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Immune Mediated Conditions in Autism Spectrum Disorders

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Abstract

We conducted a case-control study among members of Kaiser Permanente Northern California (KPNC) born between 1980 and 2003 to determine the prevalence of immune-mediated conditions in individuals with autism, investigate whether these conditions occur more often than expected, and explore the timing of onset relative to autism diagnosis. Cases were children and young adults with at least two autism diagnoses recorded in outpatient records (n=5,565). Controls were children without autism randomly sampled at a ratio of 5 to 1, matched to cases on birth year, sex, and length of KPNC membership (n=27,825). The main outcomes - asthma, allergies, and autoimmune diseases - were identified from KPNC inpatient and outpatient databases. Chi-square tests were used to evaluate case-control differences. Allergies and autoimmune diseases were diagnosed significantly more often among children with autism than among controls (allergy: 20.6% vs. 17.7%, Crude odds ratio (OR) = 1.22, 95% confidence interval (CI) 1.13 – 1.31; autoimmune disease: 1% vs. 0.76%, OR = 1.36, 95% CI 1.01 – 1.83), and asthma was diagnosed significantly less often (13.7% vs. 15.9%; OR = 0.83, 95% CI 0.76 – 0.90). Psoriasis occurred more than twice as often in cases than in controls (0.34% vs. 0.15%; OR =2.35, 95% CI 1.36 – 4.08). Our results support previous observations that children with autism have elevated prevalence of specific immune-related comorbidities.

Keywords

Autism Spectrum Disorder; Allergies; Autoimmune disease; Asthma

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Introduction

A growing body of literature suggests that the immune system might be dysregulated in individuals affected by autism spectrum disorder (ASD) or their unaffected family members (Goines and Ashwood 2013; Stigler et al. 2009). Studies of biological markers of immune function in individuals with ASD have found neuroinflammation in brain tissues (Li et al. 2009; Pardo, Vargas, and Zimmerman 2005; Vargas et al. 2005), immunoglobulin imbalances, including increased levels of plasma IgG4 (Enstrom et al. 2009), reduced levels of IgG and IgM (Heuer et al. 2008; Heuer et al. 2012) or of total IgG (Grether et al. 2010); imbalances in cytokine/chemokine levels (Ashwood et al. 2011a; Ashwood et al. 2011b, 2011c; Suzuki et al. 2011), abnormal ratios of CD4+ to CD8+ T-cells or increased blood levels of nitric oxide metabolites (Stigler et al. 2009).

Previous studies have relied on small sample sizes and have reported conflicting results as to whether the prevalence of immune-mediated conditions is higher in children with ASD than in children without ASD. (Mostafa, Hamza, and El-Shahawi 2008; Magalhaes et al. 2009; Bakkaloglu et al. 2008; Jyonouchi et al. 2008). In one study, Mostafa et al. (2008) reported that allergic manifestations were 5 times as prevalent in children with ASD than in controls (52% vs. 10%). In a second study, Magalhaes et al. (2009) found a higher frequency of atopic dermatitis, asthma, rhinitis and serum IgE in children with Asperger compared to age-matched controls (87% vs. 7%). In contrast, Bakkaloglu et al. (2008) did not find a difference in serum IgE levels between cases and controls (Bakkaloglu et al. 2008). Jyonouchi et al. (2008) also reported no difference in atopic dermatitis, allergic rhinitis, asthma, and food allergy between 133 ASD cases and 105 controls (Jyonouchi et al. 2008). A few large studies show a higher prevalence of certain immune conditions in children with ASD. Parents of children with autism report food allergies in their affected children more often than parents whose children do not have ASD (Chaidez, Hansen, and Hertz-Picciotto 2013; Gurney, McPheeters, and Davis 2006). They also report improved behavior after changing their child's diet (Lucarelli et al. 1995). The reliability of these findings is uncertain, however, because self-reported information can be subject to reporting and recall bias. Studies utilizing medical record data also found that children and adolescents with ASD have a higher prevalence of immune-mediated conditions, including asthma, allergic rhinitis, atopic dermatitis, urticaria, type 1 diabetes, and inflammatory bowel disease (Chen et al. 2013; Kohane et al. 2012). The ability to draw conclusions from the Chen study (Chen et al. 2013) is limited by differential follow up between cases and controls.

