Research in Autism Spectrum Disorders 8 (2014) 381–386

Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

Journal homepage: http://ees.elsevier.com/RASD/default.asp

# Increased risk of autism spectrum disorder among early life asthma patients: An 8-year nationwide population-based prospective study

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ARTICLE INFO

*Article history:*
Received 28 October 2013
Accepted 26 December 2013

*Keywords:*
Autism spectrum disorders
Allergy
Asthma
Wheezing

ABSTRACT

Previous research has suggested an association between autism spectrum disorder (ASD) and allergic disorders, but epidemiological evidence regarding asthma remains limited. We conducted a nationwide population-based prospective cohort study (1:4 case:control patients, age- and gender-matched), hypothesizing that asthma in infancy or toddlerhood increased the risk of ASD. The participants comprised 2134 asthmatic infants and children and 8536 controls aged 0–3 years in 2002. We identified cases of ASD that occurred near the end of the follow-up period (December 31, 2010), determining that asthmatic infants and children exhibited a higher accumulative incidence rate of ASD than did the controls (1.3% vs 0.7%, $P = .007$). After adjusting for age at enrollment, gender, level of urbanization, and comorbid allergic diseases (i.e., allergic rhinitis and atopic dermatitis), asthmatic infants and children exhibited an elevated risk of developing ASD (hazard ratio: 2.01, 95% confidence interval: 1.19–3.40). This prospective study indicated a temporal relation between asthma and subsequent ASD diagnosis, supporting the immune hypothesis of ASD pathogenesis. Further studies are required to clarify the probable interactional effects between these disorders and define a homogenous ASD subgroup.



## 1. Introduction

Numerous scholars have reported the clinical implications of medical illnesses in infants and children with autism spectrum disorder (ASD); common medical disorders have included gastrointestinal system abnormalities (e.g., malabsorption, food intolerance, inflammatory bowel disease), impaired kidney function, metal ion transportation disorders, chronic infections, and allergic diseases (Cubala-Kucharska, 2010). Combined with the behavioral and psychiatric manifestations of ASD, these conditions generate clinical care challenges regarding recognizing, assessing, and managing the illness (Olivie, 2012). The medical expenditures for ASD patients were 4.1–6.2 times greater than for non-ASD patients (Shimabukuro, Grosse, & Rice, 2008). In the National Health Interview Survey in the United States, children with autism attained significantly higher estimates regarding health care use and unmet needs measures and their prevalence of most

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http://dx.doi.org/10.1016/j.rasd.2013.12.022

medical conditions (e.g., asthma and skin and food allergies) were moderately higher compared with those who lacked developmental disabilities (Schieve et al., 2012). A large-scale epidemiologic study by our group showed a significantly higher prevalence of asthma, allergic rhinitis, atopic dermatitis, and type I diabetes in ASD patients compared with non-ASD patients (Chen et al., 2013a).

Among these medical disorders, the association between allergic diseases (i.e., asthma, allergic rhinitis, and atopic dermatitis) and ASD has been further investigated to elucidate the underlying biological aspects of autism. Numerous studies have described the immunological disturbances in ASD patients; one study determined an imbalance the T-helper (Th)1/Th2 subsets toward Th2 in autistic children, implying a predisposition to allergic and autoimmune disorders and a decreased ability to combat infections (Cohly & Panja, 2005). Evidence has also suggested alterations in the pattern of the serum immunoglobulin (Ig) subclass profile, such as increased serum IgE (Magalhaes et al., 2009; Mostafa, Hamza, & El-Shahawi, 2008) and IgG4 subclass levels (Enstrom et al., 2009) in ASD patients. Moreover, in the National Survey of Children's Health in the United States, the parents of autistic children reported more allergy symptoms than did those of healthy controls (Gurney, McPheeters, & Davis, 2006). An alternate case–control study indicated that maternal asthma during pregnancy yielded a twofold or greater elevated risk for subsequent ASD diagnoses in children (Croen, Grether, Yoshida, Odouli, & Van de Water, 2005). These studies have provided hereditary evidence suggesting the association between allergic diseases and ASD. By contrast, in one case–control study ($N = 30$), newly diagnosed autistic children (aged 2–4 years) were surveyed and their allergic features were determined to be similar to those of the control population regarding serum IgE levels and a history of wheezing or asthma as reported by the parents (Bakkaloglu et al., 2008). These variable results may reflect that methodological limitations (e.g., small sample sizes, the cross-sectional design, ill-defined ASD populations, and subsets of allergic manifestations) obscure the relations among allergic diseases and ASD.

