Iranian Red Crescent Medical Journal

ORIGINAL ARTICLE

Risk Factors Associated with Cerebral Palsy in Children Born in Eastern and Northern Districts of Tehran

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Abstract

Background: Cerebral palsy is a group of non-progressive motor impairment syndromes caused by lesions of the brain arising early in development. In this study, we evaluated perinatal risk factors of children born in eastern and northern districts of Tehran city, when perinatal records were widely available.

Methods: This was a case-control study performed on one to six year-old children living in Tehran, at health-care centers of Shahid Beheshti University of Medical Sciences and Asma Rehabilitation Center, over 12 months.

Results: During the study period, 112 subjects in the case and 3465 in the control groups were studied. The main factors associated with cerebral palsy were (odds ratios, confidence interval): neonatal convulsion (81.35, 35.09-188.6), low Apgar score (<5) at 5 min or beyond (21.83, 13.13-36.26), low birth weight (5.83, 3.47-9.77), mother's complication during pregnancy (7.83, 4.23-14.50) and maternal age over 35 years (3.88, 2.03-7.42).

Conclusion: Neonatal encephalopathy, low birth weight, and high risk pregnancy were the most powerful independent predictors of cerebral palsy in this population. The majority of infants with cerebral palsy were born at term; therefore, cerebral palsy is quantitatively mainly an issue of term infants.

Keywords: Cerebral palsy (CP); Low birth weight (LBW); Neonatal encephalopathy; High risk pregnancy

Introduction

Cerebral palsy (CP) is the most common and costly form of chronic motor disability which is caused by damage in the very young brain and begins in childhood and is characterized by non-progressiveness.[1] The etiology is mostly unknown and the prevalence is between 1.0 and 2.4 per 1000 live births.[2-4] The prevalence has not decreased in comparison to the past decades, although many advances have occurred in obstetric and neonatal care.[2,3,5] In fact, it seems that the prevalence might have even increased in term infants.[3]

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Received: January 4, 2010 Accepted: April 12, 2010

The increasing prevalence of neuro-developmental disorders in the extremely low birth weight (ELBW) infants, i.e. those with a birth weight of <1000 g, and the extremely immature infants, i.e. those with a gestational age of <26 weeks, has constantly raised concerns.[6-8] Although mortality has decreased in these groups of infants, the neurological disability rate has not changed or has only slightly decreased.[9]

Cerebral palsy was clinically defined even before the etiology of the disorder was known, and actually the diagnosis is still a clinical one.[10] Little suggested that perinatal factors were etiologically important late in the year 1862.[2] Today many experts believe that prenatal factors are mainly involved and the role of perinatal factors is controversial. On the other hand, some investigators such as Hagberg *et al.*[4, 11] have suggested birth asphyxia as a relatively frequent cause of CP in term infants. Anyway, it is important to consider

CP as a heterogeneous group of brain disorders with different possible risk factors and etiologies.[11]

Since it seems that the prevalence of cerebral palsy does not differ in different cultural environments,[12] it can be estimated that 1300-3000 children with CP are born annually in Iran, on the basis of an annual birth rate of 1.3 million according to the national census of 2007.[13]

Unlike Europe, Scandinavia, and Australia, where active CP registries exist, this is not the case in Iran, where even population-based studies on CP infants have rarely been performed. Given the paucity of up-to-date data on CP in the country, this research was performed to study the perinatal risk factors of children with CP in the eastern and northern districts of Tehran city.

Materials and Methods

This was a case-control study performed on one to six year-old children living in Tehran, at health-care centers of Shahid Beheshti University of Medical Sciences and Asma Comprehensive Rehabilitation Center (affiliated to the University of Social Welfare and Rehabilitation Sciences), over 12 months from March 1, 2007 to February 30, 2008. Tehran is divided into 4 health districts. Although Asma can be considered as a referral center for all of Tehran city, the study was carried out exclusively on children referred to Asma center from health –care centers located in the eastern and northern parts of the city. The subjects included 112 children with documented cerebral palsy (as the case group) referring to Asma for assessment and 3465 children without CP, who were apparently healthy with no overt abnormalities such as congenital anomalies, chromosomal, metabolic, and neurodegenerative disorders, had attended only for well-being check-ups (as the control group), and were examined in the same health-care centers by the research team.

All the children diagnosed as having CP were evaluated by a single pediatrician (trained in developmental assessment) with one year follow-up monitoring. CP is a diagnostic term used to describe a group of motor syndromes resulting from disorders of early brain development. CP is caused by a broad group of developmental, genetic, metabolic, ischemic, infectious and other acquired etiologies that produce a common group of neurological phenotypes.

