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Serum Anti-Myelin–Associated Glycoprotein Antibodies in Egyptian Autistic Children

Gehan Ahmed Mostafa, MD, Zeinab Awad El-Sayed, MD, Manal Mohamed Abd El-Aziz, MD, and Mohamed Farouk El-Sayed, MB, BCh

Autoimmunity to brain could play an etiopathogenic role in a subgroup of autistic patients. The frequency of serum anti-myelin–associated glycoprotein antibodies, as an index for autoimmunity to brain, and their relation to family history of autoimmunity were investigated in 32 autistic and 32 healthy matched children. Autistic children had significantly higher serum anti-myelin–associated glycoprotein antibodies than healthy children (2100 [1995] and 1138 [87.5] Buhlmann titre unit, $P < .001$). Anti-myelin–associated glycoprotein positivity was elicited in 62.5% of autistic children. Family history of autoimmunity in autistic children (50%) was significantly higher than controls (9.4%). Anti-myelin–associated glycoprotein serum levels were significantly higher in autistic children with than those without such history ($P < .05$). In conclusion, autism could be, in part, one of the pediatric autoimmune neuropsychiatric disorders. Further studies are warranted to shed light on the etiopathogenic role of anti-myelin–associated glycoprotein antibodies and the role of immunotherapy in autism.

Keywords: anti-myelin–associated glycoprotein antibodies; autism; autoimmunity

Autism, a severe neurodevelopmental disorder, is characterized by impairment in verbal and nonverbal communication, imagination, and reciprocal social interaction.[1] Medical and psychiatric co-occurrences with autism include sleep disorders, epilepsy, food intolerance, gastrointestinal dysfunction, mood disorder, and aggressive and self-injurious behaviors.[2] The prevalence of autism has surged in recent years.[3] Contrary to notion in vogue in the past, autism is not influenced by parents. The etiology of autism is not well understood. Genetic factors play a significant role, but what is actually inherited is not entirely clear. Autism may occur as a result of exposure to environmental factors in the presence of genetic predisposition.[1]

A possible role of abnormalities in immune system in pathogenesis of some neurologic disorders, including autism, was recently postulated. Autoimmunity to central nervous system is the commonest of these abnormalities.[4,5] The most important clue for the possible etiopathogenic role of autoimmunity in autism is the presence of brain-specific autoantibodies in many autistic children.[6,7] Immunotherapy should be initiated when a clue of autoimmunity is evidenced by the presence of autoantibodies to central nervous system.[8] Other clues for the occurrence of autoimmunity in autism include the increase of autoimmune disorders among autistic families.[9] Also, there is a strong association between autism and the major histocompatibility complex for the null allele of complement 4B in class III region. This results in low production of complement 4B protein leading to repeated infections, which play an important role in the development of autoimmunity.[10,11] In addition, in some autistic children, there is an imbalance of T-helper 1/ T-helper 2 subsets toward T-helper 2, which are responsible for allergic response and production of antibodies.[5] Furthermore, a new form of inflammatory bowel disease (ileocolonic lymphonodular hyperplasia or autistic enterocolitis) was reported in some autistic children, leading researchers to suspect a gut–brain connection in autism.[12]

Myelin-associated glycoprotein, a minor myelin protein, is located in the most periaxonal oligodendrocytes processes.[13] It controls neurofilament phosphorylation and, hence, controls the axon caliber, which is crucial for efficient impulse transmission.[14] In contrast to mature central nervous system, myelin-associated glycoprotein promotes regeneration of young neurons.[15] Circulating anti-myelin–associated

From the Departments of Pediatrics (GAM, ZAE-S, MFE-S) and Clinical Pathology (MMAE-A), Faculty of Medicine, Ain Shams University, Cairo, Egypt.

Address correspondence to: Gehan Ahmed Mostafa, MD, 9 Ahmed El-Samman Street off Makram Ebaid, Nasr City, Cairo, Egypt 11511; e-mail: hafezg@softhome.net.

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glycoprotein antibodies may play an etiopathogenic role in some autoimmune disorders as autoimmune chronic demyelinating neuropathy, which is characterized by a distal and symmetric, mostly sensory neuropathy.[16] Furthermore, complement-mediated demyelination of nerves has been induced experimentally in animals by intranerval or systemic injection of anti-myelin–associated glycoprotein antibodies.[17]

Autism is a cognitive disorder that includes among its distinguishing symptoms a deficit in the pragmatic component of language.[18] Demyelination may be responsible for cognitive dysfunction (memory, attention, language, concept formation, problem solving, executive and visuospatial dysfunctions).[19] The severity and rate of myelin breakdown correlates positively to cognitive dysfunction.[20]

Because autism may be one of the pediatric autoimmune neuropsychiatric disorders, this study was conducted to investigate the frequency of serum anti-myelin–associated glycoprotein antibodies, as index for autoimmunity to brain, in autistic children. The relationship between these antibodies and family history of autoimmunity was also studied.

