



Is atopy in early childhood a risk factor for ADHD and ASD? A longitudinal study



Mu-Hong Chen^{a,b}, Tung-Ping Su^{a,b,d}, Ying-Sheue Chen^{a,b}, Ju-Wei Hsu^{a,b}, Kai-Lin Huang^{a,b}, Wen-Han Chang^{a,b}, Tzeng-Ji Chen^{c,e}, Tai-Long Pan^{f,g}, Ya-Mei Bai^{a,b,d,*}

^a Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

^b Department of Psychiatry, College of Medicine, National Yang-Ming University, Taipei, Taiwan

^c Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

^d Institute of Brain Science, National Yang-Ming University, Taipei, Taiwan

^e Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan

^f School of Traditional Chinese Medicine, Chang Gung University, Taoyuan, Taiwan

^g Research Center for Industry of Human Ecology, Chang Gung University of Science and Technology, Taoyuan, Taiwan

ARTICLE INFO

Article history:

Received 20 March 2014

Received in revised form 13 June 2014

Accepted 14 June 2014

Keywords:

Atopy

ASD

ADHD

ABSTRACT

Objective: Previous studies have found a temporal concordance in the increased prevalence of atopic diathesis/atopic diseases, attention-deficit hyperactivity disorder (ADHD), and autistic spectrum disorder (ASD) worldwide. But, the temporal association among these 3 distinct diseases is unknown.

Method: 14,812 atopic subjects diagnosed with any atopic disease (asthma, atopic dermatitis, allergic rhinitis, or allergic conjunctivitis) before the age of 3 (atopic cohort) and 6944 non-atopic subjects with no lifetime atopic disease (non-atopic cohort), born between 1997 and 2000, were enrolled and followed to December 31, 2010 to identify the development of ADHD and ASD.

Results: The presence of any atopic disease in early childhood increased the risk of developing ADHD (hazard ratio [HR]: 1.97) and ASD (HR: 3.40) in later life. Greater numbers of atopic comorbidities (4 comorbidities: ADHD: HR: 2.53; ASD: HR: 4.29) were significantly related to a greater risk of developing ADHD and ASD.

Discussion: Atopic diathesis in early childhood elevated the risk of developing ADHD and ASD in later life, with the dose-dependent relationship of more atopic comorbidities with a greater likelihood of ADHD and ASD.

© 2014 Elsevier Inc. All rights reserved.

Introduction

Atopic diseases of childhood consist of atopic dermatitis, allergic rhinitis, allergic conjunctivitis, and asthma, and have been regarded as the most common chronic disorders of childhood [2,34,35,37]. The prevalence rates of atopic diseases rose gradually over the past several decades, and have been reaching epidemic proportions in both the developed and developing world [1,17,19,36]. The International Study of Asthma and Allergies in Childhood reported that from the 1990s to early 2000, the prevalence of asthma, allergic rhinitis, and atopic dermatitis rose significantly in Australia, from 4.4%, 3.7%, and 10.1% to 5.1%, 4.5%, and 13.8%, respectively, among children [31]. In the United States, the prevalence of childhood asthma doubled from approximately 3% in early 1980 to 7.5% in 1995 [40]. Atopic diathesis or atopic disease has become an important public health problem among children [1,17,19,36].

Similar to the increased prevalence of atopy worldwide over the last few decades, the prevalence rates of childhood neurodevelopmental disorders, including attention-deficit hyperactivity disorder (ADHD) and autistic spectrum disorder (ASD), have risen gradually and simultaneously [4,9]. The 1997–2008 National Health Interview Surveys in the United States reported that the prevalence of ADHD and ASD increased, respectively, from 5.69% to 7.57% and 0.19% to 0.74% over 12 years [9]. A Danish birth cohort study followed all children born from 1990 through 1999 to the end of 2004 and reported that the cumulative incidence of ADHD and ASD across specific birth years showed statistically significant increases [4]. The temporal concordance of the increased prevalence of atopy, ADHD, and ASD has inspired many scientists in recent years to investigate the possible etiological association between these 3 clinically distinct diseases.