In this study, we defined CP as a non-progressive congenital motor dysfunction with examination finding of increased tone (spasticity, rigidity, and dystonia) or choreoathetosis. Inclusion criteria were non-progressive motor dysfunction, examination the findings of increased tone or choreoathetosis. Because we were interested in perinatal risk factors for unexplained etiologic CP, children with postnatal brain injury or known developmental abnormalities were excluded. The exclusion criteria were postnatal central nervous system insult occurring after 1 week of age, or a neurological condition not typically considered to be CP, such as a myopathy or neural tube defect. We also excluded the infants with a known developmental or genetic syndrome or chromosomal anomaly, and evidence of a congenital viral infection.

Additional covariate information was obtained by a single general physician (trained by the research team), in both groups, by means of a questionnaire. The questionnaire had been previously evaluated for content validity and pilot studies had been carried out. The completion of the questionnaire was based on the thorough evaluation of the child's medical and health records and statements of their mothers, including prenatal and perinatal histories.

Data including gestational age (completed weeks), infant gender, maternal age at delivery, infant's weight and head circumference at birth, plurality (singletons or multiple gestation), parity (number of previous deliveries plus 1), parental consanguinity, history of handicap in the family, miscarriages, pregnancy complications, birth method, Apgar score, neonatal convulsion and postnatal epilepsy, hyperbilirubinemia leading to phototherapy or blood exchange transfusion and whether the infant was admitted to the NICU were obtained. Maternal age was categorized as <34 years, or ≥35 years.

Preterm delivery was defined as delivery before 37 completed weeks of gestation. Gestational age duration was estimated according to the last menstrual cycle. Parity was dichotomized as primiparous or multiparous. Complication during pregnancy meant one or more of the following risk conditions: uterine bleeding, premature rupture of membrane, poly-oligohydraminios, acute medical or surgical illness, multiple gestation, medication during pregnancy, infections, uterine or cervical anomalies, pre – eclampsia or eclampsia and diabetes mellitus.

In this study, neonatal convulsion was defined as a convulsion during the neonatal period based on clinical diagnosis of a physician, occurring at least once and without metabolic disorders such as hypoglycemia or hypocalcaemia, and with no need to long-term

treatment with anti-epileptic drugs, and converting to normal EEG after 2-3 months of treatment. Postnatal epilepsy indicated a convulsive condition based on clinical diagnosis and EEG that resulted from perinatal insults (but not congenital, CNS infection, toxic/metabolic conditions, CNS neoplasm, and traumas). In our definition, febrile seizures are included.

Neonatal sepsis was defined as positive blood culture during neonatal period, with any organism causing neonatal sepsis. Parental consanguinity indicated first or second degree relation of parents. The history of handicap condition in the family, including prior infant or first and second degree relatives with cerebral palsy, mental retardation, birth trauma, hereditary disease (inborn error of metabolism), congenital anomalies, and a history of genetic, chromosomal or non-acquired and unknown disabilities. National Center for Health Statistics (NCHS) reference chart was used to measure the head circumference.[14]

Chi-Square test and independent samples-t-test were used for comparison of the two groups. We calculated univariate odds ratios (ORs) and 95% confidence intervals (CIs), using the exact method. The significance level was 0.05 in the univariate analysis. We calculated multiple odds ratios using backward stepwise selection method with logistic regression analysis. The data were analyzed, using SPSS software for windows (Version 13; SPSS Inc, Chicago, IL, USA). Oral consent was obtained from all the parents whose children were studied, and the research was approved by the "Ethics Committee of the University of Social Welfare and Rehabilitation Sciences".

Results

In the study period, 112 (47.3% males, and 52.7% females) cases and 3465 (50.6% males, and 49.4% females) controls were studied. The mean age ±standard deviation (SD) in the males was 33 ±3.5 months and that of the females was 25±2.2 months. Head circumference <5th percentile was found in 35.1% of the subjects in the case group during the exam and 10.7% at birth. It is noteworthy that the mean head circumferences (cm) at birth in the two groups were: 32.4±3.3 in the case and 34.4±1.2 in the control groups (p<0.001).

The mean weight at birth was 2491 gr in the case group and 3187 gr in the controls; the p-value was significantly meaningful (p<0.001), and the frequency of premature males was 23(43.4%) in the case group, being higher than that of the premature females 19(31%) (p< 0.001).

Demographic data and the results obtained regarding the risk factors for CP can be observed in Table 1 and 2. As demonstrated in Table 2, birth weight under 2500 g (LBW), neonatal convulsion and postnatal epilepsy, low Apgar score (<5) at 5 minutes or beyond, preterm delivery, multiple gestations, neonatal sepsis, maternal complications during pregnancy, history of handicap condition in the family were significantly associated with CP.

