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Risk factors for cerebral palsy

Faktori rizika od nastanka cerebralne paralize

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Abstract

Background/Aim. Cerebral palsy (CP) etiology is multifactorial and heterogeneous, manifesting as damage to the developing brain. The associated risk factors can arise in the prenatal, perinatal, or postnatal period. The aim of this study was to determine the risk factors for CP and examine the associations between CP type, gestational age, and perinatal risk factors. **Methods.** The study sample comprised 206 children with CP. Pertinent data were collected from medical records and included participants' gestational age at birth, medical history, and CP clinical characteristics. Risk factors were divided according to the timing of brain injury into prenatal, perinatal, and neonatal. **Results.** Hormonally maintained pregnancy (55.3%), twin pregnancy (28.9%), vaginal bleeding after the 20th week of gestation (21.1%), threatened abortion in the first half of pregnancy (13.2%), and maternal infection (10.5%) were identified as the main prenatal risk factors for CP. Prematurity (54.5%) was the leading perinatal risk factor, followed by low birthweight (50.8%), Apgar score < 7 (41.7%), assisted delivery (41.4%), and breech presentation (13.5%). Respiratory distress syndrome (16%), need for treatment in the Neonatal Intensive Care Unit (22.3%), assisted ventilation (18.4%), hypoxic-ischemic encephalopathy (11.2%), and neonatal convulsions (5.8%) were identified as the leading neonatal risk factors for CP. A statistically significant difference was found in the total number of perinatal risk factors in relation to gestational age ($p < 0.001$) and CP type ($p = 0.006$). Perinatal risk factors were most prevalent in preterm infants and children affected by the CP of spastic bilateral type. A statistically significant difference was noted in the distribution of CP types depending on the gestational age ($p < 0.001$). In particular, spastic bilateral CP type was most prevalent in the group of preterm-born children. **Conclusion.** CP is characterized by heterogeneous risk factors and is a result of interaction among multiple risk factors.

Key words:
cerebral palsy; gestational age; infant, premature; pregnancy complications; pregnancy, twin; risk factors.

Apstrakt

Uvod/Cilj. Etiologija cerebralne paralize (CP) je multifaktorijalna i heterogena i karakteriše je oštećenje mozga u razvoju. Faktori rizika mogu se javiti u prenatalnom, perinatalnom i postanatalnom periodu. Cilj rada bio je da se utvrde faktori rizika od nastanka CP i istraži odnos između oblika CP, gestacijske starosti i perinatalnih faktora rizika. **Metode.** Istraživanjem je obuhvaćeno ukupno 206 dece obolelih od CP. Iz medicinske dokumentacije obolele dece dobijeni su podaci o njihovoj gestacijskoj starosti, kliničkim i ostalim karakteristikama. Faktori rizika su podeljeni prema trenutku nastanka oštećenja mozga na prenatalne, perinatalne i neonatalne. **Rezultati**. Najčešći prenatalni faktori rizika za nastanak CP bili su hormonski održavana trudnoća (55,3%), blizanačka trudnoća (28,9%), vaginalno krvarenje nakon 20. nedelje gestacije (21,1%), preteći abortus u prvoj polovini trudnoće (13,2%) i infekcija majke (10,5%). Među perinatalnim faktorima rizika najčešće su bili zastupljeni prevremeno rođenje (54,5%), praćeno niskom telesnom masom na rođenju (50,8%), Apgar skor < 7 (41,7%), asistirani porođaj (41,4%) i karlična prezentacija novorođenčeta (13,5%). Vodeći neonatalni faktori rizika za nastanak CP bili su respiratorni distres sindrom (16%), potreba za lečenjem na Odeljenju intenzivne nege i terapije (22,3%), asistirana ventilacija (18,4%), hipoksično-ishemijska encefalopatija (11,2%) i neonatalne konvulzije (5,8%). Utvrđena je statistički značajna razlika u ukupnom broju perinatalnih faktora rizika u odnosu na gestacijsku starost ($p < 0,001$) i tip CP ($p = 0,006$). Perinatalni faktori rizika bili su učestaliji kod prevremeno rođene dece i dece sa bilateralnom spastičnom formom CP. Utvrđena je statistički značajna razlika u distribuciji tipova CP u odnosu na gestacijsku starost ($p < 0,001$). U grupi

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prevremeno rođene dece najzastupljeniji je bio spastični bilateralni tip CP. **Zaključak.** Etiologija CP je heterogena i ova bolest nastaje kao rezultat interakcije mnogobrojnih faktora rizika.