Previous findings regarding the association among atopy, ASD, and ADHD have been inconsistent [6,7,21,27,32,42]. Biederman et al. failed to validate the association between asthma and ADHD among 140 ADHD children aged 6–17 years and controls [7]. Bakkaoglu et al. found that young autistic children ($n = 30$) did not present more allergic features, based on history, skin tests, and serum immunoglobulin (Ig)-E levels, than the normal controls ($n = 39$) [6]. However, several

* Corresponding author at: Department of Psychiatry, No. 201, Shih-Pai Road, Sec. 2, 11217, Taipei, Taiwan. Tel./fax: +886 2 28344012.
E-mail address: ymbi@mail2000.com.tw (Y.-M. Bai).

larger sample-size studies supported the relationship of atopy with ADHD and ASD [27,32,42]. The 2007 National Survey of Children's Health in the United States, composed of 92,642 children aged 0 to 17 years, demonstrated that the odds of having ADHD (odds ratio [OR]: 1.87, 95%CI: 1.54–2.27) and ASD (OR: 3.04, 95%CI: 2.13–4.34) were significantly increased in children with atopic dermatitis compared with the control subjects [42]. Mogensen et al. found that children with asthma at age 8–9 years had an almost twofold increased risk (OR: 1.88, 95%CI: 1.18–3.00) of having one or more symptoms of hyperactivity/impulsivity, and a more than twofold increased risk (OR: 2.73, 95%CI: 1.49–5.00) of having 3 or more symptoms of hyperactivity/impulsivity at age 13–14 years [27]. However, the limitations in those previous studies included that the diagnoses of ADHD and ASD were given by parental reports or questionnaires, and not by board certificated psychiatrists, and that a cross-sectional study design, and not a longitudinal follow-up design was used.

In our study, utilizing the Taiwan National Health Insurance Research Database (NHIRD) with a large sample size and a longitudinal follow-up study design, we followed newborns between 1997 and 2000 to the end of 2010, and investigated the association between atopic diathesis in early childhood (before the age of 3) and the risk of ADHD and ASD in later life. We hypothesized that subjects who had any atopic disease in early childhood had an increased risk of developing ADHD and ASD in later life.

Methods

Data source

The National Health Insurance (NHI) program was implemented in 1995 and covers up to 99% of the 23,000,000 residents of Taiwan (<http://www.nhi.gov.tw/>). The NHIRD was audited and released by the National Health Research Institute. Comprehensive information on insured subjects, such as demographic data, dates of clinical visits, and disease diagnoses, is included in the database. To guarantee privacy, all subjects included in the NHIRD are anonymous. The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan [5,12,13,41].

Inclusion criteria for atopic and non-atopic cohorts

For the study, 1,000,000 subjects, approximately 4.3% of the population of Taiwan, were randomly selected from the NHIRD. Subjects with any atopic disease, including asthma (ICD-9-CM codes: 493) diagnosed by emergency room doctors, pulmonologists, rheumatologists, or pediatricians, 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 defined as those with atopic diathesis. We combined above atopic diseases, including asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis, into a category representing the presence of atopic diathesis because much evidence has supported the frequent comorbidity of atopic diseases, and their sharing of a similar pathophysiology. Subjects born between 1997 and 2000 with the diagnosis of any atopic disease given by corresponding specialists before the age of 3 and without history of any psychiatric disorder (ICD-9-CM codes: 290–319) were enrolled as the atopic cohort ($n = 14,812$). Subjects who had any psychiatric disorder before any diagnosis of atopic disease and those who developed atopic diseases after age of 3 were excluded in the case (atopic) group. Subjects born between 1997 and 2000 without any atopic disease anytime at enrollment or during the follow-up and without any psychiatric disorder before the enrollment were included as the non-atopic cohort ($n = 6944$). The atopic and non-atopic cohorts

were followed to December 31, 2010 or the death, and those who developed ASD (ICD-9-CM codes: 299) or ADHD (ICD-9-CM codes: 314) as diagnosed by psychiatrists were identified. All diagnoses were given at least twice by corresponding physicians to achieve diagnostic validity. Level of urbanization (level 1 to level 5; level 1: most urbanized region; level 5: least urbanized region) was also assessed in our study [23].

Statistical analysis

For between-group comparisons, the independent t test was used for continuous variables and Pearson's χ^2 test for nominal variables, where appropriate. Due to the longitudinal follow-up study design, two Cox proportional hazard regression models were used to investigate the HR with 95%CI of ASD and ADHD. The death (withdrawal from the NHIRD) and the study end were set as the censor. The proportional hazard assumption was met in both regression models. The primary model investigated the presence or absence of any atopic disease as a categorical variable with the risk of ASD and ADHD; the secondary model investigated the numbers of atopic comorbidities as a categorical variable with the risk of ASD and ADHD. Two models were adjusted by demographic data. A two-tailed P -value of less than 0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC).

