ARTICLE

Maternal Autoimmune Diseases, Asthma and Allergies, and Childhood Autism Spectrum Disorders

A Case-control Study

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Objective: To investigate the association between physician-documented diagnoses of maternal autoimmune diseases, allergies, and asthma around the time of pregnancy and subsequent diagnoses of autism in children.

Design: A case-control study nested within a cohort of infants born between January 1995 and June 1999.

Setting: Northern California Kaiser Permanente Medical Care Program.

Participants: Cases (n=420) were children with at least 1 diagnosis of an autism spectrum disorder (ASD) recorded in Kaiser Permanente outpatient clinical databases. Controls (n=2100) were children without an ASD diagnosis who were frequency matched to cases on sex, birth year, and hospital of birth.

Main Outcome Measures: Frequencies of maternal immunologic disorders were compared between cases and controls with a χ^2 statistic, and relative risks were estimated by crude and adjusted odds ratios and 95% confidence intervals using logistic regression.

Results: The final study population included 407 cases and 2095 controls. A similar proportion of case and control mothers had a diagnosis of any autoimmune disease in the 4-year period surrounding pregnancy (10.3% vs 8.2%, $P=.15$). After adjustment for maternal factors, only 1 autoimmune condition, psoriasis, was significantly associated with ASDs (adjusted odds ratio, 2.7; 95% confidence interval, 1.3-5.8). A greater than 2-fold elevated risk of ASD was observed for maternal asthma and allergy diagnoses recorded during the second trimester of pregnancy.

Conclusions: These findings suggest that maternal autoimmune disorders present in women around the time of pregnancy are unlikely to contribute significantly to autism risk. Further etiologic investigations are needed to confirm these results and should include objective documentation of diagnoses and consider a larger set of maternal immune-related conditions, including asthma and allergies.

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AUTISM IS A NEURODEVELOPMENTAL disorder characterized by social and communication impairments and restricted and stereotyped patterns of behavior.[1] Contrary to early beliefs that autism resulted from adverse parent-child interactions,[2] it has become widely accepted that aberrant brain development in the prenatal or early postnatal period underlies autism pathogenesis. Data from twin and family studies suggest a strong genetic component in the etiology of autism[3] with the involvement of multiple gene loci.[4] Observations from case reports and small case series provide some evidence of the potential etiologic role of both prenatal and early postnatal environmental factors, presumably interacting with genetic factors.[5] The dramatic temporal trend in autism prevalence reported in different locales has shifted the focus of research to include an exploration of nongenetic risk factors and an evaluation of gene-environment interactions.

A variety of immune system disturbances have been reported to be present in autistic individuals,[4,6-12] although findings remain largely unreplicated. A case report by Money et al[13] that described an autistic child with a strong family history of autoimmune disorders offered the first suggestion that autoimmunity may be etiologically important in autism. Since then, some studies of autistic individuals have found an increased frequency of autoantibody production[6,14-19] and genes implicated in autoimmune disorders.[20-24] Results from 2 recently conducted epidemiologic studies also suggest that a family history of autoimmune disorders is

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Table 1. Therapeutic Drug Classes Prescribed Significantly More Often Among Women With Autoimmune Diseases, Asthma, or Allergies in the 12 Months Before Delivery

Therapeutic Class Name
Cephalosporins
Erythromycins or related macrolides
Penicillins
Sulfonamides
Narcotic analgesic combinations
Antirheumatics
Antispasmodics, single entities
Antispasmodics, combinations
Antiemetics, antivertigo agents
Adrenocorticosteroids, single entities
Respiratory sympathomimetics
Xanthine derivatives
Respiratory steroids
Respiratory anticholinergic agents
Antihistamines, single entities
Antihistamine or decongestant
Expectorant or decongestant
Antitussive or antihistamine
Topical anti-infectives
Nasal products
Ophthalmic (anti-infectives)
Ophthalmics (miscellaneous)

more common among children with autism than healthy control children.[25,26] In both studies, first-degree relatives, especially mothers, were most often affected. However, interpretation of these findings is hampered by limitations in study design, including small sample sizes and reliance on self-reported autoimmune disease history.

