Epilepsy Research (2013) **107**, 61—74

journal homepage: www.elsevier.com/locate/epilepsyres

Childhood epilepsy and maternal antibodies to microbial and tissue antigens during pregnancy

Yuelian Sun[a,*], **Jakob Christensen**[b], **Jørn Olsen**[a,c]

[a] *Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus 8000C, Denmark*
[b] *Department of Neurology and Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus 8000C, Denmark*
[c] *Department of Epidemiology, School of Public Health, University of California at Los Angeles, Los Angeles, CA, USA*

Received 17 January 2013 ; received in revised form 23 July 2013; accepted 14 August 2013
Available online 7 September 2013

KEYWORDS
Epilepsy;
Infection;
Antibodies;
Molecular mimicry;
Microbial antigen;
Tissue antigen

Summary
Introduction: Several epidemiologic studies show associations between mother's infections during pregnancy and an increased risk of mental and neurological disorders in the offspring. Such associations could be due to the direct or indirect effects of infectious agents, including immune responses to infectious agents that display molecular mimicry with host antigens. We measured a range of antigen-specific maternal IgG antibodies to examine if any were associated with risk for childhood epilepsy in offspring.
Methods: We used a case-cohort design within the Danish National Birth Cohort (DNBC) to examine maternal IgG antibodies to 25 microbial and tissue antigens during pregnancy and their association with the risk of epilepsy in offspring. The source population of this study was 68,250 live born singletons with up to 10 years of follow up. We randomly identified a sample of 282 children as a subcohort and included 275 children with a verified diagnosis of epilepsy as cases. Maternal antibodies were categorized into 6 groups (<50, 50—59, 60—69, 70—79, 80—89, ≥90 percentile) according to the level in the subcohort. We used a Prentice-weighted Cox regression model to estimate the hazard ratio (HR) and 95% confidence interval (CI) for epilepsy according to measured antibodies.
Results: Higher levels of maternal antibodies against herpes simples virus type 1 (anti-HSV1) were associated with a slightly higher risk of childhood epilepsy (HR for trend = 1.09, 95% CI:

Abbreviations: BMI, body mass index; CI, confidence interval; DNBC, Danish National Birth Cohort; HR, hazard ratio; ICD, International Classification of Diseases; HSV1, simples virus type 1; PnPS18, pneumococcal polysaccharide 18.

* Corresponding author at: Section for Epidemiology, Department of Public Health, University of Aarhus, Bartholins Allé 2, Aarhus 8000C, Denmark. Tel.: +45 8716 7985; fax: +45 8613 1580.
E-mail address: ys@soci.au.dk (Y. Sun).

0920-1211/$ — see front matter
http://dx.doi.org/10.1016/j.eplepsyres.2013.08.019

0.99—1.21), while higher levels of maternal antibodies against pneumococcal polysaccharide 18 (anti-PnPS18) were associated with a lower risk of childhood epilepsy (HR for trend = 0.90, 95% CI: 0.81—1.01). Among the subtypes, a significantly higher risk associated with anti-HSV1 antibodies was seen for childhood absence epilepsy (HR for trend = 2.08, 95% CI: 1.12—3.85) and for epileptic encephalopathies (HR for trend = 1.49, 95% CI: 1.01—2.22). The significantly lower risk associated with anti-PnPS18 antibodies was observed for infantile spasms (HR for trend = 0.47, 95% CI: 0.27—0.83).

Conclusions: Maternal anti-HSV1and anti-PnPS18 antibodies during pregnancy may be associated with the risk of epilepsy in offspring, but any potential etiologic and preventative implications of these associations warrant further exploration.

Introduction

Several epidemiologic studies show associations between infections during pregnancy and an increased risk of mental and neurological disorders in the offspring, such as cerebral palsy (Gibson et al., 2006; Grether and Nelson, 1997; Wu et al., 2013), schizophrenia (Brown et al., 2004; Buka et al., 2001; Mortensen et al., 2007), and autism (Atladottir et al., 2010). Recent findings indicate that some maternal infections during pregnancy are also associated with a higher incidence of epilepsy in childhood (Casetta et al., 2002; Glass et al., 2009; McDermott et al., 2010; Nørgaard et al., 2012; Sun et al., 2008a; Whitehead et al., 2006; Wu et al., 2013).