Results

In all, 14,812 atopic subjects (atopic cohort) with a mean 1.33 ± 0.86 years of diagnosis of any atopic disease and 6944 non-atopic subjects (non-atopic cohort) with no lifetime atopic disease, born between 1997 and 2000, were enrolled in our study, and followed to the onset of events (ASD or ADHD), the study end (December 31, 2010), or the death. During the follow-up, 557 (2.6%) subjects died and withdrew from NHIRD. The atopic cohort was more male-predominant than the non-atopic cohort (55.6% vs. 44.8%, $p < 0.001$). Of the total atopic subjects, 9438 (63.7%) were diagnosed with asthma, 10,701 (72.2%) with allergic rhinitis, 9395 (63.4%) with allergic conjunctivitis, and 8310 (56.1%) with atopic dermatitis. Furthermore, 1809 atopic patients (12.2%) were diagnosed as having only one atopic disease, 5513 (37.2%) had 2 atopic comorbidities, 4951 (33.4%) had 3 atopic comorbidities, and 2539 (17.1%) had 4 atopic comorbidities. Follow-up from birth to the end of 2010 revealed that the atopic cohort had a higher incidence of ADHD (6.3% vs. 2.9%, $p < 0.001$) and ASD (0.8% vs. 0.2%, $p < 0.001$) than the non-atopic cohort (Table 1). Furthermore, among a total number of 130 patients with ASD, 84 (64.6%) had a comorbid diagnosis of ADHD; among a total number of 1138 with ADHD, 7.4% were comorbid with ASD. Besides, the atopic cohort resided in more urbanized regions than the non-atopic cohort ($p < 0.001$) (Table 1).

Two Cox regression models were used, after adjusting gender and level of urbanization, to study the association between atopic diathesis in early childhood and the risks of ADHD and ASD between the atopic and non-atopic cohorts. The primary Cox regression model showed that the presence of any atopic disease in early childhood increased the risk of developing ADHD (HR: 1.97, 95%CI: 1.69–2.29) and ASD (HR: 3.40, 95%CI: 1.95–5.93) in later life (Tables 2 and 3). The secondary Cox regression model showed a dose-dependent effect between atopic comorbidities in early childhood and the risk of developing ADHD (1 atopic disease: HR: 1.32, 95%CI: 1.01–1.73; 2 atopic comorbidities: HR: 1.64, 95%CI: 1.37–1.97; 3 atopic comorbidities: 2.26, 95%CI: 1.90–2.69; 4 atopic comorbidities: HR: 2.53, 95%CI: 2.09–3.07) and ASD (1 atopic disease: HR: 2.14, 95%CI: 0.90–5.11; 2 atopic comorbidities: HR: 2.70, 95%CI: 1.44–5.05; 3 atopic comorbidities: HR: 4.08, 95%CI: 2.24–7.43; 4 atopic comorbidities: HR: 4.29, 95%CI: 2.25–8.19) (Tables 2 and 3). In addition, male gender was an independent risk factor for ADHD (primary model: HR: 3.34, 95%CI: 2.89–3.85; secondary model: HR: 3.27, 95%CI: 2.83–3.77) and ASD (primary model: HR: 4.14, 95%CI: 2.62–6.55; secondary model: HR: 4.04, 95%CI: 2.55–6.40) in the two Cox regression models (Tables 2 and 3).

Discussion

Our results supported the study hypotheses that atopic diathesis in early childhood (before the age of 3) increased the risk of developing ADHD and ASD in later life, and that there was a dose-dependent relationship between more atopic comorbidities with a greater likelihood of ADHD and ASD.