The aim of this study is to investigate the association between a history of maternal autoimmune diseases, allergies, and asthma around the time of pregnancy and subsequent diagnoses of autism spectrum disorders (ASDs) in children. We hypothesize that the maternal immune response during pregnancy, as measured by physician-documented diagnoses of autoimmune or allergic diseases, may affect fetal brain development, contributing to autism in some genetically susceptible individuals.

METHODS

We conducted a case-control study nested within the cohort of all infants born alive at a Kaiser Permanente Medical Care Program (KPMCP) facility between January 1995 and June 1999 and who remained health plan members for at least 2 years following birth. The KPMCP is a large integrated health care organization that provides care for more than 3 million residents of northern California, representing approximately 30% of the insured population in the region.

CASE ASCERTAINMENT

All children with at least 1 diagnosis of an ASD, including autism (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 299.0) and Asperger disorder or pervasive developmental disorder not otherwise specified (*ICD-9-CM* code 299.8), were identified by electronically scanning the KPMCP clinical databases, which contain all diagnoses made at outpatient visits that occurred at plan facilities and outside approved facilities and were recorded between January 1995 and November 2002. From a denominator population of 88 163 children born at Kaiser facilities who remained in the health plan for at least 2 years following birth, we identified 420 children between 3 and 7 years of age with an ASD diagnosis.

CONTROL SELECTION

We randomly selected 5 controls per case from the cohort of births without an ASD diagnosis. No other exclusions were made. Controls (n=2100) were frequency matched to cases on sex, birth year, and hospital of birth.

SIBSHIPS

To ensure independence of observations with respect to characteristics of the mother, we included each woman only once in the final analytic file. For women who had 2 children included in the original study cohort (13 case mothers, 5 control mothers), we randomly sampled 1 child for each woman for inclusion.

We identified all siblings of both case and control children born at a KPMCP facility between 1990 and 1999. To assess the hypothesis that a genetic etiology may be more likely in families with more than 1 ASD-affected child, we divided study sibships into 3 categories as follows: *unaffected* (no ASD-affected children in the sibship), *simplex* (1 ASD-affected child [case or sibling of control] in the sibship), and *multiplex* (more than 1 ASD-affected child in the sibship). Sibships were defined as births to the mother, without regard to paternity.

MATERNAL DIAGNOSES

Maternal autoimmune diseases (n=44), asthma, and allergies diagnosed at inpatient and outpatient visits in the period of 2 years preceding delivery through 2 years following delivery were identified from inpatient and outpatient databases (*ICD-9-CM* codes available from authors). The 2 years following delivery were included in the exposure window because of the increased incidence of onset in the puerperium of many autoimmune disorders.[27]

COVARIATES

Information on several maternal characteristics (age at delivery, race/ethnicity, educational attainment) and infant characteristics (sex, plurality [ie, singleton or multiple]) was obtained from health plan and vital statistics databases. Detailed information on prescriptions dispensed at KPMCP pharmacies was obtained to identify medications prescribed significantly more often during the 12 months before delivery among women with autoimmune, asthma, and allergic conditions compared with women without these conditions. Women were classified as using medications if prescriptions were dispensed for any of the therapeutic drug classes listed in **Table 1** or not using medications if none of the medications were given.

