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Original Article

Neonatal Infection in Children With Cerebral Palsy: A Registry-Based Cohort Study

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ABSTRACT

BACKGROUND: The goal of this study was to explore the association between neonatal infection and outcomes in children with cerebral palsy. **METHODS:** We conducted a retrospective cohort study using the Canadian CP Registry. Neonatal infection was defined as meeting one of the following criteria: (1) septicemia, (2) septic shock, or (3) administration of antibiotics for ≥10 days. Phenotypic profiles of children with cerebral palsy with and without an antecedent neonatal infection were compared. Subgroup analysis was performed, stratified by gestational age (term versus preterm). **RESULTS:** Of the 1229 registry participants, 505 (41.1%) were preterm, and 192 (15.6%) met the criteria for neonatal infection with 29% of preterm children having a neonatal infection compared with 6.5% in term-born children. Children with prior neonatal infection were more likely to have a white matter injury (odds ratio 2.2, 95% confidence interval 1.5 to 3.2), spastic diplegic neurological subtype (odds ratio 1.6, 95% confidence interval 1.1 to 2.3), and sensorineural auditory impairment (odds ratio 2.1, 95% confidence interval 1.4 to 3.3). Among preterm children, neonatal infection was not associated with a difference in phenotypic profile. Term-born children with neonatal infection were more likely to have spastic triplegia or quadriplegia (odds ratio 2.4, 95% confidence interval 1.3 to 4.3), concomitant white matter and cortical injury (odds ratio 4.1, 95% confidence interval 1.6 to 10.3), and more severe gross motor ability (Gross Motor Function Classification System IV to V) (odds ratio 2.6, 95% confidence interval 1.4 to 4.8) compared with preterm children. **CONCLUSIONS:** Findings suggest a role of systemic infection on the developing brain in term-born infants, and the possibility to develop targeted therapeutic and preventive strategies to reduce cerebral palsy morbidity.

Keywords: cerebral palsy, neonatal infection, neurodevelopment, registry, retrospective cohort

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Introduction

Cerebral palsy (CP) is the leading cause of physical impairment in children, with an estimated prevalence of two per 1000 live births.[1] CP comprises a spectrum of outcomes sharing objective neuromotor impairment caused by congenital or acquired disturbances to the developing brain.

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These disorders vary in severity and may be associated with a range of comorbidities, including epilepsy, visual, auditory and cognitive impairments, as well as behavioral and communication difficulties.[2] Risk factors include prematurity, multiple gestations, intrauterine growth restriction, intrauterine infection or inflammation, and male gender, yet the specific causal mechanism remains elusive for some children with CP.[3-5]

Neonatal central nervous system infections are one of many risk factors for the development of CP. Systemic infections are increasingly recognized as having an effect on the developing brain, even in the absence of a concurrent central nervous system infection.[6,7] Systemic neonatal infections may be associated with white matter injury (WMI)—especially in preterm infants—and widespread impairments in brain development.[8] The prevailing hypothesis concerning the pathogenesis of WMI is that preoligodendrocytes are specifically vulnerable as a function of gestational age (GA) to inflammation and ischemic injury in the developing brain.[9] Preterm infants are more vulnerable to WMI than term-born infants because preoligodendrocytes comprise the majority of the oligodendrocyte population in the premature period.[10] WMI is predominantly associated with the bilateral spastic neurological subtype of CP, although it has also been associated with the unilateral spastic subtype.[11,12]

The heterogeneity of CP creates substantive challenges in identifying targeted disease modifying interventions to improve the child's health and functional outcomes. The objectives of the present study were to explore the association between systemic neonatal infections and later outcomes in children with CP, and to identify differences in this association by GA. We hypothesized that among children with CP, those with a history of a neonatal infection would more frequently have evidence of WMI on imaging and the bilateral spastic neurological subtype than those without a history of a neonatal infection.

