Parental Autoimmune Diseases Associated With Autism Spectrum Disorders in Offspring

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Background: Autism spectrum disorders are often idiopathic. Studies have suggested associations between immune response and these disorders. We explored associations between parental autoimmune disorders and children's diagnosis of autism by linking Swedish registries.

Methods: Data for each participant were linked across 3 Swedish registries. The study includes 1227 cases and 25 matched controls for each case (30,693 controls with parental linkage). Parental diagnoses comprised 19 autoimmune disorders. We estimated odds ratios (ORs) using multivariable conditional logistic regression.

Results: Parental autoimmune disorder was weakly associated with autism spectrum disorders in offspring (maternal OR = 1.6 [95% confidence interval = 1.1–2.2]; paternal OR = 1.4 [1.0–2.0]). Several maternal autoimmune diseases were correlated with autism. For both parents, rheumatic fever was associated with autism spectrum disorders.

Conclusions: These data support previously reported associations between parental autoimmune disorders and autism spectrum disorders. Parental autoimmune disorders may represent a critical pathway that warrants more detailed investigation.

Autism spectrum disorders comprise a group of developmental disorders defined by a constellation of behavioral, communication, and social deficits.[1] Altered autoimmune responses have been reported among persons with autism,[2,3] as well as among their parents[4–6] and other family members.[7] Autoimmune disorders represent specific types of immune dysfunction in which the immune system activates against self-antigens. Autoimmune conditions previously reported in association with autism include type 1 diabetes, rheumatoid arthritis, ulcerative colitis, and celiac disease.[4–17] Molloy et al[18] reported regressive autism as a subtype that may be more strongly associated with familial autoimmune disorders. The current study examines associations of maternal and paternal autoimmune disease with autism spectrum disorders in offspring, using comprehensive data from Swedish medical records.

METHODS

This study is based on record linkage of the Swedish registry system, described previously by Daniels et al.[19] Briefly, cases were identified as children born between 1977 and 2003 who were diagnosed by age 10 with an autism spectrum disorder (autism, Asperger syndrome, or pervasive developmental disorder-not otherwise specified) in the Swedish Hospital Discharge Registry. The Register includes nearly-complete data on hospital discharges and diagnoses made by the treating physician according to the International Classification of Diseases (ICD).[20] The Swedish health care system includes a strong network of school health services, inpatient care, and outpatient care.

The children's diagnostic records were linked to the Swedish Medical Birth Registry, operated by the National Board of Health and Welfare, using the unique national registration number assigned to all Swedish residents at the time of birth or immigration. Each case child was matched by sex, birth year, and birth hospital to 25 living control children in the Registry who did not have a record of autism spectrum disorders diagnosis.

Among the 1237 cases and 30,925 controls who met all eligibility criteria, 1227 (99%) of the cases and 30,693 (99%) of the controls were linked to both biologic parents, using the Swedish Multi-Generation Register. The register assumes paternity for the husband of the mother at the time of birth or the man identified "by acknowledgment" of unwed mothers. The Swedish Hospital Discharge Register was used to identify all diagnoses related to autoimmune disorders for each parent (using ICD Codes) between 1968 and 2003. Parental autoimmune disorders were classified a priori according to

Submitted 13 November 2009; accepted 2 June 2010; posted 26 August 2010.
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Supported partially by the US Centers for Disease Control and Prevention (Grant # U50/CCU422345–04) and the US National Institute of Health Sciences (Grant # T32 ES007018).

SDC SDC Supplemental digital content is available through direct URL citations in the HTML and PDF versions of this article (www.epidem.com).

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ISSN: 1044-3983/10/2106-0805
DOI: 10.1097/EDE.0b013e3181f26e3f

ICD code (eTable, http://links.lww.com/EDE/A422). Statistics Sweden provided data on parents' country of birth and socioeconomic status.

