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Maternal Infections During Pregnancy and Cerebral Palsy in the Child

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Abstract

INTRODUCTION—Chorioamnionitis is a risk factor for cerebral palsy. The relationship between extra-amniotic infections and cerebral palsy is less well studied. We examined maternal intra- and extra-amniotic infections and risk of cerebral palsy in the child.

METHODS—Among a retrospective cohort of six million Californian births, 1991–2001, we analyzed administrative maternal and newborn hospital discharge abstracts linked to records of all children receiving services for cerebral palsy at the California Department of Developmental Services. We identified maternal hospital diagnoses of intra-amniotic (chorioamnionitis) and extra-amniotic (other genitourinary and respiratory) infections occurring up to twelve months before delivery. Using multivariable logistic regression, we determined the independent association between maternal infections and cerebral palsy, adjusting for infant sex, maternal age, race, education, socioeconomic status, and obesity.

RESULTS—5.5% of mothers had a hospital discharge diagnosis of at least one of the following: chorioamnionitis (2.0%), other genitourinary (3.1%), and respiratory infection (0.6%). An infection diagnosis was more common in mothers of the 8,473 infants with cerebral palsy than in mothers of unaffected children (13.7% vs. 5.5%, P<0.001). All three types of maternal infections (chorioamnionitis, OR 3.1, 95% CI 2.9–3.4; other genitourinary infection, OR 1.4, 95% CI 1.3–1.6; and respiratory infection, OR 1.9, 95% CI 1.5–2.2) were associated with cerebral palsy in multivariable analyses. Maternal extra-amniotic infections, whether diagnosed during prenatal or birth hospitalizations, conferred an increased risk of cerebral palsy.

CONCLUSIONS—Maternal extra-amniotic infections diagnosed in the hospital during pregnancy are associated with a modestly increased risk of cerebral palsy in the child.

Keywords

cerebral palsy; neonatal neurology; prenatal infection; epidemiology; chorioamnionitis

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Introduction

Cerebral palsy, a static encephalopathy syndrome of motor dysfunction due to intrauterine or perinatal brain lesions, affects approximately 2 per 1,000 births resulting in substantial human and economic costs[1-3]. Despite improvements in infant mortality and perinatal care leading to improved outcomes in preterm births, the incidence of cerebral palsy has remained nearly unchanged in term infants for the past three decades[4,5]. Efforts to explain the persistent incidence of cerebral palsy have led to a body of literature exploring social, demographic, and environmental risk factors including male gender, preterm birth, low birth weight, advanced maternal age, and low educational attainment[1,6-9]. The causal pathways, however, have remained incompletely understood.

In the 1990s, new research emerged demonstrating an association between inflammatory markers and the risk of cerebral palsy[10]. From these early studies has emerged an active area of research exploring the role of an inflammatory milieu on neonatal development. Mouse models have shown increased susceptibility to hypoxic insults when the fetus is exposed to bacterial endotoxin leading to a systemic inflammatory response[11-13]. In human studies, fetal systemic inflammation as a response to intra-amniotic infection has been strongly associated with cerebral palsy[14,15]. Epidemiological studies have generally shown an increased incidence of cerebral palsy in infants whose mothers had infections of the genitourinary (GU) tract during pregnancy, with the strongest and most consistent associations seen between chorioamnionitis and cerebral palsy in term infants[16-21].

The relationship between maternal infections other than chorioamnionitis and cerebral palsy is less clear. While some studies have reported increased rates of cerebral palsy in the setting of maternal urinary tract infections (UTIs) and/or sexually transmitted infections (STIs)[19,22], others did not confirm these associations[2], and maternal respiratory infections and gastroenteritis were not associated with cerebral palsy in a large population study[8]. Non-infectious causes of maternal inflammation, such as maternal obesity[23,24], might also contribute to the risk of cerebral palsy and other forms of neurologic injury. The purpose of this study was to examine prenatal and intra-partum maternal infections and to test the hypothesis that extra-amniotic infections during pregnancy are associated with increased risk of cerebral palsy in the child.

Patients and Methods

We analyzed a retrospective cohort of 6,018,504 Californian births during an 11-year period (January 1, 1991, to December 31, 2001) using linked data from the following administrative databases: 1) newborn hospital discharge abstracts from the California Office of Statewide Health Planning and Development (OSHPD); 2) maternal hospitalization discharge abstracts from OSHPD, beginning twelve months prior to delivery; and 3) records of all children receiving services for cerebral palsy from the California Department of Developmental Services (DDS) through 2006. All study procedures were approved by the California Protection of Human Subjects Committee and by the institutional review boards

at the California OSHPD, the University of California, San Francisco, and the University of California, Davis.

