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Prospective Evaluation of Perinatal Risk Factors for Cerebral Palsy and Delayed Development in High Risk Infants

Jeong Nyun Kim[3], Ran Namgung[1], Wook Chang[1], Chang Hee Oh[1], Ji Chul Shin[2], Eun Sook Park[2], Chang Il Park[2], Min Soo Park[1], Kook In Park[1], Chul Lee[1], and Dong Gwan Han[1]

Abstract

Prematurity, intrauterine infection and perinatal brain injury have been reported to be significant risk factors of cerebral palsy (CP). We examined the perinatal predictors of cerebral palsy and delayed development (DD) in 184 high risk infants. Thirty-five infants were diagnosed as cerebral palsy and delayed development at 12 months corrected age. Antenatal, intrapartum, and neonatal factors were prospectively evaluated in 2 groups of high risk infants compared with controls; Group A (n=79), infants weighing less than 2,000 g; Group B (n=43), infants weighing 2,000 g or more. In univariate analysis, there were no significant antenatal and intrapartum factors associated with cerebral palsy and delayed development in either group. We found that significant postnatal risk factors of CP in group A included sepsis (p=0.008), BPD (bronchopulmonary dysplasia) (p=0.028), IVH (intraventricular hemorrhage) (p=0.042), ventriculomegaly (VM) (p=0.001) and a longer duration of mechanical ventilation (p=0.001); while in group B, sepsis (p=0.047) and neonatal seizure (p=0.027) were significant risk factors. In multivariate analysis, sepsis in group B was a moderate risk factor of CP (OR (odds ratio) 1.47; 95% CI (confidence interval) 1.02−2.13). In conclusion, neonatal sepsis may contribute to the development of cerebral palsy and delayed development. We suggest that high risk infants who have sepsis should be carefully followed for cerebral palsy and delayed development. The prevention of cerebral palsy may be feasible by decreasing neonatal risk factors such as sepsis during the neonatal period.

Key Words: Cerebral palsy, delayed development, risk factors, neonatal sepsis

INTRODUCTION

Improved survival of high risk neonates in recent years has been accompanied by an increased incidence of cerebral palsy (CP).[1] The etiology of CP is still poorly understood. Recent evidence suggests that antenatal rather than intrapartum factors are the major determinants of CP among term infants.[2] In preterm infants, both antenatal variables and neonatal complications have been associated with neurologic impairment.[3] Investigations of the etiology of CP have shown that many adverse processes leading to CP, but which were not direct causes of it, have however been identified as causes in case-control studies. Recent reports have shown that the emphasis has shifted from neonatal to antenatal events. Antenatal factors such as maternal chorioamnionitis and prolonged rupture of membrane were reported to be significant risk factors of CP.[4] Nelson et al. showed that a decrease in CP was associated with antenatal magnesium sulfate therapy in maternal preeclampsia, reflecting a neuroprotective effect of magnesium.[5] Others reported that neonatal risk factors such as severe cranial ultrasound abnormalities and sepsis may play an important role in the development of CP.[6,7]

We previously found that periventricular leukomalacia was a significant risk factor of CP and delayed development (DD) in very low birth weight infants.[8] We also found that significant risk factors of CP and DD in term infants were the number of abortions, neonatal seizure and hypoxic ischemic encephalopathy.[9] To investigate this further, we carried out a prospective cohort study in 2 groups, one with a birth

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Departments of [1]Pediatrics, [2]Rehabilitation Medicine, Yonsei University College of Medicine, and [3]Department of Pediatrics, Inje University College of Medicine, Sanggye Paik Hospital, Seoul, Korea.

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Address reprint request to Dr. R. Namgung, Department of Pediatrics, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea. Tel: 82-2-361-5525, Fax: 82-2-393-9118, E-mail: ranng@yumc.yonsei.ac.kr

weight of less than 2,000 g and one with a birth weight 2,000 g or more.