Because most autoimmune disorders are rare, we restricted our analysis of specific autoimmune conditions to disorders occurring in parents of at least 2 cases. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using conditional logistic regression, with adjustments for child's age, sex, and hospital of birth, and for parents' country of birth and age at delivery. The study was approved by the University of North Carolina at Chapel Hill Office of Human Research Ethics Institutional Review Board and by the Karolinska Institutet Research Ethics Committee.

RESULTS

Matching characteristics were similar among autism spectrum disorders cases and controls. Control parents were younger, more likely to originate from Nordic countries, and less likely to originate from Asian and African countries than parents of children with autism spectrum disorders (as noted previously by Daniels et al[19]). A majority (63%) of the Autism spectrum disorders cases were diagnosed before 1998, using ICD-9 criteria for diagnosis (Table 1).

Collectively, autoimmune disease in both parents was associated with an increased likelihood of autism spectrum disorders diagnosis in offspring (for maternal diagnosis OR = 1.6 [95% CI =1.1–2.2]; for paternal diagnosis, OR = 1.4 [95% CI = 1.0–2.0]) (Table 2). Several specific diagnoses among mothers had elevated odds ratios, including type-1 diabetes, idiopathic thrombocytopenic purpura, myasthenia gravis, and rheumatic fever; however, most were quite rare and effect estimates were imprecise. Fewer associations were noted for fathers.

DISCUSSION

This study supports previous reports that the prevalence of autoimmune disorders is elevated in families of persons diagnosed with an autism spectrum disorders,[18,21] especially for mothers of children with autism.[4–6] This study was large and population-based, and it used complex record linkages to provide extensive health data on individuals for many years, which may have avoided some selection and recall issues of earlier studies.

Our results are generally similar to other published studies,[4,5] although varying methods, case definitions, and prevalences of autoimmune disorders limit direct comparison. Two registry-based studies from Denmark reported elevated prevalence of type-1 diabetes, ulcerative colitis, and psoriasis among parents of children with autism.[6,7] However, one of these studies relied primarily on a narrower, ICD-8 classification for autism.[5,6] The other was methodologically similar to ours but included only parental disorders that occurred before children's diagnoses.[7] Another study from the United States also reported an association between type-1 diabetes mellitus; that study evaluated several additional maternal autoimmune disorders that were not prevalent in our study.[4]

There is some concern that childhood disease might be differentially ascertained when parents have chronic disease.

TABLE 1. Demographic Characteristics From Swedish Medical Birth Registry and Statistics Sweden

	Autism Spectrum Disorder (n = 1237) No. (%)	Controls (n = 30,925) No. (%)
Maternal age (years)		
<25	327 (27)	8485 (28)
26–30	414 (34)	11,450 (37)
31–35	317 (26)	7511 (24)
36–40	146 (12)	2783 (9)
41–50	23 (2)	464 (2)
Paternal age (years)		
<25	128 (10)	4407 (14)
26–30	346 (28)	9846 (32)
31–35	385 (32)	9136 (30)
36–40	226 (18)	4759 (16)
41–50	125 (10)	2345 (8)
>50	17 (1)	200 (1)
Maternal country of origin		
Nordic countries	1029 (84)	27,588 (90)
Europe and North America	59 (5)	1364 (4)
Africa	42 (3)	403 (1)
Asia	77 (6)	1016 (3)
South America	18 (1)	254 (1)
Other	2 (0.2)	68 (0.2)
Paternal country of origin		
Nordic countries	1013 (83)	27,136 (88)
Europe and North America	66 (5)	1622 (5)
Africa	49 (4)	514 (2)
Asia	82 (7)	1094 (4)
South America	17 (1)	282 (1)
Other	0	45 (0.1)
Sex of child		
Boy	939 (77)	23,478 (76)
Girl	288 (23)	7215 (24)
Age at diagnosis/reference (years)		
1	12 (1)	300 (1)
2	62 (5)	1562 (5)
3	0 (14)	4161 (14)
4	240 (20)	6012 (20)
5	213 (17)	5286 (17)
6	158 (13)	3947 (13)
7	148 (12)	3693 (12)
8	88 (7)	2258 (7)
9	94 (8)	2335 (8)
10	44 (4)	1139 (4)
Diagnosis		
ICD-9 (diagnosed before 1998)	776 (63)	
ICD-10 (diagnosed in or after 1998)	451 (37)	