Materials and Methods

We conducted a retrospective cohort study using the Canadian CP Registry (CCPR), a national database that draws on a population sample of 18 million Canadians and 180,000 annual births (360 cases of CP annually), from the birth year 1999 until 2011. Children with CP are recruited from across Canada (Newfoundland, Nova Scotia, Quebec, Ontario, Alberta, and British Columbia) from pediatric rehabilitation centers and university-based hospitals where provincial pediatric neurology and developmental pediatric services are offered. To be enrolled in the CCPR, the child must be at least two years of age and must meet current diagnostic consensus criteria for CP (i.e., a clinical diagnosis of a nonprogressive neuromotor impairment of early onset).[2] Once parental consent is obtained, the records of the mother and the child are reviewed and standardized collected data are supplemented by a parental interview. The CCPR provides a comprehensive source of clinical (antepartum, intrapartum, and postpartum risk factors) and sociodemographic variables. Children found to no longer meet the criteria for CP at five years of age are removed from the registry. Local ethics board approval was obtained from each participating institution. The Montreal Children's Hospital-McGill University Health Center research ethics board provided central approval for data storage, analysis, and overall operations.[13]

Children with CP participating in the CCPR were then categorized according to the presence or the absence of a neonatal infection. A neonatal infection was defined as the presence of at least one of the following neonatal variables: (1) documented septicemia, (2) septic shock, or (3) administration of antibiotics for ≥10 days. This latter criterion increases specificity by excluding children who were placed on antibiotics at birth for 48 hours until cultures were proven negative. For the purposes of group assignment, a child was categorized as not having had a neonatal infection when there was no indication of septicemia, septic shock, or administration of antibiotics. In the case of missing data, indication of a negative response for at least one of the three parameters was categorized as no infection. Those for whom the presence or the absence of a neonatal infection was uncertain were excluded from the study.

Prenatal and neonatal characteristics were analyzed according to the presence or the absence of neonatal infection. Neonatal outcome variables of interest included GA, birth weight, head circumference, and Apgar scores at one and five minutes. Children with a birth weight below the tenth percentile for their gender and GA were categorized as being small for GA. Children with a head circumference below the third percentile for their gender and age were categorized as having congenital microcephaly. Apgar scores were categorized as low-moderate (scores less than 7) and normal (scores of 7 or greater).[14] Phenotypic outcome variables of interest were neurological subtype, gross motor function as measured by the Gross Motor Function Classification System (GMFCS), and four specific comorbidities: cortical visual impairment, sensorineural auditory impairment, communication difficulties, and coexisting epilepsy.

The neurological subtype was classified based on the topographic pattern of neuromotor impairment documented at five years of age. When the CP subtype at five years was not available, the CP subtype diagnosed at the time of registry enrollment was carried forward. The following clinical scheme was employed: (1) spastic diplegia, (2) spastic hemiplegia, (3) spastic triplegia and quadriplegia, (4) ataxia and hypotonia, and (5) dyskinesia. The motor function was classified according to the GMFCS, allowing us to distinguish ambulation (levels I to III) from more severe motor function (levels IV and V). Cortical visual impairment was limited to visual impairments attributed to cortical brain injury, such as hemianopsia. Sensorineural auditory impairment was broadly defined regardless of the severity. As for communication difficulties, the following clinical scheme was employed: verbal and nonverbal communication skills, nonverbal communication skills only, and no communication. Epilepsy was defined as the occurrence of nonfebrile convulsions at any point in time in the child's life. Subgroup analysis was performed according to GA: term (37 weeks or less) and preterm (less than 37 weeks). Children for whom the preterm versus the term status was unknown were excluded from this analysis. Analysis of subcategories of prematurity, including extremely preterm (less than 28 weeks), very preterm (28 to 31 weeks), and moderate to late preterm (32 to 36 weeks), was also performed. Magnetic resonance imaging (MRI) neuroimaging findings were classified into one of eight mutually exclusive categories based on a classification system previously developed for another CCPR study by coauthor JG. Each category is further described in Supplemental Table S1.[13]

SPSS Statistics software (version 20.0, IBM Corp, Armonk, NY) was used for all statistical analyses. Variables were compared between those with and without neonatal infection using the Student *t* tests and the chi-square tests for continuous and categorical variables, respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) were used where appropriate. Statistical significance was set as an alpha of 0.05. Bonferroni correction was used for multiple outcomes.