STATISTICAL ANALYSES

Frequencies of immunologic disorders were compared with a χ^2 statistic for conditions that occurred in the mothers of at least 5 cases and 5 controls. A χ^2 test for trend with unitary weighting was used to test for genetic dosage effects across unaffected, simplex, and multiplex sibships.[28] Relative risks were

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Table 2. Characteristics of the Study Population, Kaiser Permanente Northern California Births, 1995-1999*

Characteristics	Autism Cases, No. (%) (n = 407)	Controls, No. (%) (n = 2095)	*P* Value
Male	333 (81.8)	1709 (81.6)	NA
Multiple birth†	24 (5.9)	58 (2.8)	.001
Maternal age, mean (SD), y	31.1 (5.4)	29.8 (5.7)	<.001
Maternal race			.04
White, non-Hispanic	210 (51.6)	945 (45.1)	
White, Hispanic	66 (16.2)	476 (22.7)	
Black	35 (8.6)	187 (8.9)	
Asian	42 (10.3)	218 (10.4)	
Other	54 (13.3)	269 (12.8)	
Maternal education			<.001
<High school graduate	21 (5.2)	207 (9.9)	
High school graduate	79 (19.4)	602 (28.7)	
Undergraduate college	223 (54.8)	994 (47.4)	
Postgraduate	81 (19.9)	259 (12.4)	
Months of KPMCP membership for study child, mean (SD)	73.2 (19.3)	68.1 (21.5)	<.001
Months of KPMCP membership for study mother, mean (SD)‡	26.5 (15.2)	26.9 (15.1)	.60

Abbreviations: KPMCP, Kaiser Permanente Medical Care Program; NA, not applicable.

*Data are number (percentage) of patients unless otherwise indicated.

†Includes 79 twins (22 cases, 57 controls) and 3 triplets (2 cases, 1 control).

‡Before delivery of the study child.

Table 3. Frequency of Autoimmune Diseases, Asthma, and Allergies Diagnosed at the Time of Pregnancy in Mothers of Children With Autism and Control Children*

Disorder	Autism Cases, No. (%) (n = 407)	Controls, No. (%) (n = 2095)	χ^2 *P* Value
Autoimmune diseases	42 (10.3)	171 (8.2)	.15
Alopecia	8 (2.0)	30 (1.4)	.40
Autoimmune thyroid disease†	8 (2.0)	66 (3.2)	.23
Idiopathic thrombocytopenic purpura	4 (1.0)	11 (0.5)	
Inflammatory bowel disease‡	2 (0.5)	9 (0.4)	
Psoriasis	11 (2.7)	20 (1.0)	.003
Rheumatoid arthritis	1 (0.2)	6 (0.3)	
Type 1 diabetes mellitus	5 (1.2)	9 (0.4)	.04
Uveitis	1 (0.2)	5 (0.2)	
Vasculitis	1 (0.2)	1 (0.0)	
Vitiligo	1 (0.2)	1 (0.0)	
Asthma	63 (15.5)	219 (10.5)	.003
Allergies	102 (25.1)	388 (18.5)	.002
Allergic rhinitis	85 (20.9)	303 (14.5)	.001
Anaphylaxis	9 (2.2)	36 (1.7)	.37
Angioedema	1 (0.2)	1 (0.0)	
Atopic eczema	15 (3.7)	46 (2.2)	.04
Conjunctivitis	9 (2.2)	41 (2.0)	.58

*The conditions shown are only those where at least 1 case and 1 control were represented. Additional autoimmune conditions that we examined included Addison disease, ankylosing spondylitis, autoimmune anemia, autoimmune disorders, autoimmune hepatitis, Behçet syndrome, celiac disease, connective tissue disorder, cryoglobulinemia, discoid lupus, Goodpasture syndrome, Guillain-Barré syndrome, IgA nephropathy, idiopathic pulmonary fibrosis, juvenile rheumatoid arthritis, lichen planus, Meniere disease, multiple sclerosis, myasthenia gravis, optic neuritis, pemphigoid, polychondritis, polymyalgia rheumatica, polymyositis, primary biliary cirrhosis, Raynaud disease, Reiter arthritis, rheumatic fever or rheumatic heart disease, sarcoidosis, Sjögren syndrome, Stevens-Johnson syndrome, Still disease, systemic lupus erythematosus, systemic sclerosis, and thrombocytopenic thrombotic purpura. Additional allergic conditions that we examined included atopy and urticaria.

†Includes hyperthyroidism, Graves disease, hypothyroidism, and Hashimoto thyroiditis.

