

Increased Prevalence of Familial Autoimmunity in Probands With Pervasive Developmental Disorders

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ABSTRACT. *Objectives.* Increased prevalence of familial autoimmune disease is a common finding among probands with various autoimmune disorders. Autistic disorder (autism) is a highly genetic disorder with known immune and immunogenetic abnormalities. Previous research has found an increased frequency of autoimmune disorders in families with autistic probands. We further investigated this association by determining the frequency of autoimmune disorders in families that have probands with pervasive developmental disorders (PDDs), including autism, compared with 2 control groups.

Methods. Three well-defined study groups, including 1) families that have a child with a PDD, 2) families that have a child with an autoimmune disorder, and 3) families with a healthy control child, constituted the sample. A questionnaire inquiring about which first- and second-degree family members had received a diagnosis of having specific autoimmune disorders was completed by 101 families in each group.

Results. The frequency of autoimmune disorders was significantly higher in families of the PDD probands compared with families of both the autoimmune and healthy control probands. Autoimmunity was highest among the parents of PDD probands compared with parents of the healthy control subjects. Hypothyroidism/Hashimoto's thyroiditis and rheumatic fever were significantly more common in families with PDD probands than in the healthy control families.

Conclusions. Autoimmunity was increased significantly in families with PDD compared with those of healthy and autoimmune control subjects. These preliminary findings warrant additional investigation into immune and autoimmune mechanisms in autism. *Pediatrics* 2003;112:e420–e424. URL: <http://www.pediatrics.org/cgi/content/full/112/5/e420>; autism, Asperger's disorder, pervasive developmental disorder, pervasive developmental disorder-not otherwise specified, autoimmune disease, family history, prevalence.

ABBREVIATIONS. PDD, pervasive developmental disorder; NOS, not otherwise specified; SLE, systemic lupus erythematosus; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; SD, standard deviation.

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Autistic disorder (autism) is currently categorized as 1 of a group of related disorders known as pervasive developmental disorders (PDDs). Autism is described behaviorally by deficits in communication and social interaction combined with stereotyped or restricted behaviors or interests. Symptoms become manifest before 3 years of age, and mental retardation is typically a comorbid diagnosis. Asperger's disorder is distinct from autism in that it is not associated with early language delay or mental retardation. PDD not otherwise specified (NOS) describes patients who demonstrate a pattern of development and social impairment similar to autism and Asperger's disorder but who do not meet all of the specific diagnostic criteria for another PDD.

Many theories have been proposed and investigated regarding the cause of autism, although in the majority of cases, no cause is identified. One hypothesis suggests that autoimmune mechanisms may be involved.¹ Immunogenetic research shows that genes long implicated in autoimmune disorders such as rheumatoid arthritis² and systemic lupus erythematosus (SLE)³ are significantly increased in autistic populations.^{4–6} The frequency of 1 of these genes, the complement C4B null allele, has been found to be increased in individuals with autism in 2 studies.^{4,7}

Recently, we found evidence suggestive of immune activation in autistic children in the form of increased blood monocyte counts and neopterin levels compared with healthy control children.⁸ Although evidence of immune activation in autism was inconsistent in earlier studies, more recent research indicates activation of inflammatory processes and cell-mediated immunity.^{9–11}

The autoimmune theory of autism was first proposed by Money et al¹² after observing an unusually high number of autoimmune disorders in a family with an autistic child. Comi et al¹³ followed up this observation on a larger scale by surveying families with autistic children and families with healthy children regarding the occurrence of autoimmune disease in first- and second-degree relatives. The frequency of autoimmune disorders in the families with autistic children was found to be higher than in control subjects, particularly among parents, especially mothers, of autistic children. Increased prevalence of autoimmune disease in family members is common among probands with autoimmune disorders in general.^{14,15} Therefore, if increased familial

autoimmune disease in autistic probands were verified, then additional research into immunologic contributions to the pathophysiology of some individuals with autism would seem warranted.