Results

Of the 1415 children with CP registered in the CCPR as of August 18, 2015, 186 (13.1%) were excluded from the analysis as the presence or the absence of a neonatal infection was unknown. The children excluded from analysis were comparable with the rest of the cohort in gender, GA, and GMFCS level (Supplemental Table S2). Ultimately, 192 of the remaining 1229 registered participants (15.6%), met the criteria for a systemic neonatal infection, and 1037 (84.4%) met

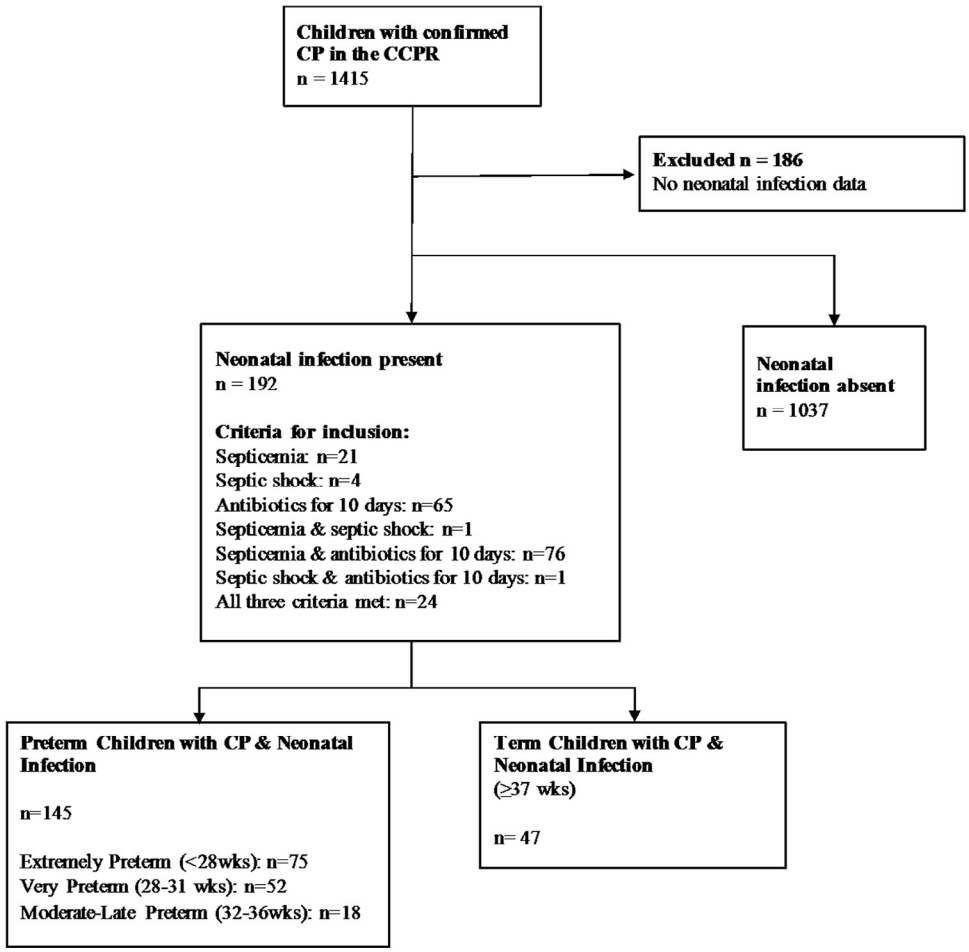

FIGURE.
Participant flowchart. CP, cerebral palsy; CCPR, Canadian CP Registry.

sufficient criteria to be classified as not having had an apparent systemic neonatal infection (Fig).

Table 1 presents the perinatal characteristics according to the presence or the absence of neonatal infection. Pre-eclampsia (OR 1.9, 95% CI 1.2 to 3.2), chorioamnionitis (OR 3.3, 95% CI 2.2 to 5.0), maternal fever (OR 1.9, 95% CI 1.2 to 3.1), delivery by Caesarean (OR 1.9, 95% CI 1.4 to 2.6), resuscitation at birth (OR 5.3, 95% CI 3.8 to 7.5), seizures