‡Includes Crohn disease and ulcerative colitis.

estimated by crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression. Statistical significance was evaluated without correction for multiple comparisons, because we sought to identify all possible associations between the conditions under study and autism. Analyses by period compared women with a diagnosis in a particular period with women with no diagnoses in the entire 4-year period (date of delivery ± 2 years). Periods were defined as *history* (diagnosis in the 2 years before delivery), *first trimester*, *second trimester*, *third trimester*, and *postdelivery* (diagnosis only in 2 years after delivery). Maternal and infant characteristics associated with both maternal disease status and infant case status (maternal age, maternal race/ethnicity, maternal education, plurality) were included as covariates in multivariate analyses. All study procedures were approved by the institutional review board of the KPMCP and the California State Committee for the Protection of Human Subjects.

RESULTS

Characteristics of the 407 cases and 2095 controls in the final study population are given in **Table 2**. Because of frequency matching on sex, 82% of both case and control children were male. The frequency of multiple births among cases was more than double that among controls. The mean age at delivery was higher for case mothers compared with control mothers, and a greater proportion of case mothers were white and had more than a high school education. Length of membership in KPMCP was, on average, 5 months longer for cases than controls. The frequency distribution of birth year and hospital of birth was similar for cases and controls (data not shown).

The frequency of maternal autoimmune, asthma, and allergic diseases diagnosed any time in the 4-year period is given in **Table 3**. A similar proportion of case and control mothers had a diagnosis of any autoimmune disease in this period (10.3% vs 8.2%, *P*=.15). Specific autoimmune conditions occurred with low frequency in this population. Only 2 conditions were reported with greater frequency among mothers of ASD-affected children compared with controls: psoriasis (2.7% vs 1.0%, *P*=.003) and type 1 diabetes mellitus (1.2% vs 0.4%, *P*=.04). After adjustment for maternal factors, only psoriasis remained significantly associated with ASD (adjusted OR, 2.7; 95% CI, 1.3-5.8) (**Table 4**). When we extended the period to also include conditions recorded before or after the 4-year period surrounding the delivery, we found a substantially higher overall frequency of maternal autoimmune diseases for both cases and controls, although the case-control difference remained unchanged (17.7% vs 14.3%; adjusted OR, 1.2; 95% CI, 0.9-1.6).

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Table 4. Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Autism Associated With Maternal Autoimmune Diseases, Asthma, and Allergies

Disorder	Crude OR (95% CI)	Adjusted OR (95% CI)*
Autoimmune diseases	1.3 (0.9-1.8)	1.2 (0.8-1.7)
Alopecia	1.4 (0.6-3.1)	1.4 (0.6-3.0)
Autoimmune thyroid disease	0.6 (0.3-1.3)	0.6 (0.3-1.2)
Psoriasis	2.9 (1.4-6.1)	2.7 (1.3-5.8)
Type 1 diabetes mellitus	2.9 (1.0-8.8)	2.6 (0.8-7.9)
Asthma	1.6 (1.2-2.1)	1.6 (1.2-2.2)
Allergies	1.5 (1.1-1.9)	1.5 (1.2-1.9)
Allergic rhinitis	1.6 (1.2-2.1)	1.6 (1.2-2.1)
Anaphylaxis	1.4 (0.7-2.9)	1.5 (0.7-3.1)
Atopic eczema	1.8 (1.0-3.3)	1.8 (1.0-3.4)
Conjunctivitis	1.2 (0.6-2.6)	1.2 (0.6-2.6)

*These ORs were adjusted for maternal age, maternal education, maternal race/ethnicity, and plurality.