To investigate further the frequency of autoimmunity in families with autistic children, we randomly administered a questionnaire to 3 well-defined groups: 1) families that have a child with a PDD, 2) families that have a child with an autoimmune disorder, and 3) families with a healthy control child. We hypothesized that autoimmune disease would occur most often in the families that have a child with an autoimmune disorder and least often in families with healthy children, with the prevalence in the autism families falling somewhere in between these 2 groups.

METHODS

This study was approved by the Indiana University Human Subjects Institutional Review Board. After a complete description of the study, written informed consent was obtained from the probands and their parent(s). For those subjects who had PDD and were unable to provide written consent, assent was obtained. Our target sample size was 100 families from each group. A total of 101 families with a child or an adolescent with a PDD were recruited from the Christian Sarkine Autism Treatment Center at the James Whitcomb Riley Hospital for Children (Indianapolis, IN). The PDD group met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*¹⁶ criteria for autistic disorder, Asperger's disorder, or PDD NOS on the basis of a thorough diagnostic interview conducted by a board-certified child and adolescent psychiatrist as part of their assessment and treatment at the center. Subjects were recruited consecutively at the time of scheduled appointments.

A total of 101 families with a child or an adolescent who had a diagnosis of autoimmune disease were recruited consecutively during scheduled appointments at the Pediatric Rheumatology Clinic at the James Whitcomb Riley Hospital for Children. Diagnoses were established during previous visits to this clinic. A total of 101 families with healthy children were recruited consecutively during visits to the Riley Hospital for Children's General Pediatric Clinic or to the office of a local pediatrician in the community. The age range for recruitment in each of the 3 groups was 3 to 20 years, inclusive.

Parents were asked to fill out a 45-item questionnaire regarding which first- or second-degree relatives had received a diagnosis of specified autoimmune disorders. The disorders inquired about in the questionnaire included rheumatoid arthritis, juvenile rheumatoid arthritis, rheumatic fever, psoriatic arthritis, ankylosing spondylitis, SLE, dermatomyositis, polymyositis, psoriasis, vitiligo, myasthenia gravis, multiple sclerosis, amyotrophic lateral sclerosis, ulcerative colitis, Crohn's disease, hyperthyroidism/Graves' disease, hypothyroidism/Hashimoto's thyroiditis, idiopathic thrombocytopenic purpura, scleroderma, uveitis, polyarteritis nodosa, Wegener's granulomatosis, Takayasu's arteritis, vasculitis, type 1 diabetes, Addison's disease, Sjögren's syndrome, pemphigus, and Guillain-Barré syndrome. These disorders were chosen

because all have a known or suspected autoimmune cause. Researchers were available to answer questions and clarify responses; however, there was no verification of the diagnosis of family members via medical record review or direct clinical examination. Data indicating family size or whether second-degree relatives were from maternal or paternal lineage was not obtained, to simplify the questionnaire for respondents. Demographic information was collected on a form separate from the questionnaire to maintain confidentiality.

All statistical analyses were performed using SPSS statistical software.¹⁷ For numerical data, such as the age of probands or the mean number of autoimmune disorders per family, 1-way analysis of variance or analysis of covariance was performed comparing all 3 groups. When the resultant *P* value was <.05, post hoc pairwise comparisons were performed using the least significant difference test. Two-tailed *P* < .05 was considered significant.

For binomial data, such as whether a family had a specific member with an autoimmune disorder or not, frequency tables were created to calculate χ^2 values and associated *P* values. Group-wise comparisons with *P* < .05 were further investigated using pairwise χ^2 comparisons. In cases with low expected cell counts, Fisher exact test was used. In χ^2 analyses involving multiple comparisons, a Bonferroni correction of significance was applied. All statistical tests were 2-tailed.

RESULTS

Descriptive Data

The mean age \pm standard deviation (SD) of the PDD (10.2 ± 4.2 years) and autoimmune (10.3 ± 4.8 years) probands was similar; however, probands from both of these groups were older than the healthy control probands (6.5 ± 4.0 years; $t = 7.13$, $P < .0001$). Group sex differences also existed. As expected, the PDD probands consisted of fewer girls (18) than boys (83). The autoimmune probands included 70 girls and 31 boys, and the healthy control probands consisted of 41 girls and 60 boys. Ethnically, the groups were similar, each being >90% white (Table 1).