Table 1
Demographic data of atopic and non-atopic cohorts

	Total (n = 21,756)	Atopic cohort (n = 14,812)	Non-atopic cohort (n = 6944)	p-value
Gender (% M)	11,339 (52.1)	8230 (55.6)	3109 (44.8)	<0.001
Age at any atopy (year, SD)	–	1.33 (0.86)	–	–
Asthma (n, %)	9438 (43.4)	9438 (63.7)	0 (0)	<0.001
Allergic rhinitis (n, %)	10,701 (49.2)	10,701 (72.2)	0 (0)	<0.001
Allergic conjunctivitis (n, %)	9395 (43.2)	9395 (63.4)	0 (0)	<0.001
Atopic dermatitis (n, %)	8310 (38.2)	8310 (56.1)	0 (0)	<0.001
Number of atopic comorbidities (n, %)				<0.001
0	6944 (31.9)	0 (0)	6944 (100%)	
1	1809 (8.9)	1809 (12.2)	0 (0)	
2	5513 (25.3)	5513 (37.2)	0 (0)	
3	4951 (22.8)	4951 (33.4)	0 (0)	
4	2539 (11.7)	2539 (17.1)	0 (0)	
Average number of atopic comorbidities (n, SD)	1.74 (1.41)	2.55 (0.91)	0 (0)	<0.001
ADHD (n, %)	1138 (5.2)	936 (6.3)	202 (2.9)	<0.001
Age at ADHD diagnosis (year, SD)	8.13 (2.34)	8.01 (2.29)	8.69 (2.48)	<0.001
ASD (n, %)	130 (0.6)	116 (0.8)	14 (0.2)	<0.001
Age at ASD diagnosis (year, SD)	7.63 (3.03)	7.82 (3.03)	6.03 (2.61)	0.037
Level of urbanization (n, %)				<0.001
1 (most urbanized)	6005 (27.6)	4355 (29.4)	1650 (23.8)	
2	6724 (30.9)	4736 (32.0)	1988 (28.6)	
3	3828 (17.6)	2500 (16.9)	1328 (19.1)	
4	3109 (14.3)	1983 (13.4)	1126 (16.2)	
5 (most rural)	2090 (9.6)	1238 (8.4)	852 (12.3)	

ADHD: attention-deficit hyperactivity disorder; ASD: autistic spectrum disorder; SD: standard deviation.

Atopy and ADHD

The comorbid or causal role of atopy and atopic immunological responses in the development of ADHD has been debated for a long time [7,12,13,27,32,42]. In the late 1980s, Marshall et al. proposed a potential neuro-immunological model of ADHD, and hypothesized that atopic reactions engendering cholinergic/adrenergic activity imbalances in the central nervous system led to ADHD symptoms in some children [26]. As mentioned in the [Introduction](#), several small sample-size studies in the 1990s failed to support this relationship, but some large sample-size nationwide studies in the 2000s found a significant association between atopy and ADHD [12,13,32,42]. A recent Korean study investigated the association between atopy and psychological and behavioral problems (Child Behavior Checklist) in a large sample of preschoolers (n = 780), and reported that atopy, including asthma, atopic dermatitis, and allergic rhinitis was associated with preschoolers' psychological and behavioral problems, and especially, that those with atopic dermatitis had more attention problems and higher ADHD scores [11]. Mogensen et al.'s cohort study suggested that asthmatic children exhibited more symptoms of hyperactivity/impulsivity in adolescence

than the controls [27]. Asthma-related physical symptoms, including wheezing attacks, shortness of breath, and coughing after exertion, were significantly related to the greater risk of inattention and hyperactivity problems in asthmatic children [8,10]. Schmitt et al. further suggested that the clinical severity of atopy was related to the elevated risk of ADHD [32].

The pathophysiology of ADHD and its relation to atopic diseases are still unclear. Previous immunological studies on the relationship of proinflammatory cytokines and related genes with ADHD elucidated the possible role of atopic diathesis/atopic diseases in the pathophysiology of ADHD. Oades et al. reported that 6 cytokines, including IL-2, IL-6, IFN- γ , IL-16, IL-10, and IL-13, showed a marginal increase in the ADHD group, compared to the control group [28]. Segman et al., investigating the role of the IL-1 receptor antagonist (IL-1Ra) gene variable number tandem repeat (VNTR) polymorphism in patients with ADHD, reported that the 4-repeat allele was associated with a significantly increased risk of ADHD, and 2-repeat alleles with a decreased risk of ADHD [33]. A genome-wide study genotyped 958 parent-offspring trios on the Perlegen 600,000 SNP array, and found that the C-allele SNP of nuclear factor, IL-3 regulated (NFIL3) was associated with an earlier age at

Table 2
Cox regression analyses of the risk of developing ADHD among atopic and non-atopic cohorts

