



## Is autism an autoimmune disease?

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### Abstract

Autism spectrum disorder (ASD) is a spectrum of behavioral anomalies characterized by impaired social interaction and communication, often accompanied by repetitive and stereotyped behavior. The condition manifests within the first 3 years of life and persists into adulthood. There are numerous hypotheses regarding the etiology and pathology of ASD, including a suggested role for immune dysfunction. However, to date, the evidence for involvement of the immune system in autism has been inconclusive. While immune system abnormalities have been reported in children with autistic disorder, there is little consensus regarding the nature of these differences which include both enhanced autoimmunity and reduced immune function. In this review, we discuss current findings with respect to immune function and the spectrum of autoimmune phenomena described in children with ASD.

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## 1. Introduction

The autistic spectrum disorders (ASD) are complex developmental disorders that are characterized by impairments in social interaction, deficits in communication and stereotyped patterns of behavior [1]. ASD describes a range of conditions including autism and Asperger's syndrome, in which, for the majority of cases the cause of remains unknown. So far, unequivocal evidence for a genetic association with ASD has yet to be established, with the most likely genetic models predicting multiple and weak gene interactions of 15 or more. Equally, ASD has been linked with environmental factors such as congenital rubella infection, anticonvulsants and antiemetics taken during pregnancy, perinatal hypoxia and post-natal infections such as encephalitis [2,3]. Various genetic, prenatal and early postnatal environmental or biochemical factors have been implicated in ASD, but neither a definitive pattern of its etiology nor its pathophysiology has emerged to date.

## 2. The neuroimmune system in ASD

Systemic immunologic aberrations in ASD have been linked with both autoimmunity, describing antibodies reactive for central nervous system (CNS) proteins with the potential for neuronal tissue destruction, and with dysfunctional immunity such as abnormalities or deficits of function in immune cell subsets. The relationship between the various immune abnormalities that have been reported in individuals with ASD and the development of neurologic changes is not yet clear. There has been speculation, however, that exposure of the developing neuronal system during critical periods to enhanced or aberrant immune activation may result in the brain pathology of ASD and/or in phenotypic differences in the disease dependent upon rates of neuronal and immune development.

The plausibility of hypotheses concerning immune system alterations in ASD is derived from the recognized roles of the immune system in early neurodevelopment and the ability of these alterations to influence patterns of behavior. The immune and nervous system are both complex, highly evolved systems that confer signals through the release of

chemical mediators such as neuropeptides, neurotrophins and cytokines. There is continual cross communication between the immune and nervous systems, with many peptides playing a critical role in both. This is evident based on the presence of immune functional cells in the CNS, as well as nerves that terminate in both the lymph node and spleen. In ASD, a number of neuroactive compounds that also share immunomodulatory properties have been implicated in the disease process, for example, elevated platelet serotonin levels are observed in approximately one-third of children with autism [4–6]. Similarly, it has been hypothesized that autism may be a result of abnormal levels or activity of opioid peptides, which can act as cytokines conferring their actions through receptors on peripheral blood and/or glial cells. In addition, neuropeptides, such as oxytocin and vasopressin, have been implicated in social recognition, affiliation and attachment behaviors. Oxytocin is present in the thymus at high levels and is expressed on thymic epithelial cells, where it is thought to play a role in immune tolerance [7]. Moreover, neuropeptides may act synergistically with cytokines to alter immune or neuronal function. For example vasoactive intestinal polypeptide (VIP) synergizes with TNF- $\alpha$  to induce dendritic cell maturation [8]. Various immune function abnormalities have been widely reported in autistic individuals [9,10].

## 3. Autoimmunity in ASD

The first suggestion that autoimmunity may be etiologically important in autism was noted in a case report in 1971 describing an autistic child with a strong family history of autoimmune disorders [11]. Common genes may contribute to a number of different autoimmune states in families [12], and immune dysfunction and brain development may be governed by similar genes (e.g., MHC third hyper-variable region sequences 1 and 2, which have been associated with both autism and rheumatoid arthritis [13,14]. Studies of autistic individuals have found an increased frequency of autoantibody production (Table 1). Analysis of data from small but representative groups of ASD patients has shown that approximately 30–70% of autistic patients have circulating anti-brain autoantibodies [10,15–21]

Table 1  
Autoantibodies against CNS proteins reported in ASD patients

Antibody specificity	Reference
Antibodies to neuron-axon filament proteins (NAFP)	Singh et al. [37]
Antibodies to cerebellar neurofilaments	Plioplys et al. [21]
Antibodies to myelin basic protein (MBP)	Singh et al. [38]
Antibodies to caudate nucleus	Singh and Rivas [20]
Antibodies to serotonin receptor	Singh et al. [39]
Antibodies to brain endothelial cells	Connolly et al. [40].
Antibodies to brain tissue (unknown antigens)	Todd et al. [18]; Silva et al. [24]; Van de Water et al., manuscript in preparation

including autoantibodies to a serotonin receptor [22], myelin basic protein [23] and, most recently, as yet unknown antigens from adult brain tissue extract [24]. We have recently described specific cells staining the Purkinje layer of the monkey cerebellum when treated with plasma from patients with ASD (Fig. 1, manuscript in preparation).