Of the autoimmune probands included in this study, 70 had a diagnosis of juvenile rheumatoid arthritis, 9 had juvenile dermatomyositis, 9 had SLE, 4 had psoriatic arthritis, 3 had scleroderma, 2 had mixed connective tissue disease, 2 had ankylosing spondylitis, 1 had vasculitis, and 1 had an episode of rheumatic fever.

The response rate to the questionnaire was similar between the PDD and healthy control groups but higher in the autoimmune group. Of the 196 questionnaires distributed to PDD families, 101 (52%) were returned. In the healthy control group, 101 (55%) of 182 questionnaires were returned. The group with the highest response rate was the autoimmune group in which 101 (75%) of 135 question-

TABLE 1. Descriptive Data for Probands and Response Rates to the Questionnaire*

	PDD	Autoimmune	Healthy
Mean age (y \pm SD)	10.2 \pm 4.2†	10.3 \pm 4.8†	6.5 \pm 4.0
Sex: male/female	83/18	31/70	60/41
Race			
White	96	94	92
Black	2	5	4
Other	3	2	5
Response rates‡	101/196 (52%)	101/135 (75%)	101/182 (55%)

* Each group consists of 101 families.

† Compared with healthy: $t = 7.13$, $P < .0001$.

‡ Response rate indicates the proportion of questionnaires completed of the number distributed to each group.

naires were returned (Table 1). Thus, across the 3 groups, 25% to 48% of the questionnaires were not returned. Occasionally, a questionnaire and/or demographic form was returned with an incomplete response. In the large majority of these cases, the family was able to be recontacted and the missing information was obtained. In approximately 2% of the cases, this was not possible, so those data were not included in the statistical analyses.

General Frequencies

Among the 3 groups, the mean \pm SD number of family members with autoimmune disease was 1.87 ± 1.6 for the PDD families, 1.44 ± 1.5 for the autoimmune families, and 0.93 ± 1.1 for the healthy control families. The PDD families had a significantly higher frequency of autoimmune disorders than both the autoimmune ($t = 2.03, P = .03$) and the healthy control ($t = 4.90, P = .000003$) families. As expected, the frequency of autoimmune disorders in the autoimmune families was significantly higher than in the healthy control families ($t = 2.72, P = .01$; Table 2). Analysis of covariance with subject age as the covariate was not significant ($F = 1.94, df = 1, P = .165$).

Family Members

Analysis of occurrence of autoimmune disease in specific family members revealed that parents of children with PDD were more likely than parents of healthy children to have autoimmune disease ($\chi^2 = 10.97; P = .0009$; Table 3). After a Bonferroni correction for multiple comparisons was applied (Bonferroni $\alpha = 0.0015$), this was the only such significant difference among the groups. Mothers ($\chi^2 = 8.73, P = .003$), total siblings ($\chi^2 = 4.04, P = .044$), brothers ($\chi^2 = 7.01, P = .059$), grandmothers ($\chi^2 = 7.72, P = .005$), and uncles ($\chi^2 = 6.04, P = .014$) of the PDD families were found to have more autoimmune disease than their respective counterparts in the healthy control families; however, these values only approached statistical significance (Table 3).

Types of Autoimmune Disorders

Among the various autoimmune disorders, hypothyroidism/Hashimoto's thyroiditis and rheumatic fever were more common in the families with chil-

TABLE 2. Mean Number of First- or Second-Degree Family Members With Autoimmune Disorders per Family and Number of Families in Each Group With a Specific Autoimmune Disorder*

	PDD	Autoimmune	Healthy
Mean Number per Family	1.87 ± 1.6 †‡	1.44 ± 1.5 §	0.93 ± 1.1
Hypothyroidism/Hashimoto's thyroiditis	36¶¶	11	14
Rheumatic fever	23#	10	6
Multiple sclerosis	7	2	1

* Each group consists of 101 families.

† Compared with autoimmune: $t = 2.03; P = .03$.

