Autoimmune connection of autism in Central Saudi Arabia

Laila Y. Al-Ayadhi, MBChB, PhD.

ABSTRACT

Objective: Autism is a neurodevelopmental disorder with unknown etiology. The etiology of autism is complex, and the underlying pathologic mechanisms are unknown. This study tests the autoimmune mechanisms in the pathogenesis for autism in autistic children in the Riyadh area.

Methods: The study took place in the Riyadh area of the Kingdom of Saudi Arabia between September 2003 and April 2004. Sixty-five autistic children, with a confirmed diagnosis according to E-2 diagnostic criteria for autistic spectrum disorders, participated in the study. Serological examination of antibodies to measles, mumps, rubella (MMR), and myelin basic protein (MBP) was carried out in autistic and control children.

Results: The level of MBP antibodies was significantly higher in autistic children as compared to controls ($p<0.01$). Furthermore, the level of antibodies to measles but not mumps or rubella was significantly higher in autistics compared to the control group ($p<0.05$). Moreover, 82% of autistic sera positive for measles IgG was also positive for MBP.

Conclusion: The current study supports the hypothesis that autoimmunity plays a role in the pathogenesis of autism. However, results from the current study are not enough to support that immunization by MMR is playing a role in the autoimmune process in autistism.

Neurosciences 2005; Vol. 10 (4): 265-267

Autism is a childhood disorder with age of onset 1½-3 years. Autism is as common as 1 in 2500 live births worldwide, and Saudi Arabia is no exception. Although there is no known unique cause of autism, there is growing evidence that a variety of disorders can cause autism.[1,2] Current theories include genetic, immune, neural, and many factors which all remain under investigation. In the current study, we focused on the autoimmune mechanisms in the pathogenesis of autism.[3,4] Scientists believe that viral infections trigger autoimmune responses and eventually lead to organ-specific autoimmune diseases. We do not know the trigger mechanism, but viral infections have been suspected in autism.[5] Several factors contribute to autoimmune diseases. Microbes such as viruses can trigger autoimmune diseases. They induce the production of pathogenic antibodies, especially the organ-specific auto-antibodies. Autoimmune diseases are generally linked to certain genes that control immune responses. Furthermore, autoimmune diseases generally show a gender preference. This is also the case with autism, which leads the scientists to believe that autism is very likely an autoimmune response against the brain.[5-7] There is controversy in the literature regarding the possibility of an autoimmune role in the pathogenesis of autism of a viral origin, particularly due to immunization by the measles, mumps, rubella (MMR) vaccine. Madsen et al[8] rule out this possibility, while Singh et al supports it.[3-5] So, the aim of the current study is to investigate the possibility that a virus induced

From the Department of Physiology, Faculty of Medicine, King Saud University, *Kingdom of Saudi Arabia*.

Received 21st September 2004. Accepted for publication in final form 1st December 2004.

Address correspondence and reprint request to: Dr. Laila Y. Al-Ayadhi, Department of Physiology, Faculty of Medicine, King Saud University, PO Box 2925, Riyadh 11461, *Kingdom of Saudi Arabia*. Tel. +966 504295974. Fax. +966 (1) 4786798/4671046. E-mail: ayadh2@hotmail.com

immune response may play a causal role in autism in the Riyadh area in Saudi Arabia. Keeping in view the literature available, we conducted the present study to determine the serological response of 3 viruses, MMR, and an antibody against the brain, myelin basic protein (MBP), exploring a possible correlation between MMR and MBP.

Methods. The study was conducted in the Department of Physiology, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia between September 2003 and April 2004. Sixty-five children, age up to 14 years old, with confirmed professional diagnoses were selected. The diagnosis was carried out either by a qualified psychologist, psychiatrist of neurologist, according to diagnostic criteria E-2.[9] A written consent was obtained from their parents prior the start of the study, and then the parents were asked to fill a questionnaire regarding child's medical and behavioral history. Healthy age and sex matched control volunteers were recruited from King Abdul-Aziz University Hospital. Blood samples were collected by venipuncture in plain tubes, and after gentle mixing were allowed to clot at room temperature, and then centrifuged at 1,500 g for 10 minutes. Then serum was collected and stored at –70°C until assay time. Samples were assayed in a single large batch, in duplicate. None of the children recruited in this study had any history of measles rash or wild type measles infection, but all have had their MMR immunization. Anti-measles, anti-rubella and anti-mumps were measured by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Dade-Behring, Marburg, Germany). Anti-myelin basic protein (anti-MBP) was measured by a commercially available ELISA kit (Diagnostic Systems, Texas, USA). The results were analyzed using SPSS for windows and expressed as percentage. A statistical analysis for differences among the groups was assessed by t-test. P values equal to or less than 0.05 were considered significant.