TABLE 1.
Perinatal Characteristics of the Cohort

Characteristics, n (%)	N	Neonatal Systemic Infection (n = 192)	No Infection (n = 1037)	*P* Value	Odds Ratio (95% CI)
Pre-eclampsia	1150	19 (10.5)	58 (6.0)	0.026	1.9 (1.2-3.2)
Chorioamnionitis	918	48 (32.9)	98 (12.7)	<0.0001*	3.3 (2.2-5.0)
Prolonged rupture of membranes	1183	34 (18.2)	109 (10.9)	0.005	2.0 (1.3-3.2)
Delivery by Caesarean	1226	112 (58.3)	441 (42.6)	<0.0001*	1.9 (1.4-2.6)
Maternal fever	1020	23 (14.8)	73 (8.4)	0.012	1.9 (1.2-3.1)
Shoulder dystocia	631	5 (4.3)	34 (6.6)	0.343	0.68 (0.3-1.7)
Resuscitation at birth	1210	138 (73.0)	342 (33.5)	<0.0001*	5.3 (3.8-7.5)
Seizures in the first 72 hours	1203	38 (20.4)	151 (14.8)	0.054	1.5 (1.0-2.2)
Multisystem involvement	1157	127 (72.7)	297 (30.3)	<0.0001*	5.9 (4.1-8.5)
Apgar <7 at one minute	1178	126 (67.7)	396 (39.9)	<0.0001*	3.1 (2.3-4.4)
Apgar <7 at five minutes	1178	78 (41.5)	208 (21.0)	<0.0001*	2.6 (1.9-3.7)
Small for gestational age	1204	29 (15.3)	156 (15.4)	0.966	1.0 (0.7-1.5)
Congenital microcephaly	930	4 (2.8)	28 (3.6)	0.806	0.8 (0.3-2.3)
Umbilical cord pH < 7.00	864	15 (10.6)	67 (9.3)	0.633	1.2 (0.7-2.1)
Preterm	505	145 (75.5)	360 (34.8)	<0.001*	5.7 (4.0-8.1)

Abbreviation:
CI = Confidence interval
* Significant after Bonferroni correction ($P < 0.003$).

during the first 72 hours of life (OR 1.5, 95% CI 1.0 to 2.2), and multisystem involvement (OR 5.9, 95% CI 4.1 to 8.5) were all more likely in children with CP who had a neonatal infection ($P < 0.001$). Children with CP with a neonatal infection were more likely to be born preterm (OR 5.7, 95% CI 4.0 to 8.1) and to have a low-moderate Apgar score at one minute (OR 3.1, 95% CI 2.3 to 4.4) and five minutes (OR 2.6, 95% CI 1.9 to 3.7). There were no significant differences between the two groups in the proportion of either children born small for GA or congenital microcephaly.

Table 2 outlines the phenotypic profile and neuroimaging of children with CP, comparing those with and without a neonatal infection. Children with a neonatal systemic infection were more likely to have bilateral WMI (OR 2.2, 95% CI 1.5 to 3.2), to have spastic diplegia (OR 1.6, 95% CI 1.1 to 2.3), and to have a sensorineural auditory impairment (OR 2.1, 95% CI 1.4 to 3.3) ($P < 0.002$ with Bonferroni correction).

Because having a neonatal infection was strongly associated with prematurity, a subgroup analysis was performed, according to GA (term versus preterm). Of the 1229 children included for analysis in this study, 722 (58.7%) were born at term, 505 (41.1%) were born preterm, and two (0.2%) had to be excluded from the subgroup analysis as their GA was unknown. Table 3 presents perinatal characteristics, comparing those with and without a neonatal infection within each group. Of the 505 children born preterm, 145 (28.7%) had a neonatal infection and 360 (71.3%) did not have a neonatal infection. In children born preterm, chorioamnionitis (OR 2.5, 95% CI 1.6 to 4.0), resuscitation at birth (OR 3.1, 95% CI 2.0 to 5.0), and multisystem involvement (OR 3.1, 95% CI 2.0 to 4.8) were more likely in those with systemic neonatal infection. Preterm children with a neonatal infection were more likely to have low-moderate Apgar scores (low-moderate Apgar score at one minute; OR 2.0, 95% CI 1.3 to 3.1) and significantly lower birth weights (1162 ± 475 g vs 1706 ± 670 g, $P < 0.001$) and placental weights (335 ± 165g vs 448 ± 211g, $P < 0.001$). Among the 722 children born at term, 47 (6.5%) had a neonatal infection and 675 (93.5%) did not have a neonatal infection. The perinatal characteristics found to be more strongly associated with the presence of a neonatal infection in children born at term were maternal fever (OR 2.8, 95% CI 1.2 to 6.6), resuscitation at birth (OR 3.7, 95% CI 2.0 to 6.7), seizures in the first 72 hours (OR 3.2, 95% CI 1.7 to 5.9), low-moderate Apgar score at one minute (OR 2.1, 95% CI 1.2 to 3.9), and multisystem involvement (OR 7.0, 95% CI 3.6 to 13.6).

