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Maternal thyroid autoantibody and elevated risk of autism in a national birth cohort

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ABSTRACT

Objective: Autoimmune disruption may contribute to risk for autism; however, since previous studies relied upon clinical diagnoses, exposure misclassification and recall bias are limitations. Thyroid peroxidase antibody (TPO-Ab) is an autoantibody involved in autoimmune thyroiditis. We aimed to test the a priori hypothesis that positivity to maternal serum TPO-Ab (TPO-Ab+) (defined as >156 IU/ml) during pregnancy is related to childhood autism.
Method: The study was based on a nested case-control design of the Finnish Prenatal Study of Autism (FiPS-A), a national birth cohort that includes prospectively drawn archived maternal serum specimens from virtually the entire pregnant population of Finland beginning in 1983. Cases of childhood autism (ICD-10F84.0) born from 1987 to 2005 were ascertained by performing linkages between national birth and inpatient/outpatient registries. All diagnosed cases in Finland over the birth years, and comparison subjects without ASD or severe/profound intellectual disability were matched 1:1 on date of birth, sex, birthplace, and residence in Finland. Maternal serum specimens were assayed in 967 matched case–control pairs for TPO-Ab by a chemiluminescent microparticle immunoassay blind to case/control status. Data were analyzed by conditional logistic regression for matched sets.
Results: The prevalence of maternal TPO-Ab+ was significantly increased in pregnancies giving rise to autism cases (6.15%) compared to controls (3.54%). The odds of autism were increased by nearly 80% among offspring of mothers who were TPO-Ab+ during pregnancy (OR = 1.78, 95% CI = 1.16–2.75, $p = 0.009$), compared to mothers negative for this autoantibody. There was also a significant relationship between maternal TPO-Ab defined as a continuous variable and odds of autism (OR = 1.09, 95% CI = 1.01, 1.17, $p = 0.02$). Measures of maternal thyroid hormones did not differ between groups.
Conclusions: These findings provide the first biomarker-based evidence that a class of known maternal autoimmune disorders is related to autism in offspring.

1. Introduction

Autism is a complex neurodevelopmental disorder characterized by impaired language, disrupted reciprocal social interactions, and stereotyped behaviors and interests (Fombonne, 2009). Genetic factors are known to play a major role in autism though its etiology is still largely unknown (Persico and Napolioni, 2013). Recent evidence has also implicated an emerging role for environmental factors (Volk et al., 2013; Patterson, 2011; Newschaeffer et al., 2007; Braunschweig and van De Water, 2012; Croen et al., 2011; Atladóttir et al., 2010; Reichenberger et al., 2006; Hamlyn et al., 2013; Hallmayer et al., 2011).

Thyroid peroxidase (TPO), a thyrocyte apical plasma membrane glycoprotein, is an antigenic epitope that, in susceptible individuals, may induce formation of thyroid peroxidase antibody (TPO-Ab), an autoantibody involved in autoimmune thyroiditis including Hashimoto's thyroiditis (Ruf and Carayon, 2006; Hadj-Kacem et al., 2009). Maternal TPO-Ab positivity (TPO-Ab+) has been associated with sensorineural hearing loss in children (Wasserman et al., 2008). In addition, five year old offspring of mothers with TPO-Ab+ during late gestation had diminished verbal, perceptual, cognitive, and motor performance (Pop et al., 1995).

Moreover, some autoimmune disorders may be more frequent in mothers and other relatives of autism probands. Early studies, based

Abbreviations: TPO, Thyroid peroxidase; TPO-Ab, Thyroid peroxidase antibody; FiPS-A, Finnish Prenatal Study of Autism; PDD, Pervasive developmental disorder; FHDR, Finnish Hospital and Outpatient Discharge Registry; ADI-R, Autism Diagnostic Interview-Revised; TSH, Thyroid stimulating hormone; fT4, Free thyroxine; ASD, Autism spectrum disorder.

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on questionnaires of family members, reported that the prevalence of any autoimmune disorder, and one or more of a number of specific autoimmune disorders was significantly higher in families of autism probands than comparison subjects (Comi et al., 1999; Sweeten et al., 2003). With regard to autoimmune thyroid disorders, the frequency of "hypothyroidism/Hashimoto's thyroiditis" was greater in family members of probands with pervasive developmental disorder (PDD) and probands with autoimmune disorders than healthy comparison subjects (Sweeten et al., 2003). In another study, autoimmune thyroiditis in only the maternal lineage was significantly related to regressive autism (Molloy et al., 2006). Other specific autoimmune diagnoses associated with ASD included parental rheumatoid arthritis (Comi et al., 1999) and rheumatic fever (first degree relatives) (Sweeten et al., 2003). These studies were limited, however, by use of diagnoses from family member self-reports and lack of validation of responses predisposing to diagnostic misclassification, by recall bias, and by low response rates to questionnaires, increasing the likelihood of selection bias.

More recent studies utilizing health plan databases and registries have demonstrated associations between ASD and maternal psoriasis, type I diabetes (Croen et al., 2005; Mourdisen et al., 2007; Keil et al., 2010), ulcerative colitis, and celiac disease (Atladóttir et al., 2009). Overall, maternal autoimmune disorders were more commonly associated with autism than paternal autoimmune disorders, suggesting effects during pregnancy on autism risk, though the type of autoimmune disorders related to autism varied between studies.

