



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.

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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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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).

2.2. Inclusion criteria for the asthma and control cohorts

In this study, 1million insurants, approximately 4.3% of the population of Taiwan, were randomly selected from the NHIRD. Insurants aged 0–3 years who were identified as newly diagnosed asthmatics (ICD-9-CM codes: 493) by emergency room doctors, pulmonologists, rheumatologists, or pediatricians between January 1, 2002 and December 31, 2002, and exhibited no history of psychiatric disorders before enrollment, were included in the asthma cohort. The age- and gender-matched control cohort (4 per patient in the study cohort) was randomly identified from insurants in the cohort after excluding children who were diagnosed with asthma anytime or psychiatric disorders before enrollment. Psychiatrists diagnosed ASD (ICD-9-CM code: 299) during the follow-up period until December 31, 2010.

Because of the high comorbidity among asthma and other allergic diseases, allergic rhinitis (ICD-9-CM code: 477; diagnosed by internists, pulmonologists, rheumatologists, otolaryngologists, or pediatricians), atopic dermatitis (ICD-9-CM codes: 691 or 691.8; diagnosed by dermatologists or pediatricians), and allergic conjunctivitis (ICD-9-CM codes: 372.05, 372.10, and 372.14; diagnosed by ophthalmologists) were identified to investigate how various comorbid allergic diseases affect the risk of developing ASD. All diagnoses were verified at least twice by corresponding physicians to ensure diagnostic validity. We also assessed the level of urbanization (Level 1 = most urbanized regions; Level 5 = least urbanized regions) (Liu et al., 2006). Furthermore, we investigated how the duration of asthma related to the risk of ASD. The duration of asthma was defined as the time between the first and final asthma diagnoses. The age of the final asthma diagnosis was defined as the age at which asthma remission occurred.

2.3. Statistical analysis

Regarding the between-group comparisons, an independent *t* test was used for the continuous variables and a Pearson's χ^2 test was used for nominal variables. A multivariate Cox regression analysis was performed to investigate the hazard ratios (HRs), using 95% confidence intervals (CIs) of ASD after adjusting for age at enrollment, gender, urbanization level, and allergic comorbidities. A 2-tailed *P* value of less than .05 was considered statistically significant. All data processing and statistical analyses were performed using the Statistical Package for Social Science software, version 17 (SPSS Inc.) and Statistical Analysis Software, version 9.1 (SAS Institute, Cary, NC, USA).

3. Results

The participants comprised 2134 infants and children aged 0–3 years (mean age: 1.35 ± 1.02 years) who were newly diagnosed with asthma. The asthmatic group exhibited higher incidence rates of ASD (1.3% vs 0.7%, $P = .007$) and comorbid allergic diseases, namely, allergic rhinitis (69.4% vs 27.8%, $P < .001$), atopic dermatitis (28.3% vs 11.5%, $P < .001$), and allergic conjunctivitis (36.7% vs 26.3%, $P < .001$), than did the control group. The members of the asthma group resided in more urbanized regions than did members of the control group ($P = .006$). Although nonsignificant, the mean age of ASD diagnosis was higher in the asthma group compared with the control group (5.63 ± 2.58 years vs 4.57 ± 2.23 years, $P = .056$) (Table 1).

The Kaplan–Meier survival curve indicated that the asthmatic group exhibited a significantly higher risk of ASD ($P = .004$) than did the controls (Fig. 1). Male gender was an independent risk factor (HR: 4.43, 95% CI: 2.27–8.64); furthermore, compared with the controls, the asthmatic patients were more likely to exhibit ASD (HR: 2.01, 95% CI: 1.19–3.40) during the follow-up period after adjusting for age at enrollment, gender, urbanization level, and allergic comorbidities. By contrast, urbanization level yielded no significantly increased risk of ASD (Table 2).

To elucidate the relations between asthma and ASD, we analyzed the age of asthma remission and the duration of asthma during an 8-year follow-up period. Regarding the asthmatic patients, compared with the non-ASD patients, those who

Table 1
Distribution of characteristics of the asthma and the control groups.

