

Selected risk factors for spastic cerebral palsy in a retrospective hospital-based case control study

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ABSTRACT

Introduction: Cerebral palsy (CP) is caused by damage to the motor control centers of the developing brain and can occur during pregnancy, during childbirth, or following birth.

Purpose: To study the selected risk factors for spastic CP in a retrospective study involving children with CP.

Materials and methods: The study population included 92 children with spastic CP. The analysis of data from the case records of both groups included the following: child's age, gender, pregnancy order, birth order, type of birth, time of birth, Apgar scores, birth weight, epilepsy, and psychomotor development.

Results: CP occurred more often in boys. A total of 27 children had congenital hemiplegia, 35 had diplegia, and 30 had spastic tetraplegia. The mean gestational age at birth for children with CP was 35.96 ± 4.2 weeks versus a mean of 39.2 ± 1.4 ($p < 0.001$) for the control group. The mean number of pregnancies and deliveries for mothers of children with CP compared to the control group did

not differ significantly. Vaginal births and cesarean sections in the group of children with CP and controls occurred in similar percentages. The birth weight of children with CP (2615.8 ± 935.1) was significantly lower than the birth weight among the control group (3343.2 ± 497) ($p = 0.04$). Almost 40 percent of the children with CP were born to mothers who had preterm labours compared to only 5.2 percent of controls. A mean Apgar score for children with CP (5.9 ± 3.3) at 1 minute was significantly lower than that for children without CP (9.10 ± 1.5) ($p < 0.001$). Of the children with CP, 20 percent had epilepsy; none of the children without CP had epilepsy; 22 percent had slight delays, 17 percent had moderate delays, and 12 percent had severe delays.

Conclusions: Gender, prematurity, low birthweight, asphyxia and epilepsy were related to the development of CP.

Key words: Risk factors; cerebral palsy; retrospective study

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INTRODUCTION

Cerebral palsy (CP) is one of the most common causes of physical disability in children. The prevalence of CP in the general population is 1.5 to 2.5 per 1,000 live births [1, 2]. The prevalence of CP in the Polish population is estimated at 2 to 3 per 1,000 live births [3]. In Poland, during their first year approximately 1,200 to 1,300 children are diagnosed with CP based on observed symptoms. Despite the development of monitoring technology and life-saving interventions for newborns, including those with low birth weight, the prevalence of CP has remained largely unchanged for the past 30 years. In preterm infants, an increasing prevalence of CP has been documented and is believed to be related to the improvement in survival rates [4].

CP is not an independent disease, but a syndrome associated with various etiologies affecting the central nervous system. CP describes a group of disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occur in the developing fetal or infant brain [5]. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception, behaviour, and/or by a seizure disorder. CP is associated with prenatal, perinatal, and neonatal risk factors. Premature birth is recognized as the main risk factor for CP, while perinatal asphyxia accounts for less than 10 to 20 percent of cases [6-10].

A number of pre-pregnancy risk factors have been described including maternal age, parity and maternal diseases including epilepsy, diabetes, and thyroid disease [11,12].

Risk factors occurring early or late in pregnancy are assisted fertilization, male gender, congenital malformation, multiple pregnancy and intrauterine growth restriction [13,14].

CP describes a group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain [5]. The motor disorders of CP are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behaviour, and/or by a seizure disorder.

Increasingly, more very low birth-weight infants in the developed world are now expected to survive the neonatal period than was previously the case. According to the UK Network of Cerebral Palsy Registers, Surveys, and Databases, low birth-weight infants are at greater risk of developing CP than higher birth-weight babies [15]. The CP rate amongst children with birth weights <2500 g was significantly higher at 16 per 1,000 live births than 1.2 per 1,000 live births for normal birth-weight

children. Despite being at greater risk of developing CP, smaller birth-weight babies are proportionately less likely to develop the most severe forms of motor impairment. Furthermore, CP rates for each motor impairment group in the 1990s were similar to those in the late 1970s. The CP rate for infants weighing 1,000 to 1,499 g at birth decreased from around 180 per 1,000 live births in 1979 to around 50 per 1,000 live births from the early 1990s onwards.

