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Full Length Research Paper

Risk factors of cerebral palsy during the perinatal period

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Cerebral palsy (CP) is an umbrella term encompassing a group of non-progressive motor impairment syndromes caused by lesions of the brain in early development. This study was to investigate the risk factors of CP. A total of 632 children with CP were retrospectively investigated in the present study. In addition, 931 children without CP aged <1~14 years (4.31±2.3 years) were recruited as controls. Risk factors investigated including preterm birth, multiple pregnancy, infection during pregnancy, neonatal convulsion, etc. Logistic regression model was used to analyze these risk factors of CP. The main risk factors increasing the prevalence of CP included neonatal convulsion (80.34, 34.75 to 182.64), low Apgar score (19.98, 10.85 to 34.96), low birth weight (5.83, 3.47 to 9.77), Infection during pregnancy (6.24, 5.01 to 12.25) and maternal age of ≥35 years (4.69, 2.54 to 5.59). Our findings confirm that neonatal convulsion, low Apgar score, low birth weight, infection during pregnancy and advanced reproductive age are the risk factors that can increase the prevalence of CP.

Key words: Cerebral palsy, low birth weight, neonatal convulsion, infection during pregnancy, advanced reproductive age.

INTRODUCTION

Cerebral palsy (CP) is the most common and costly form of chronic motor disability which is caused by the damage to the brain of very young children, often develops in childhood and characterized by non-progressiveness (Mutch et al., 1992)]. The pathogenesis of CP is mostly unknown and its prevalence is about 1.0~2.4 per 1000 live births (Nelson, 2002; Winter et al., 2002; Hagberg et al., 2001). The prevalence is remained, although great advance has been made in the obstetric and neonatal care in the past decades (Nelson, 2002; Winter et al., 2002; Colver et al., 2000). In deed, it seems that the prevalence might even increase in term infants (Winter et al., 2002). The increasing prevalence of neuro developmental disorders in the extremely low birth weight (ELBW) infants, especially those with a birth weight of <1000 g, and the extremely immature infants, particularly those with a gestational age of <26 weeks, has constantly raised concerns (Darlow et al., 2003; Meadow et al., 2004; Mikkola et al., 2005). Although the mortality of CP is decreased in these infants, the neurological disability is only slightly or even not improved (Doyle et al., 2001).

CP is clinically defined even before the pathogenesis of this disorder is known and actually the diagnosis is still a clinical challenge (Stanley et al., 2000). Little suggested that perinatal factors were etiologically important late in the year 1862 (Nelson, 2002). Nowadays, numerous experts speculate that some prenatal factors are involved in the pathogenesis of CP, but the roles of perinatal factors are still controversial. On the other hand, some investigators such as Hagberg et al. (2001) have suggested that birth asphyxia is a relatively frequent cause of CP in term infant. Anyway, it is important to consider CP as a heterogeneous group of brain disorders with different risk factors and etiologies (Himmelmann et al., 2005). This study was performed to investigate the risk factors of CP during the perinatal period.

MATERIALS AND METHODS

Patients

This was a case-control study performed in a total of 632 children with CP and the age ranged from <1 to 14 years (mean: 4.33±2.4 years). This study was registered at the General Hospital of Armed Police Forces from 2006 to 2010. In addition, 931 children without CP aged <1~14 years (4.31±2.3 years) were recruited as controls. These children were apparently healthy and no overt abnormalities such as congenital anomalies, chromosomal, metabolic, and neurodegenerative disorders, were found. Informed consent was obtained from the parents of all children, and the study was approved by the Ethics Committee of the General Hospital of Armed Police Forces. All the children diagnosed as CP were evaluated by the same pediatrician who had been trained in the developmental assessment. CP refers to 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 factors producing a common group of neurological phenotypes.

Definition of cerebral palsy

In this study, the CP was defined as a non-progressive congenital motor dysfunction characterized by increased tone (spasticity, rigidity and dystonia) or choreoathetosis.

Inclusion criteria (Mutch et al., 1992)

1. The damage in the CP is non-progressive.
2. The damaged area is located in the brain.
3. The symptoms occur in infancy.
4. Other concomitant handicaps such as intelligent retardation, epilepsy, sensation disabilities, etc are observed.

Exclusion criteria

1. Children with postnatal brain injury or known developmental abnormalities.
2. Children with postnatal central nervous system insult, occurring after 1 week of age.
3. Children with neurological conditions that are not typically considered to be symptoms of CP, such as myopathy or neural tube defect.
4. Children with central nervous system motor dysfunction caused by progressive diseases.

Data collection

Additional covariate information was obtained by a single general physician from all children through a questionnaire survey. The completion of the questionnaire was based on the thorough evaluation of the child's medical and health records and complains of their mothers, including prenatal and perinatal histories.

