



Comorbidity of allergic and autoimmune diseases in patients with autism spectrum disorder: A nationwide population-based study

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ABSTRACT

Previous clinical and genetic studies have suggested autism spectrum disorders (ASDs) is associated with immunological abnormalities involving cytokines, immunoglobulins, inflammation, and cellular immunity, but epidemiological reports are still limited. Patients with ASDs were identified in the National Health Insurance Database from 1996 to 2010, and compared with age and gender-matched controls (1:4) in an investigation of the association between ASDs and allergic/autoimmune diseases. A total of 1596 patients with ASDs were identified, and were found to have a significantly higher prevalence of allergic and autoimmune diseases than the control group. Patients with ASDs had increased risks of asthma (OR = 1.74, 95%CI = 1.51–1.99), allergic rhinitis (OR = 1.70, 95%CI = 1.51–1.91), atopic dermatitis (OR = 1.52, 95%CI = 1.30–1.78), urticaria (OR = 1.38, 95%CI = 1.12–1.69) and type 1 diabetes (OR = 4.00, 95%CI = 1.00–16.00), and a trend toward increasing comorbidity with Crohn's disease (OR = 1.46, 95%CI = 0.90–2.35). Our results support the association between ASDs and allergic diseases, and autoimmune comorbidities (type 1 diabetes and Crohn's disease). Further basic study is required to elucidate the possible underlying mechanisms and roles of allergy immunity and autoimmunity in the etiology of ASDs.

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1. Background

Autism spectrum disorders (ASDs) are complex neurodevelopment disorders that begin in childhood. Individuals with ASDs manifest qualitative impairments in social cognition, deficient verbal and non-verbal communication, restricted interests, and stereotyped/repetitive behaviors, ranging in severity from patients with profound deficits to individuals that are highly functioning (Rapin, 1997, 2002). The prevalence of ASDs has increased gradually, from 4 to 60–100/10,000 over the last decade, with a 3–4:1 male-to-female ratio (“Prevalence of Autism Spectrum Disorders – Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008,” 2012; Prevalence of Autism Spectrum Disorders – Autism and Developmental Disabilities Monitoring Network, United States, 2006,” 2009; Stankovic, Lakic, & Ilic, 2012). Although significant genetic links have been found, with evidence from monozygotic twin and family studies showing concordance rates for ASDs at least up to 60 percent and a familial risk 5–10 times higher than that for the general

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population (Bailey et al., 1995; Rutter, 2000; Szatmari, 1999), the underlying etiology of ASDs is still unknown. Many different theories researching the biological basis of ASDs have been suggested, including multiple genetic mutation, chromosomal abnormalities, epiphenomena (pre- and peri-natal complications interact with genetic factors), and immune hypotheses (Ashwood & Van de Water, 2004; Brimacombe, Ming, & Lamendola, 2007; Kolevzon, Gross, & Reichenberg, 2007; Newschaffer, Fallin, & Lee, 2002; Santangelo & Tsatsanis, 2005; Zwaigenbaum et al., 2002).

Similar to the substantially increased prevalence of ASDs worldwide over the last few decades, the prevalence rates of asthma, allergic rhinitis (AR), and atopic dermatitis (AD) have risen gradually and simultaneously. In the United States, the prevalence of childhood asthma doubled from approximately 3% in early 1980 to 7.5% in 1995 (Woodruff et al., 2004). In Australia, the International Study of Asthma and Allergies in Childhood reported that from the 1990s to early 2000, the prevalence of asthma, AR, and AD rose significantly, from 4.4%, 3.7%, and 10.1% to 5.1%, 4.5%, and 13.8% among children aged 6–7 (Schernhammer, Vutuc, Waldhor, & Haidinger, 2008). The time concordance of the increased prevalence of allergic diseases and ASDs has inspired many scientists in recent years to investigate the etiological association between these 2 clinically distinct diseases.

There is a growing awareness of an immunological involvement in individuals with ASDs. Numerous studies have described the dysregulation and the imbalances in immune and inflammatory processes in patients with ASDs, including decreased antibody levels of total plasma Immunoglobulin-G and Immunoglobulin-M (Heuer et al., 2008), lower levels of transforming Growth Factor- β (a cytokine in regulation of cellular proliferation and differentiation), and higher levels of macrophage migration inhibitory factor (a cytokine in regulation of macrophage function) (Grigorenko et al., 2008; Okada et al., 2007). Recent studies have reported a higher frequency of HLA-A2 and HLA-DR4 antigens, which are related to human immune system functioning, in patients with ASDs (Lee et al., 2006; Torres et al., 2006).