Ključne reči:
cerebrana paraliza; gestacijska starost; nedonošče; trudnoća, komplikacije; trudnoća, blizanačka; faktori rizika.

Introduction

Cerebral palsy (CP) is the most severe and the most common cause of disability in childhood, and because of that, it imposes the greatest burden on the healthcare system [1]. The extent of its severity is evident from the fact that 40% of children affected by CP are unable to walk independently [2], one-third have epilepsy [3], and about half have cognitive impairments [2, 4]. As a result, the lifetime cost of CP per patient is estimated at about one million USD. Given that prenatal and perinatal complications increase the risk of CP, their prevention and recognition is a public health priority [1]. The CP prevalence is estimated at 1.5–4 cases per 1,000 live births [1, 5–8].

Although CP is a result of nonprogressive brain damage which occurs before birth, during childbirth, or in the first two years of a child's life [9], the initial brain damage most commonly arises in the early fetal period [10] as a result of a congenital brain anomaly, infection, trauma, or an acute hypoxic-ischemic stroke [9]. CP etiology is multifactorial and heterogeneous, and although it cannot be established in many cases, it manifests as damage to the developing brain [5, 10]. The associated risk factors can arise in the prenatal, perinatal, or postnatal period and include multiple pregnancies, intrauterine infections, intrauterine stasis, preterm birth, cesarean section, perinatal stroke and infection, asphyxia, placental malformations, and congenital malformations [5, 8–10]. Thus, while accurately determining and clearly categorizing CP causes is not feasible, every effort must be made to identify and evaluate possible contributing factors or causal pathways [5].

The aim of this study was to determine the risk factors for CP and investigate the association among CP type, gestational age, and perinatal risk factors.

Methods

This work is part of a larger classical clinical-epidemiological qualitative study conducted at the Clinic for Child Habilitation and Rehabilitation, the Institute for Child and Youth Health Care of Vojvodina in Novi Sad, Serbia. The main study (involving 206 children) and all its components were approved by the Ethics Committee of the Institute (No. 400/1 from March 05, 2009). The data collection methods used are already described in our previous publication [11] and focused on participants' gestational age at birth, medical history, and CP clinical characteristics. For each child, Surveillance of Cerebral Palsy in Europe (SCPE) [12] and European commission guidelines (https://eu-rd-platform.jrc.ec.europa.eu/scpe/data-collection/cp-subtypes_en) [13] were used to determine clinical CP type. The risk factors identified from patients' medical records were categorized under the prenatal, perinatal, or neonatal category, depending on the timing of the brain injury [14].

Once the data was entered into our database as previously described [11], descriptive and inferential statistics were calculated, and findings were reported as percentages and frequencies. Observed frequencies in the attributive characteristics were compared to the expected values via the χ^2 test, whereas Spearman's ρ was calculated to assess pairwise correlations between characteristics. SPSS Statistics 17.0 commercial software was used in all statistical analyses.

Results

Of the 38 children with CP for whom data on some of the aforementioned prenatal risk factors were available, in 55.3% of these cases, mothers had hormonally maintained pregnancies, in 21.1%, the mother had vaginal bleeding after the 20th gestational week, in 13.2%, the mothers had threatened abortion in the first half of pregnancy, and in 10% of the cases, the mother had an infection during pregnancy. In a smaller percentage (5.3%) of children, the mother developed anemia in the second half of pregnancy, and in 2.6% of cases, the mother had hypertension in this period (Table 1).

As shown in Table 2, premature birth (54.5%) or low birthweight (50.8%) – both of which are perinatal risk factors – were also registered in more than half of the children

Table 1

Distribution of prenatal risk factors (PRF) in children with cerebral palsy

PRF	All examined patients n = 206	Patients with any PRF n = 38
Anemia (second half of pregnancy), n = 2	1.0	5.3
Threatened abortion (first half of pregnancy), n = 5	2.4	13.2
Bleeding (vaginal) (after 20th week of gestation), n = 8	3.9	21.1
Hypertension (second half of pregnancy), n = 1	0.5	2.6
Hormonally maintained pregnancy, n = 21	10.2	55.3
Maternal infection, n = 4	1.9	10.5
Twin pregnancy, n = 12	5.8	28.9

All values are expressed as percentages.

with CP. Moreover, 41.4% and 41.7% of these children had assisted delivery and a low Apgar score (AS), while in 13.5% of cases, the fetus had a breech presentation at delivery.

