Ann Allergy Asthma Immunol 118 (2017) 570–576

Contents lists available at ScienceDirect

How does autism spectrum disorder affect the risk and severity of childhood asthma?

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ARTICLE INFO

Article history:
Received for publication November 29, 2016.
Received in revised form February 16, 2017.
Accepted for publication February 20, 2017.

ABSTRACT

Background: Autism spectrum disorder (ASD) and asthma are among the most common chronic disorders in childhood. Both are associated with altered immune regulation and share several risk factors. The effects of ASD on risk for later asthma and asthma severity remain unclear.
Objective: To determine whether ASD in children increases the risk of incident asthma and worsens asthma severity.
Methods: We performed 2 distinct analytic designs (case-control and retrospective longitudinal cohort) using a multistate electronic health records database to assess the odds of new asthma and asthma severity among children with ASD. In both designs, children with ASD were matched with children without ASD according to sex, age, race, ethnicity, location, and insurance status. Pulmonary function, controller medication prescriptions, asthma exacerbations, and asthma-related hospitalizations were collected. The effects of ASD on asthma risk and severity were assessed using multivariable linear and logistic regression.
Results: Among children with asthma, ASD was associated with reduced exacerbations (odds ratio [OR], 0.71; 95% confidence interval [CI], 0.54–0.92), better forced expiratory volume in 1 second/forced vital capacity ratio (0.876 vs 0.841, $P < .001$), and lower odds of airflow obstruction (OR, 0.53; 95% CI, 0.31–0.90) but had higher odds of asthma controller prescription (OR, 2.18; 95% CI, 1.62–2.93). In a longitudinal analysis of children without asthma, ASD was found to be protective for new asthma (OR, 0.44; 95% CI, 0.26–0.74).
Conclusion: Among children with asthma, concomitant ASD is associated with better asthma-related outcomes but a higher controller treatment burden. In addition, our data did not support ASD as a risk factor for incident asthma.

Introduction

Autism spectrum disorder (ASD) and asthma are among the most common chronic diseases in childhood.[1] Both conditions involve altered immune regulation[2–11] and typically present during early childhood,[12,13] most often in young boys. Recent decades have seen an increase in asthma and ASD prevalence that has not yet been conclusively explained.[14,15] Both conditions also share similar risk factors, including prematurity, low birth weight, urban environment, phthalate exposure, and firstborn birth order.[16–24] A shared inflammatory origin could explain an association between the 2 conditions. In addition, a direct association from ASD to asthma might partially explain the recent increased prevalence in childhood asthma. The gene *CD38* has been implicated in both asthma and ASD,[25,26] whereas several of the genes that have been linked to ASD encode proteins involved in the respiratory cilia of the airway barrier system.[27] Branching anomalies of the subsegmental airways, possibly leading to obstruction, have been described among children with ASD.[28] Three cross-sectional, population-based studies using parents' report found higher asthma prevalence among individuals with ASD (odds ratios [ORs], 1.35–1.74),[29–31] which would be consistent with but not conclusive of ASD increasing the risk of incident asthma. However, other studies have found no association between ASD and asthma risk.[32–34] Three case-control and 1 cross-sectional population-based study did not find a significant difference in asthma prevalence between those with and without ASD, using maternal reports or physician diagnoses. Another retrospective study using clinical diagnoses from outpatient records determined asthma to be significantly *less* common among children with ASD compared with those without ASD.[35] A recent meta-analysis found a significant association between ASD and asthma among cross-sectional studies, whereas among case-control studies no association was

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Disclosures: Authors have nothing to disclose.

http://dx.doi.org/10.1016/j.anai.2017.02.020
1081-1206/

found.[36] Longitudinal cohort studies are needed to better measure the risk of incident disease. Thus, the association between ASD and subsequent asthma risk remains very much unclear. Considering the high morbidity related to childhood asthma and the recent increased prevalence of ASD, it is important to understand the association between ASD and the risk of incident asthma.

Another related question is whether ASD among patients with asthma is related to more severe asthma outcomes. Coexistence of 2 or more chronic conditions can interact and lead to greater combined disease severity.[37] Children with ASD have impaired communication skills.[38] Their reduced ability to recognize and verbalize symptoms can make early disease diagnosis and disease management more difficult. Discomfort related to other disease comorbidities (including asthma) can result in worsening and exacerbations of ASD symptoms.[39,40] The association between ASD and asthma severity is not known, but considering the population prevalence of each condition, many children worldwide would be expected to have both conditions. Few studies have examined the effect of ASD on severity of asthma in children affected by both conditions. Therefore, to address these 2 important epidemiologic and clinical questions, we sought to conduct 2 separate studies using a large multistate electronic health database: (1) to determine whether ASD serves as a risk factor for incident asthma and (2) to compare the severity of asthma among children with and without ASD.