The TORCH concept (Toxoplasmosis, Other, Rubella, Cytomegalovirus, and Herpes infections) (Nahmias et al., 1971) arose from clinical observations of specific microorganisms possibly affecting the fetal brain, but the concept also states there may be ''other'' unknown microorganisms that have this capacity. Molecular mimicry between infectious agents and brain antigens is a possible causal mechanism (Nahmias et al., 2006). Molecular components of nervous system tissues, such as polysialic acid, gangliosides, and protein, have antigenic epitopes in common with various infectious agents (Schoenfeld and Rose, 2004; Wraith et al., 2003), and these nerve tissue molecules play a major role in brain development and function (Ni Dhuill et al., 1999; Rutishauser, 1996; Svennerholm et al., 1989). The Guillain—Barre syndrome has, for example, been associated with several infectious agents that have ganglioside epitopes similar to molecular epitopes in the nervous system (Sheikh et al., 1998). Further, the fetal blood brain barrier is not fully efficient throughout the entire pregnancy and may become more permissive under certain conditions like inflammation, trauma or fever (Kowal et al., 2006; Nahmias et al., 2006). Maternal antibodies to microbial and tissue antigens may cross the placenta and the fetal blood brain barrier, and potentially interfere with the brain development. The consequences of this interference will depend on the stage and the area of the brain development and epilepsy could be one of several potential outcomes.

Epilepsy is one of the most common neurological disorders, but the etiology for most cases of childhood epilepsy is still unknown (Hauser et al., 1993). However, we and others have shown that pre- or perinatal factors are risk indicators for epilepsy in childhood (Sun et al., 2008a,b; Whitehead et al., 2006). Fever, cytokine release, autoimmunity, or other immune functions may be part of the etiologic pathway (Bartolomei et al., 1996; Hagberg et al., 2012; Khandaker et al., 2013; Meyer et al., 2006; Takahashi et al., 2006). In this study, we examined the potential role of antigen-specific maternal IgG antibodies against a wide range of microbial and tissue antigens as risk factors for childhood epilepsy.

Methods

Study population

We conducted a case-cohort study basing on the Danish National Birth Cohort (DNBC) (Olsen et al., 2001). The DNBC is a nation-wide population-based cohort including 101,033 pregnancies and their offspring (Olsen et al., 2001). Pregnant women were recruited to the cohort between March 1996 and November 2002 ending with 96,862 live births including 92,676 singletons. Data on exposures during pregnancy and after birth were collected in four computer-assisted telephone interviews (around pregnancy gestational week 12 and 30, and 6, 18 months after the delivery). Blood samples were collected twice during pregnancy (first trimester and second trimester). The source population of this study was 68,250 live born singletons with an available maternal blood sample collected in the second trimester. During up to 10 years of follow up, 277 children had a verified diagnosis of epilepsy from the source population and were included in the study as a case group. We randomly identified 282 children from the source population as a representative sample of the cohort (subcohort). The study was approved by the Research Ethic Committee in Denmark, the Danish Data Protection Agency (J.nr. 2008-41-2115), and the UCLA Institutional Review Board.

Blood samples

In this study, we used the second blood sample collected during pregnancy. Blood samples were collected at the general practitioner clinic (GP) when pregnant mothers came for antenatal care. Blood samples were collected in EDTA (Ethylenediaminetetraacetic acid) vials and were transported to the biobank in State Serum Institute, Copenhagen, Denmark by regular mail within 4—48 h, but most of the samples arrived within 28 h. At the biobank, blood samples were separated into plasma and buffy coats and were stored in freezers at −20 °C or in liquid nitrogen (Olsen et al., 2001). The mean date for maternal blood sampling was 24.9 gestational weeks (range: 18—36 gestational weeks) in this study,