While significantly higher levels of autoantibodies are detected in autistic patients when compared with controls, the pathophysiological significance of these antibodies reported in children with autism is uncertain. Taken together, the findings of autoimmunity in families and the plethora of anti-brain antibodies suggest that in some patients, autoantibodies that target the CNS may be a pathological or exacerbating factor in neuronal development in children with ASD. It is also important to note that for each antibody tested reported the number of autistic children showing incidence was far from 100%. It is also unclear whether individual autistic children are positive for more than one antibody. In addition, potentially increased autoimmunity may be confined to only a subset of autistic patients. Indeed, large cohort studies with thoroughly defined and specifically phenotyped autistic patient groups and well matched age and sex controls, need to be performed to confirm the role of autoantibodies in the pathology of either all or subsets of autistic patients. Moreover, their presence does not correlate with an anticipated pathological effect. For example, autoantibodies to myelin basic protein are frequently detected in autistic

patients, but no signs of concomitant demyelination have been described to date [25]. Anti-brain autoantibodies were also found for patients with neurological disorders other than autism, as well as in normal individuals. This raises the question of pathogenic significance and disease-specificity of the antibodies found in the serum of patients with autism. Production of these antibodies may be secondary to the innate CNS pathology and may simply be a marker of an event in the CNS that allowed the presentation of self-antigens. Indeed, glial fibrillary acidic protein (GFAP) is significantly elevated in the CSF of ASD children compared to controls, suggesting that gliosis and unspecific brain damage may occur in autism [26]. However, characterization of CNS-specific autoantibodies in the serum of patients with autism may help further define the site of neurologic disturbance or injury. There remains the possibility that a sub-phenotype of patients with autism do in fact have pathogenic antibodies.

An association with autoimmune enteropathies with specific antibodies targeted to gut epithelial cells has been shown in ASD [27]. In a recent paper, serum from a mother with an autistic child, when injected into gestating mice, induced behavioral changes including altered exploration, motor coordination and changes in cerebellar magnetic resonance spectroscopy in the offspring. In contrast, mice injected with sera from mothers with typically developing children showed no such changes in behavior [28]. This study supports the notion that maternal anti-

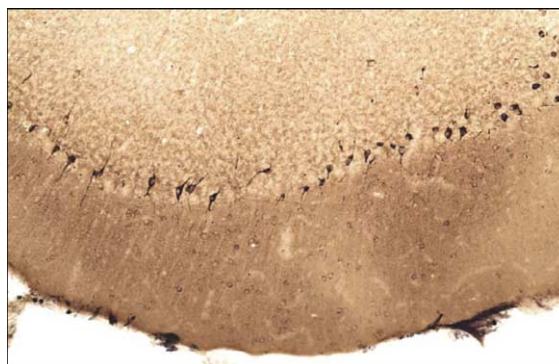


Fig. 1. Immunohistochemistry of monkey cerebellum following staining with plasma from a patient with ASD. Note the intense cytoplasmic staining of cells in the Purkinje layer of the cerebellum ( $\times 160$ ).

bodies may influence the neurodevelopmental process in autism. Several autoimmune diseases can be transferred from mother to fetus by pathogenic IgG antibodies. These include myasthenia gravis, Graves' disease, thrombocytopenic purpura, neonatal lupus rash and/or congenital heart block, and pemphigus vulgaris. Alternatively, the maternal immune response may directly impact fetal brain development and produce pathology via altered levels of circulating cytokines which demonstrate assorted effects on neuronal tissue such as the modulation of systemic and CNS responses to infection, injury and inflammation [29].