Risk factors

Information including gestational age, infant gender, maternal age at delivery, infant's body weight, plurality (singletons or multiple births), parity (number of previous deliveries plus 1), infection during pregnancy, mode of delivery, Apgar score, neonatal convulsion and postnatal epilepsy, and to the presence of treatment in the NICU was collected. Maternal age was categorized as <34 years or 35 years.

Preterm delivery was defined as the delivery before 37 completed weeks of gestation. Gestational age was estimated according to the last menstrual cycle. Parity was dichotomized as primiparous and multiparous delivery.

In this study, neonatal convulsion was defined as a convulsion during the neonatal period based on the clinical diagnosis, occurring at least once, without metabolic disorders such as hypoglycemia or hypocalcaemia, with no need of long-term treatment with anti-epileptic drugs and with normal EEG after 2 to 3 months of treatment. Postnatal epilepsy was defined as a convulsive condition based on clinical diagnosis and EEG resulting from perinatal insults (but not congenital insults, CNS infection, toxic/metabolic conditions, CNS neoplasm, or traumas).

Statistical Analysis

Chi-Square test and independent t-test were used for the comparisons of two groups. Univariate odds ratio (OR) and 95% confidence interval (CI) were calculated using the exact method. A value of P<0.05 was considered statistically significant. Multiple OR was calculated using backward stepwise selection method with logistic regression analysis. Statistical analysis was performed with SPSS version 11.5 statistical software package.

RESULTS

In the present study, 632 (341 males and 291 females) and 931 (480 males and 451 females) patients controls were recruited. The mean age of males was 4.7±2.5 years and that of females was 3.9±2.2 years.

Demographic information and the characteristics of risk factors of CP are presented in Tables 1 and 2. As shown in Table 2, birth body weight of <2500 g (LBW), neonatal convulsion, postnatal epilepsy, low Apgar score (<5) at 5 min or beyond, preterm delivery, multiple gestations, neonatal sepsis, maternal complications during the pregnancy and family history of handicap were significantly associated with CP.

Of note, the maternal age of over 35 years (*P*=0.067) was found to have a borderline association with CP. The risk factors included in the multivariable model were gender, low birth weight, low Apgar score, neonatal convulsion, preterm delivery, infection during the pregnancy and advanced maternal age (≥35 years). The factors in Table 3 were independent risk factors of CP in the multivariate analysis.

DISCUSSIONS

Our results showed that perinatal risk factors, such as

Table 1. Demographic characteristics.

Characteristics	CP	Control	P
Maternal age in pregnancy (years)	27±6	25±5	<0.001
Gender (male/female)	341/291	480/451	0.81

The mean body weight at birth was 2491±28 g in the CP group and 3187±36 g in the control group showing significant difference (*P*<0.001).

Table 2. Univariate analysis of risk factors for CP.

Factor	CP, No. (%)	Control, No. (%)	*P*	OR (95% CI)
Low birth weight	322 (50.9)	70 (7.5)	<0.001	11.10 (8.09 to16.57)
Neonatal convulsion	167 (26.4)	6 (0.6)	<0.001	69.87 (34.46 to 134.80)
Postnatal epilepsy	202 (32.0)	16 (1.7)	<0.001	27.00 (16.157 to 44.47)
Low Apgar score [α]	331 (52.4)	40 (4.3)	<0.001	23.58 (15.80 to 38.00)
Preterm delivery	219 (34.7)	20 (2.1)	<0.001	23.58 (15.80 to 36.07)
Neonatal sepsis	152 (24.1)	16 (1.7)	<0.001	28.53 (12.13 to 33.71)
Multiple gestation	76 (12.0)	9 (1.0)	<0.001	9.92 (5.67 to 20.01)
Infection during pregnancy	192 (30.4)	29 (3.1)	<0.001	12.87 (8.46 to 20.30)
Parental consanguinity	227 (35.9)	255 (27.4)	0.013	1.67 (1.17 to 2.55)
History of handicap in the family	99 (15.7)	79 (8.5)	0.003	2.74 (2.07 to 3.44)
Birth weight >4000 gram	21 (3.3)	32 (3.4)	0.9	–
Caesarian	504 (79.7)	746(80.1)	0.14	–

[α] Low Apgar score <5.

Table 3. Multivariate analysis of risk factors of CP.