Methods

Study Population

This case-control study was conduced on 64 children, of whom 32 had classic-onset autism and 32 were healthy children, over a period of 1 year from the beginning of December 2006 to the end of November 2007. The local Ethical Committee of the Faculty of Medicine, Ain Shams University, approved this study. In addition, an informed written consent of participation in the study was signed by the parents or the legal guardians of the studied subjects.

The autistic group comprised 32 children (25 boys and 7 girls) recruited from the Outpatients and Psychiatric Pediatric Clinics, Faculty of Medicine, Ain Shams University, Cairo, Egypt. Patients were fulfilling the criteria for the diagnosis of autism according to the Diagnostic and Statistical Manual of Mental Disorders-IV criteria for research.[21] Their ages ranged between 3 and 8 years (median [interquartile range] = 4 [2] years). Patients who had associated neurological diseases (such as cerebral palsy, tuberous sclerosis, and so on) and metabolic disorders (eg, phenylketonuria) were excluded from the study.

The control group comprised 32 age- and sex-matched apparently healthy children (25 boys and 7 girls) who had no clinical findings suggesting immunological or neuropsychiatric disorders. Their ages ranged between 3 and 8 years (median [interquartile range] = 4 [2.75] years).

Study Measurements

Clinical evaluation of autistic patients. This was based on clinical history taking from caregivers, clinical examination, and neuropsychiatric assessment. In addition, disease severity was assessed using Childhood Autism Rating Scale,[22] which rates the child on a scale from 1 to 4 in each of 15 areas (relating to people; emotional response; imitation; body use; object use; listening response; fear or nervousness; verbal communication; nonverbal communication; activity level; level and consistency of intellectual response; adaptation to change; visual response; taste, smell, and touch response and general impressions). According to the scale, children who have scored 30-36 have mild to moderate autism (n = 18, all were males), whereas those with scores ranged between 37 and 60 points have a severe degree of autism (n = 14; 7 were males and 7 were females).

In addition, family history of autoimmune diseases in controls and autistic subjects were ascertained in an identical manner but not in a blinded manner. Parents were asked to fill out a questionnaire regarding which first- or second-degree relatives had received a diagnosis of specified autoimmune disorders. The questionnaire was formulated with the assistance of 2 experienced immunologists. A list of autoimmune diseases with descriptions was provided. There was a verification of the diagnosis of autoimmune diseases by means of medical record review or direct clinical examination.

Assessment of mental age of autistic children. This was done by using Stanford-Binet test[23] to calculate the intelligence quotient. This test is used to measure the child's cognitive abilities. It is suitable for children from 2 to 16 years of age. The test has 2 items, the verbal and the performance, and the test item is chosen according to the child's abilities. Intelligence quotient was calculated by dividing the mental age by the chronological age multiplied by 100. Subnormal intellectual function is diagnosed when intelligence quotient is below 70.

Measurement of regional brain electrical activity of autistic children. This was done by using sleep-deprived interictal electroencephalogram.

Assessment of serum anti-myelin–associated glycoprotein antibodies. This assay uses the quantitative sandwich-type enzyme immunoassay technique (Buhlmann Laboratories AG, Baselstrasse 55, CH-4124 Schonenbuch, Switzerland). The samples were run in a blinded manner and they were run together, in parallel on the same run with the same internal standards. Highly purified myelin-associated glycoprotein from human brain has been precoated into a microtiter plate. Calibrators and patient sera were incubated in the microtiter wells, and any anti-myelin–associated glycoprotein autoantibodies present were bound by the immobilized human myelin-associated glycoprotein. After washing away any unbound substances, horseradish peroxidase–labeled antibodies against human immunoglobulin M were added to the wells and incubated. After a wash step, the substrate solution containing tetramethylbenzidine was added. The color developed in proportion to the amount of anti-myelin–associated glycoprotein autoantibodies bound in the initial step was stopped by adding an acidic stop solution. The intensity of the color absorbance was measured in a microtiter plate reader at a wavelength of 450 nm.[24]

Statistical Analysis

The results were analyzed by commercially available software package (Statview, Abacus concepts, Inc., Berkley, California). The data were nonparametric, thus, they were presented as median and interquartile range, which are between the 25th and 75th percentiles. Mann-Whitney test was used for comparison between these data. The χ^2 test was used for comparison between qualitative variables of the studied groups. Spearman's rank correlation coefficient "r" was used to determine the relationship between different variables. For all tests, a probability (P) of less than .05 was considered significant. Because data distribution was nonparametric, patients were considered to have anti-myelin–associated glycoprotein positivity if the levels of these antibodies were above the calculated highest cutoff value (the 95th percentile of the control values which was 1313.5 Buhlmann titre unit).

