

Comorbidity of Allergic and Autoimmune Diseases Among Patients With ADHD: A Nationwide Population-Based Study

Mu-Hong Chen, Tung-Ping Su, Ying-Sheue Chen, Ju-Wei Hsu, Kai-Lin Huang, Wen-Han Chang, Tzeng-Ji Chen and Ya-Mei Bai

Journal of Attention Disorders published online 11 February 2013

DOI: 10.1177/1087054712474686

The online version of this article can be found at:

<http://jad.sagepub.com/content/early/2013/02/08/1087054712474686>

Published by:



<http://www.sagepublications.com>

Additional services and information for *Journal of Attention Disorders* can be found at:

Email Alerts: <http://jad.sagepub.com/cgi/alerts>

Subscriptions: <http://jad.sagepub.com/subscriptions>

Reprints: <http://www.sagepub.com/journalsReprints.nav>

Permissions: <http://www.sagepub.com/journalsPermissions.nav>

>> [OnlineFirst Version of Record](#) - Feb 11, 2013

[What is This?](#)

Comorbidity of Allergic and Autoimmune Diseases Among Patients With ADHD: A Nationwide Population-Based Study

Journal of Attention Disorders
XX(X) 1–9
© 2013 SAGE Publications
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1087054712474686
http://jad.sagepub.com


Mu-Hong Chen¹, Tung-Ping Su^{1,2}, Ying-Sheue Chen¹, Ju-Wei Hsu¹, Kai-Lin Huang^{1,2}, Wen-Han Chang¹, Tzeng-Ji Chen^{3,4}, and Ya-Mei Bai^{1,2}

Abstract

Objective: Patients with ADHD have been suggested to have increased risks of allergic diseases but without consistent results, and limited studies about the association between ADHD and autoimmune diseases were noted in the literature. **Method:** Utilizing the Taiwan National Health Insurance Research Database, ADHD patients were identified and compared with age- and gender-matched controls (1:4). **Results:** In all, 8,201 participants were identified as having ADHD, and an increased prevalence of allergic diseases, including asthma (odds ratio [OR] = 1.53), allergic rhinitis (OR = 1.59), atopic dermatitis (OR = 1.53), and urticaria (OR = 1.39), compared with the control group. Although the comorbidity of autoimmune diseases with ADHD was low, ADHD patients had a significantly greater prevalence of ankylosing spondylitis (OR = 2.78), ulcerative colitis (OR = 2.31), and autoimmune thyroid disease (OR = 2.53) than the controls. **Conclusion:** Our results supported the association between ADHD and allergic/autoimmune diseases. The further studies will be required to clarify the underlying mechanisms. (*J. of Att. Dis.* 2013; XX(X) 1–XX)

Keywords

ADHD, allergy, autoimmune diseases, comorbidity

ADHD is a pervasive neurodevelopmental disorder that begins in childhood, and manifests the inability to marshal and sustain attention, modulate the activity level, and moderate impulsive actions. ADHD affects approximately 5% of children and adolescents and approximately 3% of adults, with a male-to-female ratio between 3:1 and 4:1 (Rappley, 2005; Swanson et al., 1998). The pathophysiology of ADHD is unclear and it appears to have a complex etiology. Multiple genetic and environmental factors act together to develop a spectrum of neurobiological vulnerability.

The association, whether comorbidity or causality, between allergic diseases and ADHD has been a focus of public and clinical interest and concern since the 1980s, though with controversial results, because the increase in the prevalence of allergic diseases (i.e., atopic dermatitis [AD], asthma, and allergic rhinitis [AR]) has been matched by a worldwide increase in ADHD diagnoses (Belfer, 2008; Wittchen & Jacobi, 2005). The neurochemical model of ADHD and allergic diseases was proposed in late 1980, and hypothesized that allergic reactions engendering cholinergic/adrenergic activity imbalances in the central nervous system led to ADHD symptoms in some children (Marshall, 1989). However, in the 1990s, Biederman, Milberger, Faraone, Guite, and Warburton (1994) studied 140 ADHD

patients (aged 6–17) and controls, and reported that the risk of asthma did not differ meaningfully between the ADHD and control children, arguing against the substantial pathophysiological association between the two diseases. Gaitens, Kaplan, and Freigang (1998), using skin prick tests on 312 ADHD children, did not support an association between atopic responsiveness and ADHD. In the 2000s, some studies with a larger sample size revalidated the significant association between allergic diseases and ADHD. Schmitt, Romanos, Schmitt, Meurer, and Kirch (2009) studied 1,436 patients with AD and matched controls, and found

¹Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan

²Department of Psychiatry, College of Medicine, National Yang-Ming University, Taipei, Taiwan

³Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan

⁴Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan

Corresponding Author:

Ya-Mei Bai, Taipei Veterans General Hospital, No. 201, Shih-Pai Road, Sec. 2, 11217 Taipei, Taiwan
Email: ymbi@mail2000.com.tw

that ADHD was significantly associated with AD but not with other allergic diseases (i.e., asthma and AR). Fasmer, Halmoy, Eagan, Oedegaard, and Haavik (2011) supported the significant association between ADHD and asthma, finding that the prevalence of asthma was higher in patients with ADHD, and that controls with asthma that scored higher on the ratings presented more symptoms of ADHD. In another recent study of 1,480 twin pairs born from 1985 to 1986, and assessing asthmatic children and adolescents at ages 8 to 9 and 13 to 14 to investigate the prevalence of two core symptoms of ADHD (hyperactivity/impulsivity and inattention), Mogensen, Larsson, Lundholm, and Almqvist (2011) found that asthmatic participants, both children and adolescents, had an increased risk of having symptoms of hyperactivity/impulsivity.

In contrast to the allergy/hypersensitivity hypothesis of ADHD, autoimmunity is rarely mentioned together with ADHD. Some genetic and basic studies have shown the possible role of major histocompatibility complex (MHC) genes involving various autoimmune diseases, including HLA-DR4, HLA-DRB1, and the complement C4B gene, in the etiology of ADHD (Aureli et al., 2008; Odell, Warren, Warren, Burger, & Maciulis, 1997; Ogdie et al., 2003). Odell et al. (1997) demonstrated that approximately 55% of ADHD participants carried both of these alleles, the C4B gene and DRB1 gene, compared with only 8% of the controls. Aureli et al. (2008) found a positive association between the HLA-DR4 gene and ADHD. HLA-DR4 may play important roles in many autoimmune diseases (i.e., juvenile rheumatic arthritis [RA], type 1 diabetes mellitus [type 1 DM], autoimmune hepatitis, lupus erythematosus [LE]; Matsushita, Fujisao, & Nishimura, 1996; Noble & Valdes, 2011; Poupon, 2003; Van Jaarsveld et al., 1998). Reviewing the past literature, only a few studies and case reports on ADHD and autoimmune comorbidity were noted. For example, Niederhofer (2011) examined the association between celiac disease and ADHD by examining anti gliadin and anti endomysium antibodies and found that 10 of 67 ADHD patients were positive for celiac disease. Banerjee, Bhojani, and Emcy (2011) reported a girl with ADHD with many behavioral problems who was comorbid with autoimmune hypothyroidism and pituitary macroadenoma. However, the clinical association between autoimmune diseases and ADHD is still unknown and epidemiological results are lacking.

