Prevalence of autism spectrum disorders in relatives of patients with selective immunoglobulin A deficiency

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Background: An association of selective IgA (immunoglobulin A) deficiency in individuals with autism has been previously described. The objective of this study was to examine the incidence of autism spectrum disorders (ASD) in children and siblings of selective IgA deficient patients.

Objective: to assess the likelihood of parents with the most common type of primary immunodeficiency (selective IgA deficiency) having children with ASD and to investigate the occurrence of ASD in siblings of the immunodeficient patients.

Methods: A study was conducted in 31 selective IgA deficient patients and 62 age and gender-matched controls. Children and siblings of IgA deficient patients and controls were screened for an ASD (autism spectrum disorder) using a standard questionnaire.

Results: Only one patient in the IgA deficient group had classical autism. Three children in that group (10.3%) had an ASD compared to only one in the control group (1.6%) and this difference was statistically significant. In terms of siblings, there was a higher occurrence of an ASD in the IgA deficient group than in the control group, but the difference was not statistically significant. A high incidence of allergies (71%) was documented in IgA deficient patients. All individuals with allergies had food sensitivities. There was a predominance of the male gender in cases identified with an ASD in all groups.

Conclusions: A lower prevalence of ASD was observed in the IgA deficient group, as compared to other reports. The study suggests that screening for an ASD seems appropriate for children of IgA deficient patients.

Key words: Autism, Autism spectrum disorders, Selective IgA deficiency.

Autism (sometimes called "classical autism") is the most common condition in a group of developmental disorders known as the autism spectrum disorders (ASD). These disorders are characterized by impairments in social interaction, verbal and nonverbal communication skills, and the presence of restricted and repetitive stereotyped behaviors (1). ASD also includes: Asperger syndrome, Rett syndrome, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified.

Autism is considered, at present, the fastest growing serious developmental disability in children. It has been estimated that more children will be diagnosed with autism this year in the United States than with AIDS, diabetes, and cancer combined.

Determination of the exact number of children with ASDs has been difficult, due in part to the absence of a medical record system that uniformly incorporates data identified by different sources, and that many studies have had limitations regarding the number and appropriateness of their control groups. Identification of individuals with these disorders is frequently made at schools by education specialists that do not convey the gathered information to a healthcare-related record system. The Centers for Disease Control and Prevention (CDC) has published an evaluation of the methodology used for collaborative multiple source surveillance of ASD (ADDM Network) for tracking the prevalence and characteristics of ASD in the United States (2). This system should provide a better estimate of the prevalence of these disorders in the population aside from that obtained through wide population screening. The CDC has reported a prevalence of 6.6 children out of 1,000 from analysis of multiple U.S. communities participating in the ADDM Network (3). Studies from

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different countries describe a wide range of prevalence of 1 in 500 to 1 in 166 children. Males are four times more likely to have autism than females.

The only mentioned prevalence among Hispanics has been 0.3 per 1,000 in Wisconsin and 9.7 per 1,000 in New Jersey (3). It is noteworthy to mention that none of the reported studies have included a significant Latino population.

At present, the etiology of ASD is unknown although genetic, environmental, immunological, and neurological factors have been implied. Studies show a higher concordance rate of autism among monozygotic twins, and a higher rate among siblings than in the general population (4). However, some monozygotic twins have also been found to be discordant for autism, and the causative role of a number of environmental factors has been considered (5). A higher incidence of prenatal stressors has been correlated with autism with a peak at 25-28 weeks of gestation, consistent with the embryological age suggested by neuroanatomical findings seen in the cerebellum of autistic individuals (6). Chemicals, metals and toxic agents have all been related to autism, including pesticides, mercury, lead, alcohol, nicotine and illicit drugs. Inability to metabolize key fatty acids and alterations in serotonin production, have also been implicated. It has been argued that prenatal and neonatal testosterone exposure can also influence the development of ASD (7).