Table 4 outlines the phenotypic profile and neuroimaging of children by GA. Term-born children with a neonatal infection were more likely to have concomitant white matter and cortical injury (OR 4.1, 95% CI 1.6 to 10.3), spastic triplegia or quadriplegia (OR 2.4, 95% CI 1.3 to 4.3), and GMFCS levels IV and V (OR 2.6, 95% CI 1.4 to 4.8). Several comorbidities were also more common in this group

TABLE 2.
Phenotypic Profile and Neuroimaging of the Cohort

Characteristic, n (%)	Neonatal Systemic Infection (n = 192)	No Neonatal Systemic Infection (n = 1037)	Chi-Square *P* Value	Odds Ratio (95% CI)
Neurological subtype, n (%)	n = 190	n = 1026	$P < 0.002$*	
Spastic diplegia	54 (28.4)	202 (19.7)		1.6 (1.1-1.3)
Spastic hemiplegia	47 (24.7)	394 (38.4)		0.5 (0.4-0.8)
Spastic triplegia and quadriplegia	69 (36.6)	302 (29.4)		1.4 (1.0-1.9)
Ataxia and hypotonia	5 (2.6)	26 (2.5)		1.1 (0.4-2.8)
Dyskinetic	15 (7.9)	102 (9.9)		0.8 (0.5-1.5)
MRI	n = 126	n = 809	$P < 0.001$*	
Normal	9 (7.1)	90 (11.1)		0.6 (0.3-1.3)
Deep gray matter injury	4 (3.2)	28 (3.5)		1.0 (0.4-2.8)
White matter injury (bilateral)	59 (46.8)	232 (28.7)		2.2 (1.5-3.2)
Concomitant white matter and cortical injury	7 (5.6)	31 (3.8)		1.5 (0.7-3.5)
Near-total brain injury	14 (11.1)	92 (11.4)		1.0 (0.6-1.8)
Focal insult	19 (15.5)	222 (23.7)		0.5 (0.3-0.8)
Malformation	3 (2.4)	79 (9.8)		0.3 (0.1-0.8)
Other	11 (8.7)	54 (6.7)		—
GMFCS	n = 183	n = 998	0.073	
I-III	122 (66.7)	724 (73.2)		0.8 (0.5-1.0)
IV-V	61 (33.3)	267 (26.8)		1.4 (1.0-1.9)
Cortical visual impairment	n = 171	n = 943	0.827	
	31 (18.1)	164 (17.4)		1.1 (0.7-1.6)
Sensorineural auditory impairment	n = 180	n = 949	$P < 0.001$*	2.1 (1.4-3.3)
	31 (17.3)	85 (9.0)		
Communication difficulties	n = 174	n = 956	0.190	1.3 (0.9-1.8)
	124 (71.3)	632 (66.2)		
Communication skills	n = 173	n = 944	0.05	
Verbal and nonverbal	129 (74.6)	722 (76.5)		0.9 (0.6-1.3)
Nonverbal only	14 (8.1)	114 (12.1)		0.8 (0.4-1.2)
No communication	30 (17.3)	108 (11.4)		1.6 (1.1-2.5)
Epilepsy	n = 191	n = 1014	0.936	1.0 (0.7-1.4)
	74 (38.7)	397 (39.2)		

Abbreviations:
CI = Confidence interval
GMFCS = Gross Motor Function Classification System
MRI = Magnetic resonance imaging
* Significant after Bonferroni correction ($P < 0.003$).

