

FINDINGS IN IMMUNOLOGY

Vijendra K. Singh, Ph.D. : Selected Research on Autism
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Dr. V. K. Singh received his doctorate from the University of British Columbia, Vancouver, Canada. His post-doctoral fellowship was completed in neurochemistry and neuroimmunology. Spanning over twenty years' experience in neurobiology and immunology research, Dr. Singh studied brain diseases, particularly infantile autism and Alzheimer's disease. Having authored over a hundred scientific publications, he is both a pioneer and an international authority on autoimmunity in autism. Dr. Singh is a member of the American Association for the Advancement of Sciences, the American Association of Immunologists, and the New York Academy of Sciences. He is listed in American Men and Women in Science (United States, R. R. Bowker, publisher) and The International Who's Who of Intellectuals (Cambridge, England, International Biographical Centre).

Introductions to the Work of V. K. Singh, Ph.D.

"*Neuro-immunopathogenesis in Autism*," Vijendra K. Singh, Ph.D., Ch. 6, Clinical Neuroimmune Biology (*New Foundation of Biology* series, Elsevier Science, 2001).

"*Autism, Autoimmunity and Immunotherapy: a Commentary*," by Vijendra K. Singh, Ph.D., reprinted from the Autism Autoimmunity Project Newsletter, December 1999, <http://lib.tcu.edu/www/staff/lruede/singhfeature.html>.

"*Autoimmunity and Neurologic Disorders*," an interview with V. K. Singh, Ph.D. in Latitudes (newsletter of the Association for Comprehensive NeuroTherapy, <http://www.latitudes.org/index.html>, vol. 4, no. 2, Spring 1999), by Sheila Rogers, is viewable at <http://lib.tcu.edu/www/staff/lruede/latitudes.html>.

"*Vijendra K. Singh, Ph.D.: Selected Work on Alzheimer's Disease*" lists immunological discoveries relating to Alzheimer's disease (<http://lib.tcu.edu/www/staff/lruede/alzheimers.html>).

V. K. Singh's "*Immunotherapy for Brain Diseases and Mental Illnesses*" (Progress in Drug Research), vol. 48, 1997, pp. 129-146) is a lengthy scientific article addressing the rationale for immunotherapy in brain diseases and possible applications of specific immunological therapies in Multiple sclerosis; Guillain-Barre syndrome; Rasmussen's encephalitis; Obsessive-compulsive disorder (OCD); Alzheimer's disease; and Autistic syndrome. The introduction to this article notes the growing comprehension among scientists of the reciprocal relationship between the nervous and immune systems, categorizes the various diseases of the nervous system, and observes that nearly all central nervous system diseases respond to immunotherapy.

Selected Research on Autism

"*Serological Detection of Measles Virus in Relation to Autoimmunity in Autism*," 102nd General Meeting of the American Society for Microbiology, May 19-23, 2002, Salt Lake City, Utah, Presentation V-5. Autoimmunity to brain myelin protein (MBP) secondary to a measles infection may cause autistic regression in some children with this neurodevelopmental disorder. ...there is a strong correlation between MMR

antibodies and MBP autoantibodies in autism. By using monoclonal antibodies, we characterized that the MMR antibodies are due to the measles subunit, but not due to mumps or rubella subunits, of the polyvalent vaccine. In light of the new evidence presented here, we suggest that the MMR vaccine in some cases of autism might cause autoimmunity and it might do so by bringing on an atypical measles infection that does not produce a typical measles rash but manifests neurological symptoms upon immunization. It is confirmed here (in an additional population) that this antibody is not typically produced during normal immune response to the vaccine.

"Abnormal Measles Serology and Autoimmunity in Autistic Children," Journal of Allergy and Clinical Immunology, vol. 109, no. 1, S232, January 2002 (abstract #702). Immunoblotting analysis in recent work showed the presence of an unusual MMR antibody in 60% (75 of 125) of autistic children, but in none of 92 normal children. By using MMR blots and monoclonal antibodies, we found that the specific increase of MV antibodies or MMR antibodies was related to measles hemagglutinin antigen (MV-HA), but not to the mumps or rubella viral proteins within the MMR vaccine. In addition, over 90% of MMR antibody-positive autistic sera were also positive for MBP autoantibodies, suggesting a causal association between MMR and brain autoimmunity in autism. Stemming from this evidence, we suggest that an "atypical" measles infection in the absence of a rash but with neurological symptoms might be etiologically linked to autoimmunity in autism.

