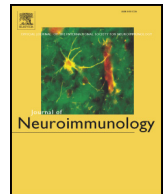




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The possible relationship between allergic manifestations and elevated serum levels of brain specific auto-antibodies in autistic children^{☆,☆☆}

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ABSTRACT

Etiology of autism has become an area of a significant controversy. Allergy induced autism is an area of research wherein immune responses to some allergens may play a pathogenic role in autism. Allergy may induce the production of brain specific auto-antibodies in a subgroup of autistic children. We are the first to investigate the possible link between allergic manifestations and serum levels of both anti-myelin basic protein (anti-MBP) and anti-myelin associated glycoprotein (anti-MAG) brain-specific auto-antibodies, which were measured by ELISA method, in 42 autistic children in comparison to 42 healthy-matched children. Allergic manifestations (bronchial asthma, atopic dermatitis and/or allergic rhinitis) were found in 47.6% of autistic patients. Increased serum levels of anti-MBP and anti-MAG auto-antibodies were found in 57.1% and 66.7%, respectively of autistic children. In addition, 78.5% of autistic children had increased serum levels of both anti-MBP and/or anti-MAG auto-antibodies. Autistic patients with allergic manifestations had significantly higher serum levels of anti-MBP and anti-MAG auto-antibodies than those without these manifestations ($P < 0.001$ and $P = 0.001$, respectively). In conclusion, allergy may be a contributing factor to the increased serum levels of anti-MBP and anti-MAG auto-antibodies in some autistic children. Indeed, we need to know more about the links between allergy, immune system and brain in autism for finding new therapeutic modalities in autism.

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1. Introduction

Some autistic children may have an imbalance of the T-helper (Th) 1/Th2 lymphocytes toward Th2 (Cohly and Panja, 2005). Th2 cells are responsible for the allergic response and the production of antibodies. This may predispose autistic children to allergic and autoimmune disorders (Jepson, 2003).

Autoimmunity may have a role in the pathogenesis of autism in a subgroup of patients (Cohly and Panja, 2005). This may be indicated by the presence of brain-specific auto-antibodies in some autistic children (Singh et al., 1993, 1997, 1998; Singh and Rivas, 2004; Mostafa et al., 2008a, 2008b, 2008c; Mostafa and Al-Ayadhi, 2011a, 2011b; Mostafa and Al-Ayadhi, 2012). There is also an increase in the frequency of autoimmune disorders among autistic families (Comi et al., 1999; Sweeten et al., 2003; Atladóttir et al., 2009; Mostafa and Kitchener, 2009; Mostafa and Shehab, 2010; Mostafa et al., 2010a, 2010b). In spite of the fact that the origins of autoimmunity in autism are unknown, the major histocompatibility complex genes and their products might be

involved (Warren et al., 1991; Odell et al., 2005; Mostafa and Shehab, 2010; Mostafa et al., 2013).

Allergy induced autism is an area of research wherein immune responses to some proteins may play a causal role in autism (Dochniak, 2007). A marked improvement in the behavioral symptoms of autistic patients after a period of 8 weeks on an elimination milk and wheat diet with worsening of autistic symptoms after their reconsumption has been reported in some autistic children (Lucarelli et al., 1995). In addition, immune response to *Hevea brasiliensis* (Hev-b) proteins in natural rubber latex (NRL) may induce immunoglobulin E (IgE) secreting lymphocytes to form antibodies that target some endogenous (e.g., brain) and exogenous (e.g., food stuff) proteins through cross react mechanism (Dochniak, 2007).

This study was the first to investigate the possible link between the allergic manifestations and serum levels of both anti-myelin basic protein (anti-MBP) and anti-myelin associated glycoprotein (anti-MAG) brain-specific auto-antibodies, as possible indicators of autoimmunity to CNS, in autistic children.

2. Materials and methods

2.1. Study population

This cross-sectional study was conducted on 42 children with autism. They were recruited from the Pediatric Neuropsychiatric Clinic, Children's

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Hospital, Faculty of Medicine of Ain Shams University, Cairo, Egypt, during their follow up visits. Patients were fulfilling the criteria of the diagnosis of autism according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders ([The American Psychiatric Association, 1994](#)). The autistic group comprised 32 males and 10 females. Their ages ranged between 6 and 11 years (mean $\pm$ SD = 8.12 ± 2.03 years). Patients who had associated neurological diseases (such as cerebral palsy and tuberous sclerosis) and metabolic disorders (e.g. Phenylketonuria) were excluded from the study.

