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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.

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 (Atladottir 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, Atladottir 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