Results

Autistic children had significantly higher levels of serum anti-myelin–associated glycoprotein antibodies than controls. In addition, autistic children with severe disease had significantly higher levels of serum anti-myelin–associated glycoprotein antibodies than those with mild to moderate autism (Table 1). Furthermore, female autistic children "all had severe autism" had significantly higher levels of serum anti-myelin–associated glycoprotein antibodies than male autistic patients "72% had mild to moderate autism and 28% had severe autism" (median [interquartile range] = 4300 [2000] Buhlmann titre unit and 1400 [1320] Buhlmann titre unit, respectively $Z = 2.4$, $P < .05$).

Anti-myelin–associated glycoprotein positivity was elicited in 62.5% (20/32) of all autistic children, in 50% (9/18) of patients with mild to moderate autism, and in 78.5% (11/14) of those with severe autism.

Only 1 control child (1/32: 3.25%) had a value of serum anti-myelin–associated glycoprotein (1320 Buhlmann titre unit) above the calculated highest cutoff value (1313.5 Buhlmann titre unit). Fortunately, the lowest value of serum anti-myelin–associated glycoprotein in autistic patients who were seropositive for this antibody was 1400 Buhlmann titre unit. Thus, all anti-myelin–associated glycoprotein seropositive patients had serum values of this antibody above that value of the control child who had serum anti-myelin–associated glycoprotein above the calculated highest cutoff value.

Fifty percent (16/32) of the studied autistic children had a first- or a second-degree relative with an autoimmune disease (rheumatoid arthritis in 10 patients, insulin-dependent diabetes mellitus in 3 patients, systemic lupus erythematosus in 2 patients, and rheumatic fever in 1 patient). Of the 16 patients with positive family history of autoimmunity, 6 had mild to moderate autism and 10 had severe disease. In addition, Of the 16 autistic children with positive family history of autoimmune diseases, 6 had a mother with an autoimmune disease (4 had rheumatoid arthritis, 1 had systemic lupus erythematosus, and 1 had insulin-dependent diabetes mellitus). On the other hand, positive family history of autoimmune diseases was found in 3 of the studied 32 healthy children "9.4%" (rheumatoid arthritis in 2 children and insulin-dependent diabetes mellitus in 1 child). The frequency of autoimmune diseases in families of autistic children was significantly higher than that of normal children ($\chi^2 = 12.6$; $P < .001$).

Autistic children with positive family history of autoimmune diseases had significantly higher serum levels of anti-myelin–associated glycoprotein antibodies than those without such history (median [interquartile range] = 2850 [2875] Buhlmann titre unit and 1290 [1052.5] Buhlmann titre unit, respectively; $Z = 2.56$; $P < .05$). In addition, the former group had significantly higher percent positivity of anti-myelin–associated glycoprotein antibodies than the latter group (Figure 1).

Of the studied 32 autistic children, 17 (53.1%) had subnormal intellectual function (intelligence quotient

Table 1. Serum Levels of Anti-Myelin–Associated Glycoprotein Antibodies in Autistic and Healthy Children and Its Relation to Autistic Severity

Studied Subjects	Anti-MAG Antibodies (BTU) Median (IQR)	Z (P)
Autism	2100 (1995)	6.35 (< .001)
Controls	1138 (87.5)	
Mild to moderate autism	1345 (872.5)	3.16 (< .05)
Severe autism	3400 (2152.5)	

Anti-MAG, anti-myelin–associated glycoprotein, BTU, Buhlmann titre unit; IQR, interquartile range.