Brooks et al. [16] assessed the trend of improved survival among individuals with (CP) in California during the 1980s and 1990s. In an observational cohort study, they evaluated individuals with CP ages 4 years and older who were clients of the California Department of Developmental Services. A total of 51,923 persons with CP were studied. Medical diagnoses, functional disabilities, and special healthcare requirements were assessed with the Client Development Evaluation. Children who did not lift their heads in the prone position who were born in more-recent years had significantly lower mortality rates than those with comparable disabilities born earlier. The authors concluded that the trend toward improved survival has continued throughout the most-recent decade.

Recently, most studies of CP have been carried out in Western countries, with very few having been conducted in the Eastern European countries. There are also few reports on risk factors for CP from our country [3]. Thus, we attempted to identify risk factors associated with CP in our retrospective study in Bialystok. A better understanding of the aetiology of CP is necessary for the development of preventive strategies and treatments. The aim of this study was to investigate the selected risk factors for CP using a hospital-based case control study.

MATERIALS AND METHODS

We evaluated 1200 medical data of the patients who were under the care of the Department of Pediatric Rehabilitation of the Medical University of Bialystok. The study was approved by the Ethics Committee at the Medical University of Bialystok, Poland. We included in the retrospective analysis 92 children with spastic CP. The control group comprised 96 healthy children. A total of 96 children without CP were included in the study. Controls were selected from the entire geographical population. Children were of similar age. The mean age of patients with CP was 10.9 ± 6.9 years with a range of 1–17 years of age. The mean age of healthy children was 12.4 ± 4.3 years with a range of 4–16 years of age and did not differ significantly. Gender, Apgar score, number of pregnancies and deliveries, cesarean sections, birth weight, preterm and term deliveries and epilepsy were analyzed We

also analyzed the type of CP, the motor and mental development of children with CP and the control group.

Motor function

Each child was classified according to the Gross Motor Function Classification System (GMFCS): level 1, walks without restrictions; level 2, walks without assistive devices, limitations in walking outdoor; level 3, walks with assistive devices; level 4, self-mobility with limitations, children are transported or use powered mobility; and level 5, self-mobility is severely limited.

Statistics

The differences between the groups were determined by the parametric t-test and nonparametric statistical tests: Fisher’s Exact test or chi-square test where appropriate. All P values were two-tailed. Statistical significance was defined as P < 0.05. To test the effects of the sex, birth weight, type of CP, mental retardation Spearman rang regression was applied.

RESULTS

A total of 92 patients with CP, 64 boys (69.6%) and 28 girls (30.4%), were recruited. In this group, the number of boys was significantly higher (p=0.003) than the number of girls. The control group included 53 girls (55.2%) and 43

Table 1. Clinical data of children with cerebral palsy and children without cerebral palsy.

Variable	Children with cerebral palsy n=92	Children without cerebral palsy n=96	P value
Boys/Girls	64/28	43/53	0.003
Gestational age (weeks)	35.96±4.2 (26-42)	39.2±1.4 (34-43)	<0.001
Number of pregnancies	2.01±1.5 (1-10)	2.09±1.3 (1-6)	NS
Number of deliveries	1.9±1.5 (1-10)	1.9±1.1 (1-6)	NS
Vaginal birth	61 (66.3%)	70 (72.9%)	NS
Cesarean section	31 (33.7%)	26 (27.1%)	NS
Prematurity	38 (41.3%)	5 (5.2%)	<0.001
Weight at birth (gram)	2616± 935 (780-5060)	3343±497 (1900-4750)	<0.001
Agar score at 1 minute	5.9±3.3 (1-10)	9.10±1.5 (1-10)	<0.001
Mental development			
Normal	45(48.9%)	96(100%)	
Small	20(21.7%)		
Moderate	16 (17.4%)		
Severe	11 (12%)		
Epilepsy	27(20.1%)	0	<0.001

boys (44.8%). The mean age of children with CP and controls was similar. The study population comprised 27 children with congenital hemiplegia (2.36%), 35 with spastic diplegia (38.04%), and 30 with spastic tetraplegia (32.6%). The mean gestational age at birth for children with CP was 35.96 ± 4.2 weeks versus a mean of 39.2 ± 1.4, (p<0.001) for the control group. The mean number of pregnancies and deliveries for mothers of children with CP compared to the control group did not differ significantly. Details are shown in Table 1.