	Asthma group (<i>n</i> = 2134)	Control group (<i>n</i> = 8536)	<i>p</i> value
Male participant (<i>n</i> , %)	1257 (58.9)	5028 (58.9)	
Age at enrollment (years, SD)	1.35 (1.02)	1.35 (1.02)	
Allergic comorbidities (<i>n</i> , %)			
Allergic rhinitis	1481 (69.4)	2370 (27.8)	<0.001
Atopic dermatitis	604 (28.3)	978 (11.5)	<0.001
Allergic conjunctivitis	784 (36.7)	2242 (26.3)	<0.001
ASD ^a (<i>n</i> , %)	27 (1.3)	57 (0.7)	0.007
Age of diagnosing ASD (years)	5.63 (2.58)	4.57 (2.23)	0.056
Level of urbanization (<i>n</i> , %)			0.006
1 (most urbanized)	580 (27.2)	2323 (27.2)	
2	679 (31.8)	2562 (30.0)	
3	342 (16.0)	1642 (19.2)	
4	305 (14.3)	1208 (14.2)	
5 (most rural)	228 (10.7)	801 (9.4)	

Bold values are significant at $p < 0.05$.

^a ASD: autism spectrum disorder.

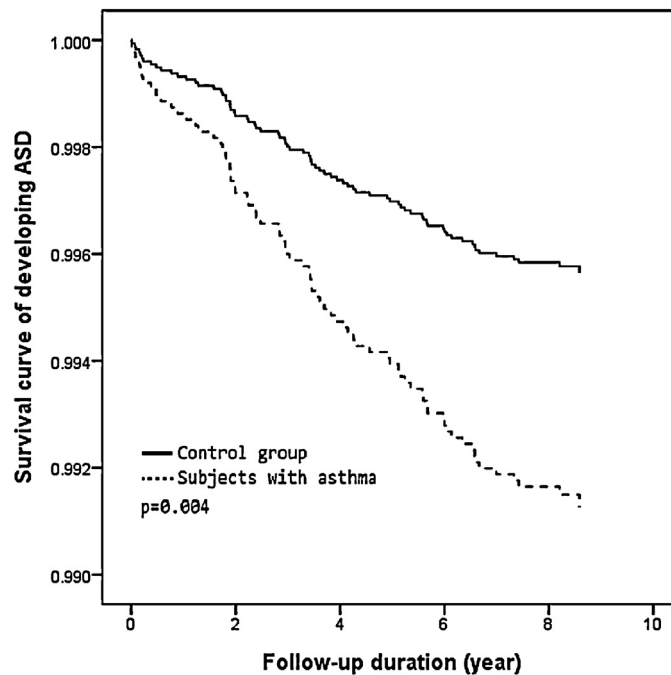


Fig. 1. Survival curve of ASD in subjects with asthma and the control group.

developed ASD exhibited an overt trend toward a later age of asthma remission (5.41 ± 3.09 years vs 4.30 ± 3.04 years, $P = .059$) and a longer duration of asthma (3.83 ± 3.25 years vs 2.97 ± 2.94 years, $P = .132$). Among the asthmatic patients, the duration of asthma as a linear variable in the Cox regression analysis exhibited a nonsignificant association with the risk of developing ASD (HR: 1.12, 95% CI: 0.98–1.28) after adjusting for age at enrollment, gender, urbanization level, and comorbid allergic diseases.

4. Discussion

We determined that asthmatic infants and children demonstrated a significantly higher incidence of ASD in the 8-year follow-up period than did those who lacked asthma (1.3% vs 0.7%, $P = .007$). The adjusted hazard ratio of developing ASD among asthmatic children was 2.01 (1.19–3.40). These results were consistent with those of the DBH study, supporting the

Table 2

Risk of developing autism spectrum disorders in subjects with asthma and the control group.

	ASD ^a		<i>p</i>
	HR ^b	95% CI ^c	
Asthma	2.01	1.19–3.40	0.009
Gender (male)	4.43	2.27–8.64	<0.001
Age at enrollment (year)	0.91	0.73–1.15	0.431
Allergic comorbidities			
Allergic rhinitis	1.20	0.73–1.98	0.479
Atopic dermatitis	0.45	0.20–1.00	0.051
Allergic conjunctivitis	1.16	0.71–1.89	0.556
Level of urbanization			
1 (most urbanized)	1	–	–
2	1.02	0.59–1.76	0.944
3	0.49	0.22–1.09	0.080
4	0.88	0.43–1.81	0.736
5 (most rural)	0.48	0.17–1.40	0.180

Bold values are significant at $p < 0.05$.

^a ASD: autism spectrum disorder.

^b HR: hazard ratio.

^c 95% CI: 95% confidence interval.

hypothesis that developing asthma in early life increases the risk of developing ASD and this temporal association remained significant after adjusting for allergic comorbidities (i.e., atopic dermatitis, allergic rhinitis, and allergic conjunctivitis). Although the DBH study assessed additional environmental factors, such as family allergic symptoms and maternal smoking behaviors, we demonstrated an obvious temporal correlation between asthma and ASD, assessing the times involved in the diseases of interest (e.g., when the diagnoses occurred) and rigorous standards of diagnostic validity (e.g., a clinical diagnosis rather than a parental questionnaire). Moreover, neither the DBH nor current study determined an association between ASD and allergic rhinitis or dermatitis.