In this nationwide population-based study with the largest case number, we attempted to retest this controversial association between ADHD and allergic diseases and investigate the possible association between ADHD and various autoimmune diseases that commonly occur in childhood or adolescence, including type 1 DM, RA, LE, inflammatory bowel disease, autoimmune thyroid disease, ankylosing spondylitis (AS), Henoch-Schönlein purpura (HSP), celiac disease, and Kawasaki disease.

Method

Data Source

This study was based on data from the Taiwan National Health Insurance Research Database (NHIRD) released by the National Health Research Institute. Taiwan's National Health Insurance (NHI) program was implemented in 1995, and has covered 96.9% of all 23,000,000 residents of Taiwan since 2001. The NHIRD includes comprehensive information on insured participants, such as demographic data, dates of clinical visits, details of prescriptions, and diagnostic codes using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan (Lin et al., 2011; Wu, Wang, Cheng, & Gau, 2011).

Inclusion Criteria for ADHD and Allergic Autoimmune Diseases

In this study, 1,000,000 participants, approximately 4.3% of the population of Taiwan, were randomly selected from the NHIRD. The study group comprised all participants who were identified by the diagnostic code "attention deficit hyperactivity disorder" (ICD-9-CM code: 314), as diagnosed by board-certificated psychiatrists between January 1, 1996 and December 31, 2010. The age- and gender-matched control group having the comprehensive medical records in NHIRD (four for every patient in the study cohort) was randomly identified from the participants after eliminating patients who had been given a diagnosis of ADHD. The comorbid allergic and autoimmune diseases were identified by specific diagnostic codes given by the corresponding board-certificated physicians: asthma (ICD-9-CM codes: 493, 493.0, 493.1, or 493.9) diagnosed by internists, pulmonologists, rheumatologists, or pediatricians; AD (ICD-9-CM codes: 691 or 691.8) diagnosed by dermatologists or pediatricians; AR (ICD-9-CM code: 477) diagnosed by internists, family physicians, or pediatricians; urticaria (ICD-9-CM code: 708) diagnosed by dermatologists or pediatricians; type 1 DM (ICD-9-CM codes: 250.X1, 250.X3, and X=0-9) diagnosed by endocrinologists or pediatricians; LE (ICD-9-CM codes: 710.0 and 695.4) diagnosed by rheumatologists, dermatologists, or pediatricians; RA (ICD-9-CM code: 714) diagnosed by rheumatologists or pediatricians; AS (ICD-9-CM code: 720.0) diagnosed by rheumatologists or pediatricians; ulcerative colitis (ICD-9-CM code: 556) diagnosed by rheumatologists, gastrointestinalists, or pediatricians; Crohn's disease (ICD-9-CM code: 555) diagnosed by rheumatologists, gastrointestinalists, or pediatricians; HSP (ICD-9-CM code: 287.0) diagnosed by hematologists, rheumatologists, or pediatricians; celiac disease (ICD-9-CM code: 579.0) diagnosed by gastrointestinalists, rheumatologists, or pediatricians; and Kawasaki disease (ICD-9-CM code: 446.1) diagnosed by pediatricians. We lumped ICD-9-CM codes, 240-242, 245, and 246 together, representing autoimmune thyroid diseases because Hashimoto thyroiditis

contributes to most patients with hypothyroidism and Graves' disease usually contributes to those with hyperthyroidism (Brent, 2008; Pearce, Farwell, & Braverman, 2003). Any depressive disorder (ICD-9-CM codes: 296.2X, 296.3X, 300.4, and 311) and any anxiety disorder (ICD-9 codes: 300.X, except 300.3 and 300.4) diagnosed by psychiatrists were identified as confounding factors because of frequent comorbidity between ADHD, depressive disorder, and anxiety disorder (Smalley et al., 2007; Taurines et al., 2010).

Statistical Analysis

When comparing the differences between the cases and controls, the independent *t* test was used for continuous variables, and Pearson's chi-square test or Fisher's exact test was applied for nominal variables, where appropriate. Multiple logistic regressions were performed to calculate the odds ratio (OR) with 95% confidence intervals (CIs) after adjusting for age, gender, and comorbid psychiatric disorders. A two-tailed *p* value of less than .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, North Carolina).

Results

Demographic Characteristics of ADHD Patients and Controls

Of the 1,000,000-person sample population, 8,201 participants were identified as having a diagnosis of ADHD between January 1, 1996 and December 31, 2010 comprising 6,251 males and 1,950 females with a significant age difference (14.89 ± 5.88 vs. 18.19 ± 10.89 years, $p < .001$). Allergic comorbidities in patients with ADHD were prevalent. Compared with the control group, the ADHD patients had a significantly greater prevalence of allergic diseases than the controls, including asthma (25.2% vs. 18.1%, $p < .001$), AR (40.6% vs. 30.1%, $p < .001$), AD (17.9% vs. 13.2%, $p < .001$), and urticaria (8.4% vs. 6.2%, $p < .001$). Differing from allergic diseases, comorbidity of autoimmune diseases with ADHD was low. Nine (0.1%) ADHD patients were diagnosed as having LE, 12 (0.1%) as having RA, 8 (0.1%) as having AS, 17 (0.2%) as having ulcerative colitis, 107 (1.3%) as having Crohn's disease, 10 (0.1%) as having type 1 DM, 22 (0.3%) as having HSP, 173 (2.1%) as having autoimmune thyroid disease, 51 (0.6%) as having Kawasaki disease, and none as having celiac disease. ADHD participants had significantly higher prevalence of AS (0.1% vs. 0%, $p = .016$), ulcerative colitis (0.2% vs. 0.1%, $p = .018$), and autoimmune thyroid diseases (2.1% vs. 0.8%, $p < .001$) than the controls. The prevalence of RA (0.1% vs. 0.1%, $p = .065$), type 1 DM (0.1% vs. 0.1%, $p = .062$), and Kawasaki disease (0.6% vs. 0.5%, $p = .094$) presented a significant trend between the cases and controls

(Table 1). Besides, ADHD participants exhibited significantly higher prevalence of any depressive disorder (5.5% vs. 0.5%, $p < .001$) and any anxiety disorder (14.8% vs. 0.4%, $p < .001$) than the controls (Table 1).