Many patients with ASDs suffer from allergic-like symptoms, but the exact prevalence remains unknown because of the lack of large-scale epidemiological studies. Only a few clinical survey studies have reported the association of allergy disorders with patients who had ASDs. Magalhaes et al. (2009) assessed 15 Asperger patients and 15 age-matched healthy controls and found that increased allergic problems (AD, asthma, and AR) were present in 70% of patients compared to 7% of controls. In a study of 30 children with mild to moderate autism and 20 with severe autism, Mostafa, Hamza, and El-Shahawi (2008) found that 52% had allergic manifestations (bronchial asthma, AD, and AR) compared to 10% of the controls, with a significantly positive correlation between symptom severity and allergic symptoms. Some studies, however, have reported negative results. In Bakkaloglu et al.'s study assessing 30 children with ASDs and 39 healthy controls, the young children with ASDs did not present more allergic features, based on history, skin tests, and serum Ig-E levels, than the normal controls (Bakkaloglu et al., 2008). Jyonouchi, Geng, Cushing-Ruby, and Quraishi (2008) also reported the ASDs group was not associated with atopic dermatitis, allergic rhinitis, asthma, and food allergy compared with the healthy controls. Therefore, previous clinical studies have had inconsistent results for the association of allergic diseases with ASDs, possibly owing to the small number of study participants, the heterogeneous patient population, and the use of parental reports instead of clinical diagnoses.

Some heredity evidence has shown that children with a maternal and familial history of autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (Atladdottir et al., 2009; Comi, Zimmerman, Frye, Law, & Peeden, 1999), have an increased risk of ASDs. For example, Comi et al. (1999) surveyed the families of 61 patients with ASDs and 46 healthy controls and reported that as the number of family members with autoimmune diseases increased from 1 to 3, the risk of autism was greater, with an odds ratio that increased from 1.9 to 5.5, respectively. In an assessment of 3325 children with ASDs with regard to the familial prevalence of autoimmune diseases, Atladdottir et al. (2009) suggested an increased risk of infantile autism was observed for children with a family history of autoimmune diseases, including type 1 diabetes, rheumatoid arthritis and celiac disease. However, data on the association between ASDs and personal autoimmune diseases is very limited. Afzal and Minor (2002) reported a possible association between Crohn's disease and autism. In a retrospective study investigating the association between type 1 diabetes and ASDs, Freeman and colleagues reported that 9 (0.9%) of 984 type 1 diabetes children were diagnosed with ASDs, a prevalence rate higher than that (0.1–0.3%) in the normal population (Freeman, Roberts, & Daneman, 2005). Holmes et al. (2011) reported a statistically significant association between Kawasaki disease and the diagnosis of disorder with ASDs (odds ratio: 15.15, $p < 0.001$). But, Pavone, Fiumara, Bottaro, Mazzone, and Coleman (1997) failed to find a positive link between autism and celiac disease in a study reporting that none of 120 celiac patients had a diagnosis of infantile autism.

In summary, although some basic and genetic evidence suggests that dysregulation of the immune system may be involved in the etiology of ASDs, the comorbidities of allergic and autoimmune diseases with ASDs are still controversial and with limited epidemiological evidence. In this study, using a large sample size from a nationwide population-based insurance database and a case-control study design, we attempted to investigate the association between ASDs and allergic and autoimmune diseases.

2. Methods

2.1. Data source

The National Health Insurance (NHI) program was implemented in Taiwan in 1995. Taiwan's NHI has covered 96.9% of all 23,000,000 residents of Taiwan since 2001. The completeness and accuracy of the NHI claims database has been audited by

the Department of Health and the Bureau of NHI. The database provides demographic and medical information on insured residents, including age, gender, prescription drugs, prescription date, and the prescription and diagnosis using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHI Research Database (NHIRD) has been used extensively in many epidemiologic studies in Taiwan (M.H. Chen et al., 2012a; S.J. Chen et al., 2012b; Li et al., 2012; Lin et al., 2011).

