



Autism 2002 : Mercury, Heavy Metals... Toxicity

AUTOIMMUNE PATHOGENESIS IN AUTISM

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Introduction

More than one million Americans suffer from autism spectrum disorders that also include an estimated one-half million people, mainly children, with a clinical diagnosis of autism. The disorder is identified not by a specific pathology but by behavioral manifestations. It is now generally believed that genetics are likely to explain no more than 10% of all autistic cases while the remainder 90% of cases is sporadic having a non-genetic etiology, and autoimmunity has a strong prospect for finding a cause and treatment of autism today. Since we developed the idea of autism as an autoimmune disorder, we are now probing autoimmunity as a prime target of drug development for autism (1-5).

Autism is generally considered to be a multi-factorial disorder. Causally speaking, immune factors, neurochemical factors, genetic susceptibility factors, and environmental factors such as viral infections have been implicated. I view autism as a very complex disorder, in which autoimmunity plays a central role. In my presentation, I will describe the role of autoimmune pathogenesis and immune therapy for autism. I have studied autism as an autoimmune disorder, in which neuro-autoimmune factors may lead to central nervous system (CNS) pathology. The essence of my hypothesis* (see below) is that the virus-induced autoimmunity to developing brain myelin may impair the anatomical development of neural pathways in children. This is mainly because there is a strong evidence to suggest that the speed of neural transmission depends essentially on structural properties of the insulating myelin sheath, connecting nerve fibers and axon diameter.

Briefly, I hypothesized that an autoimmune reaction to brain structures, in particular the myelin sheath, plays a critical role in causing the neurological impairments in individuals with autism. Furthermore, I suggested that an immune insult after a natural infection or vaccination might cause "nicks" or small changes in the myelin sheath. These anatomical changes could ultimately lead to life-long disturbances of higher mental functions such as learning, memory, communication, social interaction, etc. We have identified certain viral and autoimmune factors that led me to develop a speculative "**Neuroautoimmunity Model of Autism**" that I will discuss in my presentation. I think that autism can be treated successfully using some of the therapies proven effective in treating other autoimmune diseases; however, we need to identify and fully characterize autoimmune pathology of autism. Specifically, I am exploring the role of autoimmune factors (e.g., viruses, autoantibodies, T cells, and cytokines) because they are the well-known targets of therapy with immunomodulating agents. Thus I will focus on immune therapies for purposes of restoring brain function in autistic people through immunology.

*Hypothesis:

Environmental Factors (virus/vaccines/toxins) → Immune Dysfunction/Dysregulation → Autoimmunity to Brain → Neuro-Immune Developmental Disorders (NIDD) such as Autism

Autoimmune Features in Autism

Autoimmunity is an abnormal immune reaction in which the immune system becomes primed to react against body's own organs, and the end result is an autoimmune disease. Several factors contribute to autoimmune diseases. Microbes such as viruses can trigger them and they are generally linked to genes that control immune responses. They cause immune abnormalities of T cells - one type of white blood cell (WBC); they induce the production of autoantibodies; they involve hormonal factors; and they generally show a gender preference. This is also the case with autism, i.e., several autoimmune factors have been identified in autistic patients, supporting the pathogenic role of autoimmunity in autism (1-5). Some of the important autoimmune factors in autism are listed below:

- Autism is commonly associated with microbial infections, in particular virus infections.
- Autistic patients have immune abnormalities, especially those that characterize an autoimmune reaction in a disease.
- Autism displays increased frequency for immune response genes (e.g., HLA, C4B null allele or extended haplotypes) that render susceptibility to autoimmune diseases.
- Autism involves a gender factor as it affects males about four times more than females.
- Autism has a family history of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis and diabetes.
- Autism also involves a hormonal factor, for example secretin and endorphins.
- Autistic patients respond well to immune therapy.

Viral Studies in Autism

Because viral infections can easily be acquired during fetal life, infancy or early childhood, certain viruses have been linked to autism. Viruses can enter the brain through the nasopharyngeal membranes or induce an autoimmune response against the brain, thereby impact the development of the central nervous system (CNS). Since the onset of the disorder is quite early on in life, viruses might serve as teratogens (agents that cause developmental malfunctions) etiologically linked to autism.