OR for Allergic and Autoimmune Diseases

Multiple logistic regression analysis was used to evaluate the OR of allergic and autoimmune comorbidities among patients with ADHD, after adjusting for age, gender, and psychiatric comorbidities. ADHD patients had significantly increased OR of asthma (OR = 1.53, 95% CI = [1.44, 1.63]), AR (OR = 1.59, 95% CI = [1.51, 1.68]), AD (OR = 1.53, 95% CI = [1.42, 1.64]), and urticaria (OR = 1.39, 95% CI = [1.26, 1.52]) compared with the controls. ADHD patients presented significantly higher risks of AS (OR = 2.78, 95% CI = [1.01, 7.63]), ulcerative colitis (OR = 2.31, 95% CI = [1.26, 4.23]), and autoimmune thyroid disease (OR = 2.53, 95% CI = [2.05, 3.13]) than the controls. A significant trend of an increased OR of Kawasaki disease (OR = 1.2, 95% CI = [0.87, 1.72]) and type 1 DM (OR = 2.04, 95% CI = [0.91, 4.59]) was noted among the ADHD patients (Table 2).

Discussion

The high prevalence rates of allergic diseases among the ADHD patients in our study were compatible with those of many previous studies. The rare comorbidity of autoimmune diseases with ADHD was consistent with results from previous studies, but some potential associations between ADHD and autoimmunity were found in our results.

ADHD and Allergic Diseases

Our results, showing an increased prevalence of allergic diseases among patients with ADHD, were compatible with results from recent larger sample sized studies (Fasmer et al., 2011; Mogensen et al., 2011; Schmitt et al., 2009). Romanos, Gerlach, Warnke, and Schmitt (2010), examining the association of AD with ADHD in 13,318 children and adolescents aged 3 to 17, showed that ADHD patients, especially those with sleeping problems, had significantly increased OR of AD, independent of sociodemographic factors (i.e., parental smoking, breast-feeding, number of siblings, and perinatal health problems). Using data from the National Survey of Children's Health, involving 102,353 randomly selected children aged 0 to 17 years, Blackman and Gurka (2007) suggested that children with asthma have a higher rate of ADHD, depression, learning disability, and behavioral problems, and that the severity of asthma is positively correlated with the comorbid symptomatology. Secnik, Swensen, and Lage (2005) reconfirmed the significant risk of ADHD with asthma in a large sample sized study, revealing that ADHD patients were

Table 1. Characteristics of Patients With ADHD and Control Participants

Characteristics	ADHD	Control	p value
<i>n</i>	8,201	32,804	
Age (years)	15.68 (7.52)	15.68 (7.52)	
Sex, <i>n</i> (%)			
Male	6,251 (76)	25,004 (76)	
Female	1,950 (24)	7,800 (24)	
Associated diseases, <i>n</i> (%)			
Asthma	2,069 (25.2)	5,950 (18.1)	<.001
Allergic rhinitis	3,326 (40.6)	9,868 (30.1)	<.001
Atopic dermatitis	1,467 (17.9)	4,334 (13.2)	<.001
Urticaria	691 (8.4)	2,050 (6.2)	<.001
LE	9 (0.1)	18 (0.1)	.092
RA	12 (0.1)	25 (0.1)	.065
AS	8 (0.1)	10 (0)	.016
Ulcerative colitis	17 (0.2)	32 (0.1)	.018
Crohn's disease	107 (1.3)	413 (1.3)	.744
Type I DM	10 (0.1)	19 (0.1)	.062
Autoimmune thyroid disease	173 (2.1)	258 (0.8)	<.001
HSP	22 (0.3)	66 (0.2)	.232
Celiac disease	0 (0)	1 (0)	1.000
Kawasaki disease	51 (0.6)	155 (0.5)	.094
Any depressive disorder	449 (5.5)	156 (0.5)	<.001
Any anxiety disorder	1,212 (14.8)	140 (0.4)	<.001

Note: LE = lupus erythematosus; RA = rheumatoid arthritis; AS = ankylosing spondylitis; Type I DM = type I diabetes; HSP = Henoch-Schönlein purpura.

significantly more likely to have a comorbid diagnosis of asthma and other psychiatric disorders. In a study of 1,436 patients with AD and matched controls designed to clarify the association between atopic/allergic diseases and ADHD, Schmitt et al. (2009) reported that only AD, not asthma or AR, was significantly associated with ADHD, independent of age, gender, and comorbid psychiatric disorders. In a recent systemic review investigating the relationship between atopic/allergic diseases and ADHD by analyzing 20 relevant studies with a total of 170,175 individuals, Schmitt, Buske-Kirschbaum, and Roessner (2010) concluded that six studies consistently reported a positive association between AD and ADHD with ORs ranging between 1 and 2, and 12 studies consistently found a positive association between asthma and ADHD with ORs ranging between 1.23 and 2.42. In contrast to the significant association among ADHD, asthma, and AD, the relationship between ADHD and AR was more controversial. Brawley et al. (2004) assessed the prevalence of AR and used a skin prick test in 30 children with ADHD and dem-

Table 2. ORs Between ADHD and Allergic/Autoimmune Diseases

	Crude OR (95% CI)	mOR (95% CI) ^a
Asthma	1.52 [1.44, 1.61]	1.53 [1.44, 1.63]
Allergic rhinitis	1.59 [1.51, 1.67]	1.59 [1.51, 1.68]
Atopic dermatitis	1.43 [1.34, 1.53]	1.53 [1.42, 1.64]
Urticaria	1.38 [1.26, 1.51]	1.39 [1.26, 1.52]
LE	2.00 [0.90, 4.46]	1.62 [0.67, 3.91]
RA	1.92 [0.97, 3.83]	1.57 [0.74, 3.56]
AS	3.20 [1.26, 8.12]	2.78 [1.01, 7.63]
Ulcerative colitis	2.13 [1.18, 3.83]	2.31 [1.26, 4.23]
Crohn's disease	1.04 [0.84, 1.29]	0.97 [0.77, 1.23]
Type I DM	2.11 [0.98, 4.53]	2.04 [0.91, 4.59]
Autoimmune thyroid disease	2.72 [2.24, 3.30]	2.53 [2.05, 3.13]
HSP	1.33 [0.82, 2.16]	1.37 [0.82, 2.28]
Kawasaki disease	1.32 [0.96, 1.81]	1.22 [0.87, 1.72]

Note: OR = odds ratio; mOR = modified odds ratio; LE = lupus erythematosus; RA = rheumatoid arthritis; AS = ankylosing spondylitis; Type I DM = type I diabetes; HSP = Henoch-Schönlein purpura. Bold type means a statistically significant OR.