2.2. Inclusion criteria for ASDs and allergic and autoimmune diseases

In this study, 1,000,000 persons, approximately 4.3% of the population of Taiwan, were randomly selected from the NHIRD. The study group comprised all persons who were identified by the diagnostic code of “autism spectrum disorder” (ICD-9-CM code: 299; 299.0× for autistic disorder, 299.1× for childhood disintegrative disorder, 299.8× for Asperger disorder and other specified pervasive developmental disorder, and 299.9× for unspecified pervasive developmental disorder) between January 1, 1996 and December 31, 2010. The diagnosis was given by board-certificated psychiatrists. The age- and gender-matched control group (4 for every patient in the study cohort) was randomly identified from the persons after eliminating patients who had been given a diagnosis of ASDs. Coexistent allergic diseases were investigated by specific diagnostic codes, and included 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. Coexistent autoimmune diseases were identified as having type 1 diabetes (CD-9-CM codes: 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.71, 250.81, 250.83, 250.91, 250.93) diagnosed by endocrinologists or pediatricians; Crohn's disease (ICD-9-CD code: 555) and ulcerative colitis (ICD-9-CM code: 556) diagnosed by rheumatologists, *gastrointestinalists*, 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 combined 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). The study was approved by Institutional Review Board, Taipei Veterans General Hospital (2012-04-012BC).

2.3. Statistical analysis

For between-group comparisons, the independent t test was used for continuous variables and Pearson's χ^2 test or Fisher's exact test for nominal variables, where appropriate. Two logistic regression models were used to investigate the OR with 95%CI of allergic/autoimmune diseases in patients with ASDs. The first model was performed without adjusting for age and gender (crude OR), and the second model was performed after adjusting for age and gender (modified OR). A 2-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).

3. Results

3.1. Demographic characteristics of the ASDs study group and control group

Of the 1,000,000-person sample population identified between January 1, 1996 and December 31, 2010, 1274 males and 324 females were identified as having ASDs. Allergic diseases were prevalent in patients with ASDs. Compared with the control group, patients with ASDs had a significantly increased prevalence of allergic comorbidities, including asthma (23.3% vs. 15.3%, $p < 0.001$), AR (38.0% vs. 27.0%, $p < 0.001$), AD (17.8% vs. 13.0%, $p < 0.001$), and urticaria (8.4% vs. 6.3%, $p = 0.002$). In contrast to allergic diseases, comorbidities of autoimmune diseases with ASDs were rare. None of the patients with ASDs were identified as having celiac disease, but 18 ASDs patients were identified as having Crohn's disease, 2 had ulcerative colitis, 4 had type 1 diabetes, 17 had autoimmune thyroid disease, and five had Kawasaki disease (Table 1). No significant differences in the prevalence of autoimmune comorbidities between the ASDs patients and the controls were observed. Only a mild trend was noted for type 1 diabetes (0.3% vs. 0.1%, $p = 0.056$) and Crohn's disease (1.4% vs. 1.0%, $p = 0.088$) (Table 1).

3.2. Odds ratio for allergic and autoimmune diseases

Multiple logistic regression analysis was used to evaluate the OR of allergic and autoimmune comorbidities among patients with ASDs, after adjusting for age and gender. Compared with the control group, patients with ASDs were 1.74 times (OR = 1.74, 95%CI = 1.51–1.99), 1.70 times (OR = 1.70, 95%CI = 1.51–1.91), 1.52 times (OR = 1.52, 95%CI = 1.30–1.78), and 1.38 times (OR = 1.38, 95%CI = 1.12–1.69) more likely to have asthma, AR, AD, and urticaria, respectively. But, patients with ASDs only exhibited an increased risk of having type 1 diabetes (OR = 4, 95%CI = 1.00–16.00) and a trend toward an increased risk of having Crohn's disease (OR = 1.46, 95%CI = 0.90–2.35) (Table 2).

Table 1Independent t test and Pearson's χ^2 test for characteristics of patients with ASDs and age/gender-matched control subjects.

Characteristics	ASDs	Control	p-Value
No.	1598	6392	
Age	17.51 (11.34)	17.51 (11.34)	
Gender, N (%)			
Male	1274 (79.7)	5096 (79.7)	
Female	324 (20.3)	1274 (20.3)	
Associated diseases, N (%)			
Asthma	372 (23.3)	975 (15.3)	<0.001*
Allergic rhinitis	608 (38.0)	1728 (27.0)	<0.001*
Atopic dermatitis	284 (17.8)	830 (13.0)	<0.001*
Urticaria	134 (8.4)	400 (6.3)	0.002*
Crohn's disease	23 (1.4)	64 (1.0)	0.088
Ulcerative colitis	2 (0.1)	6 (0.1)	0.497
Type 1 diabetes	4 (0.3)	4 (0.1)	0.056
Autoimmune thyroid disease	21 (1.3)	68 (1.1)	0.423
Kawasaki disease	5 (0.3)	32 (0.5)	0.412

ASDs: autism spectrum disorders.