The California OSHPD maintains a database of discharge abstracts for all admissions to nonfederal hospitals, which represent 96% (571 of 594) of all hospitals in the state. According to the 1991–1998 California natality figures from the Centers for Disease Control and Prevention, 96.7% of all live births in California were recorded in the California OSHPD hospital discharge dataset.

We extracted the following maternal and infant sociodemographic variables from the linked California OSHPD–California Vital Statistics Birth files: maternal age, race, and education; infant gender; gestational age; and source of payment for the birth hospitalization. Source of payment was analyzed as an indicator of socioeconomic status; women who were publicly insured or uninsured were categorized as having low insurance status, whereas women with private or managed care insurance were categorized as having high insurance status. We categorized births as either preterm (< 37 weeks) or term (≥ 37 weeks) gestation. Data were excluded if the recorded gestational age was pre-viable (< 23 weeks gestation; n = 18,696) or likely erroneous (> 44 weeks; n = 181,543).

We identified the following maternal hospital discharge diagnoses by searching International Classification of Diseases-9 (ICD-9) diagnostic codes: chorioamnionitis (658.4); “other” genitourinary (venereal diseases 090–099; pyelonephritis 590; cystitis 595; inflammatory disease of female pelvic organs, 614–616; infections of genitourinary tract in pregnancy, 646.6), and respiratory (acute respiratory infections, 460–466; other diseases of the upper respiratory tract, 470–478; pneumonia and influenza, 480–487) infections. We also identified individuals with an obesity diagnosis (ICD-9 codes 646.1, 278.0, and 278.01) for use in our logistic regression model.

The DDS runs a statewide program that provides occupational and physical therapy, case management, and social services for all residents who have a substantive disability related to cerebral palsy. Cerebral palsy is defined as a non-progressive lesion or disorder in the brain occurring during intrauterine life or the perinatal period and characterized by paralysis, spasticity, or abnormal control of movement or posture that is manifest before two to three years of age, and other significant motor dysfunction appearing before age 18 years. Each year, individuals who receive services from the DDS receive a comprehensive evaluation by a staff physician who records data regarding medical diagnoses including cerebral palsy.

From DDS records, we identified all children in the study cohort and who had been diagnosed with cerebral palsy before November 30, 2006. Thus, children were at least 5 years old at the time of cerebral palsy ascertainment. Because we were interested in prenatal and perinatal risk factors for cerebral palsy, we excluded children with postnatal causes including child abuse (n = 272), motor vehicle and other vehicle injuries (n = 213), and near drowning (n = 72).

Statistical Analysis

All analyses were performed by using Stata version 12.1 (Stata Corporation, College Station, TX). We calculated univariate relative risk (RR) and 95% confidence intervals (CI) for each infection category, and stratified results by timing of diagnosis (i.e., prenatal vs. birth hospitalization) and by gestational age (preterm vs. term). We then compared demographic characteristics in different patient groups using Chi-squared analyses. Finally, we performed multivariable logistic regression analyses to estimate odds ratios (ORs) of maternal infection for cerebral palsy after adjusting for known risk factors for cerebral palsy: maternal age, race, education, and socioeconomic status; maternal hospital diagnosis of obesity[23], and infant sex. All ORs closely approximate the RR given the low prevalence of cerebral palsy.

Results

Among 6,018,504 mother-infant dyads, 5.5% received a maternal hospital discharge diagnosis of at least one of the following: chorioamnionitis (2.0%), other genitourinary (3.1%), and respiratory infection (0.6%). Women diagnosed with an infection during a pregnancy hospitalization were more likely to be younger, African American, of lower socioeconomic status, and to have a hospital diagnosis of obesity (Table 1). A hospital diagnosis of maternal infection was also more common in preterm than term births (9.9% vs. 4.9%, $P < 0.001$).

The majority (82.4%) of infections were diagnosed during the birth hospitalization (Table 2). Only 0.1% of all mothers, representing 2.3% of mothers with an infection diagnosis, were diagnosed both during a birth hospitalization and during a prenatal hospital admission. Chorioamnionitis was diagnosed almost exclusively during the birth hospitalization, while other genitourinary infections were diagnosed during the birth hospitalization in only two-thirds of cases. Maternal respiratory infections were diagnosed at a similar rate in prenatal and birth hospitalizations (Table 2).

