Original Article

Antenatal and Intrapartum Risk Factors for Cerebral Palsy in Term and Near-term Newborns

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Abstract

Background: Cerebral palsy (CP) is one of the main disabilities in term-born infants. This study attempts to investigate the maternal and neonatal factors associated with CP.

Methods: This case-control study consisted of singleton term and near-term (36 or more weeks of gestation) newborns in Tehran healthcare centers and was conducted over a 24-month period. Logistic regression analysis analyzed the data with SPSS 16.0.

Results: During the study period there were 53 infants in the case group and 106 in the control group. The main factors associated with CP were perinatal asphyxia [odds ratio (OR): 97.72; CI: 21.2–450.07], maternal age >35 years (OR: 20.89; CI: 1.05–412.62), and high risk pregnancy (OR: 0.2; CI: 0.04–0.932).

Conclusions: Several maternal, antenatal and intrapartum factors increase the risk for CP. Identifying and avoiding risks for CP may lead to lower infant neurologic morbidity.

Keywords: Asphyxia, cerebral palsy, infant

Introduction

Cerebral palsy (CP), a nonprogressive condition affecting approximately 3 in 1000 newborns, is characterized by acquired brain damage which affects motor and cognitive functions.[1–5] Perinatal asphyxia has long been believed to be a major cause of CP. Advances in perinatal care have led to decreased mortality rates among newborns. However, recent epidemiologic assessments indicate that the incidence of CP is stable or increasing in some industrialized countries.

The pathology of CP in term newborns is very different from preterm infants. Brain maldevelopments are seen in 16% of term and 2.5% of preterm infants with CP and gray matter lesions are more often seen in term (33%) than preterm (3.5%) CP infants. However periventricular white matter lesions occur significantly more often in preterm (90%) than in term (20%) infants.[6]

Neonatal encephalopathy (NE) in the term newborn is a clinical syndrome of disturbed neurologic function that presents in early life and occurs in 1−6 per 1000 live term births.[7] NE secondary to hypoxia-ischemia is the most common etiology of this condition in term newborns and is a major cause of morbidity and mortality.[7,8] As many as 20% of affected infants with NE die during the neonatal period, whereas permanent neurodevelopmental disability will be seen in 25% of the surviving children.[9]

Early brain injury in CP frequently results life-long disability, with serious adverse effects and implications for the child, family, and society.[10] In the absence of a known pathophysiological mechanism, only supportive care is provided; there is no evidence for the effectiveness of preventive strategies. Even if the pathology of NE is well-recognized, numerous questions remain regarding the causes and risk factors for pre-, peri-, and postnatal predictors of outcome.

Because risk factors for CP in term infants differ from premature infants[11] and in order to conduct preventive measures, it is necessary that the risk factors, etiology and the pathophysiology of the insult in this group be determined. However, controversy exists regarding many of these risk factors. This study aims to determine the maternal and neonatal factors associated with term infants diagnosed with CP born in Tehran, Iran.

Materials and Methods

This case-control study was conducted on all singleton term and near-term (36 or more weeks gestation) infants in Tehran, from March 2008 to February 2010. The study was carried out on 53 children with documented CP (case group) and 106 (control group) apparently healthy children without CP who had no overt abnormalities such as congenital anomalies, or chromosomal, metabolic and neurodegenerative disorders. The control group comprised infants who presented to the clinics for their well-child check-ups. All children diagnosed with CP were evaluated by a single pediatrician.

We defined CP as a nonprogressive congenital motor dysfunction with examination findings of increased tone (spasticity, rigidity, and dystonia) or choreoathetosis. The following inclusion criteria were used for patient selection: (1) singleton term and near-term newborns, (2) presence of detailed pre-, peri- and postnatal history and (3) neonatal hospitalization. Exclusion criteria were: (1) prematurity (<36 weeks gestational age), (2) postnatal central nervous system insult (infectious or trauma) that occurred after one week of age, or a neurological condition not typically considered to be CP, such as a myopathy or neural tube defect, (3)

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metabolic or genetic disorders, (4) patients whose parents did not provide informed consent, or (5) TORCH etiology.

Information was obtained by one general physician and based on a thorough evaluation of the children's medical and health records and statements by their mothers that included pre- and perinatal histories. Demographic data that consisted of maternal age, plurality (singleton or multiple gestations), parity, sex, gestational age at birth, head circumferences, and birth weight were obtained from birth certificates.

Maternal age was categorized as <18 years, 18–35 years, and >35 years. Term and near term delivery was defined as delivery ≥36 completed weeks of gestation. Gestational age duration was estimated according to last menstrual period. For detection of intrauterine growth restriction (IUGR), we used the Colorado Intrauterine Chart. Disturbances of respiration in the immediate postnatal period that originated in utero, in the delivery room, or the nursery were defined as respiratory distress. Parity was dichotomized as primiparous or multiparous. Maternal and pregnancy variables of interest included complications during pregnancy such as one or more of the following risk conditions: uterine bleeding, prolonged rupture of membranes (24 hr or more), poly-oligohydraminios, acute medical or surgical illness, medication during pregnancy, infections, uterine or cervical anomalies, pre-eclampsia or eclampsia, and diabetes mellitus.