^aAdjusted by age, sex, and psychiatric comorbidities.

onstrated that 80% of ADHD children reported AR symptoms and 61% had a positive skin prick test result. However, neither Romanos et al.'s nor Schmitt et al.'s large sample sized studies validated the possible association between AR and ADHD, although the comorbidity of asthma and AR was very high.

The association between allergic diseases and ADHD was independent of environmental and lifestyle factors such as parental smoking, breast-feeding, number of siblings, and early day care (Schmitt et al., 2010). The possible underlying mechanism of the high prevalence of allergic comorbidity and ADHD is still unknown. The cumulative incidence of allergic diseases is high within the first 2 years of life (Schmitt et al., 2009). In contrast, ADHD is rarely diagnosed before age 3 and generally, the incidence peaks at school age (Swanson et al., 1998). With the current evidence, we cannot conclude which of both diseases develops first and substantially affects the other, or whether they develop simultaneously with a shared mechanism and interact together. Immunological dysregulation and abnormality of allergic diseases may contribute to the speculative mechanism, including hypersecretion of immunoglobulin E (IgE), increased eosinophilic activity, and a predominantly T helper type 2 (Th2) cytokines secretion (Agrawal & Bharadwaj, 2005; Bieber, 2008; Kira, 2002). There is some evidence that oversecretion of inflammatory cytokines during an allergic or atopic response will penetrate the blood-brain barrier (Yarlagadda, Alfson, & Clayton, 2009) and activate neuroimmune mechanisms involving some specific neural

circuits related to behavioral and emotional modulation (Raison, Capuron, & Miller, 2006). For example, Ishiuchi et al. (2009) studied the difference in brain processing in patients with active AD and healthy controls using functional magnetic resonance imaging (fMRI) and found that patients with AD exhibited bilateral activation of the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and dorsolateral prefrontal cortex (DLPFC). Rosenkranz et al. (2005) reported the activation of ACC and insula during an allergic episode in patients with asthma. The abnormal and dysregulated neural circuitry of the prefrontal cortex, ACC, and insula has been observed in patients with ADHD (Christakou et al., 2012; Lemiere et al., 2012; Sun et al., 2012). In particular, abnormal functioning of the prefrontal cortex has been proved to account for the core symptoms of ADHD, including impulsivity and inattention (Christakou et al., 2012; Sun et al., 2012). However, the association among allergic immunity, neural circuitry, and brain function in ADHD patients requires further study.

In this study, we found an increased prevalence of asthma, AR, AD, and urticaria in ADHD patients compared with matched controls, strengthening the clinical hypothesis that allergic immunity may play an important role in ADHD. Further study will be required to clarify the underlying mechanisms, whether comorbidity or causality, between these two distinct diseases.

ADHD and Autoimmune Diseases

The relationship between autoimmunity and autoimmune diseases and ADHD has rarely been mentioned in the literature, but a slow-growing body of evidence has shown the possible roles of autoantibodies and autoimmunity in the etiology of ADHD. Examining the prevalence of antibodies against glutamic acid decarboxylase 65 (GAD65) in ADHD patients, Rout, Mungan, and Dhossche (2012) showed that serum from 20% of ADHD patients reacted with the cells in the molecular and granule cell layers and cells in the vicinity of the Purkinje neurons. Peterson et al. (2000) demonstrated that antistreptococcal antibody titer was significantly associated with ADHD and larger volumes of putamen and globus pallidus nuclei, implying the possible immune-mediated pathogenesis of ADHD. However, a recent study did not validate the role of more frequent antibasal ganglia autoantibodies in children with ADHD (Sanchez-Carpintero, Albasa, Crespo, Villoslada, & Narbona, 2009). Moreover, Bilenberg, Hougaard, Norgaard-Pedersen, Nordenbæk, and Olsen (2011) tested the hypothesis that maternal transplacentally acquired antibodies may cause ADHD symptoms years after birth, and found that Pneumococcal Polysaccharide 14 was present in the ADHD high-scoring twin more often than in the low-scoring twin. In a study on mice induced with antiphospholipid (APL) syndrome using monoclonal anticardiolipin antibodies, Ziporen, Shoenfeld, Levy, and Korczyn (1997) reported that the mice

exhibited hyperactive behavior compared with the control group. The results of a human study by Bujanover et al. (2003) did not support this association and suggested no significant difference in the level of APL antibody measured between the ADHD children and the controls. Although there was some evidence supporting the possible role of autoimmunity in ADHD, the results were still controversial.

The dysregulated secretion of many autoimmunity-related proinflammatory cytokines, including tumor necrosis factor (TNF) and interleukin (IL), may play an important role in the comorbid association. Mittleman et al. (1997) assessed the cerebrospinal fluid cytokine levels of patients with ADHD and suggested that ADHD had both cell-mediated and humoral immunity dysfunction. In Oades, Dauvermann, Schimmelmann, Schwarz, and Myint's (2010) study investigating different cytokine concentrations in ADHD compared with healthy controls, six cytokines, including IL-2, IL-6, interferon-gamma (IFN- γ), IL-16, IL-10, and IL-13, showed a marginal increase in the ADHD group. Ribasés et al. (2008), studying the association of ADHD with the 10 genes encoding neurotrophins (nerve growth factor [NGF]), the cytokine family of NGF (ciliary neurotrophic growth factor [CNTGF], including IL-6), and their receptors (nerve growth factor receptor [NGFR] and ciliary neurotrophic factor receptor [CNTFR]), offered support for the contribution of the neurotrophic factors (NTFs) and CNTFR locus as predisposing factors for the disorder. Drtilkova et al. (2008) validated Ribasés et al.'s results and reconfirmed that the polymorphisms of IL-2, IL-6, and TNF- α represent neurodevelopmental risk factors in the etio-pathogenesis of ADHD. The aforementioned cytokines are encoded from MHC genes. Current evidence has shown that ADHD is significantly associated with the HLA-DR4, HLA-DRB1, and C4B genes (Aureli et al., 2008; Odell et al., 1997; Ogdie et al., 2003).

