Comorbidity of Atopic Disorders with Autism Spectrum Disorder and Attention Deficit/Hyperactivity Disorder

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Objective To assess the relationship between allergic manifestations in early life and the occurrence of newly diagnosed autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD) throughout childhood.

Study design We collected a population-based longitudinal cohort comprising children enrolled in Taiwan's National Health Insurance Program during 2000-2010. We first identified 387 262 children who had a diagnosis of atopic dermatitis (AD) before age 2 years, with 1:1 individualized matching to children without AD. Cox regression analyses were performed to estimate the early-onset and cumulative effects of allergic manifestations on ASD and ADHD.

Results An estimated 0.5% of AD-exposed children received a diagnosis of ASD, and 3.7% were diagnosed with ADHD, significantly higher than the respective rates of 0.4% and 2.9% found in their nonexposed peers. Having AD before age 2 years was associated with an increased hazard ratio (HR) for ASD by 10% and that for ADHD by 16%; such increases were particularly prominent among those with earlier-onset or more severe AD. HRs were especially higher for children with persistent AD and emerging atopic respiratory diseases in childhood (eg, for ASD, adjusted HR, 1.75 and 2.13, respectively; $P < .001$).

Conclusion The observed increased risks of ASD and ADHD associated with AD in infancy suggest that a disordered immunologic response may exert effects on neurodevelopment and have implications for research into etiology and treatment strategies. *(J Pediatr 2016;171:248-55)*.

Over the past decade, considerable attention has been focused on the rising prevalence of diagnosed childhood-onset neurodevelopmental disorders, especially autism spectrum disorder (ASD) and attention deficit/hyperactivity disorder (ADHD).[1-3] Researchers have come to the conclusion that the etiologies of ASD/ADHD are multifactorial, including environment, genetics, and environmental–genetic interactions.[2,4-6] Notably, some studies have reported a higher prevalence of allergic manifestations among individuals with ASD or ADHD.[7-10] For instance, a cross-sectional study conducted in Germany found a 5.2% prevalence of ADHD in children affected with atopic eczema, compared with 3.4% in their nonaffected counterparts, and found a similar association pattern for asthma.[7] Another study reported that the experience of "atopic diseases" in early childhood was associated with a 3.40-fold increased risk of ASD and a 1.97-fold increased risk of ADHD.[9]

A higher incidence of allergic disorders has long been reported in individuals with neuropsychiatric disorders.[11,12] Inflammatory processes or immune dysregulation can play a role in depression, schizophrenia, and obsessive-compulsive disorders.[11-14] Allergic disorders comprise atopic dermatitis (AD) and atopic respiratory diseases (RDs). An estimated 28% of children have suffered from at least 1 clinical allergic manifestation before age 4 years.[15,16] AD is a chronic pruritic skin disease commonly observed in infants and children; 45% of affected children experience their first episode during the first 6 months of life, and 60% do so before their first birthday.[17] As for respiratory allergy, allergic rhinitis is characterized by sneezing, rhinorrhea, and nasal pruritus, whereas asthma often causes recurrent episodes of wheezing, breathlessness, and chest tightness.[16] Clinically, allergic disorders often co-occur: 20%-50% of patients with allergic rhinitis also have asthma, and more than 80% of patients with allergic asthma have concomitant symptoms of rhinitis.[18,19]

The cumulative evidence indicates that the 3 aforementioned allergic diseases may emerge gradually in temporal succession. The cutaneous manifestation of atopy often marks the entry point of atopic march, and induces epicutaneous sensitization and the migration of sensitized T cells into airways, followed by an array of atopic

AD	Atopic dermatitis
ADHD	Attention deficit/hyperactivity disorder
aHR	Adjusted HR
ASD	Autism spectrum disorder
HR	Hazard ratio
ICD-9-CM	*International Classification of Diseases, Ninth Revision, Clinical Modification*
NAD	Nonatopic dermatitis
NHIRD	National Health Insurance Research Database
RD	Respiratory disease

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RDs.[16] Because children under age 2 years are incapable of mounting humoral responses to some environmental antigens, the infantile phase of AD reflects cutaneous manifestations that may be narrowed to the window ranging from birth to age 2 years.[20]

Although a few studies have showed a positive connection between allergic disorders and ASD/ADHD, the temporal sequence underlying the intertwined relationships, possibly developmental stage–dependent, has remained less well explored. For example, previous studies that did not take the evolution of atopic conditions in childhood into account might have overestimated the contribution of certain allergic disorders to neurodevelopmental disorders and might even have inappropriately modeled the temporal sequence of etiologic processes. To tackle this omission in the literature, the present study aimed to investigate the connection between early-life atopic manifestations and subsequent diagnosed neurodevelopmental disorders. We compared the subsequent risks of ASD and ADHD over the period from toddlerhood into childhood in a cohort of children with AD in infancy and their AD-free peers, while simultaneously taking the gradual emergence of RDs (ie, rhinitis or asthma) into account.