TABLE 2. Associations of Autism Among Children in Relation to Autoimmune Disease Diagnosis Among the Parents, for Diagnoses With More Than One Case of Autism

	No. Children With Maternal Diagnosis			No. Children With Paternal Diagnosis		
Diagnosis	**Cases of Autism**	**Controls**	**OR (95% CI)[a]**	**Cases of Autism**	**Controls**	**OR (95% CI)[a]**
Autoimmune diseases						
Diabetes	16	233	1.8 (1.0–2.9)	17	288	1.4 (0.8–2.2)
Ulcerative colitis/Crohn disease	10	181	1.4 (0.8–2.7)	8	175	1.2 (0.6–2.5)
Psoriasis	3	35	2.2 (0.7–7.1)	3	32	2.3 (0.7–7.6)
ITP	2	2	22.2 (3.0–164.4)	0	2	
Systemic lupus erythematosus	2	18	3.1 (0.7–13.6)	0	1	
Myasthenia gravis	2	6	10.2 (2.0–52.6)	0	3	
Rheumatic fever	2	7	7.7 (1.6–37.9)	2	9	5.7 (1.2–26.3)
Any autoimmune disease[b]	39	631	1.6 (1.1–2.2)	34	577	1.4 (1.0–2.0)

All hypothesized associations were modeled using conditional logistic regression.
[a]Adjusted for child's age, hospital of birth, sex, and parents' ages at delivery, country of birth.
[b]Includes the above diagnoses plus Graves disease, autoimmune thyroiditis, ankylosying spondylites, Guillain-Barr é syndrome, multiple sclerosisis, AIHA, dermatopymositis, Reither disease, vasulitis, Sjögren syndrome, and pernicious anemia.

Parents may use health care more frequently, and consequently may more readily seek care for their child. Such a phenomenon might have a greater impact in studies that focus on parents' diagnoses that precede children's diagnoses. Because some previous studies rely on person-time at risk to calculate incidence rate ratios, any reduction in time at risk for children of parents with disease due to accelerated use of health care might inflate the association. Our study included parental diagnoses that occurred before as well as after the birth and diagnosis of the child; furthermore, we estimated odds ratios, which were not subject to differential time at risk.

We were unable to validate each autism spectrum disorders diagnosis in this registry-based study, unlike the California-based studies.[4,10] Nonetheless, the child's discharge diagnosis in our Registry represents the final assessment of a psychiatric specialist. During the period of study, the Swedish Hospital Discharge Register provides nationwide coverage of inpatient facilities, to which all residents have equal access. Previous estimates suggest the registry captured approximately 50% of all autism spectrum disorders cases during the study period.[20,22,23] Because the registry is based on hospital diagnoses, milder cases of both child and parental disorders may be underrepresented. Under-ascertainment of both outcome and exposure would likely underestimate the effect estimates, although the confluence of these factors could bias the results in of an unpredictable direction. Finally, we were unable to identify siblings within this analysis. Clustering within families would not bias our estimated odds ratios, but it might produce confidence intervals that are too narrow.