Our results reflected a significant relationship between ADHD and some autoimmune diseases, including AS, ulcerative colitis, and autoimmune thyroid disease. The associations of ADHD with Kawasaki disease and type 1 DM presented significant trends.

ADHD and Ankylosing Spondylitis. The association between ADHD and AS has not been reported. AS, as well as ADHD, occurs predominantly in male patients. Approximately, 90% of AS patients express the HLA-B27 genotype, but there is no evidence of a possible role of HLA-B27 in ADHD. Both ADHD and AS exhibited a dysregulated secretion of TNF- α , IL-1, and IL-6 (Mansour et al., 2007). Despite the rare prevalence of AS in the ADHD patients and controls in our study, the result may still inspire further study to test the possible association of these two male-predominant diseases.

ADHD and Ulcerative Colitis. The association between ADHD and celiac disease was proposed in a study of Caucasian participants (Niederhofer, 2011). However, in our study, we did not validate this association but found a significantly increased risk of ulcerative colitis in ADHD

patients. The racial effect on this epidemiological difference may need to be considered because the incidence of ulcerative colitis in Asian populations resident in Western countries appears to be higher than that in the native population in both children and adults (Ravikumara & Sandhu, 2006). In Sawczenko and Sandhu's (2003) large prospective national study, ulcerative colitis was found in 29% of patients with childhood inflammatory bowel disease. Furthermore, the incidence rate of ulcerative colitis has dramatically increased in recent decades, from 0.5/100,000 per year to 3.5/100,000 per year (IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, 2005), and parallels the rising incidence of ADHD. Different proinflammatory cytokines, including TNF- α , IL-6, and IL-8, contribute to the etiology of ulcerative colitis and are associated with symptomatic severity (Atreya & Neurath, 2005; Masuda, Iwai, Tanaka, & Hayakawa, 1995; Umehara, Kudo, Nakaoka, Kawasaki, & Shiomi, 2006). Our result was the first time that ADHD and ulcerative colitis were linked in a possible relationship.

ADHD and Type 1 DM. Our study results revealed an increasing risk of type 1 DM in ADHD patients. Gabbay, Sato, Duarte, and Dib (2012) reported that patients with newly diagnosed type 1 DM exhibited significantly higher concentration of IL-12, IL-6, IL-1 β , TNF- α , and IL-10 than controls, and the anti-GAD65 autoantibody was negatively associated with these cytokines. In an investigation of the association between human leukocyte antigen (HLA) genes and type 1 DM in 790 type 1 DM patients and controls, Yamashita et al. (2011) found that HLA DRB1*0405 and DRB1*0901 were positively associated with type 1 DM, whereas the DRB1*15 haplotypes were negatively associated. Skanes et al. (1986) suggested C4B*3 and HLA-DR4 were associated with type 1 DM, and that C4B*1 carriers had an increased risk of type 1 DM. ADHD and type 1 DM seemed to share the same MHC gene susceptibility for the possible comorbidity.

ADHD and Autoimmune Thyroid Diseases. The association between ADHD and autoimmune thyroid diseases was discussed more than other autoimmune diseases in previous reports, although the underlying mechanism is still unclear. One study found the prevalence of thyroid hormone abnormalities was 2.3% in ADHD patients compatible with our results (Valentine et al., 1997). But the role of thyroid function in ADHD is still controversial. In Cakaloz, Akay, Bober, and Yulug's (2011) study of 21 boys with ADHD, 26 boys with ADHD and oppositional defiant disorder (ODD), and 27 controls, thyroid-stimulating hormone (TSH) levels in the ADHD and ADHD + ODD groups were *significantly* lower compared with the control group, and significantly negatively correlated with Child Behavior Checklist (CBCL) ratings of behavioral parameters, including attention problems, delinquent behaviors, aggressive behaviors, and externalizing problems. Conversely, thyroxine concentrations were associated with mood symptoms, less strongly related to attention functioning, and

not related to hyperactivity in Stein and Weiss's (2003) study. Graves' disease and Hashimoto thyroiditis contributed to the majority of thyroid abnormalities. The role of the autoimmunity of thyroid diseases in ADHD has gained some interest in recent years. In a population-based cohort study composed of 3,139 children and their mothers, Ghassabian et al. (2012) measured maternal thyroid parameters (thyrotropin or TSH and thyroid peroxidase antibodies [TPOAbs]) at 13.5 ± 1.8 weeks of gestation and assessed children's behavior at age 3 using the CBCL, and found that children of TPOAb-positive mothers were at a higher risk of ADHD and externalizing problems after correcting for TSH. A case report presenting a girl with ADHD comorbid with autoimmune hypothyroidism and many behavioral problems proposed the possible link of ADHD with autoimmune thyroid diseases (Banerjee et al., 2011). Our result strengthened this comorbid association, but further study is required to gain understanding of the underlying mechanism.

ADHD and Kawasaki Disease. Kawasaki disease is an autoimmune disease affecting many organ systems, including the blood vessels, skin, mucous membranes, lymph nodes, and heart. It is largely seen in children less than 5 years of age. The association between ADHD and Kawasaki disease is still unclear. Tacke et al. (2012) assessed 280 children and adolescents with a history of Kawasaki disease, and reported that patients with Kawasaki disease exhibited more hyperactivity and emotional problems than the normal population. In our study, we found a significant trend of a comorbidity of ADHD with Kawasaki disease. The possible explanations may be related to the similar underlying immune abnormality and dysfunction in both ADHD and Kawasaki disease, including increased serum levels of IL-6 and TNF- α (Matsubara, 1991) and susceptible MHC genes (i.e., HLA-DRB1; Huang et al., 2007; Onouchi et al., 2012).

In contrast with allergic diseases being highly prevalent with ADHD, autoimmune diseases were rare in our study. A longer prospective study will be needed to elucidate the association, whether sporadic comorbidity or causality between ADHD and various autoimmune diseases.

Limitations

Some limitations of the study needed to be addressed. First, the prevalence rates of diagnoses may be underestimated in our study because only those having medicine-seeking behaviors were identified. However, the diagnoses were more reliable than self-reported ones because the patients included in our study were given a diagnosis by board-certified physicians. Second, NHIRD is an anonymous database, designed to protect the privacy of the insured participants, and did not provide some information, such as sociodemographic factors, personal lifestyle, social adversity, and environmental factors. We were unable to examine the influence of these factors. Third, in our study, we regarded ADHD as a complete cate-

gory, but it is composed of two subtypes: inattention and hyperactivity. The differences in allergy/autoimmune comorbidities with these two subtypes require further study.