The control group comprised 42 age- and sex-matched apparently healthy children. They included 33 males and 9 females. Their ages ranged between 6 and 11 years (mean $\pm$ SD = 8.69 ± 2.19 years). They were the healthy siblings of the children who attended the Outpatients Clinic, Children's Hospital, Faculty of Medicine, Ain Shams University, Cairo, Egypt, because of having a minor illness (e.g. common cold, tonsillitis and acute bronchitis). The control children were not related to the children with autism, and demonstrated no clinical findings suggestive of immunological, allergic or neuropsychiatric disorders.

The local Ethical Committee of the Faculty of Medicine, Ain Shams University, Cairo, Egypt, 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.

2.2. Study measurements

2.2.1. Clinical evaluation of the autistic patients

This was based on clinical history taken from caregivers, clinical examination and neuropsychiatric assessment. In addition, the degree of the disease severity was assessed by using the Childhood Autism Rating Scale (CARS) ([Schopler et al., 1986](#)) which rates the child on a scale from one to four in each of fifteen areas (relating to people; emotional response; imitation; body use; object use; listening response; fear or nervousness; verbal communication; non-verbal 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 ($n = 16$), while those with scores ranging between 37 and 60 points have a severe degree of autism ($n = 26$).

In addition, special emphasis was done on the study of the allergic manifestations in autistic children (e.g., bronchial asthma, atopic dermatitis and allergic rhinitis). The diagnosis of bronchial asthma was based on the clinical symptoms and signs of episodic wheezing, chest tightness, dyspnea and nocturnal symptoms that improved at least partially after bronchodilator therapy. In addition, a 20% or more of improvement of prebronchodilator peak expiratory flow rate (PEFR) after inhalation of a bronchodilator was used in the diagnosis of asthma. Assessment of asthma severity (mild intermittent, mild persistent, moderate and severe persistent) was done ([National Heart, Lung and Blood Institute, 2010](#)). Diagnosis of atopic dermatitis (AD) was based on the standardized diagnostic criteria ([Hanifin and Rajka, 1980](#)) and its severity (mild, moderate and severe) was determined by objective Scoring Allergic Dermatitis (obj-SCORAD) index system ([Kunz et al., 1997](#)). The diagnosis of allergic rhinitis was based on the occurrence of nasal itching, sneezing, watery discharge and nasal obstruction after exposure of the membranes of the nose to allergens ([Bousquet et al., 2001](#)).

2.2.2. Measurement of serum anti-myelin basic protein (anti-MBP) antibodies

This was done by using ELISA kit that allows for the specific measurement of human anti-MBP (Diagnostic Systems, Texas, USA). To increase accuracy, all samples were analyzed twice in two independent experiments to assess inter-assay variations and to ensure reproducibility of the observed results. No significant cross-reactivity or interference was observed ($P > 0.05$).

2.2.3. Assessment of serum anti-myelin associated glycoprotein (anti-MAG) antibodies

This assay employs the quantitative sandwich-type enzyme immunoassay (EIA) technique (Buhlmann Laboratories AG, Baselstrasse 55, CH-4124 Schönenbuch, Switzerland). To increase accuracy, all samples were analyzed twice in two independent experiments to assess the interassay variations and to ensure reproducibility of the observed results. No significant cross-reactivity or interference was observed ($P > 0.05$).

2.3. Statistical analysis

The results were analyzed by the commercially available software package (Statview, Abacus Concepts, Inc., Berkeley, CA, USA). The parametric data were presented as mean and standard deviation (SD). In addition, non-parametric data were presented as median and interquartile range (IQR), which is the difference between the 75th and 25th percentiles. Student's *t*-test was used for comparison of parametric data, while Mann–Whitney *U*-test was used for comparison of non-parametric data. Chi-square test was used for comparison between qualitative variables of the studied groups. Spearman's rho correlation coefficient “*r*” was used to determine the relationship between different variables. For all tests, a probability (*P*) of less than 0.05 was considered significant. Patients were considered to have elevated serum anti-MBP antibodies if their levels were above the highest cut-off values (209.7 pg/ml) which were the 95th percentiles of serum anti-MBP antibody levels of healthy controls as the distribution of the data was non-parametric. On the other hand, patients were considered to have elevated serum anti-MAG antibodies if their levels were more than 2SD above the mean value of serum anti-MAG antibodies of healthy controls which was 2156.06 Buhlmann titre unit (BTU) as the distribution of the data was parametric.