MATERIALS AND METHODS

One hundred and eighty-four high risk infants who were born at Yonsei Medical Center from July 1996 to November 1997 were recruited. Among them, 122 infants (66%) were examined at 2, 6, and 12 months corrected age. Subjects were divided into 2 groups according to the birth weight; infants weighing less than 2,000 g (Group A, n=79) and infants weighing 2,000 g or more (Group B, n=43).

Entry criteria were as follows: preterm (gestational age less than 37 weeks) infants and term infants with an Apgar score of less than 6 at 5 minutes, neonatal hyperbilirubinemia (total bilirubin concentration of 20 mg/dl or more) and bacterial meningitis. Infants with chromosomal abnormalities and congenital malformation were excluded. After discharge from the Neonatal Intensive Care Unit, infants were followed up at the Department of Rehabilitation Medicine and examined periodically for possible neurologic defect or delayed development up to 12 months corrected age.

CP was defined as non-progressive, often changing motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development.[10] DD was defined as a delay in parameters for motor development of more than two months according to the stages of motor development by Vojta.[11] Diagnosis of CP or DD was made by a physiatrist.

The antenatal, intrapartum and postnatal risk factors examined were as follows: Antenatal and intrapartum factors included the numbers of gestation (G), parity (P), live birth (L), death (D), abortion (A), presence of pregnancy-induced hypertension (PIH), mothers who were treated with magnesium sulfate and tocolytics, Cesarean section, fetal distress, difficult delivery, chorioamnionitis, premature rupture of membrane (PROM), abruptio placenta, placenta previa, antepartum hemorrhage, diabetes mellitus, chronic hypertension, thyroid disease and abnormal presentation at delivery.

Fetal distress included persistent fetal tachycardia, bradycardia, late fetal heart rate deceleration, poor fetal heart rate variability on fetal monitoring, or a cord blood pH of less than 7.2. PIH was defined as blood pressure $\geq$140/90 mmHg during the second half of pregnancy in a previously normotensive mother. PROM was defined as rupture of membranes that occurred more than 18 hours before delivery. Criteria for the diagnosis of clinical chorioamnionitis was PROM with fever, leukocytosis and maternal or fetal tachycardia.

Postnatal factors included Apgar score, appropriateness of gestation, resuscitation at birth with positive pressure ventilation or ventilator care, hyperbilirubinemia, sepsis, meningitis, neonatal seizure, congenital anomaly, bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), duration of mechanical ventilation and severe cranial ultrasound abnormalities such as intraventricular hemorrhage (IVH) graded as described by Papile et al.,[12] ventriculomegaly (VM), and periventricular leukomalacia (PVL).

Sepsis was defined as at least one positive blood culture accompanied by clinical signs suggestive of infection. BPD was defined as an oxygen dependence at postnatal 28 days.[13] Air leak was defined as an extrapulmonary extravasation of air like pneumothorax, pneumomediastinum and pulmonary interstitial emphysema. The diagnosis of PDA was based on clinical and echocardiographic findings. PVL was defined as lesions characterized by foci of coagulation necrosis in the white matter near the lateral ventricle seen on at least 2 occasions in serial cranial ultrasonography.

We analyzed data using SPSS (Ver 7.0) for Windows program. On univariate analysis, we used Fisher's exact test for categorical variables like sepsis and Wilcoxon rank sum test for continuous variables such as Apgar score. We regarded $p<0.05$ as significant. Multiple logistic regression was conducted to test the independent effects of perinatal and postnatal factors; due to the small sample size, we restricted the models to include only those variables with univariate association of $p<0.10$. As a consequence of the small number of cases with cerebral palsy and controls in groups, multiple analyses were not conducted for these subgroups.