There was a special emphasis on the mother's personal and obstetric history, in particular any previous spontaneous fetal death, neonatal death, congenital malformation, cervical incompetency, miscarriage or delivery of a premature or low birth weight infant. The same features and their clinical course were recorded for the current pregnancy. Mode of delivery was categorized into three groups: routine vaginal, operative vaginal (using vacuum or forceps), and cesarean section. The term neonatal or perinatal asphyxia was used when one of the following features was present: meconium-stained amniotic fluid, Apgar score (≤5) at 5 min or beyond, need for emergency cesarean section or for resuscitation after birth, and neonatal convulsion due to hypoxic ischemic encephalopathy.

Neonatal convulsion in this study was defined as a convulsion during the neonatal period based on clinical diagnosis of a physician that occurred at least once and in the absence of metabolic disorders such as hypoglycemia or hypocalcemia, with no need for long-term treatment by any anti-epileptic medications, and converted to a normal EEG after 2–3 months of treatment.

Early onset neonatal sepsis was defined as a positive blood culture during the first week of life with any organism known to cause neonatal sepsis or clinical suspicion of sepsis. Parental consanguinity indicated first or second degree relation of parents.

Statistical analysis included the student t-test of means (for quantitative data) and Chi-square test (for qualitative data). A P-value of less than 0.05 was selected a priori as statistically significant. Multiple logistic regressions were performed to examine the effect of the independent risk factors associated with CP. All statistical analyses were performed using SPSS 16.0. Informed consent was obtained from all parents whose children were studied, and the research was approved by the Ethics Committee of the University of Social Welfare and Rehabilitation Sciences.

Results

We evaluated 114 infants for participation in the case group. After taking into consideration the inclusion and exclusion criteria, 53 children met the eligibility requirements for the case group. The reasons for exclusion were: prematurity <36 weeks (28), neonatal meningitis (2), postneonatal meningitis (4), and metabolic disorders (22). In this study, 159 cases fulfilled all the inclusion and exclusion criteria, 53 (43%) in the case group and 106 (56.2%) in the control group ($P = 0.08$). The mean age of the case group was 33 months; the mean age of the control group was 21 months. Mean head circumferences at birth in the two groups were 34.25 ± 1.99 cm in the case and 34.55 ± 1.76 cm in the control groups ($P = 0.44$). The mean weight at birth was 2984 g in the case group and 3076 g in the control group ($P = 0.35$). In terms

Table 1. Frequency and odds ratio for antenatal, intrapartum, and infant characteristics among newborns of ≥36 weeks gestational age with cerebral palsy (CP) vs. the control group.

Characteristics	Cerebral palsy, % (n = 53)	No cerebral palsy, % (n = 106)	P-value	Odds ratio (95% CI)
IUGR [a]	12 (23)	10 (9.4)	0.02	2.81 (1.12–7.01)
LBW [b]	14 (26)	18 (17)	0.12	1.75 (0.79–3.88)
Perinatal asphyxia [c]	38 (66)	12 (11)	< 0.001	58.27 (19.2–170.7)
Neonatal sepsis	8 (15)	5 (4)	0.03	3.59 (1.11–11.58)
Male sex	23 (43)	59 (56)	0.09	0.59 (0.30–1.16)
Neonatal respiratory distress	8 (15)	5 (5)	0.03	3.59 (1.11–11.58)
Mother age > 35 yrs [d]	2 (5)	2 (2)	0.35	2.34 (0.32–17.19)
Mother age < 18 yrs [d]	3 (6.7)	7 (7)	0.62	1.003 (0.25–4.07)
Parity [e]	24 (45)	49 (46)	0.90	0.96 (0.49–1.87)
Miscarriage	10 (19)	17 (16)	0.65	1.22 (0.51–2.89)
Previous high risk pregnancy	11 (20)	18 (17)	0.33	1.31 (0.56–3.02)
Current high risk pregnancy	13 (25)	33 (32)	0.20	0.67 (0.32–1.42)
Mother history of chronic disease	9 (17)	19 (18)	0.53	0.93 (0.39–2.24)
Parental consanguinity	22 (41)	39 (37)	0.34	1.21 (0.62–2.39)
Not NVD [f]	33 (62)	61 (57)	0.34	1.27 (0.62–2.39)
Hyperbilirubinemia [g]	9 (17)	20 (19)	0.47	0.88 (0.37–2.09)

[a] Intrauterine growth restriction, [b]Low birth weight, [c] Perinatal asphyxia was considered when one of the following features was present: Meconium-stained amniotic fluid, Apgar score (<5) at 5 min or beyond, need for emergency cesarean section or resuscitation after birth and neonatal convulsion, [d]In comparison with 18 to 35 years, [e]Primiparous to multiparous, [f]Normal vaginal delivery (cesarean, instrument delivery), [g]Hyperbilirubinemia leading to exchange transfusion or phototherapy.