To overcome methodological limitations of previous studies, we used diagnostic information prospectively recorded in medical records on a large population-based sample from a single healthcare plan to determine the prevalence of asthma, allergies, and autoimmune diseases in children and young adults with ASD. We also explored the timing of onset of immune-mediated conditions relative to the timing of autism diagnosis to determine if the presence of an ASD diagnosis influenced the diagnosis of an immune condition. Results from this study may help guide future research to identify clinical subgroups of ASD, such as those with immune conditions, which could aid discovery of etiologic factors and focus treatment approaches.

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Methods

Study Population

The study population consisted of 3- to 26-year-olds born between January 1, 1980, and December 31, 2003, who had been members of Kaiser Permanente Northern California (KPNC) for at least 12 months during the period 1995 –2006. The year 1995 was chosen as the earliest year because the outpatient electronic database, which was one of the sources of exposure identification, was established in 1995. KPNC is a group model, integrated health plan that provides care for over 3.5 million northern California residents. The KPNC membership represents approximately 30% of the insured population in the region and is demographically similar to the residents of the counties served by KPNC, except that the very poor and very wealthy are underrepresented (Krieger 1992).

Cases were defined as KPNC members with at least 2 ASD diagnoses (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 299.0 or 299.8) recorded in their medical record between the ages of 3–18 years. ASD diagnoses were identified by electronically scanning the KPNC outpatient clinical databases, which contain all diagnoses made at outpatient visits occurring at plan facilities and outside approved facilities. Controls were defined as KPNC members with no ASD diagnoses in their medical records. Five controls per case were randomly selected from the remaining study population, frequency matched to cases on sex, birth year, total membership months (plus or minus 12 months) in the health plan from 1986 – 2006. The KPNC inpatient database, another source of exposure identification, was established in 1986. To account for secular trends in ASD and immune condition diagnoses, we additionally matched controls to cases in 3 specific time periods (1986 –1990; 1991 – 2000 and 2001 – 2006) allowing +/− 24 months differences in membership length within each of these time periods.

Immune-mediated conditions

Immune-mediated conditions included asthma, allergies (food, dermatitis, rhinitis, and others), and a number of autoimmune diseases. Appendix A provides the list of the of ICD-9 codes included in the definition of each immune-mediated condition.

The occurrence of an immune-mediated condition was defined by at least 2 outpatient, inpatient, or emergency room diagnoses recorded in KPNC medical records between 1986 and 2006. For asthma, we required at least 2 diagnoses between the ages of 2–26 years. For allergy and autoimmune disorders, we required at least 2 diagnoses between birth and 26 years. Children with multiple immune conditions were counted in multiple categories. Information on child characteristics (sex, total length of KPNC membership) was obtained from health plan medical records.

Statistical Analysis

Demographic characteristics of cases and controls were compared with contingency tables for categorical variables and T-tests for continuous variables. We compared the prevalence of any immune-mediated condition and each condition separately (asthma, allergies, autoimmune disorders) among cases and controls using contingency tables. Case-control

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comparisons were restricted to those specific conditions for which at least 5 cases were affected. Conditional logistic regression models were fit to estimate odds ratios as a measure of association between ASD and immune-mediated conditions. In addition, stratified analyses by sex, age group, and total membership months were conducted.

To investigate the timing of immune-mediated condition diagnoses in relation to age at initial ASD diagnosis, the subset of the study population born at KPNC was analyzed separately. For each case, an index date was assigned corresponding to the date of first ASD diagnosis, and the age at index date was derived. We then assigned this age as the index date for all frequency matched controls. Prevalence of immune-mediated conditions before and after this index date was compared between cases and controls using chi-square statistics. The study was approved by the institutional review board of the Kaiser Foundation Research Institute.