	Primary model		Secondary model	
	HR (95% CI) ^a	p-value	HR (95% CI) ^b	p-value
Atopy, presence vs. absence	1.97 (1.69–2.29)	<0.001	NA	NA
Numbers of atopic comorbidities, per disease				
0	NA	NA	1	–
1	NA	NA	1.32 (1.01–1.73)	0.043
2	NA	NA	1.64 (1.37–1.97)	<0.001
3	NA	NA	2.26 (1.90–2.69)	<0.001
4	NA	NA	2.53 (2.09–3.07)	<0.001
Gender, male vs. female	3.34 (2.89–3.85)	<0.001	3.27 (2.83–3.77)	<0.001
Level of urbanization				
1 (most urbanized)	1	–	1	–
2	0.78 (0.68–0.90)	0.001	0.79 (0.69–0.92)	0.002
3	0.77 (0.65–0.92)	0.003	0.79 (0.67–0.94)	0.008
4	0.72 (0.59–0.87)	0.001	0.75 (0.62–0.90)	0.003
5 (most rural)	0.39 (0.29–0.52)	<0.001	0.41 (0.31–0.55)	<0.001

ADHD: attention-deficit hyperactivity disorder; SD: standard deviation. HR: hazard ratio; CI: confidence interval; NA: not applicable.

^a Atopic disease modeled as a categorical variable.^b Number of atopic diseases modeled as a categorical variable.

Table 3

Cox regression analyses of the risk of developing ASD among atopic and non-atopic cohorts

	Primary model		Secondary model	
	HR (95% CI) ^a	p-value	HR (95% CI) ^b	p-value
Atopy, presence vs. absence	3.40 (1.95–5.93)	<0.001	NA	NA
Number of atopic comorbidities, per disease				
0	NA	NA	1	–
1	NA	NA	2.14 (0.90–5.11)	0.086
2	NA	NA	2.70 (1.44–5.05)	0.002
3	NA	NA	4.08 (2.24–7.43)	<0.001
4	NA	NA	4.29 (2.25–8.19)	<0.001
Gender, male vs. female	4.14 (2.62–6.55)	<0.001	4.04 (2.55–6.40)	<0.001
Level of urbanization				
1 (most urbanized)	1	–	1	–
2	0.55 (0.36–0.83)	0.005	0.55 (0.37–0.84)	0.006
3	0.40 (0.22–0.71)	0.002	0.41 (0.23–0.73)	0.003
4 (most rural)	0.48 (0.29–0.78)	0.003	0.50 (0.31–0.82)	0.006

ASD: autistic spectrum disorder; HR: hazard ratio; CI: confidence interval; NA: not applicable.

^a Atopic disease modeled as a categorical variable.^b Number of atopic diseases modeled as a categorical variable.

onset of ADHD [22]. This evidence implied that atopic diathesis and ADHD may share a similar underlying pathophysiology related to the alteration of the inflammatory process and abnormal immunological reactions, but further studies are required to clarify this.

Our study, compatible with previous findings, showed that atopic diathesis/atopic diseases in early childhood increased the risk of developing ADHD in school-age children. The clinical severity of atopy indicated by the numbers of atopic comorbidities was associated with a greater risk of developing ADHD.

Atopy and ASD

The association between atopic diseases and ASD is also inconsistent. Several small sample-size studies reported no significant relationship between these 2 diseases [6,21]. Jyonouchi et al.'s case-control study ($n = 26$ in the ASD group and $n = 107$ in the control group) revealed that the clinical features of the ASD group were not associated with allergic rhinitis, asthma, atopic dermatitis, or food allergy [21]. However, Yaghmaie et al. surveyed 92,642 children aged 0 to 17 years about the association between atopic dermatitis and the mental health burden, and found that patients with atopic dermatitis had significantly increased odds of having ASD (OR: 3.04, 95%CI: 2.13–4.34), compared to those without [42]. They further observed that a dose-dependent relationship existed between the risk of ASD and the reported severity of atopic dermatitis (severe status of atopic dermatitis: OR: 3.25, 95%CI: 3.82–14.36; moderate: OR: 3.25, 95%CI: 1.79–5.90; mild: OR: 1.78, 95%CI: 1.14–2.77) [42]. Our findings are compatible with Yaghmaie et al.'s findings [42]. But, in contrast to their cross-sectional study design, we used a longitudinal follow-up study design, and potentially clarified the temporal association between these 2 distinct phenomena. We demonstrated that atopic diathesis in early childhood increased the risk of developing ASD, with a dose-dependent relationship between more atopic comorbidities and the increased risk of consequent ASD.