"Serological Association of Measles Virus and Human Herpesvirus-6 With Brain Autoantibodies in Autism." Clinical Immunology and Immunopathology, vol. 89, number 1, October 1998, pp. 105-8. This study is the first to report an association between virus serology and brain autoantibody in autism; it supports the hypothesis that a virus-induced autoimmune response may play a causal role in autism.

"Positive Titers of Measles and Measles-Mumps-Rubella Antibody Are Related to Myelin Basic Protein Autoantibody in Autism." Abstract of study prepared for the annual meeting of the American Association of Immunologists (AAI) / Federation of American Societies for Experimental Biology (FASEB), San Francisco, April 1998. A significant number of autistic children exhibit positive titers of measles and MMR [measles-mumps-rubella] antibody, which in a vast majority of cases is associated with the presence of MBP [myelin basic protein, or brain] autoantibody. A measles- and/or MMR-triggered autoimmune response to myelin may play a pathogenesis role in autism.

"Association of Anti-MBP and Anti-NAFP Antibodies With HHV-6 Antibodies in a Child With Autistic Regression." Journal of Allergy and Clinical Immunology, vol. 101, no. 1, part 2, S122, January 1998 (in section entitled, "Program and Abstracts of Papers to Be Presented During Scientific Sessions [at the] 54th Annual Meeting, March 13-18, 1998"). Children with autism have been shown to have a high incidence of circulating autoantibodies to myelin basic protein (MBP) and to neuron-axon filament protein (NAFP) compared with healthy controls or controls with other disabilities. Subacute viral infections of the central nervous system have been postulated to play a role in children who develop normally before undergoing autistic regression. In this instance, a healthy boy having a typical case of roseola (HHV-6) at 15 months experienced severe regressions of language and social behavior soon afterward. "The presence of antibodies against MBP and NAFP along with the clinical course and elevated levels of HHV-6 antibodies suggest an autoimmune response to this neurotropic virus[,] resulting in the autistic regression."

"Circulating Autoantibodies to Neuronal and Glial Filament Proteins in Autism." Pediatric Neurology, vol. 17, number 1, July 1997, pp. 88-90. A significant increase in incidence of anti-NAFP [neuron-axon-filament-protein] and anti-GFAP was seen in autistic subjects, but not in mentally retarded subjects. Clinically, these autoantibodies may be related to autoimmune pathology in autism.

"Hyperserotoninemia and Serotonin Receptor Antibodies in Children With Autism but Not Mental Retardation." Biological Psychiatry, vol. 41, number 6, March 15, 1997, pp. 753-5.

"Elevated Serotonin Levels in Autism: Association With the Major Histocompatibility Complex." Neuropsychobiology, vol. 34, number 2, 1996, pp. 72-5. Two of the most consistently observed biological findings in autism are increased serotonin levels in the blood and immunological abnormalities (including autoreactivity with tissues of the central nervous system). The major histocompatibility complex (MHC) regulates the immune system, and is associated with autoimmune disorders. In this study, a positive relationship was observed between elevated serotonin levels and the MHC types previously associated with autism.

"Plasma Increase of Interleukin-12 and Interferon-gamma. Pathological Significance in Autism." Journal of Neuroimmunology, vol. 66, numbers 1-2, May 1996, pp. 143-5. Immune factors such as autoimmunity have been implicated in the genesis of autism, a neurodevelopmental disorder. Since autoimmune response involves immune activation, the plasma levels of interferon-alpha (IFN-alpha), IFN-gamma, interleukin-12 (IL-12), and IL-6 were measured, along with tumor necrosis factor (TNF-alpha) and soluble intercellular adhesion molecule-1 (sICAM-1). The levels of IL-12 and IFN-gamma were significantly higher in autistic patients than in controls (the remaining measures were not significantly different). It is suggested that IL-12 and IFN-gamma increases may indicate antigenic stimulation of Th-1 cells pathogenetically linked to autoimmunity in autism.

