodies to nine different neuron-specific antigens and their cross-reactive proteins as well as the peptides from milk, *Chlamydia pneumoniae* and *Streptococcus* group A. Among the numerous cell differentiation antigens (CD) involved as specific markers especially on lymphocytes, CD13 is expressed on stem cells and during most developmental stages of myeloid cells, mostly associated with those derived from the bone marrow. T-cells or B-cells during the earliest stages of differentiation are CD13-positive but become negative upon maturation. With respect to the nervous system CD13 inactivates endorphins and enkephalins in synaptic membranes. Once again, there is evidence of sharing of a CD marker in the immune system sharing an association with the nervous system.

Concerning the environment, autoantibodies to nervous system antigens have been detected in populations exposed to toxic, environmental or occupational chemicals and associated with the nervous system. Still others have focused on changes in the immune response as a result of environmental exposures (5-7). Clearly there is an evolutionary basis for the role of the environment in overall health of species (8-10). Titers of antibodies against neurofilaments and myelin basic protein (MBP) correlate significantly with blood lead or urinary mercury, the typical indices of toxic exposure. Moreover, levels of these antibodies correlated with sensorimotor deficits and these antibodies are known

to interfere with neuromuscular function—again an association with the nervous system.

The lead review focuses on immune and nervous system disorders (11). Assuming that autism derives from a strong autoimmune component, as with many complex autoimmune diseases, genetic, immune and environmental factors, including diet, toxic chemicals and infections, play critical roles. Opioid peptides are considered as components in the etiology of autism; these peptides are available from a variety of food sources. These dietary proteins and peptides, including casein, casomorphins, gluten (GLU) and glietomorphins, can stimulate T-cells, induce peptide-specific T-cell responses, and abnormal levels of cytokine production, assumed to result in inflammation, autoimmune reactions and disruption of neuroimmune communications. Dietary peptides, bacterial toxins and xenobiotics bind to lymphocyte receptors and/or tissue enzymes inducing autoimmune reactions in children with autism. Linkages of diet with etiology of autism suggest a mechanism by which environmental factors modulate the immune system. This convergence should therefore contribute to a concerted focus on the development of preventive and therapeutic methods. Once clearly defined, preemptive therapies or diagnostic tools could be developed. This could implement the reduction in dietary peptides, bacterial toxins and toxic chemically induced autoimmunity involved in autism. Returning to an immune etiology with nervous components, autistic children possess the highest levels of IgG, IgM and IgA antibodies against all neurologic antigens as well as the three cross-reactive peptides (12). These antibodies are specific, since a classical immune absorption has revealed only neuron-specific antigens or their cross-reactive epitopes and that they could significantly reduce antibody levels. These antibodies may have been synthesized as a result of an alteration in the blood-brain barrier. This barrier promotes access of preexisting T-cells and central nervous system antigens to immunocompetent cells that may initiate a vicious cycle. What might be the sequence of events that serve to focus on possible mechanisms of injury in autism? There may be up to ten plausible explanations.

Touching the wider population, and lest we despair, the popular media presents rather convincing but non-testable information associating a form of autism with extreme creativity. In a recent popular report, the question was asked whether Einstein and Newton were autistic? Albert Einstein and Isaac Newton were geniuses but British scientists believe

they may have suffered from Asperger syndrome — a form of autism. The condition, first described by Viennese physician Hans Asperger in 1944, is a disorder that causes deficiencies in social and communication skills and obsessive interests. But it does not affect learning or intellect and many people with AS have exceptional talents or skills. Although it is impossible to make a definitive diagnosis in people who are dead, Simon Baron-Cohen of Cambridge University and Ioan James of Oxford University studied the personalities of Einstein and Newton to see if the two scientists had symptoms of AS. “Newton seems a classic case. He hardly spoke, was so engrossed in his work that he often forgot to eat, and was lukewarm or bad-tempered with the few friends he had,” *New Scientist* magazine said on Wednesday. Baron-Cohen said Einstein was also a loner and as a child he repeated sentences obsessively. Although Einstein made friends and spoke out on political issues, Baron-Cohen suspects he showed signs of Asperger syndrome. “Passion, falling in love and standing up for justice are all perfectly compatible with Asperger syndrome,” he told the weekly science magazine. “What most people with AS find difficult is casual chatting — they can’t do small talk,” he added. But Glen Elliott, a psychiatrist at the University of California at San Francisco, said geniuses could be socially inept and impatient with other people without being autistic. “Impatience with the intellectual slowness of others, narcissism and passion for one’s mission in life might combine to make such an individual isolative and difficult,” he told the magazine. Baron-Cohen said he hopes the research can improve understanding of Asperger syndrome and make life easier for people who suffer from the condition. This same group has taken autism into the realm of the theoretical as revealed in a recent publication concerned with AS and apparent gender differences (13). Thus there are ample avenues for research into the mechanisms of autism and some mild consolation that the syndrome is not characterized by only negative components. This should give a measure of hope for those who are afflicted and for those embracing them.

A PLAUSIBLE NEUROIMMUNE MECHANISM: DEVELOPMENT OF AUTISM

1. During maternity or early in life, the body is exposed to infectious agents, which mimic neuron-specific antigens, such as EBV, CMV, HHV-6, HTLV-1, HTLV-2, streptococcus, *Chlamydia pneumoniae*

or even milk and gluten peptides.

2. Pre-existing autoreactive T-cells may be generated by molecular mimicry that results from contact with dietary proteins as well as viral, bacterial and parasitic antigens. These antigens share sequence homologies or matched motifs with autoantigens.

3. Bacterial enterotoxins, viral antigens, and metals, e.g. mercury and lead, may increase adhesion molecules on brain endothelial cells. Toxic chemicals may also increase leukocyte function-associated antigen on activated T-cells.

4. Pre-existing autoreactive T-cells may transmigrate across the blood-brain barrier and induce the activation of local antigen presenting cells, such as microglia and astrocytes.

5. By reacting to μ , δ , κ opioid receptors on lymphocytes and nerve cells, dietary peptides such as casomorphins, gluteomorphins and others may change levels of cytokine production and interfere with neuroimmune communication.

6. Production of IL-2, INF- γ and TNF- α by T-helper-1 autoreactive cells and TNF- α by antigen presenting cells (astrocytes and microglia may result in damage to oligodendrocytes and demyelination.

7. Following this sequence of events, MBP, MAG, and MOG, α - β -crystalline and other antigens are released from neurofilaments and enter the circulatory system. Antigens gaining access to the blood, results in immune reactions; this in turn leads to the formation of plasma cells that are capable of producing IgG, IgM and IgA antibodies against neuron-specific antigens.

8. Neuron-specific antibodies may cross the blood-brain barrier and combine with brain tissue antigens to form immune complexes, thus inflicting more damage to tissues of the nervous system. Neuron-specific antibodies, along with toxic biological weaponry, such as arachidonic acid and free radicals, can also delete neuron myelin and therefore impair electrical transmission e.g. between muscles and the central nervous system. This hypothesis may explain significant differences in the levels of pathogenic anti-neurological autoantibodies between control subjects and patients exposed to toxic chemicals and metals (1-4).

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