Out of 145 children with CP for whom gestational age was recorded, 54.4% were born prematurely, out of which 30.3% were born after 32−36 weeks of gestation, 17.2% were delivered after 28−31 weeks of gestation, and 6.9% were born before the 28th gestational week. As shown in Table 3, reproduced from our earlier study [11], the difference in distribution is statistically highly significant (χ^2 = 48.572, $p < 0.001$).

A statistically significant difference was present in the total number of perinatal factors concerning gestational age (χ^2 = 83.459, $p < 0.001$). While 48.5% of all infants carried to term had no perinatal risk factors, at least one factor was noted for those born prematurely. Moreover, the percentage of children with at least one perinatal risk factor decreased significantly with gestational age, from 100% for children born before 28 weeks to 84% for those born after 28−31 weeks of gestation, to 84.1% for children born after 32−36 weeks of gestation, and finally to only 13.6% for children carried to term (Table 4).

As indicated in Table 5, a statistically significant difference was present in the total number of perinatal factors across clinical types of CP (χ^2 = 21.354, p = 0.006). Specifically, 92% of children with spastic diplegia and 81.8% of those with quadriplegia had at least one perinatal risk factor, whereby one perinatal factor was noted in 24% and 18.2% of those cases, respectively, while the remaining 68% and 63.6% had two or more perinatal factors. The presence of perinatal risk factors was less common in children with other clinical types of CP.

Data reported in Table 6 further demonstrate the presence of a statistically significant difference in the distribution of clinical types of CP in relation to gestational age (χ^2 = 33.448, $p < 0.001$). While 71.8% of children with spastic unilateral CP were born at term, this percentage slightly declined for those with the dyskinetic (69.2) and ataxic type (66.7%). In contrast, children with a spastic bilateral type of CP were more likely to have been born prematurely, which is the case for 85.4% and 51.6% of children with diplegia and quadriplegia, respectively.

Table 2

Distribution of prenatal risk factors (PRF) for cerebral palsy

PRF	All examined patients n = 206		Patients with any PRF n = 152
	%	valid %	%
Placental disorders, n = 6	2.9	-	3.9
Assisted delivery, n = 46	22.3	41.4	30.3
Breech presentation, n = 7	3.4	13.5	4.6
Prematurity, n = 79	38.3	54.5	52.0
Apgar score < 7, n = 40	19.4	41.7	26.3
Low birthweight, n = 62	30.1	50.8	40.8
Resuscitation, n = 25	12.1	-	16.4

Table 3

Distribution of children with cerebral palsy by gestational age

Gestational age (in weeks)	Total number of patients n=206	Patients with complete data n=145
< 28, n = 10	4.9	6.9
28−31, n = 25	12.1	17.2
32−36, n = 44	21.4	30.3
> 36, n = 66	32.0	45.5
Total, n = 145	70.4	100.0
No data, n = 61	29.6	

All values are expressed as percentages.
Note: Table adopted from our previous work [11].

Table 4

The total number of perinatal risk factors (PRF) concerning gestational age

Gestational age (in weeks)	Number of PRF			Total
	0	1	≥ 2	
< 28			10 (100)	10 (100)
28−31		4 (16)	21 (84)	25 (100)
32−36		7 (15.9)	37 (84.1)	44 (100)
>36	32 (48.5)	25 (37.9)	9 (13.6)	66 (100)
Total	32 (22.1)	36 (24.8)	77 (53.1)	145 (100)

All values are expressed as numbers (percentages).

Table 5

The total number of perinatal risk factors (PRF) concerning cerebral palsy (CP) type

Clinical type of CP	Number of PRF			Total
	0	1	≥ 2	
Spastic unilateral	15 (37.5)	14 (35.0)	11 (27.5)	40 (100)
Spastic bilateral diplegia	4 (8)	12 (24)	34 (68)	50 (100)
Spastic bilateral quadriplegia	6 (18.2)	6 (18.2)	21 (63.6)	33 (100)
Dyskinetic	3 (23.1)	5 (38.5)	5 (38.5)	13 (100)
Ataxic	2 (33.3)	2 (33.3)	2 (33.3)	6 (100)
Total	30 (21.1)	39 (27.5)	73 (51.4)	142 (100)

All values are expressed as numbers (percentages).