Earlier studies implicated rubella virus and cytomegalovirus (CMV). Children with congenital rubella syndrome showed certain autistic-like behaviors. Some autistic children did not produce antibodies to rubella vaccine even after the repeated rubella immunization. Although the reason for this problem has never been investigated, I think this is due to a defect in T cell-mediated immunity - a defense mechanism that helps fight virus infections. Indeed, this was indicated in our pilot study: we found that the rubella-induced lymphocyte proliferation response was considerably lower in autistic children as compared to normal children. Few cases of autism have also been described among children with congenital CMV infection. Additionally, an autistic child with CMV infection responded favorably to treatment with transfer factor (an immune- modulating agent) but there was no follow-up to the study in which this was reported.

Recently, we took a new immunological approach of studying viral etiology in autism. We studied immune response to viruses by measuring their antibody level. For this purpose, we measured antibodies to measles virus, mumps virus, rubella virus, CMV, and human herpesvirus-6 (HHV-6). To our surprise, we found that the antibody level of only the measles virus, but not of the other viruses tested, was significantly higher in autistic children than the normal children. In addition, we found an interesting

correlation between measles antibody and brain autoimmunity, which was marked by myelin basic protein (MBP) autoantibodies. The two immune markers correlated in greater than 90% of autistic children, suggesting a causal link of measles virus with autoimmunity in autism. This is one of the most important findings in autism to date, which prompted us to link measles virus in the etiology of the disorder. More recently, we expanded this study to find the source of this measles virus. And, through our laboratory research, we have now gathered experimental evidence to suggest that one possible source of this virus might be measles subunit of the measles-mumps-rubella (MMR) vaccine. Once again, there was a positive correlation (greater than 90%) between MMR antibody and MBP autoantibody. Therefore, we suggested that the measles subunit of the MMR vaccine might trigger an autoimmune reaction in autistic children. This is an excellent working hypothesis to explain autoimmune subset of autism, and it may also help us understand why some children show autistic regression after the MMR immunization (2-4).

Testing for Autoimmunity in Autism

Recent advances have clearly shown that autoimmunity plays a key role in the pathogenesis of autism. Since the brain is the affected organ in autism, the autoimmune response will be directed against this organ. Autoimmunity is commonly manifested by certain autoimmune factors that have been identified by us in children with autism. The list includes brain autoantibodies, viral and/or vaccine antibodies, cytokine profile or immune activation markers, as well as antinuclear antibodies. Taken together, they are essential for identifying a brain-specific autoimmune response, which can afterward be treated with immune therapy. By performing blood tests we can determine if a patient shows autoimmunity to brain tissue, if he or she is a candidate for experimental immune therapy, and if the response to therapy is effective. Therefore, this type of immune evaluation is very important in helping people with autism. The specific tests are:

- 1. Brain autoantibodies:** this test detects antibodies to two brain proteins, namely the myelin basic protein (MBP) and neuron-axon filament proteins (NAFP). We have found that the incidence of MBP autoantibody in the autistic population is markedly higher than that of the normal population; hence, it serves as a primary marker of the autoimmune reaction in autism. In contrast, the incidence of NAFP antibody in autistic patients is only marginally higher than that of normal controls, making it a secondary marker of choice (2,3). It is, however, recommended that the two immune markers be tested simultaneously.
- 2. Virus serology:** this test measures level of antibodies to viruses such as measles, mumps, rubella or HHV-6. We have shown that the level of measles antibody is elevated in many autistic children (2-4), which could be a sign of a present infection, past infection, or immune reaction to MMR vaccine.
- 3. Vaccine serology:** this test detects antibodies to vaccines such as MMR or DPT. Our laboratory studies showed that a significant number of autistic children, but not the normal children, harbor a unique type of measles antibody to MMR vaccine (4). This antibody might represent an abnormal or inappropriate immune reaction to this vaccine and should be tested in relation to autoimmunity in autism.
- 4. Cytokine profile:** two cytokines or immune activation markers, namely interleukin-12 (IL-12) and interferon gamma (IFN-g), play a very important role in the causation of autoimmune diseases, i.e., they initiate an autoimmune reaction via induction of Th-1 white blood cells. We have found that these two cytokines are selectively elevated in autistic children, suggesting the induction of autoimmunity via Th-1 cells in autism (6). Therefore they should be measured as a sign of altered cellular autoimmunity in patients with autism.