There is a growing awareness of an atopic immunological response in subjects with ASD, but the underlying mechanisms are still unclear. Previous studies suggested that dysregulated mast cell activation and proinflammatory cytokines during atopic responses played possible roles in the risk of ASD. Magalhães et al. reported that patients with ASD had significantly higher serum Ig-E and higher rates of positive skin allergy tests than healthy controls [25]. Children with mast cell activation syndrome appeared to have ASD at a rate tenfold higher than that of the general population [3]. Wei et al. detected IL-6 expression in the cerebellum of autistic patients, and found that the increased IL-6 altered neural cell adhesion, migration and synaptic formation in patients with ASD [39]. They further suggested that mice with elevated IL-6 in the hippocampus and somatosensory cortex display many autistic features, including impaired

cognitive abilities, deficits in learning, habituations, and decreased social interactions [38]. They hypothesized that IL-6 elevation in the brain could mediate autistic-like behaviors, possibly through the imbalances of neural circuitry and impairments of synaptic plasticity [38]. Beyond IL-6, Croonenberghs et al. measured the production of IL-6, IL-10, and IL-1 receptor antagonist (IL-1RA), interferon (IFN)- γ and TNF- α among 13 adolescents with autism and 13 matched controls, and found that autistic subjects had an increased production of IFN- γ , IL-1RA, IL-6 and TNF- α compared to the controls [14].

The impact of atopy on the brain

A growing body of evidence has disclosed that atopic diseases are systemic inflammatory diseases [18,35]. The early phase of an atopic response is predominantly mediated by Th₂ cytokines, in which IL-4 and IL-13 drive Ig-E production by promoting immunoglobulin class-switch recombination in B cells, and a cascade of proinflammatory agents, such as Th₁ immunoactive cytokines (i.e., IL-2, IL-3, TNF- α) and chemokines, are also released sequentially [18]. The over-secretion of proinflammatory cytokines during vicious atopic responses would penetrate the blood-brain barrier [43] and activate neuroimmunological mechanisms involving some specific neural circuits (i.e., anterior cingulate gyrus and insula) related to behavioral and emotional modulation [20,29,30].

Some functional magnetic resonance imaging (fMRI) studies have shown that dysregulated proinflammatory cytokines would influence brain activities in patients with atopic diseases. Ishiuchi et al. found that patients with active atopic dermatitis had bilateral activation of the anterior cingulate cortex, posterior cingulate cortex, and dorsolateral prefrontal cortex, as well as contralateral activation of the caudate nucleus and putamen [20]. They also found a significant correlation between percentage changes in brain activation in the activation of the anterior cingulate cortex and insula, and histamine-induced itch intensity as well as disease severity in patients with atopic dermatitis [20]. Similar findings were observed in Rosenkranz et al.'s study detecting changes in brain activity in patients with asthma who underwent inhaled antigen challenges [30]. They demonstrated that activity in the anterior cingulate cortex and insula was related to markers of inflammation (TNF- α production) and airway obstruction in asthmatic patients exposed to antigen [30]. These results indicated that elevated brain activity is related to the development of inflammation that likely plays a key role in modulating the sensitivity of specific brain regions to the presentation of antigen stimuli [20,30], and may explain the possible roles of atopic diathesis/atopic diseases in the brain dysfunction of ASD and ADHD [15,16]. For example, Liu et al. found that ADHD patients exhibited anterior cingulate cortex hyperactivity, which was correlated with impulsivity as rated by the Go/no-Go task

[24]. Dichter et al. suggested that patients with ASD had greater activation in a region in the dorsomedial prefrontal cortex that abuts the dorsal anterior cingulate, and further indicated that dorsal anterior cingulate cortex activation to social targets predicted the severity of social impairments in ASD patients [16]. The association among atopy, atopy-mediated brain dysfunction, and each symptomatic domain of ASD (i.e., social cognition and repetitive patterns of behavior) and ADHD (i.e., inattention and hyperactivity/impulsivity) requires more study.

Some study limitations should be listed here. First, the incidence of ASD and ADHD may be underestimated because only those individuals who sought medical help were enrolled. However, the subjects enrolled in our study had board-certified psychiatrist and physician diagnoses, yielding better diagnostic validity. Second, we combined the atopic diseases, including asthma, atopic dermatitis, allergic rhinitis, and allergic conjunctivitis, into the category of atopic diathesis, and investigated the presence of atopic diathesis in early childhood (before the age of 3) relative to the risk of ASD and ADHD. Further studies would be required to elucidate the possible individual effect of each atopic disease with the risk of ASD and ADHD. Besides, the possibility of misclassification of atopic or non-atopic cases may be existent although every atopic disease was given at least twice by corresponding physicians, with a better diagnostic validity relative to the self-reported questionnaire. Third, we did not investigate the association between atopic diathesis in later childhood (after the age of 3) and the risk of subsequent ASD and ADHD in this study. Further studies would be required to clarify this possible association. Fourth, the association between treatment of atopy and ASD and ADHD was not investigated in our study because the medications used by the study subjects would be very complicated during such a long follow-up period. This association needs further study. Fifth, the NHI database did not provide some information, such as food allergy, family history, personal lifestyle, and environmental factors. Without this information, we were unable to examine their influence.