"Immunogenetic Studies in Autism and Related Disorders." Molecular Chemistry and Neuropathology, vol. 28, numbers 1-3, May-August 1996, pp. 77-81. The major histocompatibility complex comprises a number of genes that control the function and regulation of the immune system. One of these, the C4B gene, encodes a product that is involved in eliminating pathogens such as viruses and bacteria from the body. A deficient form of the C4B gene, termed the C4B null allele (no C4B protein produced) was previously seen to have an increased frequency in autism. In this study, this finding was confirmed, and this same condition was detected in related [neurodevelopmental] disorders as well. In addition, two alleles of the DR beta 1 gene also had significantly increased representation in autistic subjects.

"Antibodies to Myelin Basic Protein in Children With Autistic Behavior." Brain, Behavior and Immunity, vol. 7, number 1, March 1993, pp. 97-103. Approximately 58% of the sera of autistic children were found to be positive for anti-MBP [anti-brain antibodies]. This result was significantly different from that of the controls, among whom were children with normal health, idiopathic mental retardation, and Down syndrome. It is possible that anti-MBP antibodies are associated with the development of autistic behavior.

"Possible Association of the Extended MHC Haplotype B44-SC30-DR4 With Autism." Immunogenetics, vol. 36, number 4, 1992, pp. 203-7. The complement C4B null allele appears to be associated with infantile autism. In this study, the incidence of B44-SC30-DR4 was increased by almost six-fold in the autistic subjects as compared with healthy controls. Moreover, the total number of extended haplotypes expressed on chromosomes of autistic subjects was significantly increased as compared with those expressed on chromosomes of healthy subjects. Conclusion: a gene related to, or included in, the extended major histocompatibility complex may be associated with autism.

"Increased Frequency of the Null Allele at the Complement C4b Locus in Autism." Clinical Experiments in Immunology, vol. 83, number 3, March 1991, pp. 438-40. Associations between C4 deficiency and autoimmune disorders have been found over the past several years. In this study, autistic subjects and their mothers had significantly increased phenotypic frequencies of the C4B null allele, compared with controls. The siblings of the autistic subjects also had an increased frequency of the C4B null allele, but this was not significant. The fathers did not display this allele. All family members had normal frequencies of the C4A null allele, all normal C4A and C4B alleles and all BF and C2 alleles.

"Changes of Soluble Interleukin-2, Interleukin-2 Receptor, T8 Antigen, and Interleukin-1 in the Serum of Autistic Children." Clinical Immunology and Immunopathology, vol. 61, number 3, December 1991, pp. 448-455. Findings indirectly indicated that the activation of a subpopulation of T cells occurs in some

children with autism, as opposed to healthy children or children with mental retardation (non-Down's syndrome).

"*Deficiency of Suppressor-inducer (CD4+CD45RA+) T Cells in Autism.*" Immunological Investigations, vol. 19, number 3, June 1990, pp. 245-51. Autistic subjects as compared to a group of 35 healthy age-matched subjects had a significantly reduced number of lymphocytes, a decreased number of CD2+ T cells and reduced numbers of CD4+ and CD4+CD45RA+ lymphocytes. Results suggest that an alteration in the suppressor-inducer T-cell subset is associated with autism.

"*CD4+ Helper T Cell Depression in Autism.*" Immunology Letters, vol. 25, number 4, September 1990, pp. 341-5. Autistic subjects had a significantly lower percentage and number of CD4+ cells, a lower number of T cells (CD2+ cells) and B cells (CD20+ cells), and a lower percentage and number of total lymphocytes than siblings and normal subjects. The level of blood values for female subjects appeared lower than those for males as compared to normal subjects of the same sex. Results suggest that a decrease in CD4+ cells is associated with autism.