TABLE 3.
Subgroup Analysis: Perinatal Characteristics

Characteristic, n (%)	n	Preterm (n = 505)				n	Term (n = 722)			
		Neonatal Systemic Infection	No Infection	*P* Value	Odds Ratio (95% CI)		Neonatal Systemic Infection	No Infection	*P* Value	Odds Ratio (95% CI)
Pre-eclampsia	472	16 (11.7)	35 (10.4)	0.696	1.2 (0.6-2.1)	677	3 (6.8)	23 (3.6)	0.288	2.2 (0.7-7.0)
Chorioamnionitis	399	44 (38.3)	56 (19.7)	<0.0001*	2.5 (1.6-4.0)	518	4 (12.9)	42 (8.6)	0.417	1.8 (0.6-5.2)
Prolonged rupture of membranes	491	30 (21.0)	69 (19.8)	0.773	1.1 (0.7-1.7)	691	4 (9.1)	40 (6.2)	0.445	1.7 (0.6-4.6)
Caesarean delivery	504	94 (64.8)	193 (53.8)	0.033	1.6 (1.1-2.4)	720	18 (38.3)	248 (36.8)	0.563	1.1 (0.6-2.0)
Maternal fever	405	16 (13.9)	31 (10.7)	0.361	1.4 (0.7-2.6)	614	7 (17.5)	42 (7.3)	0.022	2.8 (1.2-6.6)
Shoulder dystocia	275	3 (3.3)	2 (1.1)	0.204	2.8 (0.6-14.7)	354	2 (8.0)	32 (9.7)	0.778	1.0 (0.3-3.8)
Resuscitation at birth	501	115 (81.0)	206 (57.4)	<0.0001*	3.1 (2.0-5.0)	707	23 (48.9)	136 (20.6)	<0.0001*	3.7 (2.0-6.7)
Seizures in the first 72 hours	494	18 (12.8)	19 (5.4)	0.05	2.6 (1.3-5.0)	707	20 (44.4)	132 (19.9)	<0.0001*	3.2 (1.7-5.9)
Multisystem involvement	461	99 (73.9)	155 (47.4)	<0.0001*	3.1 (2.0-4.8)	694	28 (66.7)	142 (21.8)	<0.0001*	7.0 (3.6-13.6)
Apgar <7 at one minute	489	105 (73.9)	202 (58.2)	0.001*	2.0 (1.3-3.1)	689	21 (47.7)	194 (30.1)	0.014	2.1 (1.2-3.9)
Apgar <7 at five minutes	492	60 (41.7)	106 (30.5)	0.017	1.6 (1.1-2.4)	686	18 (40.9)	102 (15.9)	<0.0001*	3.6 (2.0-6.9)
Small for gestational age	501	17 (11.7)	42 (11.8)	0.982	1.0 (0.6-1.8)	703	12 (26.7)	114 (17.3)	0.114	1.8 (0.9-3.5)
Congenital microcephaly	380	3 (2.6)	8 (3.0)	*P* = 1.00	0.9 (0.3-3.3)	550	1 (3.3)	20 (3.8%)	*P* = 1.00	1.2 (0.2-6.8)
Umbilical cord pH < 7.00	369	7 (6.5)	21 (8.0)	0.628	0.8 (0.4-2.0)	495	8 (22.9)	46 (10.0)	0.019	2.8 (1.2-6.3)

Abbreviation:
CI = Confidence interval
* Significant after Bonferroni Correction ($P < 0.003$).

although not reaching significance with a Bonferroni correction: cortical visual impairment (OR 2.1, 95% CI 1.1 to 3.9), communication impairment (OR 2.5, 95% CI 1.1 to 5.6), and convulsions (OR 2.4, 95% CI 1.3 to 4.4).

There were no differences in perinatal characteristics or clinical profile identified between children with and without infection who were born very preterm. There were also no differences for moderate-to-late preterm children with and