In conclusion, our results supported the role of atopic diathesis in early childhood as a risk factor for both ADHD and ASD. Children with atopic diathesis before the age of 3 had an increased likelihood of developing ADHD and ASD in later life. Further studies would be required to elucidate the underlying pathophysiology among atopy, ADHD, and ASD, and to investigate whether the prompt intervention of atopic diathesis in early childhood would decrease these risks in later life.

Conflict of Interest

No conflict of interest.

Financial disclosure

All authors have no financial relationships relevant to this article to disclose.

Acknowledgment

The study was supported by grant from Taipei Veterans General Hospital (V103E10-001).

We thanks Dr MHC, Dr TPS, and Dr YMB, who designed the study, and wrote the protocol and manuscripts, Dr YMB, Dr TPS, Dr YSC, Dr JWH, Dr KLH, and TLP who assisted with the preparation and proof-reading of the manuscript, and Dr YMB, Dr TJC, and Ms WHC, who provided advice on statistical analysis.

We thank Mr I-Fan Hu's friendship and support.

References

- [1] Adler J. The allergy epidemic. *Newsweek* 2003;142:50–1 [53–54, 57].
- [2] Amarasekera ND, Gunawardena NK, et al. Prevalence of childhood atopic diseases in the Western Province of Sri Lanka. *Ceylon Med J* 2010;55:5–8.
- [3] Angelidou A, Alysandratos KD, Asadi S, Zhang B, Francis K, Vasiadi M, et al. Brief report: "allergic symptoms" in children with Autism Spectrum Disorders. More than meets the eye? *J Autism Dev Disord* 2011;41:1579–85.
- [4] Atladottir HO, Parner ET, et al. Time trends in reported diagnoses of childhood neuropsychiatric disorders: a Danish cohort study. *Arch Pediatr Adolesc Med* 2007;161:193–8.
- [5] Bai YM, Su TP, et al. Risk of developing diabetes mellitus and hyperlipidemia among patients with bipolar disorder, major depressive disorder, and schizophrenia: a 10-year nationwide population-based prospective cohort study. *J Affect Disord* 2013;150:57–62.
- [6] Bakaloglu B, Anlar B, et al. Atopic features in early childhood autism. *Eur J Paediatr Neurol* 2008;12:476–9.
- [7] Biederman J, Milberger S, et al. Associations between childhood asthma and ADHD: issues of psychiatric comorbidity and familiarity. *J Am Acad Child Adolesc Psychiatry* 1994;33:842–8.
- [8] Blackman JA, Gurka MJ. Developmental and behavioral comorbidities of asthma in children. *J Dev Behav Pediatr* 2007;28:92–9.
- [9] Boyle CA, Boulet S, et al. Trends in the prevalence of developmental disabilities in US children, 1997–2008. *Pediatrics* 2011;127:1034–42.
- [10] Calam R, Gregg L, et al. Childhood asthma, behavior problems, and family functioning. *J Allergy Clin Immunol* 2003;112:499–504.
- [11] Chang HY, Seo JH, et al. Allergic diseases in preschoolers are associated with psychological and behavioural problems. *Allergy Asthma Immunol Res* 2013;5:315–21.
- [12] Chen MH, Su TP, et al. Attention deficit hyperactivity disorder, tic disorder, and allergy: is there a link? A nationwide population-based study. *J Child Psychol Psychiatry* 2013;54:545–51.
- [13] Chen MH, Su TP, et al. Higher risk of developing mood disorders among adolescents with comorbidity of attention deficit hyperactivity disorder and disruptive behavior disorder: a nationwide prospective study. *J Psychiatr Res* 2013;47:1019–23.
- [14] Croonenberghs J, Bosmans E, et al. Activation of the inflammatory response system in autism. *Neuropsychobiology* 2002;45:1–6.
- [15] Curatolo P, Paloscia C, et al. The neurobiology of attention deficit/hyperactivity disorder. *Eur J Paediatr Neurol* 2009;13:299–304.
- [16] Dichter GS, Felder JN, et al. Autism is characterized by dorsal anterior cingulate hyperactivation during social target detection. *Soc Cogn Affect Neurosci* 2009;4:215–26.