Within the study cohort, 8,473 individuals were diagnosed with cerebral palsy, representing a population incidence of 1.4 per 1000 live births. Among mothers of a child with cerebral palsy, 13.7% had an infection diagnosed during a prenatal or birth hospitalization, compared to 5.5% of mothers with unaffected children ($P < 0.001$). All three maternal infection categories were more commonly diagnosed in mothers of a child with cerebral palsy (Table 3): chorioamnionitis 7.6% vs. 2.0%, $P < 0.001$; other genitourinary 5.2% vs. 3.1%, $P < 0.001$; respiratory 1.3% vs. 0.6%, $P < 0.001$). The risk of cerebral palsy in the setting of chorioamnionitis was especially high if another infection diagnosis was also present (RR 7.0, 95% CI 4.1–11.7).

Genitourinary and respiratory infections were diagnosed both during a prenatal hospital admission and during the birth hospitalization. In stratified analyses, we found that these infections were significantly associated with cerebral palsy both when diagnosed prenatally (other genitourinary infection, RR 1.4, 95% CI 1.2–1.7; respiratory infection RR 2.0, 95% CI 1.5–2.7), and when diagnosed during the birth hospitalization (other genitourinary infection, RR 1.9, 95% CI 1.7–2.1; respiratory infection, RR 2.8, 95% CI 2.2–3.6).

The rate of cerebral palsy was higher among preterm than term infants (5.0 vs. 1.0 per 1,000, P < 0.001). A maternal infection diagnosis was associated with increased risk of cerebral palsy both among preterm (RR 2.8, 95% CI 2.6–3.0) and term infants (RR 1.6, 95% CI 1.4–1.8).

In multivariable analyses, a maternal diagnosis of infection made during a hospitalization was associated with a greater than 2-fold increased risk of cerebral palsy after adjusting for known risk factors (Table 4). All three types of maternal infections (chorioamnionitis, OR 3.1, 95% CI 2.9–3.4; other genitourinary infection, OR 1.4, 95% CI 1.3–1.6; and respiratory infection, OR 1.9, 95% CI 1.5–2.2) were also associated with cerebral palsy in multivariable analyses. Adjusting for potential confounders, the association between maternal infection and cerebral palsy remained significant for both term and preterm infants (data not shown).

As described in the methods, we excluded patients whose documented gestational age was >44 weeks due to concerns regarding the accuracy of these records. A post-hoc analysis repeating the above statistical tests and including these patients in the “term” group did not significantly alter the results (data not shown).

Discussion

We found that both intrauterine and extra-uterine maternal infections diagnosed in the hospital during pregnancy were associated with a higher risk of cerebral palsy in the child. Our large population allowed us to examine the relationship between maternal infections and cerebral palsy stratified by both gestational age and timing of infection relative to delivery. We report a novel association between maternal respiratory infections diagnosed in the hospital during pregnancy and cerebral palsy, and we demonstrate that maternal infections can be associated with an increased risk of cerebral palsy whether diagnosed during a prenatal hospital admission or during the birth hospitalization. We additionally provide support for the growing evidence of an association between chorioamnionitis and other GU infections during pregnancy and cerebral palsy.

The incidence of cerebral palsy in our cohort, 1.4 per 1,000 live births, is similar to previously-published population-based estimates[1,3,5]. Our rates of maternal infection, 4.9% of women delivering at term and 9.9% of women delivering pre-term, were also similar to the 4% aggregate rate reported in a recent study of hospital-based infection diagnoses[25]. In contrast, studies that incorporate both inpatient and outpatient diagnoses have much higher rates of maternal infection[2,8,18,19]. In a study utilizing Medicaid billing data, 38% of women had a genitourinary infection diagnosis[19], and self-reported rates of prenatal maternal infections of all types ranges from 23–40%[2,8]. Similarly, a Danish study utilizing centralized antibiotic prescription records found that 31% of pregnant women filled a prescription for a GU-specific antibiotic in the prenatal period[18]. Thus, our findings only pertain to the small subset of maternal infections during pregnancy diagnosed during a hospital admission.

In agreement with previous studies[16,17,26], we demonstrated that chorioamnionitis is associated with an increased risk of cerebral palsy. While there is ample evidence linking maternal chorioamnionitis with an increased risk of cerebral palsy in the child, the causal

pathway to the development of cerebral palsy remains elusive. One proposed mechanism, supported by murine models[13,27], suggests that systemic inflammation rather than a purely local process contributes to the elevated cerebral palsy by potentiating injury in the developing brain. Prompted by this hypothesis, we examined the association of non-chorioamnionitis GU infections, which would also cause a systemic inflammatory response in the fetus. Previous literature regarding other non-chorioamnionitis GU infections has produced conflicting results with some studies finding an association with cerebral palsy[18,19] while others did not[8]. In this study, we did find a statistically significant increase in risk of cerebral palsy in the child. This association remains significant irrespective of the timing of the infection during pregnancy and the gestational age of the infant and after correction for known risk factors for cerebral palsy.