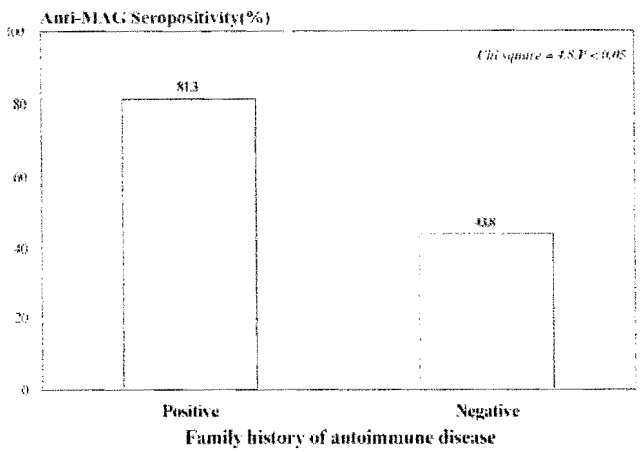

Figure 1. Anti-myelin–associated glycoprotein antibodies positivity in autistic patients with and without family history of autoimmune diseases. Anti-MAG, anti-myelin–associated glycoprotein.

Table 2. Serum levels of Anti-Myelin–Associated Glycoprotein Antibodies in Relation to Intellectual Function and Electroencephalogram Abnormalities in Autistic Children

Autistic Children	Anti-MAG Anitbodies (BTU) Median (IQR)	Z (*P*)
MR (n = 17)	2900 (2100)	3.6 (< .05)
No MR (n = 15)	1290 (710)	
Abnormal EEG (n = 12)	3150 (2125)	2.3 (< .05)
Normal EEG (n = 20)	1345 (970)	

Anti-MAG, anti-mylin–associated glycoprotein; BTU, Buhlmann titre unit; EEG, electroencephalogram; IQR, interquartile range; MR, mental retardation.

below 70), 12 had mild mental retardation (intelligence quotient = 50-69), and 5 had moderate mental retardation (intelligence quotient = 35-49). Of the 17 retarded patients, 12 had severe autism and 5 had mild to moderate autism. Electroencephalogram abnormalities were found in 37.5% (12/32) of autistic children (9 had severe autism and 3 had mild to moderate autism). These abnormalities included focal epileptogenic activity in frontal or temporal lobes in 8 patients, generalized epileptogenic activity in 2 patients and immature background in the remaining 2 patients.

Patients with subnormal intellectual function and electroencephalogram abnormalities had significantly higher serum levels of anti-myelin–associated glycoprotein antibodies than autistic patients without such manifestations (Table 2).

Serum anti-myelin–associated glycoprotein antibodies levels did not correlate significantly to the age of autistic children ($P > .05$).

An 8-year-old female child with severe autism had a very high serum anti-myelin–associated glycoprotein level (19 500 Buhlmann titre unit), which was an extreme value (more than 3 interquartile range). The serum sample of this patient was analyzed twice, the first result was 19 200 Buhlmann titre unit and the second result was 19 800 Buhlmann titre unit, an average value between these 2 values was calculated. This patient had abnormal electroencephalogram in the form of focal epileptogenic activity in the left frontal lobe and moderate mental retardation (intelligence quotient = 42). She also had a mother with rheumatoid arthritis.

Discussion

Etiology of autism presents many challenging issues, and it has become an area of a significant controversy.[25] Autism may, in part, involve autoimmune pathogenesis.[5] In our series, autistic children had significantly higher serum levels of anti-myelin–associated glycoprotein antibodies, detected by enzyme immunoassay, than healthy controls. In addition, anti-myelin–associated glycoprotein positivity was encountered in 62.5% (20/32) of autistic children.

We could not trace data in the literature concerning anti-myelin–associated glycoprotein positivity in autistic children to compare our results. Anti-myelin–associated glycoprotein antibodies are commonly found in the sera of patients with demyelinating sensorimotor neuropathy.[16] Enzyme immunoassay method of serum measurement of anti-myelin–associated glycoprotein antibodies in these patients was reported to have a higher sensitivity (97.5%) than Western blot (72.5%) and immunofluorescent assay (92.5%) methods. Enzyme immunoassay detected low titers of anti-myelin–associated glycoprotein immunoglobulin M antibodies in suspected patients sera (negative by other methods).[26] The presence of brain autoantibodies to another myelin protein (myelin basic protein), in some autistic children, has been observed to be associated to viral serology as measles and herpes virus 6[27] and *Chlamydia pneumoniae* and streptococcal M protein.[6]

In the present work, patients with severe autism had significantly higher serum anti-myelin–associated glycoprotein autoantibodies levels than patients with mild to moderate autism. This finding means that the extent of the elevation of serum anti-myelin–associated glycoprotein autoantibodies was closely linked to disease severity of autism assessed by Childhood Autism Rating Scale.