Results

Due to matching, there was no difference in the proportion of cases and controls with regard to sex, mean age, total length of KPNC membership, or length of KPNC membership in specific time periods (Table 1). Approximately 40% of both cases and controls were born at KPNC.

Asthma was less frequently diagnosed among cases than controls (13.7% vs. 15.9%; OR = 0.83, 95% CI 0.76 – 0.90). However, allergies were more frequently diagnosed in ASD cases compared to controls (20.6% vs. 17.7%; OR = 1.22, 95% CI 1.13 – 1.31). In particular, rhinitis, food allergies, and other allergies were diagnosed significantly more often among cases than among controls (Table 2). Autoimmune diseases as a group were diagnosed significantly more often among children with ASD than among controls (1.0% vs. 0.8%; OR= 1.36, 95% CI 1.01 – 1.83). Psoriasis was the most frequently diagnosed autoimmune condition among children with autism; it occurred over twice as often in cases than in controls (0.34% vs. 0.15%; OR =2.35, 95% CI 1.36 – 4.08) (Table 2).

In a stratified analysis, we found that asthma was diagnosed less often in cases than in controls only among males and children ≥6 years old (Table 3). With respect to allergies, rhinitis and food allergies were associated with ASD among both males and females, but ‘other’ allergies were associated with ASD only among males. Food allergies were significantly elevated in children with ASD only among the <=12 age group, while associations with other types of allergies were similar across the different age categories. By contrast, the association between ASD and all autoimmune disorders combined and psoriasis alone was present only among males and children ≥12 years (Table 3).

When we restricted the analysis to children born at KPNC (birth cohort), the pattern of findings was similar to those of the total population. Asthma was diagnosed significantly less often, and food allergy and psoriasis were diagnosed significantly more often among cases than among controls (Appendix B).

The pattern of results was also similar for immune-mediated conditions diagnosed before the age at first ASD diagnosis. During the period prior to the first ASD diagnosis, asthma was

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diagnosed less often (OR = 0.81, 95% CI 0.70 – 0.93), and allergy (OR = 1.06, 95% CI 0.94 – 1.20) and autoimmune disorders (OR = 1.97, 95% CI 0.94 – 4.13) were diagnosed more often among children with ASD compared to control children (Appendix C).

Discussion

In this large, population-based case-control study, we found that asthma was diagnosed less often, and allergies (in particular, food allergies and rhinitis) and psoriasis were diagnosed more often in children with ASD compared to controls. Case-control differences for asthma and autoimmune disorders were evident only among males. Furthermore, diagnoses of these immune conditions were not influenced by the ASD diagnosis.

Asthma and ASD

Our findings contrast with results from two previous large studies, each of which reported a higher prevalence of asthma among children with ASD compared to controls (Chen et al. 2013; Gurney et al. 2006). Chen et al.(2013) used data from a national health insurance database in Taiwan, and found a higher prevalence of asthma documented in medical records among 1598 children with ASD (mean age 17 years) compared to 6393 age- and sex- matched controls (23.3% vs. 15.3%). Unlike our study, however, Chen et al. (2013) did not match cases and controls on total length of membership in the health plan. As a result, if children with ASD had a longer follow up time than controls, they would have had more time to be diagnosed with asthma. Our findings also contrast with results from a national survey of child health in the U.S. (Gurney et al, 2006). In that study, prevalence of asthma as reported by parents was somewhat higher but not statistically different between 483 children with ASD and 84,789 controls between 3 – 17 years of age (17.6% vs. 13.5%). However, the Gurney study relied on parental report of asthma, which could be subject to recall bias. In the present study, we found that asthma was less frequently diagnosed in children with ASD only among males. To our knowledge, our study is the first to investigate asthma rates by child sex. In the general population, asthma is more common in boys than in girls in the preteen age, and this gender difference seems to reverse after 15 years of age (Yunginger et al. 1992). Future large studies are necessary to replicate our findings and explore potential mechanisms which might explain our observations.