In the current study, we focused on asthma, a common allergic disease in infants and children that is indicated by episodic reversible symptoms of airflow obstruction and airway hyperresponsiveness. Asthma symptoms vary substantially over time and the onset in childhood or adulthood may reflect distinct disease entities (Bel, 2004). Furthermore, a substantial group of asthmatics experience early onset in infancy or toddlerhood, followed by recurrent wheezing throughout childhood. Martinez determined that approximately 40% of children who developed asthma during the first 3 years of life continued to present wheezing at 6 years old (Martinez et al., 1995). Although autism also presents in early childhood, its diagnosis is relatively infrequent in children younger than 3 years. Recent prospective longitudinal studies of the infant siblings of ASD children have indicated that infants develop ASD based on a pattern of gradual onset throughout the first 2–3 years of life (Rogers, 2009); thus, a clinical diagnosis of asthma often precedes that of ASD. Moreover, both disorders have exhibited a similar rise in the number of cases in the previous 3 decades (Mallol et al., 2013), potentially reflecting an increase in their prevalence or merely an increased awareness of their clinical symptoms. It is difficult to determine whether this is a correlation or a coincidence.

Both ASD and asthma exhibit onset in early childhood and are considered possible epidemics; they share other features such as male preponderance (Morgan et al., 2005), a decreasing risk ratio as the number of siblings increases (Glasson et al., 2004; Matricardi et al., 1998), increased neonatal head circumference (Katz, Pocock, & Strachan, 2003; Redcay & Courchesne, 2005), and urban disease distribution (Adler, Tager, & Quintero, 2005; Lauritsen, Pedersen, & Mortensen, 2005). Despite diverse indirect evidence for the link between ASD and asthma, only one longitudinal study tested this relation: the Dampness in Buildings and Health (DBH) study (Larsson, Weiss, Janson, Sundell, & Bornehag, 2009). It was conducted in Sweden, using a population-based cohort of children aged 1–6 years. Of 4779 participants, 72 exhibited ASD at the end of the 5-year follow-up period. The researchers determined that airway symptoms in the baseline investigation, both "wheezing ever" and "physician-diagnosed asthma," were associated with ASD at the end of the follow-up period, attaining odds ratios of 1.81 (1.12–2.93) and 2.33 (1.10–4.92), respectively; allergic rhinitis or eczema failed to exhibit a significantly higher risk. However, the diagnoses of both ASD and asthma were primarily based on parental reports from questionnaires and Tourette's syndrome was included among the ASD item in the questionnaire. The DBH study also failed to mention whether ASD was diagnosed at the baseline or when ASD was diagnosed.

Therefore, we hypothesized that asthma in early life (presenting symptoms of repeated wheezing before the age of 3 years) increased the risk of ASD. A nationwide population-based database was accessed to identify numerous children (aged 0–3 years in 2002) that exhibited asthma but no psychiatric disorders. We tracked the participants from infancy and toddlerhood through later childhood until the end of 2012, evaluating the diagnosis of ASD among asthmatic and non-asthmatic infants and children in the cohort.

## 2. Methods

### 2.1. Data source

The National Health Insurance (NHI) program was implemented in 1995 and covers up to 99% of the 23 million residents of Taiwan (http://www.nhi.gov.tw). The National Health Insurance Research Database (NHIRD) was audited and released by the National Health Research Institute. The database comprises comprehensive insurant information, including demographic data, the dates of clinical visits, and disease diagnoses. The diagnostic codes were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been extensively used in epidemiologic studies in Taiwan (Chen et al., 2013b,c; Chen, Su, Li, et al., 2013; Li et al., 2012; Wu et al., 2012).