In terms of the immune system, immune alterations, consistent with a dysregulated immune response, have been reported in autistic children (8). The possibility has been raised that in a subset of children, ASD is associated with congenital immunological alterations, such as immunoglobulin A (IgA) deficiency, complement disorders, and defective cytokine production. In studies by Gupta and Warren, it was found that 20% of children with autism had selective IgA deficiency (9-10). Some authors have reported a reduction in plasma levels of the C4b complement protein (11-13). A strong association of the third hypervariable region of the HLA-DR beta 1 has also been observed in limited number of cases (14). Reduced natural killer cell activity and imbalance of serum immunoglobulin levels has also been noted (15). More recently, Jyonouchi and colleagues concluded that there are excessive innate immune responses in a number of children with ASD, based on their cytokine profile, especially their enhanced production of TNF-alpha (16). Finally, a predominance of a TH2-type cytokine response has been observed in autistic children (17). Based on these observations, investigators have postulated that aberrant immune activity during vulnerable and critical periods of neurodevelopment could participate in the generation of neurological dysfunction characteristic of ASD. The problem with the previous studies is the limited number of patients included. The counterpart has been a number of studies, also with limited number of patients, which have concluded that autistic children have normal immune function (18).

The design of the studies cited above, as well as that of others, has been the investigation of children with ASD in terms of a given immune abnormality. To our knowledge, no published study has investigated the susceptibility of ASD, if any, in children born to parents with a primary immunodeficiency. The present study was undertaken to assess the likelihood of parents with the most common type of primary immunodeficiency (selective IgA deficiency) having children with ASD and to investigate the occurrence of ASD in siblings of the immunodeficient patients.

Methods

Case definition

For the purpose of this study, the diagnostic criteria of an ASD were those established by the CDC (19). Conditions classified as an ASD were: the classical autistic disorder, Asperger disorder, childhood disintegrative disorder, Rett disorder and a pervasive developmental disorder, not otherwise specified. The diagnosis of these entities was performed based on their developmental pattern and through behavioral observation.

Study Group

The study group comprised patients followed at the Immunology Clinic of the University Hospital with a diagnosis of selective IgA deficiency over a period of fifteen years. A total of 31 patients diagnosed with IgA deficiency after an initial evaluation and willing to give informed consent were entered into the study. The evaluation consisted of a complete history, physical examination and baseline laboratory tests. Confidentiality of data was guaranteed to participants. The control population consisted of 62 age and gender-matched controls, fulfilling the same requirements as the IgA deficiency group. Since IgA deficiency is not a common condition, the number of participants in the control group was doubled in order to attain a more accurate statistical analysis. The offspring and siblings of the IgA deficient as well as the control group were screened for an ASD.

Immunological parameters

The 62 individuals in the control group were screened for IgA deficiency using an immunoturbidimetry assay performed by a reference laboratory. IgA deficiency was defined as an immunoglobulin A level less than or equal to 10 mg/dL. All cases finally identified as having an

ASD, both in the control as well as in the IgA-deficient group were tested for IgA deficiency in the same manner. Reference ranges for IgA values were considered in the case of children. No use of concomitant medications known to lower IgA levels was identified in the participants. The control group was selected from a clinic.

ASD Screening Questionnaire

A standard ASD screening questionnaire prepared by the FILIUS Institute of Disability and Rehabilitation Research of the University of Puerto Rico was used in all IgA deficient as well as in the control group. This questionnaire includes: baseline demographic data, complete family history, obstetrical history, delivery conditions, health history of the child, developmental history, and observed behavior at different ages for cases identified with a diagnosis of an ASD. For the cases identified as having an ASD with the questionnaire, evidence for the diagnosis was sought in terms of: medical record, letter from school and/or center providing services, as indicated.

The medical record of the IgA-deficient patients was not available to the personnel administering the ASD screening questionnaire.

Statistical analysis

Percent distributions were calculated for the IgA deficient and the control groups. For the outcomes comparisons between the IgA deficient groups and the control groups, the Fisher's Exact Test was used. Since the number of offspring and siblings affected with an ASD were very small (less than 5) in both groups (IgA deficient and control group), this test is more adequate than the traditional parametric test. The probabilities associated with the observed outcomes were calculated based on an $\alpha = 0.10$ or a 90% confidence.