RESULTS

Among 122 infants, CP was diagnosed in 12 infants (9 in Group A and 3 in Group B). The type of CP was 11 spastic diplegia and 1 quadriplegia. DD was diagnosed in 23 infants (8 in Group A and 15

Table 1. Subject Characteristics

Group A (birth weight <2,000 g)	CP (n=9)	DD (n=8)	CP/DD (n=17)	Controls (n=62)
Gestational age (wks)	29.6±2.7	32.3±3.8	30.8±3.5	31.4±2.2
Birth weight (g)	1333±421	1480±272	1557±252	1418±376
Male : Female	5 : 4	3 : 5	8 : 9	32 : 30
Multiple pregnancy	0	7	7	2
Group B (birth weight ≥2,000 gm)	**CP (n=3)**	**DD (n=15)**	**CP/DD (n=18)**	**Controls (n=25)**
Gestational age (wks)	37.7±2.5	36.9±2.2	37.0±2.2*	35.0±2.4
Birth weight (g)	2943±487	2504±397	2577±397	2485±495
Male : Female	2 : 1	4 : 11	6 : 12	14 : 11
Multiple pregnancy	0	0	0	4

Values are mean±SD; Number of cases for gender and multiple pregnancy.
CP, cerebral palsy; DD, delayed development.
*$p<0.05$ compared to control.

Table 2. Obstetric and Intrapartum Risk Factors in Infants Weighing Less Than 2,000 g (Group A)

	CP (n=9)	DD (n=8)	CP/DD (n=17)	Controls (n=62)
Previous obstetric history				
Chronic hypertension	2	1	3	4
Thyroid disease	0	0	0	4
Diabetes mellitus	0	0	0	1
Present obstetric history				
PIH	0	1	1	14
Chorioamnionitis/PROM	3	3	6	11
Gravida (G)	2.1±1.1	2.1±1.6	2.3±1.6	2.5±1.6
Para (P)	0.7±0.8	0.6±0.5	0.7±0.6	0.8±0.7
Live birth (L)	0.6±0.8	0.5±0.5	0.6±0.6	0.8±0.7
Dead (D)	0.2±0.4	0.3±0.5	0.1±0.3	0
Abortion (A)	0.3±0.6	0.5±1.4	0.7±1.4	0.9±1.4
Antepartum hemorrhage	0	0	0	1
Abruptio placenta	1	1	2	1
Placenta previa	0	2	2	5
Medications given to mother				
Magnesium sulfate therapy	1	1	2	11
Tocolytic therapy	2	1	3	1
Antenatal steroid	1	2	3	15
Intrapartum				
Cesarean section	6	7	13	47
Fetal distress	0	2	2	7
Difficult delivery	0	0	0	1
Breech presentation	1	1	2	4

Values are mean±SD for G, P, L, D, A; Number of cases for others.
No significant differences between groups for all risk factors.

in Group B). Sixty-two infants in group A and 25 infants in group B were selected as controls. The number of control infants in group B were relatively small due to the high drop-out rates on follow-up in this population. The total subjects with CP/DD (17 in group A and 18 in group B), and the subgroup CP and the subgroup DD in group A or group B were compared to their respective controls (62 in group A and 25 in group B) for each of the obstetric, intrapartum and postnatal factors.

In group A, gestational age and birth weight were similar. In group B, gestational age of CP/DD was significantly greater than control ($p<0.05$), but birth weight was not different in both subgroups. Gender distribution and multiple pregnancy were similar in both groups and subgroups (Table 1).

Table 2 gives a description of selected past and present obstetric history, medications given to the mother antenatally, and intrapartum and delivery risk factors in group A. A low incidence of diabetes mellitus, chronic hypertension and thyroid disease were noted in both groups. There were no significant differences between groups in the rates of PIH, chorioamnionitis and PROM, numbers of G, P, L, D, A, antepartum hemorrhage, abruptio placenta and placenta previa. Magnesium sulfate given to mothers was found in 11 cases in control, but in only one case each in CP and CP/DD groups, respectively. Rates of intrapartum risk factors such as Cesarean section, fetal distress, difficult delivery and abnormal presentation at delivery were not different in both groups.

Table 3 presents a description of the postnatal risk factors in group B. When compared to their controls, infants with CP had significantly higher rates of sepsis, BPD, IVH, VM and a longer duration of mechanical ventilation. The CP/DD group differed significantly from controls in the above risk factors, excluding VM.