‡ Compared with healthy: $t = 4.90; P = .000003$.

§ Compared with healthy: $t = 2.72; P = .01$.

¶ Compared with autoimmune: $\chi^2 = 18.06; P = .00002$.

¶¶ Compared with healthy: $\chi^2 = 13.21; P = .0003$.

Compared with healthy: $\chi^2 = 12.31; P = .0005$.

TABLE 3. Number of Families That Have at Least One Specified Member With an Autoimmune Disorder*

	PDD	Autoimmune	Healthy
Parent	31†	28	12
Mother	26	17	10
Father	5	13	2
Sibling	8	6	2
Brother	5	2	0
Sister	3	4	2
Grandparent	55	48	35
Grandmother	47	35	28
Grandfather	23	22	14
Uncle	17	11	6
Aunt	25	25	17
Cousin	12	10	8

* Each group consists of 101 families.

† Compared with healthy: $\chi^2 = 10.97; P = .0009$.

dren with PDD than in the healthy control families after statistically correcting for multiple comparisons ($\chi^2 = 12.31, P = .0005$; $\chi^2 = 13.21, P = .0003$, respectively; Bonferroni $\alpha = 0.001$; Table 2). Hypothyroidism/Hashimoto's thyroiditis was also significantly increased in the PDD families compared with the autoimmune families ($\chi^2 = 18.06, P = .00002$). Group comparisons of other autoimmune disorders revealed no other significant differences. The frequency of multiple sclerosis was increased but not significantly in the PDD families compared with the healthy control families ($\chi^2 = 5.25, P = .065$; Table 2).

PDD Subtypes

The PDD group consisted of 3 clinically defined subtypes: autism ($n = 62$), Asperger's disorder ($n = 18$), and PDD NOS ($n = 21$). Comparing the familial occurrence of autoimmune disease in these 3 subtypes revealed similar frequencies in the autism (mean \pm SD 2.1 ± 1.60) and Asperger's disorder (2.2 ± 1.67) groups. However, the frequency was lower in the PDD NOS group (0.9 ± 0.89) compared with both the autism ($t = 3.25, P = .002$) and the Asperger's disorder ($t = 3.01, P = .007$) groups. The PDD NOS families had a prevalence of autoimmunity very similar to that of the healthy control families (0.93 ± 1.1). When the PDD NOS subtype is removed from the overall PDD group, the combined autism and Asperger's disorder group differs even more from the healthy ($t = 5.64, P = .0000004$) and autoimmune ($t = 2.97, P = .001$) control families in terms of familial frequency of autoimmune disease.

DISCUSSION

The results of this study provide preliminary evidence suggestive of a possible association between autism and autoimmune disease. The use of a well-characterized control group with known autoimmune disease and a larger sample of well-diagnosed probands with PDDs were important advances on previously reported work. Similar to the results from the earlier study by Comi et al,¹³ we found an increased frequency of autoimmune disorders in first- and second-degree relatives of children and adolescents with PDDs compared with healthy control subjects. The finding of increased autoimmune disease in parents, especially mothers, of children

with PDDs is also in agreement with that of Comi et al. However, regarding which particular autoimmune disorders are increased, Comi et al found a higher familial rate of rheumatoid arthritis, whereas we found an increased occurrence of hypothyroidism/Hashimoto's thyroiditis and rheumatic fever. Rheumatic fever was not, however, included in the Comi et al survey. Previous reports have noted possible connections between autism and a family history of both rheumatoid arthritis^{18,19} and hypothyroidism,²⁰ particularly in mothers. In probands with autoimmune disease, it is not unusual to have family members with a variety of autoimmune disorders, as common genes may contribute to a number of different autoimmune states.²¹

The increased frequency of rheumatic fever in the families of autistic probands could be related to the increased expression of the B-cell antigen D8/17 previously reported in autistic subjects.²² Increased expression of D8/17 was originally found in patients with rheumatic fever²³ and subsequently in patients with obsessive-compulsive disorder and tic disorders in which autoimmune pathology is suspected.²⁴ Concerns about the sensitivity and reliability of the D8/17 assay, however, have recently been raised.²⁵