3. Results

3.1. The frequency of allergic manifestations in autistic children

Twenty autistic children (47.6%) had one or more allergic diseases. Seven autistic patients had bronchial asthma (mild intermittent in 2, mild persistent in 3 and moderate persistent in the remaining 2 patients). Three autistic patients had AD (mild in one patient and moderate in the remaining 2 patients). Two autistic patients had allergic rhinitis. Two autistic patients had AD of moderate severity and allergic rhinitis. Two autistic patients had mild persistent asthma and moderate AD. The remaining four autistic patients had bronchial asthma (mild intermittent in one patient, moderate persistent in 2 patients and severe persistent the remaining patient), AD (mild in one patient, moderate in 2 patients and severe in the remaining patient) and allergic rhinitis.

Patients with severe autism had significantly higher frequency of allergic manifestations (61.5%; 16/26) than children with mild to moderate autism (25%; 4/16), $P = 0.02$.

3.2. Serum levels of anti-MBP and anti-MAG auto-antibodies in autistic children and healthy children and their relation to the degree of the severity of autism

Autistic children, as a whole, had significantly higher serum levels of anti-MBP and anti-MAG auto-antibodies than healthy children, $P < 0.001$ and $P < 0.001$, respectively ([Tables 1 and 2](#)). Similarly, autistic children with and without allergic manifestations had significantly higher serum levels of anti-MBP ($P < 0.001$ and $P = 0.001$, respectively) and anti-MAG auto-antibodies ($P < 0.001$ and $P < 0.01$, respectively) than healthy children.

According to the highest cut-off values of serum anti-MBP and anti-MAG auto-antibodies, increased serum levels were found in 57.1% (24/42) and 66.7% (28/42), respectively of autistic patients. In

addition, 78.5% (33/42) of autistic children had increased serum levels of anti-MBP and/or anti-MAG auto-antibodies.

Autistic patients with increased serum levels of anti-MBP auto-antibodies had significantly higher frequency of seropositivity of anti-MAG auto-antibodies (79.2%; 19/24) than autistic patients with normal serum levels of anti-MBP auto-antibodies (50%; 9/18), $P = 0.049$.

Patients with severe autism had significantly higher serum anti-MBP and anti-MAG auto-antibodies than children with mild to moderate autism, $P = 0.047$ and $P < 0.001$, respectively (Tables 1 and 2).

Male and female autistic children had comparable values of serum anti-MBP and anti-MAG auto-antibodies ($P = 0.4$ and $P = 0.6$, respectively). In addition, serum anti-MBP and anti-MAG auto-antibodies had no significant correlations with the age of the children with autism ($P = 0.89$ and $P = 0.12$, respectively).

3.3. The relationship between the allergic manifestations and serum levels of both anti-MBP and anti-MAG auto-antibodies in autistic children

Autistic patients with allergic manifestations had significantly higher serum levels of anti-MBP auto-antibodies [median (IQR) = 290 (458) pg/ml] than autistic patients without such manifestations [median (IQR) = 189 (59) pg/ml], $P < 0.001$. Similarly, autistic children with allergic manifestations had significantly higher serum levels of anti-MAG auto-antibodies (mean $\pm$ SD = 2855.45 $\pm$ 656.62 BTU) than autistic children without such manifestations (mean $\pm$ SD = 2117.50 $\pm$ 386.05 BTU), $P < 0.001$.

In addition, autistic patients with allergic manifestations had significantly higher frequency of seropositivity of both anti-MBP and anti-MAG auto-antibodies [85% (17/20) and 95% (19/20), respectively] than autistic patients without allergic manifestations [31.8% (7/22) and 40.9% (9/22), respectively], $P < 0.001$ and $P < 0.001$, respectively (Table 3).

4. Discussion

Immune response to some allergens may play a pathogenic role in some patients with autism through the induction of an autoimmune reaction to CNS (Cohly and Panja, 2005). In our series, 47.9% of autistic children had one or more allergic diseases. Two studies reported allergic manifestations in 45% and 52% of autistic children which was significantly higher than that in their non-autistic control children (10% in both studies) (Mostafa et al., 2008b, 2008c). The main reason behind the increased frequency of allergic diseases in autistic children may be the imbalance of Th1/Th2 toward Th2 cells (Cohly and Panja, 2005). Th2 is the main effector cell in the pathogenesis of allergy through the induction of hyper IgE production and eosinophil survival by Th2-type cytokines such as IL-4 and 5 (Akidis, 2006).

This study revealed a significant association between the presence of one or more of allergic manifestations and the severity of autism. This was indicated by the significant increase in the frequency of allergic manifestations in patients with severe autism (61.5%) than children with mild to moderate autism (25%), $P = 0.02$. Similarly, in another study, patients with severe autism had significantly higher frequency of allergic manifestations than children with mild to moderate autism (Mostafa et al., 2008c). The causal role of allergy in autism may be enforced by worsening

Table 1

Serum levels of anti-MBP auto-antibodies in autistic children and their relation to the severity of autism.