Results. Sixty-five autistic children with confirmed diagnosis (61 males and 4 females) participated in the study. The mean age for the total number of autistic children participated in the study was 8.2±0.5 years, with 61 (93.8%) males and 4 females (6.2%). The male to female ratio was 17.2:1. In 40% (26) of the autistic children, the parents think that the autistic symptoms started following immunization. As **Table 1** demonstrates, 32% (21) of the autistic children's sera, and 35% (23) of the control sera were positive for mumps IgG antibody (not significant, $p<0.7$). Furthermore, 31% (20) of autistic children sera, and 28% (18) of control sera were positive for rubella IgG antibody (not significant, $p<0.7$). However, 51% (33) of autistic children's sera, and 18% (12) of control sera were positive for measles IgG antibody (significant, $p<0.0001$). In addition, 54% (35) of autistics sera, and 9% (6) of control sera, were positive for MBP antibody (highly significant, $p<0.0001$). Moreover, 82% (27) of autistics sera positive for measles IgG were also positive for MBP (correlation r=0.71). In contrast, only 8% (1) of control sera positive for measles IgG antibodies are also positive for MBP IgG antibodies (correlation r=0.2). Highly significant results ($p<0.0001$) for percentages of simultaneous positive IgG for measles and MBP between autistic children and control. It is interesting to note that, 20% (13) of autistic sera were positive for mumps, measles and rubella IgG. Almost the same results were reached with control sera, 18% (12) of control sera were positive for mumps, measles and rubella IgG.

Table 1 - Percentage of IgG positive antibody in sera of autistic and control children to myelin basic protein (MBP), measles, mumps and rubella.

Antibody	Autistic children		Control children	
	n	(%)	n	(%)
MBP	35	(54)	6	(9)
Measles	33	(51)	21	(18)
Mumps	21	(32)	23	(35)
Rubella	20	(31)	18	(28)

Discussion. Autism is a neurodegenerative disorder with unknown etiology. Several theories have been suggested by scientists, in an attempt to reach a causal factor in the genesis of the disease. An autoimmune reaction of the body, against brain cells, in response to infection or immunization, has been suggested. The current study demonstrates the presence of an autoimmune process in the body against the MBP, through the presence of significant levels of IgG to MBP. Moreover, the current study demonstrated a positive correlation between measles antibody and MBP antibodies in autistic children as compared to healthy control children. The result of this study is in agreement with Singh et al.[3-7,10]

Brain autoantibodies to MBP (anti-MBP) and neuron-axon filament protein (anti-NAFP) have been found to be significantly higher in autistic children when compared to controls.[6] Singh et al[6,11] examined the association between virus serology and autoantibody by simultaneous analysis of measles virus antibody (measles IgG), human herpes virus-6 antibody (HHV-6-IgG) and anti-NAFP. They found that measles-IgG and HH-6-IgG titers were moderately higher in autistic children. In addition, they found that a vast majority of virus

serology-positive autistic sera were also positive for brain autoantibody. Furthermore, researchers have drawn the link between the vaccines and demyelination, concluding that any vaccines can lead to inflammatory reaction involving the nervous system.[12]

Immunological testing of autistic children has shown certain features that are also found in patients with autoimmune disease such as systemic lupus erythematosus, thyroid disease, ankylosing spondylitis, and rheumatoid arthritis. This feature includes, genetic predisposition, autism shows a greater concordance rate in monozygotic twins than in the normal population. In addition, gender factor plays a role, autism is 4 times more common in boys than in girls. Moreover, autism might be triggered by microorganisms, rubella virus and cytomegalovirus infections have indirectly linked to autism. The parallels between autism and autoimmune disease suggest that autoimmunity may be a critical factor in the causes of autism. Since autoimmune diseases are common in our area as compared to the western world, it is likely that the ranking orders of etiological factors of autism are different in those 2 parts of the world.[6,10,13,14]

Accumulating evidence suggests that auto-immunity plays a key role in the pathogenesis of autism. The fact that autistic patients respond well to treatment with immune modulating drugs strengthens the idea that autism is an autoimmune disorder.[15,16] Autistic children do have immune abnormalities and therefore, depending on the nature of the immune abnormality, the goal of immune modulating 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 risky.

Wakefield et al,[17] demonstrated a possible link between MMR vaccination and autism. Then in 2004, these findings were retracted by Wakefield and his group through an article published, ruling out the possible link between vaccines and autism.[18,19] Despite that, several scientists demonstrated a possible link between viral infection, vaccination and the autoimmune factor in the genesis of autism,[3-6,10] which cannot be ignored from a scientific point of view.