Table 6

Distribution of cerebral palsy (CP) types by gestational age

Clinical type of CP	Preterm birth	Term birth	Total
Spastic unilateral	11 (28.2)	28 (71.8)	39 (100.0)
Spastic bilateral diplegia	41 (85.4)	7 (14.6)	48 (100.0)
Spastic bilateral quadriplegia	16 (51.6)	15 (48.4)	31 (100.0)
Dyskinetic	4 (30.8)	9 (69.2)	13 (100.0)
Ataxic	2 (33.3)	4 (66.7)	6 (100.0)
Total	74 (54.0)	63 (46.0)	137 (100.0)

All values are expressed as numbers (percentages).

Table 7

Distribution of neonatal risk factors

Neonatal risk factors	Children with CP
Respiratory distress syndrome	33 (16.0)
Hypoxic-ischemic encephalopathy	23 (11.2)
Assisted ventilation	38 (18.4)
Need for treatment in the NICU	46 (22.3)
Neonatal convulsions	12 (5.8)

CP – cerebral palsy; NICU – Neonatal Intensive Care Unit.
All values are expressed as numbers (percentages).

As indicated in Table 7, 22.3% of children with CP were treated in the Neonatal Intensive Care Unit (NICU), and 18.4% required assisted ventilation. Moreover, every sixth child with CP developed respiratory distress, hypoxic-ischemic encephalopathy was diagnosed in every ninth child, and neonatal convulsion in every seventeenth child with CP.

Discussion

CP is characterized by heterogeneous risk factors and specific etiology [14]. Although prematurity and low birthweight are the main risk factors for CP, it is also associated with congenital brain malformations, genetic predisposition, hypoxic-ischemic encephalopathy, stroke, kernicterus, maternal infection, multiple pregnancies, neonatal convulsions, neonatal or post-neonatal meningitis, and sepsis [1, 8, 14–16]. Yet, according to numerous epidemiological studies, half of the children with CP were carried to term and had none of the identified risk factors [1, 15–17].

In the cohort analyzed as a part of our study, hormonally maintained pregnancy, twin pregnancy, threatened abortion in the first half of pregnancy, bleeding after the 20th week of gestation, maternal infection, and anemia and hypertension in the second half of pregnancy were identified as the main prenatal risk factors for CP. As pregnant women are typically prescribed pharmacological therapy in order to prevent premature contractions and bleeding, the large percentage of hormonally maintained pregnancies, threatened abortions, and bleeding in our sample is not surprising. It is also worth noting that, according to Tollanes et al. [18], who studied birth outcomes in over 20,000 twins, the prevalence of CP is higher in twin pregnancies, indicating that CP in one twin increases the likelihood of CP in the other twin.

These findings concur with our data, as 28.9% of children with CP who had at least one of the prenatal risk factors were a result of twin pregnancies. The association between CP and twin pregnancy can be explained by a greater prevalence of premature birth in twins [5, 19]. In a population-based study conducted by Arnaud et al. [13] involving 2,273 premature babies, a quarter of the children were from multiple pregnancies. These authors noted that the presence of non-specific infection indicators, such as maternal fever, antibiotic use, and chorioamnionitis in the period immediately preceding labor, is associated with an increased risk of CP. This association has also been observed for maternal infections that occurred in early pregnancy, even though these findings

are inconclusive [8, 20]. In our study, every tenth mother reported having an infection during pregnancy, while in the sample analyzed by Elmagid and Magdy [5], this percentage was slightly lower (6%). Available evidence indicates that maternal infection, even in cases where there is no detectable inflammatory response, can lead to CP by transmitting the pathogen to the fetus and inducing systemic inflammation, which renders the developing brain sensitive to potential insults [21].

In our sample, prematurity was the leading perinatal risk factor, followed by low birthweight, low AS, assisted delivery (emergency cesarean section and vacuum fetal extraction), resuscitation, and pelvic presentation of the fetus. These results are in line with the available data, indicating that premature birth poses the greatest risk for the occurrence of CP, especially among extremely preterm babies [12–14, 22, 23]. For instance, about 10% of children born before 28 weeks of gestation are diagnosed with CP.

