Official Journal of the European Paediatric Neurology Society

Original article

Chorioamnionitis and cerebral palsy: Lessons from a patient registry

Allison Shevell [a], *Pia Wintermark* [b], *Ruba Benini* [a], *Michael Shevell* [a,b], *Maryam Oskoui* [a,b,*]

[a] *Department of Neurology & Neurosurgery, McGill University, Canada*
[b] *Department of Pediatrics, McGill University, Canada*

ARTICLE INFO

Article history:
Received 5 July 2013
Received in revised form
19 December 2013
Accepted 20 December 2013

Keywords:
Placenta
Chorioamnionitis
Cerebral palsy
Periventricular white matter injury

ABSTRACT

Aim: The fetal neuroinflammatory response has been linked to the development of brain injury in newborns and subsequent neurologic impairment. We aimed to explore the maternal and child factors associated with histologic chorioamnionitis in cerebral palsy.
Methods: We conducted an observational study on a cohort of children with cerebral palsy who were identified from the Quebec Cerebral Palsy Registry. Placental pathology was reported prospectively. Maternal and child factors associated with histological chorioamnionitis were explored.
Results: Placental reports were available in 455 of 534 (85%) children with cerebral palsy, and of these 12% had histological signs of chorioamnionitis on reports. These children were more likely to have large placentas over 90th percentile for gestational age (53.7% versus 30.7%, $p = 0.001$) and were born significantly more prematurely (<32 weeks in 51.9% vs 24.1%, $p = 0.007$) than children without chorioamnionitis. A clinical sign of perinatal infection was reported in 61.1% of children with chorioamnionitis, however each clinical sign was seen in a minority of these children. Children with chorioamnionitis were more likely to have spastic diplegic cerebral palsy subtype (37% vs 19.2%, $p = 0.003$) and periventricular white matter injury on neuroimaging (52.9% vs 35.8%, $p = 0.004$). However no differences in neuroimaging or subtypes were seen when stratified by prematurity.
Discussion: Histological chorioamnionitis was a frequent pathological finding in children with cerebral palsy born prematurely, with larger placentas relative to gestation and birth weight. Future case control studies are needed to shed light on the role of inflammatory placental findings in pregnancy outcomes.

* *Corresponding author*. Department of Pediatrics, McGill University, Montreal Children's Hospital, 2300 Tupper Street, A-512, Montreal, Quebec H3H 1P3, Canada. Tel.: +1 514 412 4446; fax: +1 514 412 4373.
E-mail address: Maryam.oskoui@mcgill.ca (M. Oskoui).

1090-3798/$ – see front matter © 2014 European Paediatric Neurology Society. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejpn.2013.12.005

1. Introduction

Cerebral palsy (CP) is the most common cause of childhood motor disability, affecting 2 to 2.5 children per 1000 live births.[1] CP is a permanent disorder of movement and posture that results in a non-progressive motor impairment and is often associated with epilepsy as well as deficits in sensation, perception, cognition, communication and behavior.[2] The etiology of CP is multifactorial, relating to congenital or acquired disturbances to the brain during fetal or infant development.[2] The harmful effects of prematurity and low birth weight on neurodevelopment are well described in the literature, and prematurity indeed is the best known risk factor for CP.[3] Very preterm infants (under 32 weeks) account for 2% of all births, yet make up a quarter of all cases of CP.[4] The prevalence of CP is inversely proportional to gestational age (GA), with a 60-fold higher risk of CP in children born at less than 28 weeks gestation compared to term infants.[5] Not surprisingly, low birth weight has also been found to be strongly associated with CP, with a 70-fold increased risk of CP in extremely low birth weight infants (i.e. <1500 g) compared to normal birth weight infants.[6]