Table 2. Independent risk factors for cerebral palsy (CP).

Characteristics	P-value	Odds ratio	95% CI
Perinatal asphyxia [a]	< 0.001	97.72	21.21–450.07
Mother age >35 years [b]	0.046	20.89	1.05–412.62
High risk pregnancy	0.04	0.2	0.04–0.93

[a]Perinatal asphyxia was considered when one of the following features was present: Meconium-stained amniotic fluid, Apgar score (<5) at 5 min or beyond, need for emergency cesarean section or resuscitation after birth and neonatal convulsion, [b]In comparison with 18 to 35 years.

of maternal age at pregnancy there were 6.6% of mothers under the age of 18 years, 90.8% in the 18–35 year age group, and 2.6% who were over the age of 35 years.

Table 1 shows the frequency, *P*-value and odds ratio (OR) for characteristics of infants with CP compared to the control group. By logistic regression analysis, only the following factors (Table 2) were significantly associated with CP: perinatal asphyxia, maternal age >35 years compared with the 18–35 year age group, and high risk pregnancy. Accuracy prediction of this model equaled 87.8%.

Discussion

According to the results of the present study, perinatal asphyxia, maternal age >35 years and high risk pregnancy were independent factors that correlated with CP in term and near-term newborns. In developing countries, 4 to 9 million infants experience birth asphyxia annually.[12] There are 1 million neonatal deaths attributed to birth asphyxia each year, which comprises 20%–40% of all neonatal deaths.

In hypoxic-ischemic encephalopathy, findings from previous studies suggest that antenatal risk factors such as third trimester hemorrhage and premature rupture of the membranes account for the majority of cases; intrapartum factors play only a minor role.[13–15] Recently, however, data from two prospective cohort studies of term newborns with encephalopathy as evaluated with MRI have shown that brain injury actually has imaging characteristics more consistent with acute events at or near the time of birth.[16–18] In these cohorts, most affected newborns had evidence of perinatally acquired insults on MRI, with a very low rate of established antenatal brain injury.

The clinical diagnosis of intra-partum asphyxia is complicated by a lack of objective, specific markers. Thus practice guidelines and 'expert' consensus statements define diagnosis using a number of non-specific markers that are considered alternatively essential or non-essential to an accurate diagnosis.[19–22] On the other hand, approximately 6% of term neonates with otherwise unexplained spastic CP appear to be the result of actual perinatal asphyxia as defined by strict diagnosis criteria.[23] A major factor contributing to CP in Iran is asphyxia according to recent MRI-based studies, expert opinions in Iran and similar countries,[24–27] problems such as low monitoring rates during labor and delivery and the severe shortage of skilled personnel and equipment for neonatal resuscitation.

The increased risk of CP among offspring of women over the age of 35 years in our study was significant compared with offspring of women aged 18 to 35. The increased risk of CP in this group might be related to changes in uterine function seen with advancing age and the state of high risk pregnancy and its multiple covariates.

Previous studies have demonstrated that deviation from optimum birth weight at any gestational age is strongly associated with a risk of CP. This relation is increased for males, particularly in the lowest birth weight range.[28] A similar pattern of different pre/perinatal conditions has been shown in neonatal hypoxic-ischemic encephalopathy with lower birth weight as well as with acute patterns such as the need for an emergency cesarean section, more intensive resuscitation at birth, and increased seizures.[18]

In the present study low birth weight and IUGR were significantly associated with the development of CP in univariate analysis; however we did not detect any correlation as independent risk factors. This might be due to the fact that low birth weight and IUGR are background risks for induction of perinatal insults such as birth asphyxia, followed by CP.

In accordance with previous studies,[29,30] the risk of CP is higher in the male sex. The cause for the protective effect of female gender is unknown, but may be related to differences in genetic factors. In the current study we have shown this association was borderline according to univariate analysis ($P = 0.09$) and not significant in multivariate analysis.

One of the limitations in this study was the lack of a single gold standard to accurately diagnose perinatal asphyxia due to the low specificity and sensitivity of the markers used. At present, researchers have loosely used diagnostic criteria for perinatal asphyxia and post-asphyxia encephalopathy, making the study samples heterogeneous. Clinicians and researchers are urged to use a unique consensus regarding diagnostic criteria for intrapartum asphyxia and to identify these high-risk infants for early intervention. Once these infants are accurately diagnosed, the next challenge is to examine the effectiveness of promising preventive measures and to identify suitable candidates for intervention.

Conclusion

This study shows that, perinatal asphyxia, mother's age, and any pathology during pregnancy are independent factors associated with CP in term newborns.

Previous studies have suggested that improving maternal care improves neonatal outcome. However the extent to which preventing or treating these and other risk factors would reduce the incidence of CP in newborns is unknown and merits further study.

Acknowledgments

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A view of Afjeh, a village in   Lavasanat, near Tehran, Iran. (Photo by M .H. Azizi MD)