Results

The IgA deficient population included 19 males and 12 females, from which all but two patients had offspring. In terms of the control group, all except one participant had children. One IgA deficient patient, age 21, had classical autism and he did not have children; his sister was healthy. All participants in the control group had normal IgA levels when tested.

As shown in Table 1, 87 children were born to the IgA deficient population and 193 children to the control group. The proportion of male offspring was slightly higher in the IgA deficient group (47.1%) versus that of the control group (45.1%).

Table 2 summarizes the children affected with an ASD in the IgA deficient and in the control group. In the IgA

Table 1. Gender distribution of children in the study group.

Condition of Parent	Total # of Children	Males	Females
IgA deficient group (n=29)*	87 (100%)	41 (47.1%)	46 (52.9%)
Control group (n=61)**	193 (100%)	87 (45.1%)	106 (54.9%)

*In the IgA deficient group, two did not have children.
**In the control group, one did not have children.

Table 2. Children affected with an ASD in the study group.

Condition	# parents	# children with ASD	# children healthy
IgA deficiency	9 (100%)	1 (11.1%)*	23 (88.9%)
IgA def. + allergies	20 (100%)	2 (10.0%)**	61 (90.0%)
No condition (controls)	61 (100%)	1 (1.6%) ***	192 (98.4%)

P value (all IgA def. versus control group) = 0.09045†

*IgA def. father; offspring was a girl.
**IgA def. parents in which there was one father and a mother; both offspring were boys.
***Parent was a mother; affected child was a boy.
†Using Fisher's exact test. Statistically significant at α=0.10.

deficient group, three children had an ASD (10.3%) compared to only one affected child in the control group (1.6%). This difference was statistically significant with a p value less than 0.10. Both parents of the child with an ASD in the control group had normal IgA levels. Most of the IgA deficient patients had documented allergies (71%). All patients identified with allergies had food sensitivities as obtained from their medical history.

In terms of siblings, there were more cases with an ASD in the IgA deficient group (2.0%) compared with those in the control group (0.5%), however this difference was not statistically significant. Again, there was a predominance of brothers to sisters, as indicated in Table 3. One of the siblings of an IgA deficient patient had an ASD, as well as IgA deficiency. The sibling of the only individual in the control group with an ASD had a normal IgA level.

Table 4 summarizes all the cases identified as having an ASD. The male to female ratio of individuals having an ASD was 4:1.

The final identification of the types of ASD in this study is detailed in Table 5. Overall, most cases pertained to the atypical autism (PDD-NOS) group.

Table 3. Siblings affected with an ASD.

Condition	Total number with siblings	Number of unaffected siblings	Number of siblings with an ASD
IgA deficiency	28	97 (98.0%)	2 (2.0%)*
Control	60	216 (0.5%)	1 (0.5%)**

P value (IgA deficiency versus controls) = 0.232186†

*Gender - IgA def. female in one case; IgA def. male in another case; both siblings were brothers. One was IgA deficient.
**Gender - female in this case; the sibling with ASD was male, negative for IgA deficiency.
†Using Fisher's exact test. Not statistically significant at α=0.10.

Table 4. Summary of identified ASD cases.

Group of origin	Affected relative	Number	Gender
IgA deficient	offspring (n=87)	3	Two males; one female
	sibling (n=99)	2	Males
Control	offspring (n=193)	1	Male
	sibling (n=217)	1	Male

Table 5. Type of autism spectrum disorder identified in offspring and siblings.

Type of ASD	IgA deficient (number)	Control (number)
Classical autism	2	-
Asperger disorder	-	-
Rett syndrome	-	-
Childhood disintegrative disorder	-	-
Atypical autism (PDD-NOS)[1]	3	2

[1] PDD-NOS = Pervasive developmental disorder not otherwise specified.