Chorioamnionitis and intrauterine exposure to maternal infection are risk factors for premature birth.[7,8] Although intrauterine infection appears to increase the risk of CP,[5,9–13] it is not clear if the effect is mediated solely through prematurity or through a neuroinflammatory response. A relationship between maternal infection during pregnancy and subsequent neurological sequelae in the newborn is not consistently demonstrated across all studies, especially when gestational age is adjusted for.[14–16] An observational case–control study comparing infants born to mothers with and without chorioamnionitis concluded that adverse neurological outcome was not affected by chorioamnionitis once gestational age was controlled for.[15] In a retrospective case–control study looking at placentas from very low birth weight infants with subsequent neurological impairment and placentas from matched controls, a similar prevalence of chorioamnionitis was found in both cases and controls.[17] Another case–control study examining cases of infants exposed to chorioamnionitis and control infants and assessing neurodevelopment at two years of age found that chorioamnionitis had but a minor role in the development of later neurological impairment.[18] The association between chorioamnionitis, periventricular white matter injury (PWMI) and later CP thus continues to be debated.[19,20]

Our objective was to explore the maternal and child factors associated with chorioamnionitis in a cohort of children with CP.

2. Methods

We conducted an observational study on a cohort of children with CP who were identified from a large population-based CP Registry (Registre de la Paralyse Cérébrale de Québec (REPACQ)), which includes children with CP born between 1999 and 2010 from 6 of the 17 administrative health regions in Quebec, representing approximately half of the province's pediatric population. The diagnosis of CP was based on the consensus definition of CP as previously described.[2] Children are registered in REPACQ at the age of 2 years and the diagnosis of CP is later confirmed at 5 years on follow-up along with updating their comorbidities and functional severity levels. Eligible children were ascertained by surveying specialized pediatric health or rehabilitation centers in each of the six administrative regions of Quebec, and parental consent was obtained before participation in the Registry. The birth records, the health records of both mothers and children with CP, and the children's rehabilitation records were systematically reviewed. Information from these medical documents along with information from standardized parental interviews were coded into over 200 variables and entered into a centralized encrypted computerized database (REDCap). The host institution as well as each participating health center granted ethical approval before proceeding with subject recruitment.

Macroscopic placental pathology is frequently examined in the province of Quebec, and microscopic examination is performed as clinically indicated. Categorical data from placenta pathology reports was collected within REPACQ at each center from the mother's medical chart. The sample in this study includes only the children from REPACQ where placental pathology was documented at least macroscopically. Placental pathology was classified as normal or abnormal and further subdivided by type of abnormality. Placental mass was reported in grams, and a corrected placental weight percentile was determined according to gestational age, sex and single or twin gestation.[21,22] Fetoplacental ratio (BW/PW) (ie, infant birth weight in grams divided by placental weight in grams) was also calculated, with BW/PW percentiles determined based on plurality, gestational age and sex.[22] Small for gestational age was defined as birth weight for gestational age percentile below the 10th percentile using Canadian population standards.[23]

CP subtype was categorized as ataxic/hypotonic, athetoid/dystonic/dyskinetic, spastic diplegic, spastic hemiplegic, and spastic quadriplegic. Those children with both spasticity and dyskinesia were classified as dyskinetic. Functional severity with respect to ambulation was assessed by the Gross Motor Function Classification System (GMFCS) (coded as I–III and IV–V to designate ambulant versus non-ambulant status).[24] Functional severity with respect to bimanual dexterity was assessed by the Manual Ability Classification System (MACS) (coded as levels I–III and IV–V).[25] Neuroimaging data was classified as normal or abnormal and further subdivided by type of abnormality reported on magnetic resonance images (MRI). Types of abnormalities included periventricular white matter injury, cerebrovascular accident, cerebral malformation, diffuse grey matter injury, superficial grey matter injury, deep gray matter injury, intracranial hemorrhage, and infection.

Descriptive statistics were applied to the data using SPSS Statistics (Version 20.0). The characteristics of children with chorioamnionitis on placental pathology were compared to children having any other placental findings including normality. Chi Square tests and Student *t*-tests were used for examining associations as appropriate. A subgroup analysis among children born very prematurely (32 weeks or less) was