Conclusion

Our results supported the significant association between ADHD and allergic diseases, indicating the important roles of allergic immunity in the etiopathogenesis of ADHD. We again validated the association of ADHD with autoimmune thyroid diseases. Moreover, this is the first study to link the possible relationship of ADHD with various autoimmune diseases, including AS, ulcerative colitis, type 1 DM, autoimmune thyroid disease, and Kawasaki disease. However, the role of autoimmunity in ADHD is still unknown. Further study will be required to clarify the comorbid or etiological association and the underlying mechanisms of a relationship between ADHD and allergic/autoimmune diseases.

Acknowledgment

We thank Dr. Mu-Hong Chen and Dr. Ya-Mei Bai, who designed the study, wrote the protocol and manuscripts; Dr. Ya-Mei Bai, Dr. Tung-Ping Su, Dr. Ying-Sheue Chen, Dr. Ju-Wei Hsu, and Dr. Kai-Lin Huang, who assisted with the preparation and proofreading of the manuscript; and Dr. Ya-Mei Bai, Dr. Tzeng-Ji Chen, and Ms. Wen-Han Chang who provided the advices on statistical analysis.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was supported by grant from Taipei Veterans General Hospital (V101D-001-1).

References

- Agrawal, D. K., & Bharadwaj, A. (2005). Allergic airway inflammation. *Current Allergy & Asthma Reports*, 5, 142-148.
- Atreya, R., & Neurath, M. F. (2005). Involvement of IL-6 in the pathogenesis of inflammatory bowel disease and colon cancer. *Clinical Reviews in Allergy & Immunology*, 28, 187-196.
- Aureli, A., Sebastiani, P., Del Beato, T., Marimpietri, A., Melillo, V., Sechi, E., & Di Loreto, S. (2008). Investigation on the possible relationship existing between the HLA-DR gene and attention deficit hyperactivity disorder and/or mental retardation. *International Journal of Immunopathology and Pharmacology*, 21, 985-991.
- Banerjee, J., Bhojani, S., & Emcy, N. (2011). Co-existence of ADHD, autoimmune hypothyroidism and pituitary macroadenoma presenting in a behaviour clinic: A case report and brief review of the literature. *Journal of Pediatric Endocrinology and Metabolism*, 24, 229-231.
- Belfer, M. L. (2008). Child and adolescent mental disorders: The magnitude of the problem across the globe. *Journal of Child Psychology and Psychiatry and Allied Disciplines*, 49, 226-236.
- Bieber, T. (2008). Atopic dermatitis. *New England Journal of Medicine*, 358, 1483-1494.
- Biederman, J., Milberger, S., Faraone, S. V., Guite, J., & Warburton, R. (1994). Associations between childhood asthma and ADHD: Issues of psychiatric comorbidity and familiarity. *Journal of the American Academy of Child & Adolescent Psychiatry*, 33, 842-848.
- Bilenberg, N., Hougaard, D., Norgaard-Pedersen, B., Nordenbæk, C. M., & Olsen, J. (2011). Twin study on transplacental-acquired antibodies and attention deficit/hyperactivity disorder: A pilot study. *Journal of Neuroimmunology*, 236, 72-75.
- Blackman, J. A., & Gurka, M. J. (2007). Developmental and behavioral comorbidities of asthma in children. *Journal of Developmental & Behavioral Pediatrics*, 28, 92-99.
- Brawley, A., Silverman, B., Kearney, S., Guanzon, D., Owens, M., Bennett, H., & Schneider, A. (2004). Allergic rhinitis in children with attention-deficit/hyperactivity disorder. *Annals of Allergy, Asthma & Immunology*, 92, 663-667.
- Brent, G. A. (2008). Clinical practice. Graves' disease. *New England Journal of Medicine*, 358, 2594-2605.
- Bujanover, S., Levy, Y., Katz, M., Leitner, Y., Vinograd, I., & Shoenfeld, Y. (2003). Lack of association between anti-phospholipid antibodies (APLA) and attention deficit/hyperactivity disorder (ADHD) in children. *Clinical and Developmental Immunology*, 10, 105-109.
- Cakaloz, B., Akay, A. P., Bober, E., & Yulug, B. (2011). Thyroid function and oppositional defiant disorder: More than a coincidence in prepubertal boys with attention-deficit hyperactivity disorder? *Journal of Neuropsychiatry and Clinical Neurosciences*, 23, E9-E10.
- Christakou, A., Murphy, C. M., Chantiluke, K., Cubillo, A. I., Smith, A. B., Giampietro, V., & Rubia, K. (2012). Disorder-specific functional abnormalities during sustained attention in youth with attention deficit hyperactivity disorder (ADHD) and with autism. *Molecular Psychiatry*. Advance online publication. doi: 10.1038/mp.2011.185.
- Drtilkova, I., Sery, O., Theiner, P., Uhrova, A., Zackova, M., Balastikova, B., & Znojil, V. (2008). Clinical and molecular-genetic markers of ADHD in children. *Neuroendocrinology Letters*, 29, 320-327.
- Fasmer, O. B., Halmoy, A., Eagan, T. M., Oedegaard, K. J., & Haavik, J. (2011). Adult attention deficit hyperactivity disorder is associated with asthma. *BMC Psychiatry*, 11, 128.
- Gabbay, M. A., Sato, M. N., Duarte, A. J., & Dib, S. A. (2012). Serum titres of anti-glutamic acid decarboxylase-65 and anti-IA-2 autoantibodies are associated with different immunoregulatory milieu in newly diagnosed type 1 diabetes patients. *Clinical & Experimental Immunology*, 168, 60-67.
- Gaitens, T., Kaplan, B. J., & Freigang, B. (1998). Absence of an association between IgE-mediated atopic responsiveness and ADHD symptomatology. *Journal of Child Psychology and Psychiatry*, 39, 427-431.