Table 5. Adjusted Odds Ratios (ORs) and 95% Confidence Intervals (CIs) for Autism Associated With Maternal Autoimmune Diseases, Asthma, and Allergies by Period of Diagnosis

Exposure Period	No. of Cases (n = 406)	No. of Controls (n = 2087)	Adjusted OR (95% CI)*
Autoimmune diseases			
History†	22	98	1.0 (0.6-1.7)
Trimester 1	4	16	1.2 (0.4-3.6)
Trimester 2	4	20	1.0 (0.3-3.1)
Trimester 3	14	54	1.1 (0.6-2.1)
Postdelivery‡	20	71	1.5 (0.9-2.5)
Asthma			
History	42	140	1.7 (1.2-2.4)
Trimester 1	10	20	2.8 (1.3-6.1)
Trimester 2	14	37	2.2 (1.1-4.2)
Trimester 3	23	77	1.7 (1.0-2.8)
Postdelivery	21	79	1.4 (0.8-2.3)
Allergies			
History	48	173	1.5 (1.1-2.1)
Trimester 1	7	35	1.0 (0.4-2.3)
Trimester 2	11	27	2.5 (1.2-5.2)
Trimester 3	6	18	1.9 (0.7-4.9)
Postdelivery	54	211	1.5 (1.1-2.0)

*The ORs were adjusted for maternal age, maternal education, maternal race/ethnicity, and plurality.
†In the 2 years before delivery.
‡In the 2 years after delivery.

Asthma and allergic diseases were relatively more common in both case and control mothers and were reported significantly more often for mothers of affected children (Table 3). After adjustment for maternal factors, asthma and allergic rhinitis remained significantly associated with autism (Table 4).

To evaluate the impact on the association with ASDs of the timing of the maternal diagnosis relative to the stage of pregnancy, we calculated crude and adjusted ORs associated with maternal disease diagnoses recorded before, during, and after pregnancy. After adjustment for maternal factors, no association was found for autoimmune diagnoses recorded during any of the intervals under consideration (**Table 5**). Odds ratios higher than 2.0 were observed for asthma diagnoses recorded during the first and second trimesters of pregnancy and for allergy diagnoses recorded during the second trimester of pregnancy (Table 5). After adjustment for maternal medication use, point estimates were only modestly attenuated for maternal asthma (OR, 1.9; 95% CI, 1.0-3.7) or allergy (OR, 2.3; 95% CI, 1.1-4.8) reported in the second trimester of pregnancy. No independent effect was observed for medication use.

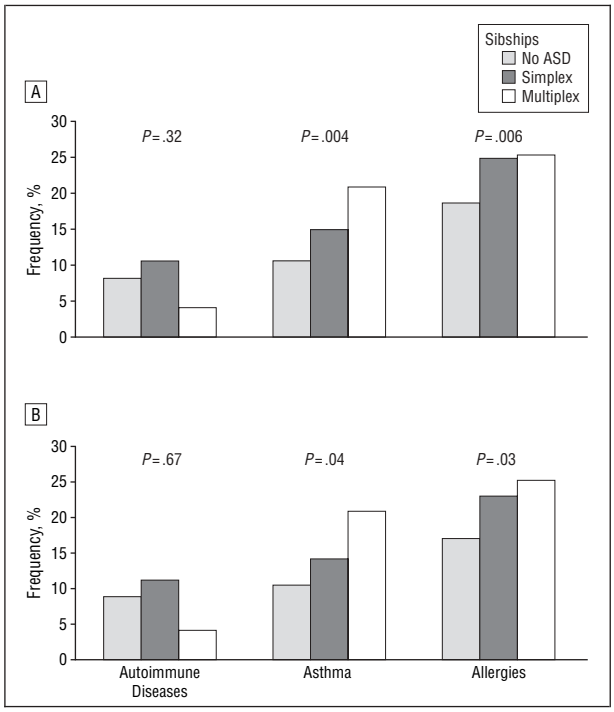

Figure. Frequency of maternal disease among all study sibships (A) and sibships with 2 or more children (B). *P* values are from the χ^2 test for trend. ASD indicates autism spectrum disorder.