Table 4 presents a description of antenatal and intrapartum factors in group B. There were no significant differences in antenatal factors between CP/DD and controls. Table 5 presents postnatal risk factors in group B. Rates of sepsis were significantly higher in the DD and CP/DD groups than in controls. Rates of neonatal seizure were significantly higher in the CP and CP/DD groups than in controls. Rates of IVH (Grade $\geq$ II) and VM were greater in the CP group than in the control group, but not for those of IVH

Table 3. Postnatal Risk Factors in Infants Weighing Less Than 2,000 g (Group A)

	CP (n=9)	DD (n=8)	CP/DD (n=17)	Controls (n=62)
Apgar score at 1 min	3.3±2.7	4.1±2.6	3.7±2.6	4.9±1.9
5 min	4.8±2.7†	6.1±2.1	5.4±2.5†	6.7±1.6
SGA	2	1	3	8
Resuscitation at birth	6	3	9	26
Neonatal hyperbilirubinemia	1	3	4	12
Sepsis	4*	1	5*	4
CRP at birth (mg/dl)	0.4±0.3	0.3±0.3	0.3±0.2	0.2±0.2
Neonatal seizure	1	1	2	2
BPD	4*	3*	7*	9
Air leak	1	1	2	4
PDA	2	3	5†	6
Days on ventilator	18.1±25.1*	11.3±8.7*	12.2±19.6*	3.3±3.3
Cranial ultrasound abnormalities				
IVH (G≥II)	4*	1	5*	6
IVH (G≥III)	2	0	2	3
VM	5*	0	5	8
PVL	1	0	1	1

SGA, small for gestational age infants; CRP, C-reactive protein; BPD, bronchopulmonary dysplasia; PDA, patent ductus arteriosus; IVH, intraventricular hemorrhage graded by Papile et al.[12]; VM, ventriculomegaly; PVL, periventricular leukomalacia.
Values are mean±SD for Apgar score, CRP at birth and days on ventilator; Number of cases for others.
* $p<0.05$ compared to control.
† $p<0.10$ compared to control.

Table 4. Antenatal Risk Factors in Infants Weighing 2,000 g or More (Group B)

	CP (n=3)	DD (n=15)	CP/DD (n=18)	Controls (n=25)
Previous obstetric history				
Chronic hypertension	0	1	1	3
Thyroid disease	0	0	0	1
Diabetes mellitus	0	0	0	1
Present obstetric history				
PIH	1	0	1	1
Chorioamnionitis/PROM	1	3	4	4
Gravida (G)	2.3±1.2	2.4±1.4	2.4±1.3	2.3±1.3
Para (P)	0.7±1.2	0.7±0.7	0.7±0.8	1.5±1.0
Live birth (L)	0.3±0.6	0.5±0.6	0.5±0.6	0.8±0.7
Dead (D)	0.7±1.2	0.3±0.8	0.3±0.8	0.1±0.3
Abortion (A)	0	0.5±0.7	0.6±0.8	0.6±0.7
Antepartum hemorrhage	0	0	0	0
Abruptio placenta	0	0	0	2
Placenta previa	0	1	1	2
Medications given to mother				
Magnesium sulfate therapy	0	1	1	3
Tocolytic therapy	0	1	1	2
Antenatal steroid	0	0	0	0
Intrapartum				
Cesarean section	2	9	11	18
Fetal distress	1	1	2	2
Difficult delivery	0	0	0	0
Breech presentation	0	0	0	1

Values are mean±SD for G, P, L, D, A; Number of cases for others.
No significant differences between groups for all risk factors.