ASD and allergies

Our finding of higher prevalence of food allergy among ASD cases compared to controls is similar to that reported by two previous studies based on data from parental report (Chaidez et al. 2013; Gurney et al. 2006). Food allergy prevalence among controls in our study population (0.5%) was much lower than the 3.2% reported by Gurney et al.(2006) and the 11% reported by Chaidez et al.(2013). Our results, which are based on physician documented diagnoses, may underestimate the true prevalence of these conditions, because milder cases may not come to the attention of doctors. However, we would expect any under ascertainment to affect cases and controls to a similar degree, and therefore the relative difference between cases and controls should be more accurate using data recorded in medical records than information from parental report.

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Prevalence of rhinitis was also higher among ASD cases compared to controls in our study. This finding is similar to that reported by Chen et al. (2013), despite methodological differences between the two studies. Although both studies used diagnoses recorded in medical records, the prevalence of rhinitis among controls in our study population (12.9%) was about half that reported in Chen's study (27%). In our study, occurrence of allergy was determined by at least two diagnoses in the medical records. Chen et al.(2013) did not provide details regarding the definition of allergies. Our finding of higher prevalence of allergies in children with ASD vs. control children is consistent with previous studies that analyzed data from skin prick test and/or allergen-specific IgE, or cellular immune reactivity including TNF-α and/or IL-12, or brain specific auto-antibody production as biological markers of allergic reactions (Magalhaes et al. 2009; Mostafa and Al-Ayadhi 2013; Mostafa et al. 2008).

ASD and autoimmune disorders

We found that children with ASD had a higher prevalence of all autoimmune disorders combined compared to controls. However, we did not find a difference in the prevalence of type 1 diabetes between ASD cases and controls in contrast to two previous studies (Chen et al. 2013; Kohane et al. 2012). In the Chen study, for example, the prevalence of type1 diabetes among cases was about 3 times higher than the prevalence among controls (0.3% vs. 0.1%). If ASD cases had a longer follow up time than controls in Chen's study, they would have had more opportunities than controls to be diagnosed with type 1 diabetes, which could account for its higher prevalence among cases. In our study, we matched controls to cases on length of KP membership to avoid such bias. Kohane et al.(2012) analyzed medical record data from 4 different health plans and found that prevalence of type 1 diabetes in cases was twice that of controls (0.67% vs. 0.29%). Our results are based on data from a single healthcare plan.

In our study, psoriasis was more prevalent in children with ASD compared to controls. The prevalence of psoriasis in our control group was similar to that reported by a previous study that estimated the prevalence of psoriasis among child and adolescents utilizing medical record data (Wu et al. 2011). In our study population, psoriasis diagnoses occurred more in children ≥12 years, consistent with expectations that prevalence increases with age (Gelfand et al. 2005; Kurd and Gelfand 2009).

We previously reported that maternal allergies and psoriasis during pregnancy were associated with increased risk of ASD in the offspring (Croen et al. 2005). Here we find that the same immune conditions are more prevalent in children with ASD compared to controls. These findings suggest that genes underlying these immune abnormalities may also be etiologically related to ASD. In the general population, the prevalence of most immune diseases, including psoriasis, is higher in females than in males (Matusiewicz et al. 2014; Voskuhl 2011). In this study, however, male ASD cases were more affected than females. Given that ASD affects vastly more males than females (Wing 1981) and that autoimmune disorders are relatively rare, larger studies are needed to confirm the gender differences observed here.

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The present findings are strengthened by the large study population; the use of prospectively collected, physician documented diagnoses of autoimmune, asthma, and allergic diseases; and the use of an appropriately matched internal comparison group. Our exposure was defined based on medical record data using ICD9 codes. As a result, minor misclassification of asthma and allergies may have occurred. While children with asymptomatic or mild immune conditions may not have been diagnosed, this possible misclassification of exposure was likely not related to case status and would therefore only bias results towards the null value. The methods used to identify cases and controls may have also resulted in some minor outcome misclassifications. ASD cases were selected based on diagnoses recorded in medical records, without validation by a standardized clinical assessment. However, a subset of 50 cases had been previously evaluated with the Autism Diagnostic Interview-Revised (ADI-R) (Lord, Rutter, and Le Couteur 1994) and the Autism Diagnostic Observation Schedule-Generic (ADOS-G) (Lord et al. 2000), and 94% met criteria for ASD on both instruments. In addition, record-review validation studies conducted by the investigators have demonstrated that at least 90% of children with an ASD diagnosis recorded in the KPNC electronic databases have documentation consistent with a diagnosis of autism based on DSM-IV criteria (Croen et al. 2008). Control subjects were selected randomly from the pool of patients who had never received an ASD diagnosis from a KP provider, but it is possible that a small number (<1%) might in fact meet diagnostic criteria for ASD. Again, there is no reason to believe that outcome misclassification would be related to exposure status, and therefore our findings may, if anything, underestimate the true magnitude of association between immune-mediated conditions and ASD.