The frequency of maternal autoimmune diseases, asthma, and allergies diagnosed any time in the 4-year period among unaffected, simplex, and multiplex sibships was also evaluated. The frequency of maternal disease increased significantly with increasing numbers of ASD-affected children in the sibship for asthma (χ^2_{trend}=8.36, *P*=.004) and allergies (χ^2_{trend}=7.51, *P*=.006) but not for autoimmune diseases (χ^2_{trend}=0.99, *P*=.3) (**Figure**). Similar relationships were observed for the subgroup of study children (n=1262) who came from sibships of at least 2 children (Figure).

COMMENT

In contrast to published reports of self-selected patients without verification of maternal self-reports of autoimmune conditions,[25] we did not find an overall association between autism risk and maternal autoimmune diseases documented in the medical records of patients in the KPMCP. Among 44 specific autoimmune conditions evaluated, only psoriasis (a chronic immune-

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mediated cutaneous disorder) occurred more frequently among mothers of children with autism compared with mothers of control children after adjustment for covariates. Two other immune-mediated conditions, asthma and allergies, were significantly more often reported for mothers of ASD-affected children compared with controls. These findings are strengthened by a large study population; the use of prospectively collected, physician-documented diagnoses of maternal autoimmune, asthma, and allergic diseases; the use of an appropriately matched internal comparison group; and the ability to examine risk for specific periods during pregnancy and to adjust analyses for several important covariates.

Until replicated in another large study population, our findings should be interpreted with caution because a true association with autoimmune diseases may be underestimated. The frequencies of specific autoimmune diseases in our study population were, in general, similar to previously reported population prevalence estimates.[29] However, reliance on diagnosed autoimmune conditions in a 4-year period surrounding pregnancy may have identified only "the tip of the iceberg" because the incidence of autoimmune diseases increases throughout adult life.[30] As these women age and their risk for autoimmune disorders increases, it is possible that continued investigation will reveal a case-control difference that we were unable to detect, even in our large population. In addition, women who were asymptomatic or experienced only mild symptoms during the study period may not have had their conditions diagnosed. Evaluations using biologic markers of immune function may be required to identify this larger pool of women with primarily subclinical conditions.

The methods used to identify case and control patients may have resulted in some misclassification. The ASD case patients were selected based on diagnoses recorded in medical records, without validation by a standardized clinical assessment, and we were unable to evaluate risk within ASD phenotypic subgroups. Control subjects were selected randomly from the pool of patients who had not had an ASD diagnosed and may include a small number of children with undiagnosed ASDs. A pilot study we conducted of a sample of 35 children with an ASD diagnosis recorded in the KPMCP outpatient databases indicates that misclassification of cases is likely to be minimal. Following a protocol closely adapted from the Metropolitan Atlanta Developmental Disabilities Surveillance Program,[31] expert review of detailed information on diagnoses, school services, behavioral and developmental history, and psychometric assessment results abstracted from all pediatric and mental health records for these children determined that 54% had an ASD according to *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria and the remaining 46% according to clinical impression. To the extent that misclassification of cases or controls occurred in our samples, the observed association between maternal immune conditions and autism may underestimate the true magnitude of risk associated with these conditions.

Our study was designed to minimize the possibility of bias due to self-selection of patients or reliance on maternal recall, since selection and recall bias may explain the findings previously reported by Comi et al[25] and Sweeten et al.[26] For those studies, the ascertainment of a family history of autoimmune disease was based on reports from parents who volunteered to participate, without verification of diagnoses by clinical examination or review of medical records. In the study by Comi et al, the proportion of case mothers who reported a history of autoimmune disorders (16%) was similar to our estimate of 18% among cases, but the reported frequency among control mothers (2%) was significantly lower than our estimate of 14% based on physician-reported diagnoses. In the more recent study by Sweeten et al, the frequency of autoimmune disorders self-reported by mothers was higher in autism families and lower in control families compared with our estimates, suggesting that recall bias may explain the observed association. Moreover, there was no overlap in the specific conditions that were elevated in these studies (hypothyroidism or Hashimoto thyroiditis,[26] rheumatic fever,[26] and rheumatoid arthritis[25]) and in our investigation (psoriasis). The inconsistencies with regard to specific autoimmune conditions may be attributed to methodologic differences between the studies but may also indicate different population frequencies of the autoimmune disorders. Additional studies with large sample sizes, proper comparison groups, and objectively collected data on maternal disease status will be required to determine whether there is a true association between maternal history of any autoimmune disorders, or of specific autoimmune disorders, and ASD.