This is the first study to demonstrate an association between maternal respiratory infection during pregnancy and risk of cerebral palsy in the fetus. The increased risk was statistically significant in both term and preterm infants, and regardless of whether diagnosed during a prenatal or birth hospitalization. The few published studies looking at extra-amniotic infections outside the genitourinary system have not shown an increased risk of cerebral palsy[8,25]. Prior studies could have underestimated the association by including less severe infections that did not require hospitalization; alternatively, a threshold level of severity as present in our study of hospitalized patients could be a necessary component of the association. Prior studies might also have been limited by smaller sample sizes. There are several potential explanations for the association between prenatal respiratory infections and cerebral palsy seen in our study. First, respiratory infections of sufficient severity to occur during a hospitalization might lead to a systemic inflammatory response that predisposes the fetal brain to injury, a mechanism that has been previously suggested for intra-amniotic infections[12]. The respiratory infection could lead to a prolonged period of maternal hypoxemia that could then cause or predispose the fetal brain to injury. The antibiotics themselves used to treat infections during the hospitalization could also contribute to the risk of developing cerebral palsy as suggested by the ORACLE II trial[28]. Further research is needed to confirm our results and to explore the etiology of the increased risk of cerebral palsy with respiratory infection exposure.

As with all retrospective research using ICD-9 codes to determine hospital diagnoses, the accuracy of our data is limited by the use of appropriate ICD-9 hospital discharge diagnostic codes. We were unable to account for comorbid diagnoses related to the hospitalization that might have been the primary reason for hospitalization or an unrecognized contributor to the risk of cerebral palsy. The use of hospitalization-based diagnoses inherently limits extrapolation of the data to outpatient illnesses. Consequently it is likely that the associations seen in our data are only true for more severe infections. Since maternal hospitalizations up to one year before delivery were included in the analyses, we may have included some maternal infection diagnoses that occurred during a hospital admission prior to conception. However, such an infection would be unlikely to affect the fetus, and therefore this misclassification would tend to bias our findings against finding an association between maternal infection and cerebral palsy. Strengths of the study include the lack of recall bias, the large population-based setting, and the ability to evaluate maternal infection diagnoses both during and prior to the birth hospitalization.

Conclusion

In addition to chorioamnionitis, GU and respiratory infections occurring during both prenatal and birth hospitalizations are also associated with an increased risk of cerebral palsy. These data support the role of the maternal inflammatory milieu in the pathogenesis of cerebral palsy, although a separate causal pathway involving hypoxemia in the setting of respiratory infections cannot be excluded. Research including both inpatient and outpatient illnesses is needed to confirm the association between extra-uterine infections and cerebral palsy, to understand how severity of disease might impact cerebral palsy risk, and to understand the biologic mechanisms leading to the increased risk.

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Abbreviations

CI	confidence interval
DDS	Department of Developmental Services
OR	odds ratio
RR	relative risk
SES	socioeconomic status
STI	sexually transmitted infection
UTI	urinary tract infection
GU	genitourinary
OSHPD	California Office of Statewide Health Planning and Development
ICD-9	International Classification of Diseases, 9th Revision

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Table 1

Maternal demographic characteristics, in relation to diagnoses of prenatal infection and cerebral palsy in the child, among 6 million California births.

	Prenatal Infection			Cerebral Palsy		
	Yes	***No***	***p* value**	***Yes***	***No***	***p* value**
n	381,056	5,637,446		8,473	6,010,031	
Age, y			<0.001			<0.001
<18	6.0	4.3		5.0	4.4	
18–34	80.4	81.7		77.3	81.6	
≥35	13.7	14.0		17.8	14.0	
Socioeconomic status			<0.001			<0.001
Low	52.2	48.5		51.3	48.7	
Middle/High	47.8	51.5		48.7	51.3	
Education			<0.001			<0.001
Primary	4.2	4.7		5.1	4.6	
Secondary	30.7	28.0		29.4	28.2	
High school	30.5	29.3		30.3	29.3	
Some college	19.0	19.6		19.2	19.5	
College graduate	15.7	18.5		16.0	18.3	
Race			<0.001			<0.001
White	30.2	35.5		35.0	35.2	
Black	11.6	6.9		9.0	7.2	
Hispanic	47.6	46.2		46.8	46.3	
Asian	9.1	10.1		7.9	10.1	
Other	1.5	1.3		1.3	1.3	

Table 2

Hospital discharge diagnoses of chorioamnionitis, other genitourinary infections, and respiratory infections among 6 million California births in 1991–2001.