* $p < 0.05$.**Table 2**

ORs between ASDs and allergic and autoimmune diseases.

	Crude OR (95%CI)	mOR (95%CI) ^a
Asthma	1.69 (1.47–1.93)*	1.74 (1.51–1.99)*
Allergic rhinitis	1.66 (1.48–1.86)*	1.70 (1.51–1.91)*
Atopic dermatitis	1.45 (1.25–1.68)*	1.52 (1.30–1.78)*
Urticaria	1.37 (1.12–1.68)*	1.38 (1.12–1.69)*
Crohn's disease	1.44 (0.89–2.33)	1.46 (0.90–2.35)
Ulcerative colitis	1.33 (0.27–6.61)	1.33 (0.27–6.60)
Type 1 diabetes	4.01 (1.00–16.04)*	4.00 (1.00–16.00)*
Autoimmune thyroid disease	1.24 (0.76–2.03)	1.23 (0.75–2.03)
Kawasaki disease	0.624 (0.24–1.60)	0.628 (0.24–1.61)

ASDs: autism spectrum disorders.

^a Adjusted by age and gender.* $p < 0.05$

4. Discussion

The ASDs patients in our study had a higher prevalence of allergic diseases than the control group, which was compatible with the findings in previous clinical observational studies and supported studies suggesting a possible shared etiology between ASDs and allergic diseases. In addition, we validated the possible association of ASDs with type 1 diabetes and Crohn's diseases (Afzal & Minor, 2002; Freeman et al., 2005), despite the low comorbid prevalence rates.

4.1. Autism spectrum disorder and allergic diseases

Our results showed that patients with ASDs had higher prevalence of allergic diseases, including asthma, AR, AD, and urticaria than control group. Furthermore, patients with ASDs were significantly prone to having the allergic diseases compared to controls.

Allergy is a hypersensitivity disorder of the immune system, in which both innate immunity and acquired immunity may contribute to the development of allergic diseases (Ledford, Pastva, & Wright, 2010; Minnicozzi, Sawyer, & Fenton, 2011). Excessive and abnormal activation of mast cells by Ig-E and related inflammatory responses account for the clinical symptoms, ranging in severity from uncomfortable to lethally dangerous (Kay, 2001a, 2001b). Higher serum Ig-E levels and dysregulated mast cell activation are widely found in asthma, AR, AD, and food allergy (Kay, 2001a, 2001b). Many studies have delineated the importance of mast cell function in both innate and acquired immunity, as well as in inflammation. Dysregulated mast cell activation leads to the secretion of different cytokines, such as tumor necrosis factor- α (TNF- α) and macrophage chemoattractant protein (MCP)-1. TNF- α and MCP-1 induce the chemotaxis of dendritic cells, which cause an inappropriate Th₂ immune to the innocent allergen, resulting in B cell production of a specific Ig-E. The allergic response becomes a vicious cycle if the antigen is always existent. Mast cells amplify this vicious allergic cycle, and many other cytokines and chemokines, including interleukin-1 (IL-1), IL-2, IL-3, IL-4, IL-6, IL-9, IL-13, and neurotensin, are released, leading to the consequent immune reaction and persistent inflammation (Amin, 2012; Weissler, Mekori, & Mor, 2008).

There is a great deal of evidence of a similar immune dysregulation and alteration with allergic diseases among patients with ASDs. Magalhaes et al. (2009) reported that ASDs patients exhibited significantly higher serum Ig-E and higher rates of