In a previous study, plasma from 11.5% of mothers of children with ASD, but no mothers of comparison subjects, demonstrated IgG-reactivity against fetal brain proteins at 37 kDa and 73 kDa (Braunschweig et al., 2008). This finding was extended in a larger sample (Singer et al., 2008). In a further study, a band reactive to brain protein in the Rhesus macaque was found at 39 kDa (Braunschweig et al., 2012). Prenatal exposure to these antibodies was related to whole body stereotypies and hyperactivity in nonhuman primates and rodents supporting a potential pathogenic role for these antibodies in autism (Martin et al., 2008). More recently, maternal anti-brain antibodies were shown to be related to a fourfold increased risk of ASD, and mothers with these antibodies exhibited an increased prevalence of anti-nuclear antibodies and certain autoimmune diseases (Brimberg et al., 2013).

In the present study, we directly quantified maternal TPO-Ab, a biomarker utilized in the diagnosis of autoimmune thyroiditis. TPO-Ab was ascertained in cases and comparison subjects from a national birth cohort. A definitive diagnosis of autoimmune thyroiditis relies on the demonstration of not only circulating antibodies to thyroid antigens but also reduced echogenicity on thyroid sonogram in a patient with clinical features (Dayan and Daniels, 1996). However, compared to other epidemiologic studies of autoimmune disorders and ASD, this reduces the possibility of inaccurate diagnoses of autoimmune disorders, bias due to preferential recall and treatment seeking behavior, and lack of inclusion of asymptomatic subjects. The large number of cases and comparison subjects enhanced statistical power to detect an association.

We tested the hypothesis that the odds of autism in offspring are related to maternal TPO-Ab + exposure documented in archived maternal prenatal sera. The investigation was conducted in the Finnish Prenatal Study of Autism (FiPS-A), which capitalizes on a large number of pregnancies from a national birth cohort with prospectively collected, archived maternal serum specimens in the Finnish Maternity Cohort (FMC), an extensive, centralized biobank. Virtually all childhood autism cases in Finland identified from national computerized registries of hospital admissions and outpatient treatment, and validated by a structured research interview, were included.

There is previous evidence that maternal hypothyroidism is associated with adverse cognitive outcomes (Haddow et al., 1999; Li et al., 2010). Although the main focus of this paper was to address maternal thyroid autoimmunity and autism, in order to assess whether associations between maternal TPO-Ab + and autism were accounted for by thyroid dysfunction, we conducted secondary analyses of maternal clinical and subclinical hypothyroidism, maternal thyroid stimulating hormone (TSH), and free T4 (fT4) levels, and autism.

2. Methods

The methods are described in detail in Lampi et al. (2011), and will be summarized here. The FiPS-A is based on a nested case–control design. The sampling frame was defined such that all members of this national birth cohort were within the age of risk of autism. Toward this end, the sampling frame consisted of all offspring born in Finland from 1987 to 2005, and subjects were followed up until 2007 (see "Case and comparison subject identification").

2.1. Description of the birth cohort, biobank, and national registries

All offspring in the FiPS-A were derived from the Finnish Maternity Cohort (FMC), which consists of greater than 1 million pregnancies with archived prenatal serum specimens drawn beginning in 1983. Sera were obtained during the first and early second trimesters from over 98% of pregnant women in Finland. One maternal serum sample was acquired for each pregnancy. Following the screening, serum samples were stored as one aliquot at minus 25 °C in a single biorepository at THL in Oulu, Finland. All samples in the FMC can be linked with offspring using a unique personal identification number (PIN), which has been assigned to all residents of Finland since 1971.

2.2. Case and comparison subject identification

The Finnish Hospital and Outpatient Discharge Registry (FHDR) was utilized to identify all recorded diagnoses from psychiatric hospital admissions and outpatient visits of childhood autism (ICD-10F84.0) among members of the FMC. We restricted the outcome to this diagnosis given that only childhood autism, not Asperger disorder or PDD NOS, was validated by interview (see next paragraph). Computerized data are available from January 1, 1987 to the present. Only singleton births were included. Cases diagnosed over the sampling frame were identified from registry linkages between the FMC and the FHDR from January 1, 1987 to December 31, 2007. During this time period, there were 1.2 million births. The total number of childhood autism cases in the FiPS-A study sample was 1132.

In order to validate the registry diagnoses, 80 cases of infantile autism from the FHDR were assessed with the Autism Diagnostic Interview—Revised (ADI-R). Among these cases, 77 (96%) met the criteria for childhood autism by this instrument (Lampi et al., 2010).

The cases were matched 1:1 to comparison subjects (singleton births only) drawn from the birth cohort who were without ASD (no F84 diagnosis) or severe/profound intellectual disability on date of birth, sex, birthplace, and residence in Finland. Serum samples were assayed for TPO-Ab (see "Laboratory assays") in the 967 matched cases with adequate quantities of sera for this assay from among the 1,132 cases, and in 967 matched comparison subjects. We utilized 1:1 matching of cases to comparison subjects given limited resources for assaying sera on a larger number of comparison subjects. For a secondary analysis aimed at testing whether a putative association between TPO-Ab and autism was accounted for by thyroid hormone abnormalities, assays were also conducted for thyroid stimulating hormone (TSH) and free thyroxine (fT4) in these same 967 matched case–control pairs. Measurements were available on 960 pairs for TPO-Ab, 954 pairs for TSH, and 958 pairs for fT4; these sample sizes differed slightly from those assayed for TPO-Ab due to sample volume constraints in a small proportion of subjects.

The study was approved by the ethical committees of the hospital district of Southwest Finland, THL, and the Institutional Review Board