	Serum anti-MBP antibodies (pg/ml) Median (IQR)	Z (P-value)
Healthy children (n = 42)	97 (63)	6.65
Patients with autism (n = 42)	227 (133)	(<0.001)
Patients with mild to moderate autism (n = 16)	195 (50)	1.98
Patients with severe autism (n = 26)	270 (330)	(0.047)

Anti-MBP, anti-myelin basic protein antibodies.

Table 2

Serum levels of anti-MAG auto-antibodies in autistic children and their relation to the severity of autism.

	Serum anti-MAG antibodies (BTU) Mean $\pm$ SD	t (P-value)
Healthy children (n = 42)	1285.9 $\pm$ 435.1	9.87
Patients with autism (n = 42)	2468.9 $\pm$ 644.4	(<0.001)
Patients with mild to moderate autism (n = 16)	2163.6 $\pm$ 360.3	2.9
Patients with severe autism (n = 26)	2656.8 $\pm$ 711.9	(0.005)

Anti-MAG, anti-myelin associated glycoprotein antibodies.

of the disease manifestations after consumption of some food as milk and wheat (Millward et al., 2004) and exposure to NRL (Dochniak, 2007).

Autoimmunity to CNS may have a pathogenic role in autism (Cohly and Panja, 2005). This may be indicated by the presence of brain-specific auto-antibodies in some autistic children (Singh et al., 1993, 1997, 1998; Singh and Rivas, 2004; Mostafa et al., 2008a, 2008b, 2008c; Mostafa and Al-Ayadhi, 2011a, 2011b). In our series, autistic children had significantly higher serum levels of anti-MBP auto-antibodies than healthy controls, $P < 0.001$. Increased serum levels of anti-MBP auto-antibodies were found in 57.1% of autistic patients. A previous study reported seropositivity of anti-MBP protein auto-antibodies in 58% of autistic children (Singh et al., 1993). A recent study reported increased serum levels of anti-MBP auto-antibodies in 80% of autistic children (Mostafa and Al-Ayadhi, 2011b). These antibodies have been observed to be associated to viral serology as measles and herpes virus 6 (Singh et al., 1998), *Chlamydia pneumoniae* and streptococcal M protein (Vojdani et al., 2002).

In this study, autistic children had significantly higher serum levels of anti-MAG auto-antibodies than healthy children, $P < 0.001$. Increased serum levels of anti-MAG auto-antibodies were found in 66.7% of autistic patients. A previous study reported anti-MAG seropositivity in 62.5% of autistic children (Mostafa et al., 2008a). In addition, 78.5% of autistic children had increased serum levels of anti-MBP and/or anti-MAG auto-antibodies. This may denote the importance of measurement of multiple brain specific auto-antibodies in autism.

MBP is a major myelin protein that is believed to be important in the process of myelination of nerves in the central nervous system. Interest in MBP has centered on its role in demyelinating diseases, particularly multiple sclerosis (MS). Several studies have shown a role for antibodies against MBP in the pathogenesis of MS (Angelucci et al., 2005; Hedegaard et al., 2009). MAG is a minor myelin protein that is located in most periaxonal oligodendrocyte processes (Aboul-Enein et al., 2003). It controls neurofilament phosphorylation and hence, controls the axon caliber which is crucial for efficient impulse transmission (Lunn et al., 2002). In contrast to mature CNS, MAG promotes regeneration of young neurons (Cai et al., 2001). Circulating anti-MAG antibodies may play an etiopathogenic role in some autoimmune disorders as autoimmune chronic demyelinating neuropathy (Steck et al., 2006).

Table 3

The relationship between the presence of allergic manifestations and serum levels of both anti-MBP and anti-MAG auto-antibodies in autistic children.

Patients with autism (n = 42)	Patients without allergic manifestations (n = 22)	Patients with allergic manifestations (n = 20)	χ^2 (P-value)
Normal serum anti-MBP (n = 18)	15 (68.2%)	3 (15%)	15.22
Elevated serum anti-MBP (n = 24)	7 (31.8%)	17 (85%)	(<0.001)
Normal serum anti-MAG (n = 14)	13 (59.1%)	1 (5%)	13.79
Elevated serum anti-MAG (n = 28)	9 (40.9%)	19 (95%)	(0.001)

Anti-MBP, anti-myelin basic protein antibodies. Anti-MAG, anti-myelin associated glycoprotein antibodies.