It is also noteworthy that over-35 year pregnancies (p= 0.067) and parental consanguinity (p=0.010) were found to have a borderline association. The risk factors entered in the multivariable model were gender, birth weight under 2500 gr, neonatal convulsion, low Apgar score (<5) at 5 minutes or beyond, preterm delivery, neonatal sepsis, maternal complications during pregnancy, maternal age at delivery, and parity. The factors demonstrated in Table 3 remained as independent risk factors for CP in the multivariate analysis.

Discussion

Our results show that perinatal risk factors such as neonatal convulsion, low Apgar score (<5) at 5 min or beyond, low birth weight, maternal complications during pregnancy and mother's age≥35 years are associated with cerebral palsy in this population. Although our results may not be able to prove a cause and effect relationship, they provide evidence in regard to many risk factors. This appears even more

Table 1: Demographic characteristics of case and control groups

Parameter	Case Group Mean±standard deviation	Control Group Mean±standard deviation	*P* value
Maternal age in pregnancy (years)	27±6	25±5	<0.001
Birth head circumference (cm)	32.41±3.30	34.43±1.19	<0.001
Birth weight (grams)	2491±887	3187.5±508	<0.001

Table 2: Univariate risks for Cerebral Palsy

Factors	Case No. (%)	Control No. (%)	*p* Value	OR (95% CI)
Low Birth Weight	54 (50)	260 (7.7)	<0.001	11.90 (7.99-17.27)
Neonatal convulsion	28 (25)	16 (0.5)	<0.001	71.85 (37.46-137.81)
Postnatal epilepsy	37 (33)	62 (1.8)	<0.001	27.07 (16.97-43.19)
Low Apgar score [α]	52 (55.9)	170 (4.9)	<0.001	24.58 (15.87-38.07)
Preterm delivery	41 (36.9)	77 (2.2)	<0.001	24.77 (15.88-38.64)
Neonatal sepsis	26 (23.2)	52 (1.5)	<0.001	29.84 (11.83-33.28)
Multiple gestation	12 (10.7)	41 (1.2)	<0.001	10.02 (5.11-19.64)
Mother complication during pregnancy	34 (30.4)	112 (3.2)	<0.001	13.05 (8.36-20.35)
Parental consanguinity	43 (38.4)	998 (28)	0.013	1.63 (1.10-2.42)
History of handicap in the family	18 (16.1)	295 (8.5)	0.003	2.14 (1.27-3.61)
Birth weight >4000grm	2 (3.4)	109 (3.4)	0.9	_
Not NVD (Caesarian, instrumental delivery)	66 (58)	1834 (52)	0.14	_
Hyperbillirubinemia[β]	6 (5.4)	248 (7.2)	0.46	_
Miscarriage	19 (17.1)	491 (14.2)	0.38	_

[α]Low Apgar score (<5) at 5 minutes or beyond, β leading to phototherapy or Exchange transfusion

Table3: Multivariate risks factors for Cerebral Palsy.

Factor	*P* value	OR (95% CI)
Low Birth Weight	<0.001	5.83 (3.47-9.77)
Neonatal convulsion	0.001	81.35 (35.09-188.60)
Low Apgar score [α]	<0.001	21.83 (13.13-36.26)
Mother complication during pregnancy	<0.001	7.83 (4.23-14.50)
Maternal age≥35 y	<0.001	3.88 (2.03-7.42)

[α]Low Apgar score (<5) at 5 minutes or beyond

meaningful when compared to other risk factor profiles in developed and developing countries. One important finding in the present study was that the majority of infants with CP were born at term and only 42 (37.5%) before 37 weeks of gestation, which shows that CP is mainly an issue of term infants.

In the present study, we found a correlation between CP and neonatal convulsion (OR; 81.35, 95%CI, 35.09-188.6). On the other hand, one finding was that low Apgar score (<5) at 5 min or beyond (OR; 21.83, 95%CI, 13.13-36.26)) increases the risk of CP. Although a low Apgar score may be the result of different damages of various origins,[15] a 5-min Apgar score below 4 at term in a normal neonate is often associated with acidemia at birth, indicating intra-partum hypoxia along with neonatal encephalopathy.[15]

Birth asphyxia is a vague and controversial term that denotes a clinical diagnosis lacking specificity for any single underlying pathological condition. We considered neonatal convulsion, and/or low Apgar score (<5) at 5 minutes or beyond the presentation of birth asphyxia, regardless of whether true hypoxia-ischemia was present.