- [17] Eder W, Ege MJ, et al. The asthma epidemic. *N Engl J Med* 2006;355:2226–35.
- [18] Galli SJ, Tsai M, et al. The development of allergic inflammation. *Nature* 2008;454:445–54.
- [19] Holgate ST. The epidemic of allergy and asthma. *Nature* 1999;402:82–4.
- [20] Ishiuchi Y, Coghill RC, et al. Distinct patterns of brain activity evoked by histamine-induced itch reveal an association with itch intensity and disease severity in atopic dermatitis. *Br J Dermatol* 2009;161:1072–80.
- [21] Jyonouchi H, Geng L, et al. Impact of innate immunity in a subset of children with autism spectrum disorders: a case control study. *J Neuroinflammation* 2008;5:52.
- [22] Lasky-Su J, Anney RJ, et al. Genome-wide association scan of the time to onset of attention deficit hyperactivity disorder. *Am J Med Genet B Neuropsychiatr Genet* 2008;147B:1355–8.
- [23] Liu CY, Hung YT, et al. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. *J Health Manag (China)* 2006;4:1–22.
- [24] Liu J, Zubieta JK, et al. Sex differences in anterior cingulate cortex activation during impulse inhibition and behavioral correlates. *Psychiatry Res* 2012;201:54–62.
- [25] Magalhaes ES, Pinto-Mariz F, et al. Immune allergic response in Asperger syndrome. *J Neuroimmunol* 2009;216:108–12.
- [26] Marshall P. Attention deficit disorder and allergy: a neurochemical model of the relation between the illnesses. *Psychol Bull* 1989;106:434–46.
- [27] Mogensen N, Larsson H, et al. Association between childhood asthma and ADHD symptoms in adolescence—a prospective population-based twin study. *Allergy* 2011;66:1224–30.
- [28] Oades RD, Dauvermann MR, et al. Attention-deficit hyperactivity disorder (ADHD) and glial integrity: S100B, cytokines and kynurenine metabolism—effects of medication. *Behav Brain Funct* 2010;6:29.
- [29] Raison CL, Capuron L, et al. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol* 2006;27:24–31.
- [30] Rosenkranz MA, Busse WW, et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proc Natl Acad Sci U S A* 2005;102:13319–24.
- [31] Schernhammer ES, Vutuc C, et al. Time trends of the prevalence of asthma and allergic disease in Austrian children. *Pediatr Allergy Immunol* 2008;19:125–31.
- [32] Schmitt J, Romanos M, et al. Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. *JAMA* 2009;301:724–6.
- [33] Segman RH, Meltzer A, et al. Preferential transmission of interleukin-1 receptor antagonist alleles in attention deficit hyperactivity disorder. *Mol Psychiatry* 2002;7:72–4.
- [34] Sly PD, Boner AL, et al. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008;372:1100–6.
- [35] Stone KD. Atopic diseases of childhood. *Curr Opin Pediatr* 2003;15:495–511.
- [36] Thalasingam M, Lee BW. Allergies in Asia: are we facing an allergy epidemic? *Asia Pac Allergy* 2013;3:1–2.
- [37] Vasar M, Julge K, et al. Development of atopic sensitization and allergic diseases in early childhood. *Acta Paediatr* 2000;89:523–7.

- [38] Wei H, Chadman KK, et al. Brain IL-6 elevation causes neuronal circuitry imbalances and mediates autism-like behaviors. *Biochim Biophys Acta* 2012;1822:831–42.
- [39] Wei H, Zou H, et al. IL-6 is increased in the cerebellum of autistic brain and alters neural cell adhesion, migration and synaptic formation. *J Neuroinflammation* 2011;8:52.
- [40] Woodruff TJ, Axelrad DA, et al. Trends in environmentally related childhood illnesses. *Pediatrics* 2004;113:1133–40.
- [41] Wu CY, Chen YJ, et al. Association between nucleoside analogues and risk of hepatitis B virus-related hepatocellular carcinoma recurrence following liver resection. *JAMA* 2012;308:1906–14.
- [42] Yaghmaie P, Koudelka CW, et al. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol* 2013;131:428–33.
- [43] Yarlagadda A, Alfson E, et al. The blood brain barrier and the role of cytokines in neuropsychiatry. *Psychiatry (Edmont)* 2009;6:18–22.