TABLE 4.
Subanalysis by Gestational Age, Phenotypic Profile, and Neuroimaging

	Preterm (n = 505)				Term (n = 722)			
	Neonatal Infection	No Infection	*P* Value	Odds Ratio (95% CI)	Neonatal Infection	No Infection	*P* Value	Odds Ratio (95% CI)
Neurological subtype, n (%)	n = 143	n = 356	0.822		n = 47	n = 668	0.006*	
Spastic diplegia	47 (32.9)	131 (36.8)		0.8 (0.6-1.3)	7 (14.9)	71 (10.6)		1.5 (0.7-3.5)
Spastic hemiplegia	35 (24.5)	74 (20.8)		1.2 (0.8-2.0)	12 (25.5)	320 (47.9)		0.4 (0.2-0.7)
Spastic triplegia or quadriplegia	47 (32.9)	119 (33.4)		1.0 (0.7-1.5)	22 (46.8)	181 (27.1)		2.4 (1.3-4.3)
Ataxia or hypotonia	2 (1.4)	7 (2.0)		0.8 (0.2-3.5)	3 (6.4)	19 (2.8)		2.6 (0.8-8.5)
Dyskinetic	12 (8.4)	25 (7.0)		1.2 (0.6-2.5)	3 (6.4)	77 (11.5)		0.6 (0.2-1.8)
MRI, n (%)	n = 89	n = 236	0.404		n = 37	n = 571	0.003*	
Normal	7 (7.9)	24 (10.2)		0.8 (0.3-1.9)	2 (5.4)	66 (11.6)		0.5 (0.1-2.0)
Deep gray matter injury	1 (1.1)	6 (2.5)		0.6 (0.1-3.6)	3 (8.1	21 (3.7)		2.6 (0.8-8.5)
White matter injury (bilateral)	51 (57.3)	141 (59.7)		0.9 (0.6-1.5)	8 (21.6)	91 (15.9)		1.5 (0.7-3.4)
Concomitant white matter and cortical injury	1 (1.1)	4 (1.7)		0.9 (0.1-5.6)	6 (16.2)	27 (4.7)		4.1 (1.6-10.3)
Near-total brain injury	5 (5.6)	17 (7.2)		0.8 (0.3-2.2)	9 (24.3)	74 (13.0)		2.2 (1.0-4.8)
Focal insult	15 (16.9)	20 (8.5)		2.2 (1.1-4.5)	4 (10.8)	183 (32.0)		0.3 (0.1-0.8)
Malformation	1 (1.1)	8 (3.4)		0.5 (0.1-2.6)	2 (5.4)	71 (12.4)		0.5 (0.1-1.8)
Other	8 (9.0)	16 (6.8)		1.4 (0.6-3.3)	3 (8.1)	38 (6.7)		1.4 (0.5-4.4)
GMFCS n (%)	n = 138	n = 350	0.670		n = 45	n = 647	0.001*	
I-III	99 (71.7)	257 (73.6)		0.9 (0.6-1.4)	23 (51.1)	474 (73.3)		0.4 (0.2-0.7)
IV-V	39 (28.3)	92 (26.4)		1.1 (0.7-1.7)	22 (48.9)	173 (26.7)		2.6 (1.4-4.8)
Cortical visual impairment, n (%)	n = 125	n = 330	0.815		n = 46	n = 611		2.1 (1.1-3.9)
	16 (12.8)	45 (13.6)		1.0 (0.5-1.7)	15 (32.6)	117 (19.1)	0.029	
Sensorineural auditory impairment, n (%)	n = 135	n = 337	0.029		n = 44	n = 611	0.335	1.7 (0.7-4.4)
	26 (19.3)	39 (11.6)		1.8 (1.1-3.1)	5 (11.4)	45 (7.4)		
Communication difficulties	n = 131	n = 344	0.211	1.2 (0.8-1.8)	n = 43	n = 612	0.021	2.5 (1.1-5.6)
	87 (66.4)	207 (60.2)			37 (86.0)	425 (30.6)		
Communication skills, n (%)	n = 130	n = 343	0.020		n = 43	n = 599	0.015	
Verbal and nonverbal	105 (80.8)	285 (83.1)		0.8 (0.5-1.4)	24 (55.8)	437 (73.0)		0.5 (0.2-0.8)
Nonverbal only	8 (6.2)	37 (10.8)		0.6 (0.2-1.2)	6 (14.0)	77 (12.9)		1.2 (0.5-2.8)
No communication	17 (13.1)	21 (6.1)		2.3 (1.2-4.5)	13 (30.2)	85 (14.2)		2.7 (1.4-5.2)
Epilepsy, n (%)	n = 144	n = 353	0.267	1.3 (0.8-2.0)	n = 47	n = 659	0.05	
	42 (29.2)	86 (24.4)			32 (68.1)	309 (46.9)		2.4 (1.3-4.4)

Abbreviations:
CI = Confidence interval
GMFCS = Gross Motor Function Classification System
MRI = Magnetic resonance imaging
* Significant after Bonferroni Correction ($P < 0.006$).

without neonatal infection. Extremely preterm children with CP who had a neonatal infection were more likely to have convulsions within the first 72 hours of life (OR 14.9, 95% CI 2.3 to 91.0). Extremely preterm children with infection were also more likely to have epilepsy later on than extremely preterm children without infection (OR 5.0, 95% CI 1.6 to 14.9).