Table 5. Postnatal Risk Factors in Infants Weighing 2,000 g or More (Group B)

	CP (n=3)	DD (n=15)	CP/DD (n=18)	Controls (n=25)
Apgar score at 1 min	4.0±2.6	6.5±1.5	6.1±1.9	5.7±2.3
5 min	4.7±3.1	7.9±1.1	7.3±1.9	7.5±1.4
SGA	0	2	2	3
Resuscitation at birth	1	4	5	2
Neonatal hyperbilirubinemia	1	4	5	8
Sepsis	1	4*	5*	1
CRP at birth (mg/dl)	0.4±0.3	0.4±0.2	0.4±0.3	0.3±0.3
Neonatal seizure	2*	2	4*	0
Days on ventilator	5.7±4.9	0.9±2.5	1.7±3.4	1.3±2.5
Cranial ultrasound abnormalities				
IVH (G≥II)	2*	0	2	0
Ventriculomegaly	2*	1	3†	0
PVL	1	0	1	0

SGA, small for gestational age infants; CRP, C-reactive protein; IVH, intraventricular hemorrhage graded by Papile et al.[12]; PVL, periventricular leukomalacia.
Values are mean±SD for Apgar score, CRP at birth and days on ventilator; Number of cases for others.
* $p<0.05$ compared to control.
† $p<0.10$ compared to control.

Table 6. Multivariate Logistic Regression Analysis of Risk Factors of CP/DD in Groups A and B*

	Beta	SE	Odd ratio	95% CI	p
Group A (birth weight <2,000 g)					
Apgar score at 5 min	−0.02	0.03	0.85	0.47−1.04	0.57
BPD	0.12	0.14	1.12	0.85−1.50	0.41
IVH	0.13	0.16	1.13	0.73−1.39	0.94
PDA	0.16	0.15	1.17	0.86−1.58	0.30
Sepsis	0.25	0.17	1.28	0.91−1.81	0.14
Duration of mechanical ventilation	0.03	0.06	1.00	0.99−1.01	0.54
Group B (birth weight ≥2,000 g)					
Gestational age	0.01	0.02	1.00	0.75−1.05	0.66
Resuscitation at birth	0.02	0.15	1.02	0.76−1.05	0.89
Neonatal seizure	0.21	0.24	1.23	0.77−1.98	0.37
Sepsis*	0.39	0.19	1.47	1.02−2.13	0.04
Ventriculomegaly	0.24	0.18	1.27	0.25−1.83	0.19

SE, standard error; CI, confidence interval.
*Risk factors from the univariates analysis which had a p values less than 0.1 were included in the multivariate logistic regression model.
*$p<0.05$ compared to control.

(Grade≥III).

Table 6 presents the results of multiple logistic regression analyses. In group A, there were no significant risk factors among 6 variables. Among 5 factors selected from univariate analysis in group B, sepsis was statistically significant ($p=0.04$); and subjects with septicemia was 1.5 times more likely to be cerebral palsy or delayed development than controls (OR 1.47; 95% CI 1.02−2.13).

DISCUSSION

In this study, we found that the significant risk factors of CP in infants whose birth weight was less than 2,000 g were sepsis, BPD, IVH, ventriculomegaly and a longer duration of mechanical ventilation by univariate analysis; and that significant risk factors for infants with a birth weight of 2,000 g or more included sepsis and neonatal seizure by univariate analysis. Multivariate analysis showed that sepsis in the group with a birth weight of 2,000 g or more had a moderate risk for CP.

Preterm infants have a higher incidence of CP than term infants. The etiologies underlying the development of CP may be different between preterm and term infants. In preterm infants, in utero ischemic insult that leads to both preterm birth and white matter damage is thought to be a major risk factor for CP. Accordingly, we analyzed the risk factors in 2 different populations according to birth weight.

We previously found that chorioamnionitis was a significant risk factor of cerebral palsy in very low birth weight infants,[8] which was consistent with the results of another study.[4] Yoon et al. demonstrated that elevated proinflammatory cytokine levels in amniotic fluid before delivery was correlated with the subsequent development of CP at 3 years of age.[14] However in this study, chorioamnionitis/PROM occurred in only 33% of CP, 35% of CP/DD and in 18% of controls, demonstrating no significant differnece between groups.