- Ghassabian, A., Bongers-Schokking, J. J., de Rijke, Y. B., van Mil, N., Jaddoe, V. W., de Muinck Keizer-Schrama, S. M., & Tiemeier, H. (2012). Maternal thyroid autoimmunity during pregnancy and the risk of attention deficit/hyperactivity problems in children: The Generation R Study. *Thyroid*, 22, 178-186.
- Huang, F. Y., Chang, T. Y., Chen, M. R., Hsu, C. H., Lee, H. C., Lin, S. P., & Lee, Y. J. (2007). Genetic variations of HLA-DRB1 and susceptibility to Kawasaki disease in Taiwanese children. *Human Immunology*, 68, 69-74.
- IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. (2005). Inflammatory bowel disease in children and adolescents: Recommendations for diagnosis: The Porto criteria. *Journal of Pediatric Gastroenterology and Nutrition*, 41, 1-7.
- Ishiuji, Y., Coghill, R. C., Patel, T. S., Oshiro, Y., Kraft, R. A., & Yosipovitch, G. (2009). Distinct patterns of brain activity evoked by histamine-induced itch reveal an association with itch intensity and disease severity in atopic dermatitis. *British Journal of Dermatology*, 161, 1072-1080.
- Kira, J. (2002). Atopy and neural damage. *Internal Medicine*, 41, 169-174.
- Lemiere, J., Danckaerts, M., Van Hecke, W., Mehta, M. A., Peeters, R., Snaert, S., & Sonuga-Barke, E. (2012). Brain activation to cues predicting inescapable delay in adolescent attention deficit/hyperactivity disorder: An fMRI pilot study. *Brain Research*, 1450, 57-66.
- Lin, G. M., Chen, Y. J., Kuo, D. J., Jaiteh, L. E., Wu, Y. C., Lo, T. S., & Li, Y. H. (2011). Cancer incidence in patients with schizophrenia or bipolar disorder: A nationwide population-based study in Taiwan, 1997-2009. *Schizophrenia Bulletin*. Advance online publication. doi: 10.1093/schbul/sbr162.
- Mansour, M., Cheema, G. S., Naguwa, S. M., Greenspan, A., Borchers, A. T., Keen, C. L., & Gershwin, M. E. (2007). Ankylosing spondylitis: A contemporary perspective on diagnosis and treatment. *Seminars in Arthritis and Rheumatism*, 36, 210-223.
- Marshall, P. (1989). Attention deficit disorder and allergy: A neurochemical model of the relation between the illnesses. *Psychological Bulletin*, 106, 434-446.
- Masuda, H., Iwai, S., Tanaka, T., & Hayakawa, S. (1995). Expression of IL-8, TNF-alpha and IFN-gamma mRNA in ulcerative colitis, particularly in patients with inactive phase. *Journal of Clinical & Laboratory Immunology*, 46, 111-123.
- Matsubara, T. (1991). Interleukin 6 activities and tumor necrosis factor-alpha levels in serum of patients with Kawasaki disease. *Arerugi*, 40, 147-154.
- Matsushita, S., Fujisao, S., & Nishimura, Y. (1996). Molecular mechanisms underlying HLA-DR-associated susceptibility to autoimmunity. *International Journal of Cardiology*, 54, S81-S90.
- Mittleman, B. B., Castellanos, F. X., Jacobsen, L. K., Rapoport, J. L., Swedo, S. E., & Shearer, G. M. (1997). Cerebrospinal fluid cytokines in pediatric neuropsychiatric disease. *Journal of Immunology*, 159, 2994-2999.
- Mogensen, N., Larsson, H., Lundholm, C., & Almqvist, C. (2011). Association between childhood asthma and ADHD symptoms in adolescence: A prospective population-based twin study. *Allergy*, 66, 1224-1230.
- Niederhofer, H. (2011). Association of attention-deficit/hyperactivity disorder and celiac disease: A brief report. *Primary Care Companion for CNS Disorders*, 13, 3.
- Noble, J. A., & Valdes, A. M. (2011). Genetics of the HLA region in the prediction of type 1 diabetes. *Current Diabetes Reports*, 11, 533-542.
- Oades, R. D., Dauvermann, M. R., Schimmelmann, B. G., Schwarz, M. J., & Myint, A. M. (2010). Attention-deficit hyperactivity disorder (ADHD) and glial integrity: S100B, cytokines and kynurenine metabolism—Effects of medication. *Behavioral and Brain Functions*, 6, 29.
- Odell, J. D., Warren, R. P., Warren, W. L., Burger, R. A., & Maciulis, A. (1997). Association of genes within the major histocompatibility complex with attention deficit hyperactivity disorder. *Neuropsychobiology*, 35, 181-186.
- Ogdie, M. N., Macphie, I. L., Minassian, S. L., Yang, M., Fisher, S. E., & Francks, C. (2003). A genomewide scan for attention-deficit/hyperactivity disorder in an extended sample: Suggestive linkage on 17p11. *American Journal of Human Genetics*, 72, 1268-1279.
- Onouchi, Y., Ozaki, K., Burns, J. C., Shimizu, C., Terai, M., & Hamada, H., U.S. Kawasaki Disease Genetics Consortium. (2012). A genome-wide association study identifies three new risk loci for Kawasaki disease. *Nature genetics*, 44, 517-521.
- Pearce, E. N., Farwell, A. P., & Braverman, L. E. (2003). Thyroiditis. *New England Journal of Medicine*, 348, 2646-2655.
- Peterson, B. S., Leckman, J. F., Tucker, D., Scahill, L., Staib, L., Zhang, H., & Lombroso, P. (2000). Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive-compulsive, and attention deficit/hyperactivity disorders. *Archives of General Psychiatry*, 57, 364-372.
- Poupon, R. (2003). Autoimmune overlapping syndromes. *Clinical Liver Disease*, 7, 865-878.
- Raison, C. L., Capuron, L., & Miller, A. H. (2006). Cytokines sing the blues: Inflammation and the pathogenesis of depression. *Trends in Immunology*, 27, 24-31.
- Rappley, M. D. (2005). Clinical practice. Attention deficit-hyperactivity disorder. *New England Journal of Medicine*, 352, 165-173.
- Ravikumara, M., & Sandhu, B. K. (2006). Epidemiology of inflammatory bowel diseases in childhood. *Indian Journal of Pediatrics*, 73, 717-721.
- Ribasés, M., Hervás, A., Ramos-Quiroga, J. A., Bosch, R., Bielsa, A., Gastaminza, X., & Bayés, M. (2008). Association study of 10 genes encoding neurotrophic factors and their receptors in adult and child attention-deficit/hyperactivity disorder. *Biological Psychiatry*, 63, 935-945.
- Romanos, M., Gerlach, M., Warnke, A., & Schmitt, J. (2010). Association of attention-deficit/hyperactivity disorder and atopic eczema modified by sleep disturbance in a large population-based sample. *Journal of Epidemiology & Community Health*, 64, 269-273.
- Rosenkranz, M. A., Busse, W. W., Johnstone, T., Swenson, C. A., Crisafi, G. M., Jackson, M. M., & Davidson, R. J. (2005). Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. *Proceedings of the National Academy of Sciences of the United States of America*, 102, 13319-13324.