Discussion

Children with CP who had an antecedent neonatal infection were found, as hypothesized, to more commonly manifest WMI on neuroimaging. This finding is consistent with the prevailing hypothesis that immature (i.e., premyelinating) oligodendrocytes are specifically gestationally vulnerable to inflammation via free radical and cytokine toxicity.[10] Our findings are consistent with other studies showing similar proportions of neonatal infections among preterm infants.[8,15] As expected, children with CP having a neonatal infection were also found to more frequently have a bilateral spastic neurological subtype, and in particular spastic diplegia.[11] Regarding comorbidities, children with CP who had a neonatal infection were more likely to have sensorineural auditory impairment. Both bacterial meningitis and antibiotics are risk factors for sensorineural hearing loss.[16]

Subanalysis, stratified by GA, addressed the strong association between prematurity and neonatal infection. Surprisingly, neurological subtypes, MRI findings, and motor deficits (GMFCS) were distributed similarly between preterm-born children with CP with and without a neonatal infection. Spastic diplegia and WMI were the most common subtype and MRI finding, respectively, in both groups of preterm-born children. The only significant differences found between these two groups were in frequency of sensorineural hearing loss and lack of communication skills, with both being more frequent in those with neonatal infection. Neonatal infection and its treatment are associated with sensorineural hearing loss in preterm-born children.[17] Treatment with aminoglycosides, such as gentamicin, has potentially ototoxic effects, which can be minimized when used in short courses with close monitoring.[18] The near absence of phenotypic differences between preterm-born children with and without a neonatal infection suggests that neonatal infection, as a pathogenic factor, does not result in a specific clinical and imaging phenotype in the preterm population. In other words, different upstream CP pathways (hypoxic injury, inflammation, etc.) may lead to similar patterns of WMI and CP subtypes.[19] Both hypoxia-ischemia and inflammation have been shown to disrupt the normal development of oligodendrocytes and white matter.[20,21] The limited imaging description available in our registry could miss potential differences in severity of injury between the two groups.

Interestingly, a different trend was observed among the term-born children with CP. Those with a neonatal infection had a more severe phenotypic profile and significantly more comorbidities than those without. Indeed, the term-born children with CP with a neonatal infection were found to more frequently have a white matter or near-total brain injury, a bilateral spastic neurological subtype, and nonambulation gross motor functional capability. Maternal fever was also more common in the group with neonatal infection, suggesting that, in some instances, the neonatal infection may have had prenatal origins. These results are consistent with current studies supporting the hypothesis that preoligodendrocytes are preferentially targeted by the inflammatory response and that the resulting WMI usually involves corticospinal tract axons.[10,11] Another cohort from Sweden has similarly found that neonatal infection was independently significantly associated with an increased risk of later spastic diplegia and quadriplegia.[22] This finding supports the notion that there are more potential causal pathways to CP in the term population than in the preterm population, leading to a wider variety of distinct phenotypic profiles, each dependent on the underlying sentinel or inciting event.[23] Term neonates have a more mature immune system than preterm neonates, which makes them more likely to mount an increasingly specific inflammatory response in the presence of an infectious agent.[24] This finding could also contribute to the phenotypic discrepancy observed between term-born children with and without an antecedent neonatal infection.

The strengths of the CCPR include its enrollment of children with CP in a geographically defined population, well-defined study groups, the use of standardized motor function classifications, and systematically reviewed phenotypic outcome variables. A potential limitation of the present study is the small percentage of registered children with CP who were excluded because of uncertainty regarding the presence or the absence of a neonatal infection. The absence of meningitis variables and the lack of information regarding the causative infectious organisms are additional limitations. Children with an antecedent neonatal infection are indeed being discussed as a group, but are in fact a quite heterogeneous one. Specifically, neonates with a central nervous system infection might differ from those with other systemic infections. Finally, another important limitation of the present study is our reliance on descriptive MRI findings, rather than a systematic review of the original neuroimaging studies by blinded experts, which could also miss differences in severity within each imaging pattern.

Conclusions

Knowledge of the most common neurological subtypes, the degree of motor deficit severity, and the most frequently observed comorbidities associated with neonatal infections will allow physicians to better discuss prognosis with families. Furthermore, the present study contributes to the expanding body of evidence suggesting that systemic infections and inflammation can promote injury to the term-born infant's developing brain.[25] Finally, given the findings that term-born children with CP with an antecedent neonatal infection are more likely to have a more severe phenotypic presentation, the present study highlights the need to improve upon strategies to mitigate the risk of neonatal infection.

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Supplementary data

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