Factor	*P*	OR (95% CI)
Low birth weight	<0.001	5.94 (4.47 to 9.77)
Neonatal convulsion	0.001	80.34 (34.75 to 182.64)
Infection during pregnancy	<0.001	6.24 (5.01 to 12.25)
Low apgar score [α]	<0.001	19.98 (10.85 to 34.96)
Maternal age≥35 y	<0.001	4.69 (2.54 to 5.59)

neonatal convulsion, low Apgar score, low birth weight, infection during the pregnancy and advanced maternal age (≥35) were associated with CP. Although our results did not prove a causal relationship, they provided evidence for many risk factors of CP. This appears even more important when compared to other risk factors in developed and developing countries.

In the present study, in CP group 54.0% were males, while 51.6% males is in control group. It seems that males have a higher morbidity of CP, but statistical analysis did not reveal the gender was an independent risk factor of CP, which was in accordance with another study in USA, in which some perinatal, neonatal and early childhood factors were found to increase the risk in or protect boys and girls (Hintz et al., 2006).

In the present study, our results showed a correlation between CP and neonatal convulsion (OR: 80.34, 95%CI: 34.75 to 182.64) and low Apgar score (<5) at 5 min or beyond (OR: 19.98, 95%CI: 10.85 to 34.96) increased the risk for CP. Although, a low Apgar score may be as a result of different insults, a 5 min Apgar score below 4 at term in normal neonates is usually associated with acidemia at birth, indicating intra-partum hypoxia along with neonatal encephalopathy (Moayedi et al., 2007).

It is important to note that despite a very significant decrease in the occurrence of birth asphyxia in recent years, the incidence of CP remains stable, suggesting that birth asphyxia is not a major contributor to CP (Cowan et al., 2003). However, the fact that, in tertiary care centers most infants with neonatal encephalopathy show radiological evidence of acute brain injury at birth (Wu et al., 2006) should not be overlooked.

In a study of Wu et al (2006), about one third (32%) of infants with CP showed strong evidence of perinatal acute brain injury. Hagberg et al. (2001) reported that in respect of the timing of the injury resulting in CP, perinatal or neonatal events were responsible for the development of CP in 36% of term infants. A Swedish study revealed about 58% of CP was attributed to birth asphyxia in term infants. Also, experts in developing countries, such as Iran, have recognized asphyxia as a major cause of CP in their countries (Hermansen and Hermansen, 2006; Soleimani et al., 2009).

In this study, low birth weight was an independent risk factor of CP. According to previous studies, the risk for CP increases with the decrease in birth weight (Jarvis et al., 2003; Soleimani and Dadkhah, 2007). In our study, the risk for CP in LBW infants was 5.83 times higher than that in infants with birth weight of 2500 to 4000 g (OR; 5.83 95% CI, 3.47 to 9.77).

It is still unclear whether growth retardation is a cause or consequence of the disability. In developed countries, LBW is predominantly related to the premature birth whereas in developing countries, LBW is more commonly associated with intrauterine growth retardation (IUGR) (Berg, 1989). However, the underlying mechanism, by which growth restriction related to CP, is still poorly understood. There may be a higher vulnerability in fetus with growth restriction to intrapartum hypoxic-ischemic stress (Uvebrant and Hagberg, 1992), or IUGR may be a result of chronic intrauterine hypoxia resulting in white matter injury (Gaffney et al., 1994; Blair and Stanley, 1990). Wu et al. (2006) demonstrated that the growth-restricted infants had evidence in neuro-imaging suggestive of white matter injury, which was not caused by intra-partum hypoxic-ischemic injury (McManus et al., 2006).

In the present study, a significant correlation between CP and preterm birth was noted in univariate analysis but not in multivariate analysis. Prematurity has been shown to correlate with high mortality and morbidity, not only in the neonatal period, but throughout infancy. This can be explained by the fact that the prematurity related neurodevelopmental disorders can itself be as a result of or co-existent with other neonatal risk factors and the prematurity is a dependent risk. In addition, the possibility that many preterm infants die in the first few months of life may be another explanation.

In the univariate analysis of correlation between multiple gestations and CP, a well known risk factor of poor perinatal outcomes was identified (Johnston and Hegberg H, 2007; Glinianaia et al., 2006; Topp et al., 2004). However it was not significantly associated with CP in multivariate analysis. This may be attributed to the fact that multiple gestations cannot be considered as an independent risk factor and that it only increases the risk for CP through other comorbidities.

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 in CP, but further studies are required to confirm our findings.

There were still limitations in the present study. For example, there was the possibility of overlooking other confounders, lack of enough information from neuro-imaging, incomplete information of risk factors obtained from mothers and medical records where not all factors of interest such as the acid-base status at birth and chorioamnionitis have been recorded, and lack of assessment of risk factors in term and preterm infants.

Our results show that low birth weight, neonatal convulsion, low Apgar score (<5) at 5 min or beyond, advanced maternal age and high risk pregnancy are risk factors of CP and CP is mainly an issue of term infants.

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