Joint Bone Spine xxx (2017) xxx–xxx

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Original article

Risk of autism spectrum disorder in children born to mothers with systemic lupus erythematosus and rheumatoid arthritis in Taiwan

Ping-Han Tsai[a,1], Kuang-Hui Yu[a,1], I-Jun Chou[b,c], Shue-Fen Luo[a], Wen-Yi Tseng[d,e], Lu-Hsiang Huang[a], Chang-Fu Kuo[a,f,*]

[a] Division of Rheumatology, Allergy and Immunology, Chang-Gung Memorial Hospital, 333 Taoyuan City, Taiwan
[b] Division of Clinical Neuroscience, School of Medicine, University of Nottingham, NG7 2RD Nottingham, UK
[c] Division of Paediatric Neurology, Chang-Gung Memorial Hospital, 333 Taoyuan City, Taiwan
[d] Kennedy Institute of Rheumatology, University of Oxford, OX3 7FY Oxford, UK
[e] Division of Rheumatology, Allergy and Immunology, Chang-Gung Memorial Hospital, 204 Keelung City, Taiwan
[f] Division or Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, NG7 2RD Nottingham, UK

ARTICLE INFO

Article history:
Accepted 8 November 2017
Available online xxx

Keywords:
Systemic lupus erythematosus
Rheumatoid arthritis and autism spectrum disorder

ABSTRACT

Objectives: To determine whether offspring of Taiwanese mothers with systemic lupus erythematosus or rheumatoid arthritis have a higher risk of autism spectrum disorder.
Methods: Using the National Health Insurance database and National Birth Registry, we identified a cohort of all live births in Taiwan between 2001 and 2012. Children born to mothers with systemic lupus erythematosus or rheumatoid arthritis were identified and matched with up to 8 controls by maternal age, 1-minute Apgar score, 5-minute Apgar score, mode of delivery, sex of the child, gestational age, birth weight and place of residence. Marginal Cox proportional hazard models were used to estimate relative risk (RR) with 95% confidence intervals (CI) for ASD in offspring.
Results: Of 1,893,244 newborns, 0.08% (n = 1594) were born to systemic lupus erythematosus mothers, and 0.04% (n = 673) were born to rheumatoid arthritis mothers. Overall, 5 of 673 (0.74%) offspring of rheumatoid arthritis mothers, 7 of 1594 (0.44%) offspring of systemic lupus erythematosus mothers and 10,631 of 1,893,244 (0.56%) offspring of all mothers developed autism spectrum disorder. Autism spectrum disorder incidence (per 100,000 person–years) was 140.39 (95% CI, 45.58–327.62) for the rheumatoid arthritis group and 76.19 (95% CI, 30.63–156.97) for the systemic lupus erythematosus group. Autism spectrum disorder risk was not significantly higher for children born to mothers with rheumatoid arthritis (HR, 1.42; 95% CI, 0.60–3.40) or systemic lupus erythematosus (HR, 0.76; 95% CI, 0.36–1.59).
Conclusions: Children born to women with systemic lupus erythematosus or rheumatoid arthritis do not have a higher risk of autism spectrum disorder.

1. Introduction

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are common autoimmune diseases and are characterised by autoantibody production and systemic involvement of multiple organs [1,2]. Both diseases primarily affect young women during their reproductive years and thus may adversely affect pregnancy outcomes [3–5]. Few studies have investigated the effects that these maternal diseases and their treatment have on the health of children. The available data generally pertain to complications at birth, such as early foetal loss, complications during delivery, prematurity, stillbirth and congenital malformation. Although studies have rarely investigated the long-term health of children born to parents with autoimmune rheumatic diseases, emerging evidence suggests that such children have higher risks of neuropsychiatric diseases [6,7].

Autism spectrum disorder (ASD) is a set of complex neurodevelopment disorders characterised by mild to severe problems in social interaction and communication along with restricted, repetitive behaviour patterns [8]. Most cited traditional risk factors of ASD are foetal conditions at birth, for instance low gestational age, low birth weight and Apgar score [9–14]. Recently, accumulating evidence suggests that autoimmunity has a role in ASD pathogenesis.

* Corresponding author. Division of Rheumatology, Allergy and Immunology, Chang-Gung Memorial Hospital, No.5, Fuxing Street, Guishan District, 333 Taoyuan City, Taiwan.
E-mail address: zandis@gmail.com (C.-F. Kuo).
[1] Dr Ping-Han Tsai and Kuang-Hui Yu contribute equally to this manuscript.

https://doi.org/10.1016/j.jbspin.2017.11.005
1297-319X/

The sharing of a specific human leukocyte antigen locus between rheumatic diseases and autism has been reported [15]. In addition, maternal autoantibodies were found to alter foetal brain development and induce behavioural anomalies in offspring in an animal model [16]. Furthermore, children born to women with SLE in Quebec had an increased risk of ASD [7]. However, data on ASD risk among the offspring of mothers with SLE have not been reported for other populations, and no study has evaluated ASD risk in the offspring of mothers with RA. In this study, we used data from a linkage between the National Health Insurance (NHI) database and National Birth Registry in Taiwan to determine if the offspring of Taiwanese mothers with SLE or RA had a higher risk of developing ASD.

2. Methods

Ethical approval was obtained from the Institutional Review Board of the Chang Gung Memorial Hospital (IRB number 104-2447B). This study analysed completely anonymised data, and patient consent was thus not required.