Two separate epidemiologic studies suggest that a family history of autoimmune disorders is more common among children with autism than healthy control children [30,31]. The frequency of autoimmune disorders was increased in the ASD group with over 40% of families with two or more close family members having autoimmunity. In both studies, first-degree relatives, especially mothers, were most often affected. However, interpretation of these studies is hampered by limitations in study design, sample size, and the reliance on self-reporting rather than medical records and thus may have a significant margin of reporting error. A more recent study reported an elevation in the frequency of psoriasis, type I diabetes and asthma not previously reported in ASD mothers using medical records for diagnosis confirmation [32]. In this study, we observed that asthma and maternal atopy were more strongly associated with autism in families with more than one ASD-affected child, thus suggesting that genes underlying atopy may also be etiologically related to autism. In addition, the observation that the risk of having a child with autism was highest among women with diagnoses of asthma or allergies recorded during the second trimester may indicate that disease severity or disease flare may be more strongly correlated with fetal neuropathology.

#### 4. The role of xenobiotics in autism

Recently, it has been hypothesized that environmental exposure to various xenobiotics may contribute to ASD etiology either through direct or indirect effects on the immune system and/or the

developing CNS. A variety of interactions among environmental agents, immune system dysfunction and ASD can be envisioned. The neuropathology of ASD may be induced and/or exacerbated by infectious agents or other toxicants as a direct consequence of activation of the immune system. Neurotoxicity may occur as a consequence of an immune system that is inherently dysfunctional, such that endogenous immune-related molecules create toxicity in the absence of defined exogenous exposures. Alternatively, heritable variation in characteristics of the immune system could create vulnerabilities for such effects.

The reported increases in the prevalence of autism have intensified the focus on environmental exposures such as thimerosal. The effects of heavy metals such as lead and mercury on the immune system have been studied extensively and attest to the ability of environmental agents to perturb immune function [33,34]. Moreover, the effects of mercury exposure on immune development in both pre-natal and post-natal rat models suggest that placental and lactational transfer of methylmercury adversely affects the developing immune system of the exposed offspring [35]. Recent studies by Hornig et al. [36] describe a subset of autoimmune disease susceptible mice that express several aspects of the behavioral and neuropathologic features of autism spectrum disorders following thimerosal exposure. Major alterations in immune function, such as those occurring during immune development, are long lasting and may result in an increased likelihood of development and/or progression of autoimmune and/or allergic diseases.

#### 5. Summary

In conclusion, numerous world-wide studies have demonstrated immunological abnormalities in children with ASD. These include the presence of autoantibodies to several antigens pertinent to the nervous system. However, as yet, no definitive autoantibody pattern in ASD has emerged. Admittedly, ASD encompasses a broad spectrum of behavioral anomalies and as such several sub-phenotypes may be represented. In addition, the presence of autoantibodies in the serum of these patients may be a secondary phenomenon. The continued identification

and verification of the altered immune response seen in patients with ASD is clearly required.

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### Take-home messages

- Patients show evidence of immune dysregulation.
- Autoantibodies have been described in patients with autism to brain antigens.
- There is an increased incidence of autoimmune disease in the families of patients with autism.

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### *The World of Autoimmunity; Literature Synopsis*

#### **Anti-CD154 in treatment of murine lupus nephritis**

Anti-CD154 antibody treatment can ameliorate murine lupus nephritis when given early in the disease. Quezada et al. (*Arthritis Rheum* 2003;48:2541) report that the early treatment produced long-term survival in BW mice, with abrogation of renal immune complex deposition for months after treatment was stopped. On the other hand, late anti-CD154 treatment, which started after development of nephritis, could halt disease in approximately 40% of mice, and the remissions induced by late treatment with anti-CD154 occurred despite ongoing renal immune complex deposition. These responding mice had reductions in renal mRNA levels of transforming growth factor beta, interleukin-10, and tumor necrosis factor alpha. The authors concluded that amelioration of murine lupus by anti-CD154 therapy is mediated by distinct mechanisms in early versus late intervention. It is possible that anti-CD154 therapy prevents autoantibody production and renal immune complex deposition in early disease, whereas it limits secondary tissue damage in situ in the late phase.

#### **Seronegative antiphospholipid syndrome**

Hughes and Khamashta discuss the term 'seronegative antiphospholipid syndrome (APS)' (*Ann Rheum Dis* 2003;62:1127). They refer to subsets of patients with clinical manifestations highly suggestive for APS, but without detectable levels of antiphospholipid antibodies. They suggest 3 possibilities for this phenomenon: a wrong diagnosis, a laboratory problem as an explanation for the failure of detection of autoantibodies directed against different phospholipids or protein cofactors, or previously positive antiphospholipid antibody tests that have reverted to negative. As previously the terms seronegative rheumatoid arthritis and seronegative lupus have been used, the authors suggest seronegative APS should be a new entity, as even though a classification criteria may be missing (presence of antiphospholipid antibody), the diagnosis seems obvious in the presence of characteristic manifestations.