Our finding of an association with maternal asthma and allergic diseases has not, to our knowledge, been previously reported. If supported by further study, our observation that these conditions were more strongly associated with autism in families with more than 1 ASD-affected child may suggest that genes underlying atopy may also be etiologically related to autism. The observation that autism risk was highest among women with diagnoses of asthma or allergies recorded during the second trimester may indicate that disease severity or disease flare-up may be more strongly correlated with fetal neuropathologic conditions or that a critical period for dysregulation in neurodevelopment occurs in midpregnancy. It is possible that the period during which maternal diagnoses were recorded may not reflect the period during which symptoms were experienced, although since more than 80% of women received regular medical care during each period, diagnoses recorded during specific periods may well reflect when the symptoms appeared. Because of the similarity of symptoms, it is also possible that maternal respiratory infections were misdiagnosed as atopic reactions. Numerous studies[32,33] have suggested an association between perinatal exposure to infection and autism risk.

Although we do not find a strong association between autism and maternal immune dysfunction, an etiologic link is biologically plausible in the context of current scientific understanding of possible mechanisms. Relevant mechanisms to consider include a shared genetic susceptibility to both immunologic diseases and autism[22,32,34] or passive transfer of antibodies to neural tis-

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sue. A more likely scenario is direct impact on fetal brain development via altered levels of circulating cytokines.[35] There is strong evidence that the inflammatory cytokine interleukin 6 (IL-6) can cross the placenta,[36] and dysregulation of IL-6 has been implicated in the pathology of nervous system disturbances.[37] Recent data indicate that T cells and proinflammatory cytokines, including IL-6, are of major importance in the pathophysiology of psoriasis.[38-40] Among pregnant women with psoriasis, this elevation of the IL-6 level would similarly result in higher levels of IL-6 in fetal circulation.

Allergic rhinitis is a frequent problem during pregnancy[41] that may be due in part to the shift from T_H1 to T_H2 cytokines during gestation such that levels of regulatory cytokines are elevated and proinflammatory cytokines are reduced.[42] Allergy is typically associated with a T_H2 cytokine profile. Moreover, during an acute allergic episode or exacerbation of asthma, histamine is released through mast cell degranulation, which enhances IL-1–induced production of IL-6 by monocytes.[43] In individuals with chronic allergic disease or allergic asthma, IL-6 has been implicated in the inflammation associated with airway remodeling,[43,44] and IL-6 has repeatedly been found to be elevated in biologic fluids and tissues of individuals with asthma. In women with a dysregulated immune response, evidence suggests the potential for altered cytokine production toward an inflammatory phenotype during pregnancy.[45] This can result in the transfer of several factors to the fetus during critical periods of gestation. It is also possible that the immune response of the child, rather than that of the mother, may be the primary abnormality in autism, leading secondarily to brain dysregulation. Finally, autism and immunologic diseases may have shared environmental risk factors. Similarity in observed temporal increases[46-52] and in demographic patterns[53-58] between autism and some immune conditions suggests that an exploration of environmental factors may be etiologically informative.

CONCLUSIONS

These findings from a large, contemporary population of members of the Kaiser Permanente integrated health care system suggest that maternal autoimmune disorders present in women around the time of pregnancy are unlikely to be significant contributors to the development of autism in their children and that further etiologic investigations should not only include objective documentation of diagnoses but also consider a larger set of immune-related conditions in the mother that includes asthma and allergies. Further investigations in large populations are needed to unravel the relationships between autism and the complex and interacting roles of genetic factors, environmental influences, and the immune status of fetuses, young children, and their mothers.

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