Discussion

The dysregulated immune condition described in autism has included the production of low levels of immunoglobulin A. In a series of 25 cases with autism (in which its type was unspecified), Gupta reported a 20% concomitant IgA deficiency. Similarly, Warren and collaborators described the same percent of cases with decreased serum IgA in individuals with autism in a group of 40 cases with unspecified type of autism.

In our study, from the 31 individuals in the IgA deficiency group only one had classical autism. A lower incidence of autism was observed in our study when compared to the combined series reported by Gupta and Warren. A possible explanation for this difference is the reduced number in the IgA deficient group studied.

Overall, in our study, an ASD was more commonly found in the offspring and siblings of IgA deficient patients than in the control group, although it was only statistically significant in the case of children born to the immunodeficient group. One possible explanation is that the recall of whether a child had an ASD was more precise for parents with offspring than for participants regarding siblings. Also, it was easier to certify the diagnosis by parents, since they possessed the documentation about their child's condition.

The predominance of male to female individuals with ASD observed in this study is in agreement with that published in the medical literature. The finding of a significant proportion of allergies in the IgA deficient group identified in our study is in agreement with what has been reported in previous publications. People with autism have also been found to be more susceptible to allergies and food sensitivities especially to grains and dairy products (20). The predominance of a TH2-type of cytokine profile may be the explanation for the increased incidence of allergies, low IgA levels and autoimmune phenomena observed in autism. An interesting fact is that the TH2 axis predominates throughout pregnancy, and apparently it is perpetuated in autistic children by unknown mechanisms.

Although, our study relied on patient reports, information from other sources, and data obtained through a questionnaire, it included a larger number of cases screened for specific types of ASDs as compared to those previously published.

It is important to stress that immunoglobulin A is the protective antibody in the digestive tract. It would be interesting to correlate that fact to the reported high incidence of gastrointestinal manifestations, such as diarrhea, abdominal pain, bloating, gastroesophageal reflux, dysbiosis, fat malabsorption, intestinal lining abnormalities, enterocolitis reported in autistic children (21). This study suggests that screening for an ASD seems appropriate for children of IgA deficient patients.

Another pertinent suggestion of this study is the desirability to investigate the children of patients with IgA deficiency and food sensitivities for an ASD. In addition, genetic analysis of IgA deficient patients and their relatives may be appropriate to assess the possible association of the HLA-DR beta 1 region as a susceptibility region for autism as hinted by prior studies.

Resumen

La asociación entre la deficiencia selectiva de inmunoglobulina A con el autismo ha sido previamente descrita. El objetivo de este estudio fue examinar la incidencia del espectro de desórdenes asociados al autismo (ASD, por sus siglas en inglés) en hijos y hermanos de pacientes con deficiencia selectiva de IgA. En éste se evaluaron 31 pacientes con deficiencia selectiva de IgA y 62 controles pareados por edad y género. Los hijos y los hermanos de los pacientes con deficiencia de IgA y los controles fueron examinados con respecto al ASD mediante un cuestionario estándar. Un solo paciente del grupo con deficiencia selectiva de IgA se identificó con autismo clásico. En tres hijos del grupo de pacientes con deficiencia de IgA se halló un ASD (10.3%) en comparación con sólo uno en el grupo control. Esa diferencia fue significativa desde el punto de vista estadístico. En hermanos de pacientes con deficiencia de IgA, también se identificaron más casos de ASD que en el grupo control, pero la diferencia no fue significativa desde el punto de vista estadístico. La mayoría de los pacientes con deficiencia de IgA presentaron alergias (71%) y todos los pacientes con alergias mostraron sensibilidad a alimentos. Hubo una predominancia de varones en todos los casos con ASD en ambos grupos estudiados. En resumen, el estudio mostró una incidencia menor de ASD en el grupo de pacientes con deficiencia de IgA al compararse con otros informes en la literatura. Sin embargo, se insinúa el aspecto beneficioso de efectuar una evaluación para ASD en hijos de pacientes con deficiencia de IgA.

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