In the present study, we did not stratify our results by ASD subtypes. Future studies with accurate data on ASD subtype should address this limitation by comparing a more homogenous group of individuals with autism to those without autism. An additional limitation of this study is that we did not match ASD cases and controls on race/ethnicity, which may be associated with certain autoimmune diseases, including psoriasis (Helmick et al. 2014).

Our finding of no relationship between the timing of diagnosis of immune-mediated conditions and ASD indicate that our results are less likely to be affected by exposure ascertainment bias. That is, the knowledge of ASD diagnosis did not affect the diagnosis of the immune mediated-conditions.

Conclusion

In a population-based study, our results support previous observations that children with autism have elevated prevalence of specific immune-related comorbidities. Allergies to food and rhinitis, and autoimmune diseases, in particular psoriasis, occur more often than expected in children with autism. The presence of an ASD diagnosis does not appear to influence the diagnosis of the immune condition. More research is needed into the biologic mechanisms underpinning the association between immune-mediated conditions and autism spectrum disorders. Findings from such research could aid discovery of etiologic factors and help focus treatment approaches for individuals with autism spectrum disorders and immune comorbidities.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Allergies were more frequently diagnosed in autism spectrum disorder (ASD) cases compared to controls.
- Asthma was less frequently diagnosed among ASD cases than controls.
- Autoimmune diseases as a group were diagnosed significantly more often among children with ASD than controls.
- Psoriasis was the most frequently diagnosed autoimmune condition among children with autism; it occurred over twice more often in cases than controls.
- The presence of an ASD diagnosis did not influence the diagnosis of the immune condition.

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Table 1

Characteristics of study population, Kaiser Permanente Northern California members born 1980–2003.

Characteristics	ASD Cases (n = 5565) N (%)	Controls (n = 27825) N (%)	Chi-square P-value
Sex			
Female	1,002 (18)	5,010 (18)	1.0
Male	4,563 (82)	22,815 (82)	
Mean age in years in 2006 (SD)	12.15 (5.2)	12.15 (5.2)	1.0
Total length of KP membership in months (1995 – 2006)	107.72 (59.7)	107.73(59.7)	0.9
Total length of KP membership in months in specific time periods			
1986– 1994	15.27 (28.1)	15.25 (28.1)	1.0
1995 – 2000	35.44 (29.6)	35.11 (29.6)	1.0
2001 – 2006	57.01 (20.5)	57.02 (20.5)	1.0
Birth year			
1980 – 1985	372 (6.7)	1,860 (6.7)	1.0
1986 – 1990	1,102 (19.8)	5,510 (19.8)	
1991 – 1995	1,854 (33.3)	9,270 (33.3)	
1996 – 2000	1,642 (29.5)	8,210 (29.5)	
2001 – 2003	595 (10.7)	2,975 (10.7)	
Born at KPNC, %	41.7	42.6	0.2

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Table 2

Frequency of Immune- mediated Conditions in Children with Autism Spectrum Disorder (ASD) and Controls, Kaiser Permanente Northern California members born 1980–2003.