Although the specificity of these findings for hypoxia-ischemia is unknown because there is no way to directly measure intrapartum blood flow and oxygen delivery to the brain, these findings are often implying the presence of perinatal hypoxia-ischemia in the neonates with encephalopathy.

Thus, if we consider neonatal convulsion and low Apgar score (<5) at 5 min or beyond as clinical symptoms of birth asphyxia, we can conclude that birth asphyxia or "neonatal encephalopathy" was a strong predictor of CP in our study population.[16]

It is important to note that despite a very significant decrease in the occurrence of birth asphyxia in recent years, the incidence of CP has been unchanged, which suggests that birth asphyxia is not the major contributor to CP.[17] However, the fact that in tertiary care centers most infants with neonatal encephalopathy show radiological evidence of acute brain injury around the time of birth[18] should not be overlooked.

In Yvonne et al.'s study,[19] one third (32%) of infants with CP showed strong evidence of an acute brain injury perinatally, using neuro-imaging techniques. Hagberg *et al.*[4] reported that relying on clinical parameters for timing the injury in CP, it seems that in 36% of the term infants, perinatal or neonatal

events were responsible for its development. A Swedish report attributed 58% of CP incidences in the term infants to birth asphyxia. Also, experts in developing countries, such as Iran, have recognized asphyxia as a major cause of CP in their countries.[20,21]

In this study, low birth weight was an independent risk of CP. According to relevant literature, the risk of CP increases with birth weight that is well below normal.[22,23] In our study, the risk of CP in LBWs was 5.83 times higher than 2500-4000gr birth weight infants, respectively (OR; 5.83 95% CI, 3.47-9.77).

It is still not exactly known whether this growth retardation is the cause or effect of the disability. In developed countries, LBW is predominantly related to premature birth whereas in developing countries LBW is more commonly associated with intra- uterine growth retardation (IUGR).[24] However, the underlying mechanism by which growth restriction related to CP is not clearly identified. There may be a higher vulnerability of the growth restricted fetus to intra-partum hypoxic-ischemic stress,[25] or IUGR may be the result of chronic intrauterine hypoxia causing white matter injury.[26, 27] Yvonne *et al.*[19] demonstrated that the growth-restricted infants in their study had neuro-imaging findings suggestive of white matter injury, that was not caused by intra-partum hypoxic-ischemic injury.[28]

In the present study, we found a significant correlation between CP and preterm birth in univariate but not in multivariate analysis. Prematurity has been shown to correlate with high rates of mortality and morbidity, not only in the neonatal period, but also throughout infancy.[1- 3] This can be due to the fact that the neurodevelopmental disorders with prematurity can itself be the result of or co-existent with other neonatal risk factors and the prematurity is a dependent risk. Also, the possibility that many pre-term infants die in the first few months of life can be another explanation.

The risk of CP in premature males (OR=0.4) was higher than that in females in the present study. This finding has been supported by similar findings in recent literature.[29, 30]

In the univariate analysis correlation between multiple gestations, we also found a well-known risk factor for adverse perinatal outcomes,[31-33] which was not significantly associated with CP in multivariate analysis. This can be due to the fact that multiple gestations cannot be considered as an independent risk factor and that it only increases the risk of CP through other co-morbidities.

The results of multivariate analysis due to maternal age and maternal complications during pregnancy in the present study emphasize the importance of prenatal risk factors which need to be assessed with more precision and in more detail in further studies and better high risk pregnancy care and follow-ups.

The main strength of the present study was in its vast range of data that was collected on the past and present medical situation of the children studied, in comparison to many other registration systems in other countries.

Our main limitations consisted of the possibility of overlooking other confounders, lack of adequate neuro-imaging data, limitation of our risk factor data to information obtained from mothers and from documented records where not all factors of interest such as the acid-base status at birth or chorioamnionitis had been assessed, lack of assessment of the risk factors in groups of term and preterm infants, and finally disregarding the subgroups of CP.

Our study showed the correlation between low birth weight, neonatal convulsion, low Apgar score (<5) at 5 min or beyond, mother's age ≥35 years and high risk pregnancy with cerebral palsy. We also showed that CP was mainly an issue of term infants.

Acknowledgement

We would like to express our appreciation to the following for their contributions to this project: The health- care centers of Shahid Beheshti University of Medical Sciences & Health Services for their valuable logistic cooperation in carrying out this study. The Pediatric Neurorehabilitation Research Center of University of Social Welfare and Rehabilitation Sciences for their full financial support. Mrs Compani for her assistance in editing the manuscript and Dr Biglarian for management of the statistical team.

Conflict of interest: None declared.

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