The effects of antenatal magnesium sulfate therapy in preventing CP are controversial. Some authors have reported lower rates of CP among VLBW infants born to mothers with PIH, especially those with in utero exposure to magnesium sulfate.[5,15] These results are supported by other reports of a decrease in mortality,[16] periventricular hemorrhage[17] and CP associated with antenatal magnesium sulfate therapy. However, in this study, we did not find magnesium to be neuroprotective, which was consistent with the find-

ings of others.[18,19]

Mechanical ventilation in preterm infants was reported to be associated with the increased incidence of CP.[20] Hypocarbia during mechanical ventilation may lead to PVL and subsequently to CP.[21] In this study, we found that the duration of mechanical ventilation was significantly longer in the CP group than in the control group. Possible associations of hypocarbia and CP were not examined in this study.

BPD has been reported to be a risk factor of CP. The mechanism as to the linkage of BPD to CP is unclear. O'Shea et al. reported that BPD was an independent risk factor for CP in very preterm infants without cranial ultrasound abnormalities.[22] Yoon et al. reported that elevated proinflammatory cytokine levels in amniotic fluid before delivery were associated with BPD and PVL, and subsequently with CP.[23,24] However, we could not find any link between BPD and CP in this study.

Several authors have reported an association between neonatal sepsis and cerebral palsy.[6,7] In this study, sepsis was a significant risk factor in groups A and B in univariate analysis, and in group B in multivariate analysis. Nelson et al.[25] recently reported that neonates with high postnatal blood levels of various cytokines, particularly interferons,[26] subsequently developed CP, indicating that inflammation during the neonatal period is important regarding the etiology of CP. Although the mechanism of neonatal sepsis leading to CP is not clear, CP may be associated with postnatal events like neonatal sepsis during the newborn period. Since the prevention of chorioamnionitis may not be feasible in the near future, efforts to decrease the incidence of CP have been made possible by decreasing the neonatal risk factors associated with CP.

Cranial ultrasound abnormalities are an important risk factor for CP. In previous studies, infants with severe IVH of Grade II or more developed neurologic disabilities in 60−75% of cases.[27,28] Pinto-Martin et al. reported that severe IVH in VLBW infants can predict disabling CP by multivariate logistic regression analysis.[29] In previous reports and in this study, IVH was a significant risk factor in univariate analysis, but not in multivariate analysis.

PVL is the infarction of periventricular white matter. Studies have shown that PVL is the most important cause of CP in very low birth weight infants.[8,29,30] In this study, PVL was detected in only one case each in the CP and control groups, respectively. Some cases were lost to follow-up. Premature infants with VM have an increased risk of cerebral palsy. The incidence of VM was higher in infants with CP in this study. Of note, since preterm infants who died with unexplained VM have early histologic evidence of PVL,[31,32] it is possible that some infants with VM in whom CP subsequently developed will have PVL below the detection level of cranial ultrasonography. This theory is supported by the findings that MRI (magnetic resonance imaging) study can detect PVL in infants with VM.[33] As MRI was not routinely performed in our study, we could not rule out this possibility.

Recurrent neonatal seizure was reported to be a sensitve predictor for the development of CP.[34,35] However, the incidence of CP was not greater in patients with a longer duration of seizure than in those with a shorter duration of seizure,[36] implying that neonatal seizure is not the cause but could be the process leading to CP. In this study, neonatal seizure was significantly associated with CP and CP/DD in group B only in univariate analysis. Others have reported that cord blood pH may or may not be associated with the development of CP.[37,38] In this study, we were unable to analyze cord blood pH as a risk factor, since cord blood pH was not measured in all subjects.

In conclusion, neonatal sepsis contributes to the development of cerebral palsy and delayed development. We suggest that high risk infants who have sepsis should be carefully followed for cerebral palsy and delayed development. The prevention of cerebral palsy may be feasible by decreasing neonatal risk factors such as sepsis during the neonatal period.

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