An unanticipated finding was that the families of PDD probands had a greater frequency of autoimmune disorders than the families of children with known autoimmune disease. Another unexpected result was a slight increase of autoimmune disease in the brothers of autistic probands compared with brothers of healthy children. Although this finding did not reach statistical significance, it is notable because of the rarity of autoimmune disorders in young boys, the close genetic relationship of these brothers to the PDD probands, and the male preponderance in autism. Another observation of possible importance is the numerical increase of autoimmunity in grandmothers and uncles, as well as mothers and brothers of PDD probands, compared with their respective counterparts in the healthy control families. This suggests a possible mother-to-son transmission of susceptibility to autoimmune disease in the PDD families.

With regard to the analysis of the PDD subtypes, the increased frequency of autoimmunity in the autism and Asperger's disorder families compared with the PDD NOS families suggests that patients with PDD NOS may not have as strong a connection to autoimmunity as patients with autism and Asperger's disorder. Nevertheless, caution must be maintained when interpreting these results because of the low number of subjects in each group and the relatively subtle diagnostic differences among these disorders.

Although this work replicates, in part, the results of a previous, similar study,¹³ limitations of self-response questionnaires must be taken into account. Families from the 3 study groups may respond differently to the questionnaire as a result of differing motivations or a dissimilar knowledge base of autoimmune disease. This could account for the higher rate of return of questionnaires from the autoimmune families who are personally familiar with au-

toimmune disease and terminology. The responses of the autoimmune families may also be accompanied by greater specificity. That is, such parents are likely to be more familiar with specific autoimmune disorders and may be less likely to report false positives than parents of children from the 2 other groups. Responses are also likely to be hampered by recall bias. A similar study measuring familial history of autoimmune disease in patients with multiple sclerosis found that approximately 30% of the responses could not be verified by checking medical records.¹⁴ We suspect that a similar rate of error may have occurred in this study. Although not directly assessed, it is also possible that any psychopathology present in the parents, especially within the PDD group, may have contributed to bias in the completion of the questionnaire.

Another potential confounding factor is the lower age of healthy control probands compared with the PDD and autoimmune probands. The mean age of the healthy control children was approximately 3.75 years below that of the PDD and autoimmune groups. As a result, family members in the healthy control group may tend to be younger than those in the 2 other groups and perhaps, therefore, less likely to have members who have received diagnoses of autoimmune disorders. However, when subject age was included as a covariate in the statistical analysis, it did not contribute significantly to the difference detected between groups. Although the age difference might account for the reduced rate of autoimmunity observed in the healthy control families, we believe that this is a minor contributing factor. However, the PDD and autoimmune probands were almost identical in age. Although the sex ratio differed for probands in each group, we do not believe that this had a significant effect on family histories, especially because autoimmune data on probands were not included in the statistical analysis.

Autoimmunity or chronic immune activation could help to explain some peripheral biochemical abnormalities reported in autistic subjects. For instance, hyperuricemia and iron deficiency anemia reported in subclasses of autistic subjects^{26,27} both are commonly found in autoimmune disease.^{28,29} It is possible that elevated blood serotonin reported in autism could also be related to immune factors.³⁰⁻³²

Autism is 4 times more common in boys than in girls. Altered sex ratios are common in autoimmune disease, with girls being overrepresented in the majority of disorders. Our data are consistent with these expected sex differences. The overrepresentation of boys in autism is inconsistent with the female preponderance of most autoimmune disorders. However, a substantial subset of predominately male autoimmune disorders does exist, including amyotrophic lateral sclerosis, ankylosing spondylitis, and type 1 diabetes.³³ The high rate of autoimmune disease in the mothers of the children with PDD 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. Finally, much attention has been focused lately on a possible increase in the incidence of autism.³⁴ If this is the case, then the rise would coincide with recent increases in the incidence of type 1 diabetes in children reported by some investigators.³⁵

To date, a definitive relationship between autism and autoimmunity has not been established. On the basis of the preliminary results reported in this study, however, there seems to be 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.

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