Methods

This study uses real-world clinical data obtained from the Nemours Children's Health System electronic health records (Epic, Verona, Wisconsin) using 2 separate designs: a case-control design (asthma severity) and a retrospective longitudinal cohort design (asthma risk). Patient data originated from more than 11 clinical sites that involved primary and subspecialty care from 3 main sites in Florida (Jacksonville, Orlando, and Pensacola) and throughout the Delaware Valley (Delaware, New Jersey, Maryland, and Eastern Pennsylvania). The Nemours data warehouse includes clinical care data which reflects pragmatic care patterns. The Nemours data network has taken advantage of advances in data collection methods adhering to the PEDSNet common data model[41,42] to increase data validity, database size and diversity, and data linkage (connecting clinical diagnoses to laboratory data to pulmonary function tests to medication use to health care use) and has been able to uncover accurate and hidden value from longitudinal analyses. In developing the common data elements across the network, we have considered the entire life cycle of the clinical data, the source of the data, the challenges arising from missing data, and possible inaccuracies in the data itself.[43,44] Our methodologic approach addresses the traditional limitations that have challenged database research in the past, including adequate and compatible computer systems, inconsistent data standards across sites, lack of quality-control checks during data collection, and entry and large-scale data cleaning. The study was approved by the Nemours Institutional Review Board.

Participant Selection

To assess *asthma severity* among children with asthma and ASD, we conducted a cross-sectional case-control analytic study that involved children 2 to 17 years of age with asthma with and without ASD. Cases were children with confirmed asthma and ASD seen from January 1, 2008, through March 30, 2016. Children were considered to have confirmed asthma if they had 2 or more clinical diagnoses of asthma and at least 1 antiasthma drug prescription in the previous 12 months. ASD and asthma diagnoses were collected using the *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 299.x and the *International Classification of Diseases, 10th Revision* (*ICD-10*) codes F84.0-5 and F84.8-9 and *ICD-9* codes 493.x and *ICD-10* codes J45.x, respectively. Each patient with ASD and asthma was matched with one comparator (control) patient with confirmed asthma but without ASD diagnosis. Comparators were matched for sex, race (white, black, Asian, other), ethnicity (Hispanic/Latino), insurance status (private, Medicaid, none), and current age (within 12 months). Patients with cystic fibrosis were excluded.

To assess *risk of asthma* attributed to ASD diagnosis, we conducted a separate retrospective cohort study of children with and without ASDs. Both groups were without asthma at baseline. The ASD risk group included all children seen at Nemours from January 1, 2008, through April 30, 2016, with at least 2 visits with an ASD diagnosis before the age of 6 years and without asthma at or before the time of the first ASD diagnosis. Children in the ASD cohort must have had at least 4 total Nemours visits, 2 or more of which must have been after the age of 5 years, and with a total observation period of at least 5 years. The total observation period was defined as the time between the first ASD diagnosis and last Nemours visit. Each patient with ASD was matched with 2 similar comparator patients with no ASD diagnosis at or before their initial visit, defined as the visit that corresponds to within 12 months of matched ASD patient's initial diagnosis visit. Comparators were matched for age (date of birth $\pm$12 months), date of initial visit ($\pm$12 months), sex, race (black, white, or other), ethnicity (Hispanic/Latino or other), insurance status (private, Medicaid, or none), and Nemours location (Delaware, Jacksonville, Orlando, or Pensacola). Patients with cystic fibrosis were excluded.

Clinical Data

Asthma *severity* was measured using forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), forced expiratory ratio (FER), the number of asthma exacerbations, the number of asthma-related hospitalizations, and prescriptions for asthma controller medications. Controller medications included any inhaled corticosteroid (ICSs) with a long-acting β-agonist (ICS-LABA) or a leukotriene receptor antagonist (LTRA). Spirometry results were used to create the binary variables airflow obstruction and bronchodilator responsiveness, defined as an FER less than 0.85 and FEV_1 or FVC percent change of 12% or greater after bronchodilator, respectively. When multiple spirometry results were available for a single patient, the best set that included both pre and postbronchodilator results were used.

To assess asthma *risk* and compare rates of incident asthma, patients and comparators had all subsequent Nemours visits assessed for incident asthma diagnosis, defined by *ICD-9* or *ICD-10* codes. Absolute and relative risks of asthma were calculated for each risk group. Other variables collected included number of prescriptions for controller medications, number of visits with an asthma diagnosis, age at first asthma diagnosis, length of observation period, number of prescriptions for the most common medications prescribed to patients with ASDs (sleep, antipsychotic, and attention-deficit/hyperactivity disorder medications), any cause visits (primary care, emergency department, hospitalization, and specialty visits), gestational age at birth, number of diagnoses of known comorbidities of asthma (eczema, gastroesophageal reflux disease, allergic rhinitis, and obstructive sleep apnea), and spirometry results when available. We collected individual race, ethnicity, sex, location, observation period, and insurance status on all participants.

Statistical Analysis

The χ^2 test was used for comparing percentages, whereas the *t* or Wilcoxon tests were used comparing continuous variables, as appropriate. For analysis of asthma severity, we performed simple