Vaginal births and cesarean sections in the children with CP and controls occurred in similar percentages (p=0.568). The birth weight of children with CP (2615.8 ± 935.1) was significantly lower than birth weight among the control group (3343.2 ± 497) (p=0.04). Almost 40 percent of the children with CP were born to mothers who had preterm labour, compared to only 5.2 percent of the children without CP (p<0.001). A mean Apgar score for children with CP (5.9 ± 3.3) at 1 minute was significantly lower than for children without CP (9.10 ± 1.5) (p<0.001). Of the children with CP, 27 (20.1%) had epilepsy; none of the children without CP had epilepsy. Almost 52 percent of patients with spastic tetraplegia, 22 percent with spastic diplegia, and 15.5 percent with spastic hemiplegia had epilepsy. Of children with CP, 45 (48.9%) had normal mental development and all children (100%) of the control group had normal development. In regard to delayed development, 20 patients with CP (21.7%) had small delays, 16 (17.4%) had moderate delays, and 11(12%) had severe delays. The children with CP were more frequently classified into levels II (n=25) and V (n=20) of the GMFCS; other patients were classified into levels I (n=18), III (n=14), and IV (n=15).

Table 2. Psychomotor development of children with cerebral palsy and controls.

Variable	Children with cerebral palsy n=92	Children without cerebral palsy n=96	P value
Sitting	1.1 ± 0.8 (0.6-3) years	0.6 ± 0.25 (0.5-2) years	<0.001
Standing	1.2 ± 0.9 (0.9-3.6) years	0.97 ± 0.2 (0.9-2) years	0.0045
Walking	1.5 ± 0.7 (1-5) years	1 ± 0.3 (1-3) years	<0.001
Speech	1.4 ± 0.98 (1-4)	1.1 ± 0.4 (1-3)	0.003

Of children with CP, 12 (13%) were unable to sit independently. The mean age for

sitting independently was 1.1 ± 0.8 years and was significantly delayed compared to the control group. Details are shown in Table 2.

Of children with CP, 19 (20.1%) were unable to stand independently. The average age for standing independently in children with CP was 1.2 ± 0.99 years and differed significantly ($p=0.0045$) compared to controls. Of children with CP, 20 (21.7%) were unable to walk independently. The mean age for walking independently in children with CP was 1.5 ± 0.7 years and differed significantly ($p<0.001$) compared to the control group. Of children with CP, 18 (19.6%) were

unable to speak. The average age for speaking in children with CP was 1.4 ± 0.98 years and differed significantly compared to the control group ($p=0.003$).

Gender, number of pregnancies and deliveries, birth weight, and preterm versus term deliveries were not related to psychomotor development in children with CP. (Details are shown in Table 3). Birth by cesarean section, Apgar score at 1 minute, epilepsy, and mental retardation were related to psychomotor development in children with CP.

Table 3. Correlations between variables and psychomotor development in children with cerebral palsy.

Variable	Sitting		Standing		Walking		Speech	
	R	P value	R	P value	R	P value	R	P value
Gender	0.127	0.227	-0.034	0.740	0.067	0.524	-0.046	0.660
Number of pregnancies	-0.107	0.306	-0.051	0.627	-0.110	0.294	0.028	0.789
Number of deliveries	-0.099	0.347	-0.014	0.894	-0.044	0.671	-0.051	0.623
Cesarean section	0.213	0.041	0.062	0.553	0.063	0.550	0.058	0.581
Week of pregnancy	0.151	0.149	0.006	0.951	0.075	0.473	0.029	0.782
Prematurity	-0.173	0.097	-0.028	0.786	-0.063	0.547	-0.022	0.832
Apgar score at 1 minute	0.301	0.003	0.119	0.255	0.171	0.101	0.112	0.284
Asphyxia	-0.302	0.003	-0.078	0.459	-0.128	0.225	-0.127	0.229
Weight at birth	0.200	0.055	-0.033	0.750	0.124	0.238	0.029	0.781
Epilepsy	-0.315	0.002	-0.289	0.005	-0.301	0.003	-0.080	0.449
Mental retardation	-0.420	0.000	-0.478	0.000	-0.617	0.000	-0.221	0.034

R- Spearman's rank correlation coefficient

DISCUSSION

In the present study, we demonstrated that maleness, perinatal asphyxia, low birthweight, premature birth, and epilepsy were independent factors correlated with CP. The psychomotor development of children with CP was also correlated with these factors.

This study's result that the risk of CP is significantly greater in males than in females agrees with earlier findings [17–19]. Males born preterm also appear to be more vulnerable to white matter injury and intraventricular hemorrhage than females. Experimental studies of adult animals and data from adult patients who have experienced a stroke indicate that sex hormones such as estrogens protect against hypoxic–ischemic injury and influence the neonatal brain.