In the present work, patients with severe autism had significantly higher serum anti-MBP and anti-MAG auto-antibodies than children with mild to moderate autism, $P = 0.047$ and $P < 0.001$, respectively. These results may indicate that the extent of the elevation of serum anti-MBP and anti-MAG auto-antibodies were possibly linked to the degree of the disease severity assessed by CARS. Further studies, on a large scale, are warranted to reveal if these auto-antibodies have a role in the pathogenesis of autism.

In the current study, autistic children with and without allergic manifestations had significantly higher serum levels of anti-MBP ($P < 0.001$ and $P = 0.001$, respectively) and anti-MAG auto-antibodies ($P < 0.001$ and $P < 0.01$, respectively) than healthy children. These results indicated that autistic children, whether allergic or not, had significantly higher serum levels of both anti-MBP and anti-MAG auto-antibodies than healthy children.

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 the induction of autoimmune reaction against brain in some patients with autism. Additional investigation designed to expand on these data is warranted. Therapy in patients who are seropositive for serum auto-antibodies 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 (Steck et al., 2006). Preliminary results suggest that this line of therapy is well tolerated and is promising in the treatment of some patients (Renaud et al., 2006; Benedetti et al., 2007). Thus, we suggest that further studies with a larger subject population should be conducted to investigate the possible role of this therapy in autistic patients who have increased serum levels of anti-MBP and anti-MAG auto-antibodies.

In this study, we have tried to find a possible link between the presence of allergic manifestations and the elevated serum levels of anti-MBP and anti-MAG auto-antibodies in autism. Autistic patients with allergic manifestations had significantly higher serum levels of anti-MBP and anti-MAG auto-antibodies than autistic patients without such manifestations, $P < 0.001$ and $P < 0.001$, respectively. In addition, there was a significant positive association between the presence of one or more of allergic manifestations and the seropositivity of both anti-MBP and anti-MAG auto-antibodies in autistic children as 85% and 95% of autistic patients with allergic manifestations had concomitant elevated serum levels of anti-MBP and anti-MAG auto-antibodies, respectively. On the other hand, only 31.8% and 40.9% of autistic patients without allergic manifestations had concomitant elevated serum levels of anti-MBP and anti-MAG auto-antibodies, respectively ($P < 0.001$ and $P < 0.001$, respectively).

We could not trace data in the literature concerning the possible relationship between the presence of allergic manifestations and brain auto-antibodies in autistic patients to compare our results. We are the first to study such a relationship. The results of this study may indicate that the presence of allergy is a possible contributing factor to the increased frequency of serum anti-MBP and anti-MAG auto-antibodies in some autistic children. However, this is an initial report that warrants further research to determine the possible link between the increased frequency of allergic manifestations and brain-specific auto-antibodies in autism.

The mechanism by which allergy may have a role in autism is possibly through the induction of the production of brain specific auto-antibodies secondary to exposure to allergens. Allergic responses in autistic children are associated with increased number of Th2 cells (Cohly and Panja, 2005) which stimulate B lymphocytes to produce antibodies to allergens (Mok and Lau, 2003) that may cross-react with sequence homologies with brain resulting in neuronal damage with subsequent release of neuronal antigens. These neuronal antigens may result in induction of autoimmune reactions through the activation of inflammatory cells in

genetically susceptible individuals (Vojdani et al., 2002; Cohly and Panja, 2005). The environmental allergens include food allergies to certain peptides as gliadin, cow's milk protein and soy (Jyonouchi et al., 2002) infectious agents (Cohly and Panja, 2005), heavy metal exposure such as mercury (Mutter et al., 2005) and *Hevea brasiliensis* proteins in natural rubber latex (Dochniak, 2007).

Thus, autism may be considered as one of the pediatric autoimmune neuropsychiatric disorders. Such autoimmunity may be triggered by environmental allergens exposure. Therefore, skin testing with common environmental allergen extracts should be performed for allergic autistic children for possible identification of the incriminated allergens. Avoidance of these allergens, if possible, is recommended. Immunotherapy should be tried in allergic autistic children who are candidate for this line of therapy.

In conclusion, allergy may be a contributing factor to the increased serum levels of anti-MBP and anti-MAG auto-antibodies in some autistic children. Indeed, we need to know more about the links between allergy, immune system and brain in autism. This is important to determine whether therapeutic modulation of the immune function and allergic diseases are legitimate avenues for novel therapy in selected cases of autism. Thus, further investigations are warranted to shed light on the possible link between allergy and autoimmunity in autism.

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