These findings do not imply a cause and effect relation between asthma and ASD. Because ASD is a neurodevelopment disorder, only the age of first detection and diagnosis can be identified; this is typically after the onset of asthma in infants and children. It is possible that asthma precedes ASD as a predisposing risk factor in the pathogenesis process. For example, the “mast cell activation” hypothesis implies that allergic, infection-based, environmental, and stress-related triggers release pro-inflammatory and neurotoxic molecules, disrupting the blood–brain barriers and causing brain inflammation (Angelidou et al., 2011; Theoharides et al., 2012). Asthma might also be a physical manifestation of biological abnormalities or environmental factors that predispose ASD because both disorders reflect complex interactions among environmental and genetic factors. Thus, those who exhibit both ASD and asthma may constitute a unique subgroup of patients who are likely to respond to environmental triggers or demonstrate hypersensitive mast cells (Becker & Schultz, 2010). In the current study, the confounding effects of male gender, urbanization level, and other allergic diseases were considered; however, the role of risk factors, such as early allergic sensitization, maternal smoking during pregnancy, and post-natal exposure to tobacco smoke, remained unclear because of methodological limitations (Hanrahan et al., 1996; Kalkbrenner et al., 2012; Soyseth, Kongerud, & Boe, 1995; Stein et al., 1999). Despite this, the results highlight the role of allergic responses in the pathogenesis of autism.

Furthermore, although asthma duration exhibited no overt dose-dependent effects on ASD, we discovered a trend toward later remission and longer asthma duration in those who were later diagnosed with ASD compared with non-ASD asthmatics. In addition, the asthmatics were diagnosed with ASD later than were the control group, although the difference lacked statistical significance. These findings may yield clinical significance, suggesting that the presence of asthma influences the manifestation pattern of ASD and its delayed diagnosis. For example, parental awareness of social and behavioral abnormalities may be hindered by recurrent medical problems. By contrast, impaired expressive language abilities and aberrant behaviors among autistic children influence parental medical-seeking behaviors and treatment implementation (e.g., difficulties using metered-dose inhalers), leading to suboptimal asthma interventions (Jyonouchi, 2010). Clinically, this interactional effect sensitizes practitioners to underlying allergic diseases among ASD patients or any autistic features masked by recurrent allergic symptoms. To clarify the possible causal or co-occurrence relations between asthma and ASD, additional longitudinal data regarding the symptomatology and developmental trajectories must be gathered to avoid identification bias.

Certain study limitations should be addressed. First, the NHIRD is an anonymous database, designed to protect the privacy of insurants; thus, it excludes certain information regarding disease severity, family history, personal lifestyle, social adversity, and environmental factors. Both asthma and ASD might be heterogeneous groups based on their symptom patterns and severity and various factors might influence their interactions. Second, the association between asthma medications and ASD was not investigated herein. Because the medications taken by the participants were complex during the long follow-up (8 years), the medication use patterns could be erratic and medication types might have changed frequently; thus, it was difficult to analyze medications as a factor in the current model and subsequent clinical studies are required to elucidate this influence. Third, we focused on the temporal association between asthma and the subsequent diagnosis of ASD, but not vice versa. To avoid an ascertainment bias, those diagnosed with autism before 3 years of age were excluded from the analysis. Although we determined no ASD diagnosis in those with asthma before 3 years of age, the reverse temporal relationship (i.e., first developing ASD and then asthma) was beyond the scope of this investigation. Additional studies are required to address the probable bidirectional effects between ASD and asthma.

In conclusion, the current findings suggest that asthma is a risk factor for subsequent ASD diagnosis. The interaction between these disorders must be clarified beyond simple causal effects; the underlying allergic response may imply the need for further investigations regarding the etiology and manifestations of ASD. Recognizing asthma in early life should aid in the clinical detection of and interventions for children with ASD.

Conflict of interest

None declared.

Acknowledgements

The study was supported by grant from Taipei Veterans General Hospital (V101D-001-1).

We thanks Dr. PHT, Dr. MHC and Dr. YMB, who designed the study, wrote the protocol and manuscripts, Dr. YMB, Dr. TPS, Dr. YSC, Dr. JWH, and Dr. KLH, who assisted with the preparation and proofreading of the manuscript, and Dr. YMB, Dr. TJC, and Ms. WHC, who provided the advices on statistical analysis.

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