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Review

Family history of autoimmune diseases is associated with an increased risk of autism in children: A systematic review and meta-analysis

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ABSTRACT

Background: We conducted a systematic review and meta-analysis to summarize the current evidence on the relationship between family history of autoimmune diseases (ADs) and risk of autism in children, as current evidence suggests inconsistent results.
Methods: We identified relevant studies by searching PubMed, EmBase, and Web of Science databases up to Dec 2014. Risk estimates from individual studies were pooled using random-effects models. Subgroups analyses were conducted by some study-level factors. Publication bias was assessed by funnel plots, Egger's regression test and Begg–Mazumdar test.
Results: A total of 11 articles were included in the meta-analysis, including 3 cohort studies, 6 case-control studies, and 2 cross-sectional studies. The meta-analysis showed that family history of all ADs combined was associated with a 28% (95% CI: 12–48%) higher risk of autism in children. For some specific ADs, evidence synthesis for risk of autism in children showed a statistically significant association with family history of hypothyroidism (OR = 1.64, 95% CI: 1.07–2.50), type 1 diabetes (OR = 1.49, 95% CI: 1.23–1.81), rheumatoid arthritis (OR = 1.51, 95% CI: 1.19–1.91), and psoriasis (OR = 1.59, 95% CI: 1.28–1.97). The results varied in some subgroups.
Conclusion: An overall increased risk of autism in children with family history of ADs was identified. More mechanistic studies are needed to further explain the association between family history of ADs and increased risk of autism in children.

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1. Introduction

Autism is a neurologic disorder characterized by impairments in social interaction and communication along with restricted, repetitive, and stereotyped patterns of behaviors, interests, and activities (Lord et al., 2000). The prevalence of autism is about 1–2 per 1000 children worldwide and it occurs about four times more often in boys than girls (Danasekaran et al., 2014), which has greatly increased the burden for both the family and society. While many aspects of autism remain poorly understood, major advances have been made in terms of highlighting the role of genetic and environmental factors in its etiology.

Altered autoimmune responses have been reported among children with autism (Ashwood et al., 2006), as well as among their parents (Croen et al., 2005) and other family members (Sweeten et al., 2003). Immunogenetic research shows that genes long implicated in autoimmune diseases (ADs) such as rheumatoid arthritis (RA) and systemic lupus erythematosus are associated with autism (Fielder et al., 1983; Stastny, 1978; Warren et al., 1992). However, evidence from observational and epidemiological studies suggests an inconsistent relationship between family history of ADs and risk of autism in children. Some human studies suggest that family history of ADs such as hypothyroidism, type 1 diabetes and RA was associated with higher risk of autism (Comi et al., 1999; Keil et al., 2010), while other studies failed to find this association (Chonchaiya et al., 2010; Mouridsen et al., 2007).

Prevention will entail detecting infants at risk before the full syndrome is present and implementing treatments designed to alter the course of early behavioral and brain development (Dawson, 2008). Therefore, for the prevention of childhood autism, it is crucial to investigate how the disease is impacted by family history of ADs. If family history of ADs is indeed associated with childhood autism, prevention should be made by early intervention to such children. To our knowledge, no quantitative review has been undertaken previously to summarize the relationship between family history of ADs and childhood autism. We therefore conducted a systematic review and meta-analysis of the evidence for the relation between family history of ADs and risk of autism in children.

2. Methods

2.1. Search strategy and eligibility criteria

We followed the guidelines published by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group to complete the meta-analysis (Table S1) (Stroup et al., 2000). A systematic literature search of PubMed, EmBase, and Web of Science for identification of articles published between 1965 to Dec 2014 was performed by two investigators (SW and YD). We selected synonymous terms and used these to develop the search strategy (Panel S1). No language restriction was imposed. In addition, we also manually reviewed the references of all retrieved articles and recent reviews to identify relevant studies.

The eligible studies should meet the following inclusion criteria: (1) the study population consisted of children with infantile autism or autism spectrum disorder (ASD); (2) examination of family history of ADs as the variable of interest; (3) the association between family history of ADs and autism/ASD was assessed; and (4) presented risk estimates with confidence intervals (CIs) or sufficient information to calculate these. Cross-sectional, cohort, and case-control studies were all included in the analysis. Animal experiments, review researches and mechanistic studies were excluded from the analysis.

2.2. Data extraction and study quality evaluation

Study characteristics were extracted independently by two researchers (FW and JH). We extracted risk estimates (95% CI) for different family members separately when possible. If a study reported more than one measure of ADs, each AD was extracted separately. The most adjusted estimate was included when a study reported more than one risk estimate. The quality of each study was assessed by two researchers (FW and PM), using the Newcastle–Ottawa Scale recommended by Wells and colleagues (Wells et al., 2011).

2.3. Statistical analysis

The random effects model was used in this meta-analysis to take into account heterogeneity among studies, because the study design and measuring time were different across studies. The I-squared (I^2) statistic and Q-statistic were used to explore the heterogeneity among studies. Large I^2 (>50%) or $P < 0.10$ for Q-statistic suggests substantial heterogeneity among studies. We used funnel plots to visually assess the publication bias. Egger's regression test (Egger et al., 1997) and Begg–Mazumdar test (Begg and Mazumdar, 1994) were used to further assess publication bias. Subgroup analyses were performed according to the source of family history, outcome, design and adjustment, to test the possible impact factors. Statistical analyses were conducted using Stata Version 12.0 software (Stata Corp, College Station, TX).

3. Results

3.1. Search results

The article selection procedure is shown in Fig. 1. Briefly, 149 articles were screened after excluding the duplicate articles. We excluded 112 articles by screening title and abstract and assessed 37 full-text articles for eligibility. Finally, a total of 11 articles met the inclusion criteria and were included in the meta-analysis, including 3 cohort studies (Andersen et al., 2014; Atladottir et al., 2009; Roman et al., 2013), 6 case-control studies (Comi et al., 1999; Croen et al., 2005; George et al., 2014; Keil et al., 2010; Mostafa and Shehab, 2010; Mouridsen et al., 2007), and 2 cross-sectional studies (Chonchaiya et al., 2010; Valicenti-McDermott et al., 2006). All relevant studies identified were published in the English language. Characteristics of these 11 studies are provided in Table 1, and Tables S2–S4 present the quality assessment of the included studies in detail. The pooled relative risks of autism were calculated for family history of all ADs combined and some specific ADs (hypothyroidism, type 1 diabetes, RA, and psoriasis). Relative risks for other specific ADs were not calculated due to insufficient data.