There are several plausible pathways by which immune dysfunction might affect autism spectrum disorders.[2,3,24–26] Maternal autoimmunity may influence brain development either by creating a hostile uterine environment[11,12] or by altering the child's autoimmunity in early development through immunoglobulin G (IgG), which can pass through the blood-brain barrier and is partly responsible for maternally-conferred immunity in infancy.[10] The IgG reactivity profiles of children with autism and their mothers have been shown to differ from controls.[8,27–29] Radetti et al[30] also described a transplacental pathway by which maternal autoantibodies can be introduced into the fetal environment. Animal studies have shown differential cytokine profiles and autism-like characteristics in offspring induced by prenatally exposing mice and rhesus monkeys to a human case-mother's IgG.[11,12,31] Together, these studies suggest that nonspecific autoimmune reactivity in parents, (primarily mothers) may be related to autism in offspring.[11,12,31,32] This literature could be interpreted in 2 ways: (1) some cases of autism spectrum disorders result from adverse conditions caused by altered autoimmune response during the prenatal or early postnatal period, possibly by enhancing susceptibility to other agents, or (2) some familial factors are concurrently associated with both autism spectrum disorders and autoimmunity.

We observed nearly a 50% higher odds of being diagnosed with autism by age 10 years among children whose parents had any autoimmune disease. We used a large, representative sample with extensive, lengthy follow-up of individuals through the registry system. The overall association was observed for both mothers and fathers, but high odds ratios estimated for some disorders should be interpreted with caution due to the rarity of each disorders. Our results support those from smaller studies, although the specific autoimmune disorders implicated vary by study, possibly a result of methodological differences or differing burden of specific autoimmune disorders among the source populations. The more consistently implicated and prevalent disorders, such as type 1 diabetes, warrant more in-depth investigation. Studies

could also explore familial autoimmune conditions among subclinical autism-related behaviors or the broad autism phenotype.[33] Further mechanistic work should investigate specific etiologic bases for this association.