Furthermore, female autistic patients had significantly higher serum anti-myelin–associated glycoprotein than male autistic ones. These results could be explained by the fact that all the 7 female patients had severe autism, whereas only 28% of the studied male patients had severe autism. Thus, the relationship between anti-myelin–associated glycoprotein antibodies and the severity of autism is possibly a causal one, in which these autoantibodies might be playing a role in the pathogenesis of brain damage, the extent of which will determine the clinical severity of autism.

To further understand if autoimmunity could play a role in autism, we studied the frequency of autoimmune diseases in families of autistic patients in comparison to healthy children. The frequency of autoimmune disease among families of the former group (50%) was significantly higher than that of the latter group (9.4%). In addition, 18.8% (6/32) of autistic patients had a mother with an autoimmune disease.

Previous research had also found an increased frequency of autoimmunity in families of autistic children compared with those of healthy and autoimmune control subjects.[9] Family history of autoimmune diseases was reported by some inyestigators[28] in 46% of autistic children. They also reported that as the number of family members with autoimmune disorders increased from 1 to 3, the risk of autism was greater with an odds ratio that increased from 1.9 to 5.5, respectively. Thus, this may be

an outstanding feature among autistic patients that points to their autoimmune background; the target in their case being the developing brain.

In our series, the finding of the increased frequency of autoimmune diseases in the mothers of children with autism (6/32: 18.75%) is also in agreement with that of Comi et al[28] who reported an autoimmune disease in 16% of the mothers of their studied autistic subjects. The high rate of autoimmune disease in the mothers of the children with autism could also suggest that an autoimmune process exists in the mothers that is targeted toward the developing fetus in utero. Although this would be more consistent with the female preponderance in autoimmune disorders, it does not explain the high male-to-female ratio observed in autism.[9]

The current study revealed a more significant increase of serum levels and percent positivity of anti-myelin–associated glycoprotein antibodies in autistic patients with family history of autoimmunity than those without such history. This finding suggests that, in some families, immune dysfunction, perhaps induced by certain environmental triggers, could express itself in the form of autism in one of its offsprings.

In the present study, autistic children with mental retardation and those with abnormal electroencephalogram had significantly higher serum levels of anti-myelin–associated glycoprotein antibodies than patients without such abnormalities. These results denoted that autoimmunity to brain could induce brain damage in autistic children with subsequent decrease of mental power and increase in electroencephalogram abnormalities.

To date, a definitive relationship between autism and autoimmunity has not been fully established. On the basis of the preliminary results reported in this study, however, there seems to be a suggestive evidence in support of autoimmune contributions to the pathophysiology of autism in some cases. Additional investigation designed to expand on these data is warranted.

Autoimmune reaction to myelin in autism, in genetically susceptible individuals, might be trigged by cross-reacting antigens in the environment. These environmental antigens include food allergies to certain peptides as gliadin, cow's milk protein and soy,[29] infectious agents,[5] heavy metals exposure such as mercury,[30] and *Hevea brasiliensis* proteins in natural rubber latex.[31] Cross-reacting antigens in the environment may increase adhesion molecules on brain endothelial cells. Preexisting autoreactive T-cells transmigrate across the blood–brain barrier and induce activation of local antigen-presenting cells with production of cytokines that induce oligodendrocyte damage and demyelination. These events result in release of antigens from neurofilaments that enter the circulation resulting in formation of plasma cells, which produce antibodies against neuron-specific antigens. These antibodies may cross the blood–brain barrier and combine with brain tissue antigens forming immune complexes, thus further damaging the neurological tissue.[6]

Despite that the origin of autoimmunity in autism is unknown, immune-related genes on major histocompatibility complex, which have been associated with some autoimmune diseases, may play a central role in the development of autoimmunity in autism (eg, human leukocyte antigen-DRB1 and complement 4B null alleles).[10,11]

Therapy in patients with anti-myelin–associated glycoprotein neuropathy is directed at reducing the antibody concentration, blocking the effector mechanisms and depleting the monoclonal B cells. The recent availability of a monoclonal antibody suppressing B-cell clones, which is not myelosuppressive and does not cause secondary malignancies, allows for early targeted intervention.[16] Preliminary results suggest that this new line of therapy is well tolerated and is promising in treatment of patients with anti-myelin–associated glycoprotein polyneuropathy.[32,33] Therefore, studies concerning the role of this therapy in amelioration of autistic manifestations in anti-myelin–associated glycoprotein positive autistic patients are warranted.

In conclusion, autism may be, in part, one of the pediatric autoimmune neuropsychiatric disorders. Further studies are warranted to shed light on the etiopathogenic role of anti-myelin–associated glycoprotein antibodies in autism and the role of immunotherapy in anti-myelin–associated glycoprotein positive autistic patients.

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