5. Antinuclear antibodies: this test assays for antinuclear antibodies (ANA) that are non-specific antibodies but are often present in patients with autoimmune diseases. We have found that approximately one-third of the autistic children have positive titers of ANA.

Immunotherapy in Autism

Taken together, the aforementioned findings clearly point to an autoimmune mechanism of pathogenesis of autism. The idea that autism is an autoimmune disorder is further strengthened by the fact that autistic patients respond well to treatment with immune modulating drugs (1,3). Immune interventions can produce immune modulation - a state of suppression or stimulation. Since autistic patients do not show evidence of a classical primary immunodeficiency, simply boosting their immunity is not a good strategy. However, they do have immune abnormalities and therefore depending on the nature of the immune abnormality, the goal of therapy should be to normalize or reconstitute the immune function. This will permit a more balanced immune response, avoiding major fluctuations of overt immune activity that could be detrimental to the patient. Immune therapy should always be done in consultation with a physician, preferably a clinical immunologist, allergist or hematologist.

The following immune interventions can be used:

Steroid therapy: steroids such as Prednisone and/or ACTH (adrenocorticotropin hormone) are commonly used as the first course of treatment for patients with autoimmune diseases and infantile spasm. For treating autism, there are anecdotal reports and only one study that showed improvement of autistic-like symptoms in children when they were treated with synthetic ACTH. This result indicated that steroids are potentially useful in alleviating clinical symptoms of autism, but the efficacy of this treatment has not been properly assessed in individuals with autism.

Immunoglobulin therapy: this treatment is in practice for treating patients with autoimmune diseases. It has also been used to treat children with autism. Open-label trials of both low-dose and high-dose intravenous immunoglobulin (IVIG) have shown that most but not all autistic children respond favorably to this treatment. Clinically, children so treated have shown improvements in language, communication, social interaction and attention span. However, the treatment is not for everyone, and before this treatment is administered a proper immune evaluation is highly recommended to assess the nature of the immune problem.

Autoantigen therapy: this treatment is used for treating patients with autoimmune diseases by feeding patients autoantigen. We have found that the autoantigen in autism is a myelin basic protein (MBP), suggesting the possibility of treating autistic patients with MBP-containing myelin products. Accordingly, one such product known as Sphingolin has been used with success. The school psychologists, teachers and parents have reported significant improvement of symptoms in autistic children. Obviously, these preliminary reports are quite encouraging and promising, but a well-designed clinical trial has not been conducted.

Plasmapheresis: although it is not commonly recommended, this procedure is used for treating patients with infections, autoimmune diseases, and immune complex diseases. Because this method removes harmful substances (e.g., autoantibodies) from the blood, it is considered a viable immune therapy. The method has also been used to treat certain brain disorders (for example Rasmussen's encephalitis and obsessive-compulsive disorder), in which autoimmunity has been implicated as a basis of the disorder. Plasmapheresis produced positive responses in patients with these disorders, and the responses were much better with plasmapheresis when compared to the IVIG treatment. In these patients, the rationale to administer plasmapheresis relied mainly on the anti-neuronal antibody test. Since autistic patients also

have positive titers of brain autoantibodies, they should also respond to plasmapheresis. Although the plasmapheresis treatment for autism has been suggested for last 5-6 years, it has thus far not been tried in patients with the disorder.

Conclusions

Current research suggests that autoimmunity is the core of the problem in autism. The existence of autoimmune factors and the patient responsiveness to treatment with immune therapies strengthens the idea that autism is an autoimmune disorder. The autoimmune response is most likely directed against the brain myelin perhaps secondary to an “atypical” measles infection. Considering an estimated population of 500,000 autistic people in the United States, it is tempting to suggest that the autoimmunity research may benefit between 250,000-350,000 Americans today. In a much broader sense, I conclude that the autoimmunity research will have a global impact for treating autism in America as well as in other countries worldwide, hence there is tremendous hope for autistic people through autoimmunity research.

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