Skiöld et al. [18] demonstrated that cognitive and language outcomes in infants aged 30 months were poorer in males born preterm. Sex-related differences were also observed on neonatal structural MRI, including in the patterns of correlations between brain volumes and developmental scores at both global and regional levels.

The pathogenesis of CP is multifactorial. Factors contributing to fetal brain injury may be acute (i.e., within hours) or chronic (i.e., over days or weeks), as well as either continuous or intermittent [19]. Epidemiological studies [20–22] have confirmed that the incidence of CP is inversely related to gestational age. Meanwhile, EpicURE determined the survival and neonatal morbidity rates for infants born between 22 and 26 weeks of gestation in the U.K. during 2006 and, compared to results from 1995, showed changes in outcome for infants born between 22 and 25 weeks [22]. In 2006, CP was present in 14% of survivors. Though the survival of infants born between 22 and 25 weeks of gestation had increased since 1995, the pattern of major neonatal morbidity and proportion of survivors affected remained unchanged. Furthermore, the results of the present study corroborate these earlier findings, all of which indicate a substantial increase in the population of preterm survivors at risk of later health problems.

Asphyxia at birth remains the primary cause of CP [23–24] and, accordingly, the current study showed that asphyxia was significantly correlated with CP. However, wide disparity persists in estimating the proportion of CP

attributable to asphyxia at birth. According to Ellenberg and Nelson [25], available data do not support the belief, widely held in the medical and legal communities, that asphyxia at birth can be recognized reliably and specifically, or that CP is often due to asphyxia at birth.

Previous studies have demonstrated infants with low birthweight are at greater risk of developing CP than those with higher birthweight [26–28]. The rate of CP among children with birthweights of less than 2,500 g was significantly higher (16 per 1,000 live births) than among infants born with normal weight (1.2 per 1,000 live births) [27]. In the present study, low birthweight was also significantly associated with the development of CP.

In a study of premature infants, Rutkowska et al. [29] evaluated the development of infants from birth until the age of 2 years. Of the 162 children who participated in the examination at the age of 2 years, normal development was observed among 88%, and CP of different types was diagnosed in 8%. Hustad et al. [30] examined early speech and language development in children with CP and found that 85% of 2-year-old children with CP in their study had clinical speech and/or language delays relative to expectations for their age. They suggested that children with CP receive speech and language assessment and treatment at or before 2 years of age. These findings are consistent with our results, which show that, of all children with CP, 19.6% were unable to speak. The average age for speaking in children with CP was 1.4 ± 0.98 years, which differed significantly to that of the control group.

The frequent association of epilepsy and CP is of special interest. It has been estimated that 15–90% of patients with CP suffer from epilepsy [30–31], which our results corroborate. Zafeiriou et al. [30] reported that the overall prevalence of epilepsy in children with CP was 36.1%. Patients with atonic–diplegic, dystonic, tetraplegic, and hemiplegic CP had a higher incidence of epilepsy. In all, 75.3% of patients has been seizure-free for more than 3 years and could discontinue therapy, whereas 25% of patients were still taking antiepileptic drugs. Among a cohort of 452 patients with CP, Singhi et al.'s [31] retrospective study found a 35% rate of epilepsy, which most commonly affected children with spastic hemiplegia and tetraplegia.

Several studies have identified significant relationships among mental retardation, motor impairment, and epilepsy [32,33]. Vargha–Khadem et al. [32] reported that the presence of epilepsy in patients with hemiplegia was clearly associated with more severe cognitive difficulties. Furthermore, Bruck et al. [33] found a higher rate of severe mental retardation in patients with spastic tetraplegia and who had epilepsy. In the present

study, nearly 52% of patients with spastic tetraplegia, 22% with spastic diplegia, and 15.5% with spastic hemiplegia also had epilepsy, and nearly half of our patients with CP and epilepsy had severe mental retardation. There is also an association between epilepsy in children with CP and the degree of mental impairment. The occurrence of epilepsy, mostly in children with hemiplegia and diplegia, is associated with reduced mental capacities [34].

CONCLUSIONS

Gender, prematurity, low birthweight, asphyxia, and epilepsy were related to the development of CP. The psychomotor development of children with CP significantly differed from that of the control group. Of patients with CP, nearly 20% had epilepsy, while 50% had mental retardation.

Conflicts of interest

There are no conflicts of interest.

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