The main outcome of this study is, first, the presence of statistically significant levels of MBP antibody in autistics as compared to controls, supporting an autoimmune basis in the development of autism in those children examined. The second result is the highly significant correlation between IgG measles antibody and IgG MBP antibody in autistics as compared to controls. From our point of view, this correlation on its own is not enough to support the hypothesis that a virus induced autoimmune response (through measles vaccine) may play a causal role in autism. Both outcomes need to be investigated further.

Acknowledgment. The author wishes to express gratitude to all the families and children who participated in the study, without them this work would not have been possible. Great appreciation to professor Ali Al-Tuwajri for support and help. Many thanks to Dr. Ali Sowairi, Head of the laboratory section in King Abdul-Aziz University Hospital. Special thanks for King Faisal bin Fahad Center and Special education Academy. Many thanks to Mrs. Reem Al-Sehaily. Great appreciation to Mrs. Asma Al-Zamel for her unending support.

References

1. Freeman WJ. Neurohormonal brain dynamic of social group formation implication for autism. ***Ann N Y Acad Sci*** 1997; 15: 501-503.
2. Waterhouse L, Fein D, Modahl C. neurofunctional mechanisms in autism. ***Psychol Rev*** 1996; 103: 457-489.
3. Singh VK, Warren RP, Odell JD, Warren WL, Cole P. Antibodies to myelin basic protein in children with autistic disorder. ***Brain Behavior and Immunity*** 1993; 7: 97-103.
4. Singh VK, Lin SX, Newell E, Nelson C. Abnormal measles-mumps-rubella antibodies and autoimmunity in children with autism. ***Journal of Biomedical Science*** 2002; 9: 359-364.
5. Singh VK, Jensen RL. Elevated levels of measles antibodies in children with autism. ***Pediatr Neurol*** 2003; 28: 292-294.
6. Singh VK, Lin SX, Yang VC. Serological association of measles virus and human herpes-virus with brain auto-antibodies in autism. ***Clin Immunol Immunopath*** 1998; 89: 105-108.
7. Singh VK. Warren R, Averett R, Ghaziuddin M. Circulating autoantibodies to neuronal and glial filament proteins in autism. ***Pediatr Neurol*** 1997; 17: 88-90.
8. Madsen KM, Hviid A, Vestergaard M, Schendel D, Wohl Ahrt J, Thorsen P et. al. A population study of measles, mumps, and rubella vaccination and autism. ***New Engl J Med*** 2002; 7: 1477-1482.
9. Rimland B. On the objective diagnosis of infantile autism. ***Acta Paedopsychiatr*** 1968; 35: 146-161.
10. Singh VK. Neuro-immunopathogenesis in autism. In: NeuroImmune Biology: New Foundation of Biology. New York: Elsevier Science Ltd; 2001. p. 443-454.
11 Warren RP. Detection of maternal antibodies in infantile autism. ***J Am Acad Child Adolesc Psychiat*** 1990; 29: 873-877.
12. Patja A, Paunio M, Kinnunen E, Junttila O, Hovi T, Peltola H. Risk of Guillain-Barre syndrome after measles-mumps-rubella vaccination. ***J Pediatr*** 2001; 138: 250-254.
13. Weizman A, Weizman R, Szekely GA, Wijsenbeek H, Livni E. Abnormal immune response to brain tissues antigen in the syndrome of autism. ***Am J Psychiatry*** 1982; 139: 1462-1465.
14. Kawashima H, Mori T, Kashiwagi Y. Detection and sequencing of measles virus from peripheral blood mononuclear cells from patients with inflammatory bowel disease and autism. ***Digest Dis Sci*** 2000; 322: 693-699.
15. Singh VK. Immunotherapy for brain disease and mental illnesses. ***Prog Drug Res*** 1997; 48: 129-146.
16. Singh VK. Cytokine regulation in autism. In: Kronfol Z, editor. Cytokines and Mental Health. Boston (MA): Kluwer Academic Publishers; 2003. p. 369-383.
17. Wakefield A, Murch SH, Anthony A, Casson DH, Malik M, Berelowitz M et al. Illeal-lymphoid-nodular hyperplasia, non-specific colitis and pervasive developmental disorders in children. ***Lancet*** 1998; 351; 637-641.
18. Wakefield A. A statement by Dr Andrew Wakefield. ***Lancet*** 2004; 363: 1327-1328.
19. Murch S, Anthony A, Casson DH, Malik M, Barlowitz M, Dhillon A, et al. Retraction of an interpretation. ***Lancet*** 2004; 363: 750.