	Prenatal Hospitalization		Birth Hospitalization		Any Hospitalization	
	n	%	*n*	%	*n*	%
Chorioamnionitis						
Preterm	227	0.0	24,414	4.0	24,564	4.0
Term	330	0.0	86,335	1.7	86,645	1.7
Other genituourinary						
Preterm	11,414	1.9	20,741	3.4	30,789	5.1
Term	51,243	1.0	95,913	1.9	143,137	2.8
Respiratory						
Preterm	3,039	0.5	3,433	0.6	6,345	1.0
Term	12,564	0.2	12,394	0.2	24,715	0.5
Any of the above						
Preterm	14,210	2.3	47,878	7.9	60,181	9.9
Term	62,345	1.2	193,258	3.8	250,748	4.9

Table 3

Risk of cerebral palsy (CP) associated with a hospital discharge diagnosis of maternal chorioamnionitis, other genitourinary, or respiratory infection.

	Total (N)	CP (N)	RR	95% CI
Chorioamnionitis				
Prenatal hospitalization	614	2	2.3	0.6 – 9.2
Preterm	227	1	0.9	0.1 – 6.2
Term	330	0	NA*	–
Birth hospitalization	118,074	640	4.1	3.8 – 4.4
Preterm	24,414	443	4.1	3.7 – 4.5
Term	86,335	167	2.0	1.7 – 2.4
Any hospitalization	118,578	642	4.1	3.8 – 4.4
Preterm	24,564	444	4.0	3.7 – 4.5
Term	86,645	167	2.0	1.7 – 2.3
Other genituourinary infection				
Prenatal hospitalization	66,380	130	1.4	1.2 – 1.7
Preterm	11,414	69	1.2	1.0 – 1.5
Term	51,243	49	1.0	0.7 – 1.3
Birth hospitalization	123,466	323	1.9	1.7 – 2.1
Preterm	20,741	177	1.7	1.5 – 2.0
Term	95,913	129	1.4	1.2 – 1.7
Any hospitalization	184,087	442	1.7	1.6 – 1.9
Preterm	30,789	238	1.6	1.4 – 1.8
Term	143,137	175	1.3	1.1 – 1.5
Respiratory infection				
Prenatal hospitalization	16,662	47	2.0	1.5 – 2.7
Preterm	3,039	23	1.5	1.0 – 2.3
Term	12,564	22	1.8	1.2 – 2.7
Birth hospitalization	16,981	67	2.8	2.2 – 3.6
Preterm	3,433	31	1.8	1.3 – 2.6
Term	12,394	27	2.2	1.5 – 3.3
Any hospitalization	33,248	112	2.4	2.0 – 2.9
Preterm	6,345	53	1.7	1.3 – 2.2
Term	24,715	48	2.0	1.5 – 2.6

* NA = not calculated because there were no exposed cases of cerebral palsy.

Table 4

Adjusted risks of cerebral palsy associated with maternal infection and with other known sociodemographic risk factors in a multivariable logistic regression model.*

	Odds Ratio	95% CI	*P* value
Any study infection	2.17	2.04 – 2.32	<0.001
Maternal race			
White	Reference	Reference	Reference
Black	1.02	0.94 – 1.11	0.64
Hispanic	0.96	0.09 – 1.01	0.13
Asian	0.78	0.71 – 0.85	<0.001
Other	0.92	0.75 – 1.13	0.42
Maternal age in years			
18 – 34	Reference	Reference	Reference
< 18	1.04	0.93 – 1.15	0.51
>= 35	1.29	1.22 – 1.37	<0.001
Maternal education, years			
College graduate (> 16 y)	Reference	Reference	Reference
Some college (13-15 y)	1.10	1.02 – 1.19	0.01
High school graduate (12 y)	1.15	1.06 – 1.23	<0.001
Secondary school (6-11 y)	1.15	1.06 – 1.25	0.001
Primary school or none (0-5 y)	1.22	1.07 – 1.38	0.002
Low insurance status#	0.99	0.94 – 1.04	0.73
Preterm delivery	4.78	4.57 – 5.01	<0.001
Maternal obesity	1.23	1.02 – 1.49	0.03
Male infant	1.28	1.23 – 1.34	<0.001

*Logistic regression model includes all the variables listed in the table.

#Medicare/Medicaid/Self-Insured