2.1. Study design and data sources

To obtain data on neonates, this population-based cohort study used the Taiwan NHI database, which was linked to the National Birth Registry. The NHI database was established in 1996 and contains health data for 99.5% of residents in Taiwan. Upon request, a unique personal identifier – which is encrypted before data are released to researchers – can be used to link, internally and externally, all information in the database with information in other databases. These databases include civil registration data, a death registry, birth registry and other government-held data. The NHI Research Database has records on gender, date of birth, place of residence, insurance details, family relationships, dates of inpatient and outpatient visits, medical diagnoses, medical expenditures, prescription details, vaccination status, examinations, operations, procedures and fees incurred.

Insured citizens with major diseases, including SLE, RA and ASD, are eligible to apply for a catastrophic illness certificate, holders of which are entitled to a waiver of medical co-payments. To receive the certificate, patients with a diagnosis of a catastrophic illness undergo comprehensive clinical and laboratory assessment, followed by a full board review by a panel of NHI-commissioned rheumatologists and psychiatrists. The registry of patients with catastrophic illnesses contains information on outpatient and inpatient claims of all beneficiaries who received catastrophic illness certificates and is distributed as a package to eligible researchers.

The National Birth Registry contains information on live births and stillbirths (older than 20 weeks or weighted over 500 gm) from year 2001. The variables contain in the registry include demographics of pregnant women, conditions of the pregnancy, conditions of the newborns and demographic data of spouses. Both NHI database and National Birth Registry contain unique personal identification. The linkage can be achieved by the assistance of the Collaboration Center of Health Information Application of the Ministry of Health and Welfare.

2.2. Study population and case definition

This is a cohort study, which consisted of all live births registered in National Birth Registry from 2000 to 2012. The identified children were classified according to parental history of rheumatic diseases and were followed until the end of 2013 or the occurrence of prespecified outcomes. ASD was defined as a physician diagnosis of ASD (International Classification of Diseases, 9th Revision code 299) on at least 2 ambulatory clinic visits. Maternal diagnoses of SLE and RA had to be earlier than the date of conception.

2.3. Statistical analysis

All newborns were followed until a diagnosis of ASD, death, deregistration or December 31, 2013. Marginal Cox proportional hazards models were used to estimate relative risk (RR) with 95% confidence intervals (CI) for ASD in offspring of affected mothers. This analysis considered one woman could have multiple births. The covariates were maternal age, 1-minute Apgar score, 5-minute Apgar score, mode of delivery, sex of the child, gestational age, birth weight and place of residence. All analyses were performed by using SAS v. 9.4 (SAS Institute, Cary, NC, USA).

2.4. Role of the funding source

This work was funded by theNational Science Council of Taiwan (project 105-2314-B-182A-135-MY2) and Chang Gung Memorial Hospital (project CMRPG3E1962, CMRPD1F0251, CMRPG3D1671, CMRPG3F1942, CORPG3E0142, CORPG3F0451). The sponsors (the Chang Gung Memorial Hospital and the National Science Council) mainly support the cost of the national health insurance research database and personnel costs of research assistants. They had no role in the design or conduct of the study; in the collection, management, analysis or interpretation of the data; in the preparation, review or approval of the manuscript or in the decision to submit the manuscript for publication.

3. Results

Table 1 summarises demographic, maternal and infant characteristics, current residence and ASD status of newborns for RA mothers, SLE mothers and all mothers. Among a total of 1,893,244 newborns, 673 were born to RA mothers and 1594 were born to SLE mothers. Mean maternal age was older in RA mothers and SLE mothers than in mothers without RA or SLE ($P < 0.001$). Approximately 7% of infants in Taiwan were born prematurely (gestational age < 37 weeks), and prematurity prevalence was significantly higher for infants born to mothers with RA (13.67%) and SLE (22.02%). Infant birth weight was lower in infants born to RA and SLE mothers. One-minute, but not 5-minute, Apgar scores were significantly lower for newborns born to mothers with RA or SLE than for the overall population of newborns. As compared with all mothers, RA and SLE mothers were more likely to require Caesarean delivery, had lower parity and delivered infants at a younger gestational age.

ASD was diagnosed in 5 of 673 (0.74%) children born to RA mothers, 7 of 1594 (0.44%) children born to SLE mothers and 10,631 of 1,893,244 (0.56%) children born to all mothers. ASD onset age was later in the SLE group (age 4.75 ± 1.69 years) than in the overall population (4.21 ± 2.03 years), and there was a trend toward later onset in the RA group (5.02 ± 3.22 years).

ASD incidence in RA, non-RA, SLE and non-SLE group demonstrated in Table 2. Children born to mothers with RA or SLE did not have a higher risk of ASD: the RR (95% CI) for ASD was 1.42 (0.60–3.40) for RA mothers and 0.76 (0.36–1.59) for SLE mothers (Table 3). Other risk factors for ASD are shown in Table 3. Male sex was a strong predictor of ASD development among children of RA mothers (RR, 4.97; 95% CI, 4.41–5.59) and SLE mothers (RR, 4.97; 95% CI, 4.41–5.6). There was a positive correlation between maternal age and ASD risk for children born to RA and SLE mothers. Other significant factors were 5-minute Apgar score and rural residence.

Please cite this article in press as: Tsai P-H, et al. Risk of autism spectrum disorder in children born to mothers with systemic lupus erythematosus and rheumatoid arthritis in Taiwan. Joint Bone Spine (2017), https://doi.org/10.1016/j.jbspin.2017.11.005