Methods

We obtained data from Taiwan's National Health Insurance Research Database (NHIRD). The Taiwanese National Health Insurance Program has provided comprehensive medical care coverage to all citizens and resident foreigners since March 1, 1995. In 2014, 99.5% of Taiwan's population was enrolled (http://www.nhi.gov.tw). The database contains the registration files and claims data on the insured subjects. For each subject, a unique identification number is used to link all insurance information and healthcare records. Approval of this study was granted by the Institutional Review Board of the National Health Research Institutes (EC1020403-E).

The original sample comprised children born during 2000-2004 (n = 1 262 810). Children who: (1) received any diagnosis of ASD (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code 299) or ADHD (ICD-9-CM code 314) before age 2 years; or (2) died during the follow-up period were excluded from the analytic sample. On the basis of a retrospective cohort study, children who received a first AD diagnosis (ICD-9-CM code 691) before age 2 years during 2000-2006 (n = 387 262; 30.7%) were classified as the AD-exposed group. Based on a 1:1 ratio of exposed to nonexposed children, we used the criteria of birth year, birth season, and residential region to match individual non-AD (NAD)-affected children from the NHIRD, resulting in a total of 774 524 children. The follow-up period spanned birth until December 31, 2010, in an interval of 6-10 years. The occurrence of ASD was defined as having at least 2 outpatient visits with ASD as the primary diagnosis within 1 year; the same definition was applied to ADHD.[21]

Data were obtained not only on AD occurring before age 2 years, but also on later episodes (either first or recurring instances of AD) for children categorized AD-exposed or NAD group. Guided by the atopic march model, we further ascertained the subjects' experience with RDs, comprising allergic rhinitis (ICD-9-CM code 477) and asthma (ICD-9-CM code 493). To evaluate possible time-dependent effects of atopic disorders, the occurrence of RDs was obtained separately from 3 developmental stages (ie, infancy [0-1 years], toddlerhood/preschool [2-5 years], and childhood [6+ years]).

Data concerning all medical diagnoses were retrieved from outpatient records by unique identification number. Information on individual sociodemographic variables (ie, sex, birth year, birth season, premium category, urbanization level, and residential region) was retrieved from the beneficiary registry data files. Residential regions were categorized as northern, central, southern, and eastern. Level of urbanization was classified as level 1 (rural), level 2 (suburban), or level 3 (urban).[3] The premium category, an indicator of parental income, was divided into 3 income levels: poverty and near poverty, middle income, and high income. Birth seasons were defined as spring (March, April, and May), summer (June, July, and August), autumn (September, October, and November), and winter (December, January, and February).[19]

Statistical Analyses

Descriptive statistics for individual sociodemographic and clinical characteristics were first summarized and tested in relation to AD exposure. The χ^2 test was used for categorical variables, and the Student *t* test was used for continuous variables (eg, age at diagnosis). The associations linking individual sociodemographic and clinical characteristics with ASD and ADHD were then estimated using the Cox proportional hazard model. The crude association (as indexed by hazard ratio [HR]) was obtained first, followed by multivariate regression, with simultaneous adjustment for sex, urbanization, premium category, birth year, birth season, residential region, previous history of AD diagnosis, and history of first episode of RD.

The time-dependent risks linking early AD and RD with ASD/ADHD were captured using time-dependent survival analyses. Three measures were used to assess exposure to atopic disease–diagnosis of AD before age 2 years (yes vs no), age of onset (<1 year vs 1-2 years), and number of visits (1, 2-3, or 4 or more)—to evaluate the possible critical window of exposure and clinical severity. Finally, based on age-dependent risk estimates linking atopic disorders, linear combination was used to derive the summary risk of ASD and ADHD; an episode occurring after age 2 years was added into the equations for comparison. The magnitude and strength of associations are presented in point estimates, 95% CIs, and *P* values. The data were prepared and the analyses performed using SAS version 9.3 (SAS Institute, Cary, North Carolina).