- Rout, U. K., Mungan, N. K., & Dhossche, D. M. (2012). Presence of GAD65 autoantibodies in the serum of children with autism or ADHD. *European Child & Adolescent Psychiatry*, 21, 141-147.
- Sanchez-Carpintero, R., Albesa, S. A., Crespo, N., Villoslada, P., & Narbona, J. (2009). A preliminary study of the frequency of anti-basal ganglia antibodies and streptococcal infection in attention deficit/hyperactivity disorder. *Journal of Neurology*, 256, 1103-1108.
- Sawczenko, A., & Sandhu, B. K. (2003). Presenting features of inflammatory bowel disease in Great Britain and Ireland. *Archives of Disease in Childhood*, 88, 995-1000.
- Schmitt, J., Buske-Kirschbaum, A., & Roessner, V. (2010). Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. *Allergy*, 65, 1506-1524.
- Schmitt, J., Romanos, M., Schmitt, N. M., Meurer, M., & Kirch, W. (2009). Atopic eczema and attention-deficit/hyperactivity disorder in a population-based sample of children and adolescents. *Journal of the American Medical Association*, 301, 724-726.
- Secnik, K., Swensen, A., & Lage, M. J. (2005). Comorbidities and costs of adult patients diagnosed with attention-deficit hyperactivity disorder. *Pharmacoeconomics*, 23, 93-102.
- Skanes, V. M., Barnard, J., Farid, N., Marshall, W. H., Murphy, L., Rideout, D., & Larsen, B. (1986). Class III alleles and high-risk MHC haplotypes in type I diabetes mellitus, Graves' disease and Hashimoto's thyroiditis. *Molecular Biology & Medicine*, 3, 143-157.
- Smalley, S. L., McGough, J. J., Moilanen, I. K., Loo, S. K., Taanila, A., Ebeling, H., & Järvelin, M. R. (2007). Prevalence and psychiatric comorbidity of attention-deficit/hyperactivity disorder in an adolescent Finnish population. *Journal of the American Academy of Child & Adolescent Psychiatry*, 46, 1575-1583.
- Stein, M. A., & Weiss, R. E. (2003). Thyroid function tests and neurocognitive functioning in children referred for attention deficit/hyperactivity disorder. *Psychoneuroendocrinology*, 28, 304-316.
- Sun, L., Cao, Q., Long, X., Sui, M., Cao, X., Zhu, C., & Wang, Y. (2012). Abnormal functional connectivity between the anterior cingulate and the default mode network in drug-naïve boys with attention deficit hyperactivity disorder. *Psychiatry Research*, 201, 120-127.
- Swanson, J. M., Sergeant, J. A., Taylor, E., Sonuga-Barke, E. J., Jensen, P. S., & Cantwell, D. P. (1998). Attention-deficit hyperactivity disorder and hyperkinetic disorder. *Lancet*, 351, 429-433.
- Tacke, C. E., Haverman, L., Berk, B. M., van Rossum, M. A., Kuipers, I. M., Grootenhuys, M. A., & Kuijpers, T. W. (2012). Quality of life and behavioral functioning in Dutch children with a history of Kawasaki disease. *Journal of Pediatrics*, 161, 314-319.e1.
- Taurines, R., Schmitt, J., Renner, T., Conner, A. C., Warnke, A., & Romanos, M. (2010). Developmental comorbidity in attention-deficit/hyperactivity disorder. *Attention Deficit and Hyperactivity Disorder*, 2, 267-289.
- Umehara, Y., Kudo, M., Nakaoka, R., Kawasaki, T., & Shiomi, M. (2006). Serum proinflammatory cytokines and adhesion molecules in ulcerative colitis. *Hepatology*, 53, 879-882.
- Valentine, J., Rossi, E., O'Leary, P., Parry, T. S., Kurinczuk, J. J., & Sly, P. (1997). Thyroid function in a population of children with attention deficit hyperactivity disorder. *Journal of Paediatrics and Child Health*, 33, 117-120.
- Van Jaarsveld, C. H., Otten, H. G., Jacobs, J. W., Kruize, A. A., Brus, H. L., & Bijlsma, J. W. (1998). Association of HLA-DR with susceptibility to and clinical expression of rheumatoid arthritis: Re-evaluation by means of genomic tissue typing. *British Journal of Rheumatology*, 37, 411-416.
- Wittchen, H. U., & Jacobi, F. (2005). Size and burden of mental disorders in Europe: A critical review and appraisal of 27 studies. *European Neuropsychopharmacology*, 15, 357-376.
- Wu, C. S., Wang, S. C., Cheng, Y. C., & Gau, S. S. (2011). Association of cerebrovascular events with antidepressant use: A case-crossover study. *American Journal of Psychiatry*, 168, 511-521.
- Yamashita, H., Awata, T., Kawasaki, E., Ikegami, H., Tanaka, S., & Maruyama, T., Japanese Study Group on Type 1 Diabetes Genetics. (2011). Analysis of the HLA and non-HLA susceptibility loci in Japanese type 1 diabetes. *Diabetes/Metabolism Research and Reviews*, 27, 844-848.
- Yarlagadda, A., Alfson, E., & Clayton, A. H. (2009). The blood brain barrier and the role of cytokines in neuropsychiatry. *Psychiatry (Edmont)*, 6, 18-22.
- Ziporen, L., Shoenfeld, Y., Levy, Y., & Korczyn, A. D. (1997). Neurological dysfunction and hyperactive behavior associated with antiphospholipid antibodies. A mouse model. *Journal of Clinical Investigation*, 100, 613-619.

Bios

Mu-Hong Chen is Chief resident in the Department of Psychiatry, Taipei Veterans General Hospital.

Tung-Ping Su is a Professor in the Department of Psychiatry, Taipei Veterans General Hospital and National Yang-Ming University.

Ying-Sheue Chen is Chief of Department of Psychiatry, Taipei Veterans General Hospital

Ju-Wei Hsu is the Attending physician in the Department of Psychiatry, Taipei Veterans General Hospital and National Yang-Ming University.

Kai-Lin Huang is the Attending physician in the Department of Psychiatry, Taipei Veterans General Hospital and National Yang-Ming University.

Wen-Han Chang is the Research assistant in the Department of Psychiatry, Taipei Veterans General Hospital.

Tzeng-Ji Chen is the Chief of Department of Family Medicine, Taipei Veterans General Hospital and National Yang-Ming University

Ya-Mei Bai is the Attending physician in the Department of Psychiatry, Taipei Veterans General Hospital and National Yang-Ming University.