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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 ($n = 5565$). 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.

1. 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 et al., 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, 2012) or of total IgG (Grether et al., 2010); imbalances in cytokine/chemokine levels (Ashwood et al., 2011a–c; 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 et al., 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 et al., 2013; Gurney et al., 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

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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 health-care 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.

2. Methods

2.1. 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 to 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.

2.2. Immune-mediated conditions

Immune-mediated conditions included asthma, allergies (food, dermatitis, rhinitis, and others), and a number of autoimmune diseases. Apendix 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.

2.3. 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 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

Table 1
Characteristics of study population, Kaiser Permanente Northern California members born 1980–2003.

Characteristics	ASD Cases (n = 5565) N (%)	Controls (n = 27,825) N (%)	Chi-square P-value
Sex			
Female	1002 (18)	5010 (18)	1.0
Male	4563 (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)	1860 (6.7)	1.0
1986–1990	1102 (19.8)	5510 (19.8)	
1991–1995	1854 (33.3)	9270 (33.3)	
1996–2000	1642 (29.5)	8210 (29.5)	
2001–2003	595 (10.7)	2975 (10.7)	
Born at KPNC, %	41.7	42.6	0.2