positive skin allergy tests than healthy controls. Singh, Warren, Odell, and Cole (1991) reported that the concentration of IL-2 and soluble antigens was significantly increased in the sera of children with ASDs, more so than in the healthy control children. Measuring the production of IL-6, IL-10, and TNF- α in whole blood, Croonenberghs, Bosmans, Deboutte, Kenis, and Maes (2002) found a significant trend toward an increased production of IL-6 and TNF- α in children with ASDs. Using the immunohistochemical method to detect the IL-6 expression in the cerebellum, Wei et al. (2011) suggested that IL-6 was significantly increased in the cerebellum of patients with ASDs, altering the neural cell adhesion, migration and synaptic formation. In addition, the serum TGF- β concentration in patients with ASDs was significantly low (Ashwood & Van de Water, 2004), which is important in view of the fact that TGF- β inhibits mast cell function and Ig-E receptor expression (Gebhardt et al., 2005). Some studies measuring the cytokines in the autistic brain reported a cytokine dysregulation similar to that in serum and that patients with ASDs had increased TNF- α (Chez, Dowling, Patel, Khanna, & Kominsky, 2007), IL-6 (Wei et al., 2012) and MCP-1 compared to the control group (Vargas, Nascimbene, Krishnan, Zimmerman, & Pardo, 2005). Our result supported the significant comorbidity of ASDs with allergic diseases.

4.2. Autism spectrum disorder and autoimmune diseases

In our study, we validated the association of ASDs with specific autoimmune diseases, including type 1 diabetes and Crohn's diseases. Patients with ASDs were more likely to have type 1 diabetes and Crohn's diseases compared to control groups.

Autoimmunity occurs when the immune system mistakenly exerts an exaggerated response to the body's own tissues. The exact mechanism of autoimmunity in the various autoimmune diseases is not identical, but it involves autoreactive antibodies and altered cellular immunity. Some evidence has shown autoantibodies, including brain-specific autoantibodies in the hypothalamus and cerebellum and anti-nuclear antibodies, were present at significantly higher frequencies in children with ASDs than in healthy controls (Cabanlit, Wills, Goines, Ashwood, & Van de Water, 2007; Mostafa & Kitchener, 2009; Wills et al., 2009). Singh (2009) proposed an autoimmune hypothesis for the development of ASDs, but the underlying mechanism linking autoimmune disease/autoimmunity and ASDs is still unknown. Generally speaking, the prevalence rates of surveyed autoimmune diseases in the normal population in our study were low (Kawasaki disease: 0.25%; type 1 diabetes: 0.1–0.3%; Crohn's disease: 0.05%) ("Prevalence of selected chronic conditions. United States, 1979–81," 1986; Ravikumara & Sandhu, 2006; Uehara & Belay, 2012), which may explain why few studies have investigated the potential associations. Our study supported the proposed possible association of ASDs with type 1 diabetes and Crohn's disease and failed to link ASDs with Kawasaki disease, autoimmune thyroid disease, and celiac disease.

4.2.1. Type 1 diabetes

Freeman et al. (2005) reported that 0.9% of 984 children with type 1 diabetes had ASDs, a higher prevalence than that in the general population, and suggested the possible link of ASDs with type 1 diabetes. Our result validated the hypothesis that ASDs patients had a higher risk of type 1 diabetes than the control group. In contrast, the study by Harjutsalo et al. did not support this link. They reported that 7 cases with type 1 diabetes fulfilled the criteria of ASDs, yielding a cumulative incidence of 1.35/1000, which did not differ from that of the background population (Harjutsalo & Tuomilehto, 2006). This possible but controversial association between ASDs and type 1 diabetes may be owing to the shared genetic susceptibility and dysregulated autoimmune cytokine secretion (Chien et al., 2012; King, 2008; Manzardo, Henkhaus, Dhillon, & Butler, 2012; Sayad, Akbari, Pajouhi, Mostafavi, & Zamani, 2012). For example, patients with type 1 diabetes had increased serum concentration of IL-1 and IL-6 compared to healthy controls (Grishman, White, & Savani, 2012; Snell-Bergeon et al., 2010), and this phenomenon of hypersecretion of inflammatory cytokines, including IL-1 and IL-6, was also noted in patients with ASDs (Croonenberghs et al., 2002; Wei et al., 2011). However, further studies would be required to clarify the underlying pathophysiology between ASDs and type 1 diabetes.