Immune mediated-conditions		**ASD cases (n=5565) N (%)**	**Controls (n-27825) N (%)**	**OR and 95% CI**
Any Immune-mediated Condition		1592 (28.61)	7671 (27.57)	1.05 (0.98 – 1.11)
Asthma		760 (13.66)	4432 (15.93)	0.83 (0.76 – 0.90)
Any Allergy		1148 (20.63)	4914 (17.66)	1.22 (1.13 – 1.31)
Food allergies		49 (0.90)	152 (0.50)	1.62 (1.17 – 2.23)
Dermatitis		405 (7.30)	1908 (6.90)	1.07 (0.95 – 1.20)
Rhinitis		888 (16.00)	3578 (12.90)	1.30 (1.20 – 1.41)
Others		498 (8.90)	2107 (7.60)	1.21 (1.09 – 1.34)
Any Autoimmune Disease		57 (1.02)	211 (0.76)	1.36 (1.01 – 1.83)
Specific Autoimmunedisease	Type 1 diabetes	12 (0.22)	52 (0.19)	1.15 (0.62 – 2.17)
	Psoriasis	19 (0.34)	41 (0.15)	2.35 (1.36 – 4.08)
	Alopecia	5 (0.09)	35 (0.13)	0.71 (0.28 – 1.81)
	Vitiligo	6 (0.11)	21 (0.08)	1.42 (0.57 – 3.52)

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Table 3

Association Between Immune Mediated Conditions and Autism Spectrum Disorder (ASD) Stratified by Sex and Age Categories, Kaiser Permanente Northern California Members born 1980– 2003.

	sex				Age categories (years)							
Immune condition	**Male**			**Female**	**< 6**		**6 – 11**		**12 – 18**		**19 – 26**	
	N[a]	**OR (95% CI)**	**N[a]**	**OR (95% CI)**	**N[a]**	**OR (95%CI)**	**N[a]**	**OR (95% CI)**	**N[a]**	**OR (95% CI)**	**N[a]**	**OR (95% CI)**
Asthma	643	0.81 (0.74 – 0.89)	117	0.96 (0.77 – 1.19)	63	0.96 (0.71 – 1.28)	227	0.85 (0.74 – 0.98)	338	0.78 (0.69– 0.89)	82	0.85 (0.65 – 1.09)
Any Allergies	963	1.23 (1.14 – 1.34)	185	1.16 (0.97 – 1.39)	108	1.20 (0.95 – 1.51)	403	1.16 (1.03 – 1.32)	497	1.21 (1.08 – 1.36)	140	1.52 (1.22 – 1.88)
Food allergy	41	1.53 (1.08 – 2.18)	8	2.22 (0.97 – 5.11)	11	2.11 (1.03 – 4.29)	24	2.22 (1.37 – 3.58)	14	1.32 (0.73 – 2.38)	0	-
Rhinitis	751	1.31 (1.12 – 1.40)	137	1.28 (1.04 – 1.57)	37	1.32 (0.90 – 1.92)	291	1.24 (1.08 – 1.43)	431	1.27 (1.12 – 1.43)	129	1.53 (1.23 – 1.91)
Dermatitis	319	1.04 (0.91 – 1.18)	86	1.20 (0.93 – 1.54)	79	1.06 (0.82 – 1.38)	164	1.02 (0.85 – 1.21)	137	1.13 (0.93 – 1.37)	25	1.53 (0.97 – 2.42)
Other allergies	437	1.26 (1.08 – 2.18)	61	0.95 (0.71 – 1.26)	36	1.26 (0.86 – 1.84)	203	1.27 (1.08 – 1.50)	217	1.15 (0.98 – 1.35)	42	1.29 (0.90 – 1.83)
Any Autoimmune disorders	50	1.49 (1.08 – 2.05)	7	0.83 (0.37 – 1.86)	2	-	11	0.91 (0.47 – 1.76)	32	1.70 (1.13 – 2.57)	12	1.19 (0.63 – 2.26)
Psoriasis	18	2.88 (1.60 – 5.18)	1	-	0	-	1	-	12	2.95 (1.42 – 6.10)	6	3.61 (1.25 – 0.44)
Type 1 Diabetes	10	1.14 (0.57 – 2.27)	2	-	0	-	2	-	7	1.20 (0.52 – 2.78)	3	-

[a] Number of children with ASD