REFERENCES

1. Lord C, Cook J, Edwin H, Leventhal BL, Amaral DG. Autism spectrum disorders. *Neuron*. 2000;28:355–363.
2. Ashwood P, Wills S, Van de Water J. The immune response in autism: a new frontier for autism research. *J Leukoc Biol.* 2006;80:1–15.
3. Ashwood P, Van de Water J. A review of autism and the immune response. *Clin Dev Immunol.* 2004;11:165–174.
4. Croen LA, Grether JK, Yoshida CK, Odouli R, Van de Water J. Maternal autoimmune diseases, asthma and allergies, and childhood autism spectrum disorders: a case-control study. *Arch Pediatr Adolesc Med.* 2005;159:151–157.
5. Mouridsen SE, Rich B, Isager T, Nedergaard NJ. Autoimmune diseases in parents of children with infantile autism: a case-control study. *Dev Med Child Neurol*. 2007;49:429–432.
6. Atladóttir HO, Pedersen MG, Thorsen P, et al. Association of family history of autoimmune diseases and autism spectrum disorders. *Pediatrics*. 2009;124:687–694.
7. Sweeten TL, Bowyer SL, Posey DJ, Halberstadt GM, McDougle CJ. Increased prevalence of familial autoimmunity in probands with pervasive developmental disorders. *Pediatrics*. 2003;112:e420.
8. Cabanlit M, Wills S, Goines P, Ashwood P, Van de Water J. Brain-specific autoantibodies in the plasma of subjects with autistic spectrum disorder. *Ann N Y Acad Sci.* 2007;1107:92–103.
9. Croonenberghs J, Wauters A, Devreese K, et al. Increased serum albumin, gamma globulin, immunoglobulin IgG, and IgG2 and IgG4 in autism. *Psychol Med*. 2002;32:1457–1463.
10. Croen LA, Braunschweig D, Haapanen L, et al. Maternal mid-pregnancy autoantibodies to fetal brain protein: the early markers for autism study. *Biol Psychiatry*. 2008;64:583–588.
11. Dalton P, Deacon R, Blamire A, et al. Maternal neuronal antibodies associated with autism and a language disorder. *Ann Neurol*. 2003;53:533–537.
12. Martin LA, Ashwood P, Braunschweig D, Cabanlit M, Van de Water J, Amaral DG. Stereotypies and hyperactivity in rhesus monkeys exposed to IgG from mothers of children with autism. *Brain Behav Immun*. 2008;22:806–816.
13. Lee L, Zachary AA, Leffell MS, et al. HLA-DR4 in families with autism. *Pediatr Neurol*. 2006;35:303–307.
14. Russo AF. Anti-metallothionein IgG and levels of metallothionein in autistic families. *Swiss Med Wkly*. 2008;138:70–77.
15. Silva SC, Correia C, Fesel C, et al. Autoantibody repertoires to brain tissue in autism nuclear families. *J Neuroimmunol*. 2004;152:176–182.
16. Singer HS, Morris CM, Williams PN, Yoon DY, Hong JJ, Zimmerman AW. Antibrain antibodies in children with autism and their unaffected siblings. *J Neuroimmunol*. 2006;178:149–155.
17. Todd RD, Hickok JM, Anderson GM, Cohen DJ. Antibrain antibodies in infantile autism. *Biol Psychiatry*. 1988;23:644–647.
18. Molloy CA, Morrow AL, Meinzen-Derr J, et al. Familial autoimmune thyroid disease as a risk factor for regression in children with autism spectrum disorder: a CPEA Study. *J Autism Dev Disord*. 2006;36:317–324.
19. Daniels JL, Forssen U, Hultman CM, et al. Parental psychiatric disorders associated with autism spectrum disorders in the offspring. *Pediatrics*. 2008;121:e1357–e1362.
20. Hultman CM, Sparen P, Cnattingius S. Perinatal risk factors for infantile autism. *Epidemiology*. 2002;13:417–423.
21. Comi AM, Zimmerman AW, Frye VH, Law PA, Peeden JN. Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *J Child Neurol*. 1999;14:388–394.
22. Gillberg C, Wing L. Autism: not an extremely rare disorder. *Acta Psychiatr Scand*. 1999;99:399–406.
23. Fombonne E. The epidemiology of autism: a review. *Psychol Med*. 1999;29:769–786.
24. Ashwood P, Van de Water J. Is autism an autoimmune disease? *Autoimmun Rev.* 2004;3:557–562.
25. Korvatska E, Van de Water J, Anders TF, Gershwin ME. Genetic and immunologic considerations in autism. *Neurobiol Dis*. 2002;9:107–125.
26. Wills S, Cabanlit M, Bennett J, Ashwood P, Amaral D, Van de Water J. Autoantibodies in autism spectrum disorders (ASD). *Ann N Y Acad Sci.* 2007;1107:79–91.
27. Braunschweig D, Ashwood P, Krakowiak P, et al. Autism: maternally derived antibodies specific for fetal brain proteins. *Neurotoxicology*. 2008;29:226–231.
28. Connolly AM, Chez M, Streif EM, et al. Brain-derived neurotrophic factor and autoantibodies to neural antigens in sera of children with autistic spectrum disorders, Landau-Kleffner syndrome, and epilepsy. *Biol Psychiatry*. 2006;59:354–363.
29. Weizman A, Weizman R, Szekely GA, Wijsenbeek H, Livni E. Abnormal immune response to brain tissue antigen in the syndrome of autism. *Am J Psychiatry*. 1982;139:1462–1465.
30. Radetti G, Persani L, Moroder W, Cortelazzi D, Gentili L, Beck-Peccoz P. Transplacental passage of anti-thyroid auto-antibodies in a pregnant woman with auto-immune thyroid disease. *Prenat Diagn*. 1999;19:468–471.
31. Singer H, Morris C, Gause C, Pollard M, Zimmerman A, Pletnikov M. Prenatal exposure to antibodies from mothers of children with autism produces neurobehavioral alterations: a pregnant dam mouse model. *J Neuroimmunol*. 2009;211:39–48.
32. Rose N, Bona C. Defining criteria for autoimmune diseases (Witebsky's postulates revisited). *Immunol Today (Amsterdam. Regular ed)*. 1993;14:426–430.
33. Micali N, Chakrabarti S, Fombonne E. The broad autism phenotype: findings from an epidemiological survey. *Autism*. 2004;8:21–37.