4.2.2. Autoimmune thyroid diseases

Only case reports about the association between ASDs and hyperthyroidism or hypothyroidism were found in the literature search. Gillberg, Gillberg, and Kopp (1992) reported 3 patients with ASDs that had congenital hypothyroidism and 2 had mothers who had been hypothyroid in pregnancy. Suresh, Sebastian, George, and Radhakrishnan (1999) presented 3 hyperthyroid children who exhibited developmental learning disabilities associated with behavioral disturbances (i.e., hyperactivity and autistic features). Comi et al. (1999) found that in mothers and first-degree relatives of children with ASDs, there were more autoimmune disorders (16% and 21%) than in the controls (2% and 4%), including type 1 diabetes and autoimmune hypothyroidism. However, our results, combining autoimmune hyperthyroidism (i.e., Grave's disease) and hypothyroidism (i.e., Hashimoto disease) together, could not validate a possible association between these 2 diseases.

4.2.3. Crohn's disease

Crohn's disease and ASDs have increased in prevalence concomitantly during the last decade (IBD Working Group of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition, 2005). Our result showed a significant trend toward an increasing risk of ASDs with Crohn's disease, which is compatible with previous findings (Afzal & Minor, 2002). Patients with Crohn's disease exhibited the higher levels of IL-1, IL-6, and TNF- α than healthy controls (Bene, Falus, Baffy, &

Fulop, 2011; Sanchez-Munoz, Dominguez-Lopez, & Yamamoto-Furusho, 2008), and imbalance of cytokines is contributing to the pathogenesis of Crohn's disease (Sanchez-Munoz et al., 2008). Regarding the previous studies measuring the cytokine levels in patients with ASDs (Chez et al., 2007; Wei et al., 2011, 2012), the results supported that those with ASDs had the immunological imbalance and hypersecretion of pro-inflammatory cytokines (i.e., IL-6, and TNF- α), which were consistent with the findings in patients with Crohn's disease. But, further study is needed to clarify the underlying possible comorbid mechanism.

4.2.4. Kawasaki disease

Kawasaki disease is an autoimmune vasculitis that affects children under age five predominantly and involves the blood vessels, skin, mucous membranes, lymph nodes, and even the central neural system. A case study by Tabarki, Mahdhaoui, Selmi, Yacoub, and Essoussi (2001) suggested a possible link between Kawasaki disease and autistic behavior. Holmes et al. (2011) reported a statistically significant association between Kawasaki disease and the diagnosis of autistic disorder, hypothesizing that the inflammatory response that underlies Kawasaki disease may affect neurological changes that result in autism, or the susceptibility to the underlying pathophysiology may lead to both diseases occurring independently in the same individual. However, our result failed to support this link between Kawasaki disease and ASDs.

4.2.5. Celiac disease

In our study, no cases of celiac disease were identified among the ASDs patients and the controls. Some studies have proposed a possible association between ASDs and celiac disease (Ashkenazi, Levin, & Krasilowsky, 1980; Genuis & Bouchard, 2010), but this association is disputed. Both Pavone et al. (1997) and Batista et al. (2012) did not support a possible link between ASDs and celiac disease.

To clarify the low prevalence of autoimmune comorbidities in the ASDs patients in our study, further research into the sporadic comorbidity or etiological association between ASDs and autoimmune diseases is needed, although current evidence has shown that patients with ASDs have a dysfunction and imbalance in their immune systems (Chez et al., 2007; Croonenberghs et al., 2002; Magalhaes et al., 2009; van Gent, Heijnen, & Treffers, 1997), and that a familial history of autoimmune diseases significantly increases the risk of ASDs in their offspring (Atladdottir et al., 2009; Comi et al., 1999).

5. Limitations

Some limitations of this study need to be mentioned. First, the prevalence of ASDs, allergic, and autoimmune diseases may be underestimated because only those individuals who sought for medical help were identified. However, the patients with ASDs included in our study were given a diagnosis by board-certified psychiatrists using psychiatric interviews and clinical judgments, and the diagnoses were more reliable than those that are self-reported. Second, previous studies showed that a familial history of autoimmune diseases significantly increases the risk of ASDs in their offspring (Atladdottir et al., 2009; Comi et al., 1999), but the national health insurance database was an anonymous database and did not provide that information. Without this information, we were unable to examine the influence of these factors.

6. Conclusion

In our study, with the largest case number reported thus far, the results supported the significant association between ASDs and allergic diseases, including asthma, AR, AD, and urticaria. The link between ASDs and various autoimmune diseases is characterized by mixed findings in previous studies, although patients with ASDs seem to have increased vulnerability to type 1 diabetes and Crohn's disease. Further study is required to elucidate the possible underlying mechanisms and roles of allergic immunity and autoimmunity in the etiology of ASDs.

Conflict of interest

There is no conflict of interest.

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