A meta-analysis of studies examining the relationship between CP prevalence and gestational age revealed that children born after 32−36, 28−31, and before 27 weeks of gestation had a 5−6, 32−54, and 60−130 times greater risk of developing CP in relation to children born at term, respectively [23]. In our cohort, prematurity was noted in about half of the cases, whereby 17% of children with CP were born after 28−31 weeks of gestation, and 7% were delivered before the 28th gestational week. Empirical evidence indicates that white matter damage as a result of intracerebral hemorrhage (ICH) and periventricular leukomalacia (PVL) is the most common pathological finding in premature infants who have developed CP [24, 25]. Moreover, Horber et al. [25] found that more than 80% of children born before 32 weeks of gestation had predominantly white matter damage, and its prevalence relative to gray matter damage was higher in this group of children compared to those born after 32 weeks of gestation. In extremely premature infants and those with extremely low birthweight, PVL and IVH are important prognostic factors for the development of CP [26]. The presence of infection also contributes to an increased risk of CP in premature infants [27, 28].

In our study, the prevalence of perinatal factors was high in children with CP delivered prematurely, which may be a consequence of the prenatal predisposition that led to premature birth. It is believed that children born prematurely are exposed to both perinatal and prenatal risk factors [29]. According to our data, perinatal risk factors are more prevalent in preterm infants than in those carried to term. This observation is in line with the available evidence suggesting that the number of children with at least one of the perinatal risk factors decreases significantly with gestational age, which may be associated with a gradual decline in the CP prevalence after 32 weeks of gestation [19, 26].

Our analyses further revealed that perinatal risk factors are most prevalent in the spastic bilateral type, followed by the dyskinetic type of CP. The bilateral spastic form of CP is most common in premature infants [6, 19, 30], and prematurity is recognized as the main risk factor in the perinatal period [31, 32]. Arnaud et al. [13] noted a bilateral spastic form of CP in two-thirds of preterm infants. According to our results, three-quarters of children with a diplegic form and half of the children with a quadriplegic form of CP were delivered prematurely. An ample body of evidence points to a link between premature birth and bilateral spastic diplegia [5, 30] as well as PVL occurrence [1, 15, 24, 25]. Spastic diplegia is typically attributed to damage to immature oligodendroglia during the 20–34 weeks of the gestational period, and PVL is the most common neuropathological substrate during neuroimaging [1, 15]. Spastic quadriplegia occurs in 20% of children with CP, and this clinical phenotype is also associated with premature birth and the presence of periventricular leukomalacia and multicystic cortical encephalomalacia [16].

Low AS, respiratory distress, and neonatal convulsions may be indicative of asphyxia but are also neurological signs that can indicate brain damage that occurred *in utero*. The role of asphyxia in the development of CP is related to the presence of other risk factors, such as markers of infection and placental disorders, which can result in abnormal fetal heart rate and low AS [33, 34]. In about 3% and 7% of cases analyzed as a part of our study, a placental abnormality and an AS < 7 were registered, respectively. However, when considered in isolation, these results have limited significance without determining the presence of other risk factors. According to Joud et al. [30], an AS < 7 which fails to improve after 5 min post-delivery is significantly associated with the development of CP.

Breech presentation at birth is thought to contribute to the development of asphyxia, but it may also be indicative of prenatal fetal abnormalities, such as intrauterine fetal growth retardation, fetal anomalies, oligohydramnios, gestational diabetes, and maternal thyroid dysfunction [35, 36]. In our study, 13.5% of children for whom data on the fetal position was available had breech presentations. Several authors have noted that assisted vaginal delivery or emergency cesarean section are significant risk factors for CP [5, 7, 13, 30]. Our analyses revealed that 41.4% of children with CP for whom the type of delivery was recorded required assisted childbirth, which is consistent with the findings based on a sample of 1,000 Egyptian children [5].

Based on our analyses, respiratory distress syndrome, the need for treatment in the NICU, assisted ventilation, hypoxic-ischemic encephalopathy (HIE), and neonatal convulsions emerged as the leading neonatal risk factors for CP. The first three factors noted above are causally related and are the focus of preventive measures, made possible by modern achievements in the field of intensive care and therapy that can be offered to newborns. Among the neonatal measures that can be adopted for the prevention of CP, induction of hypothermia in order to reduce intrapartum hypoxia and ischemia is particularly beneficial, according to some authors. In Sweden, this strategy was introduced in 2007 and has resulted in a significant reduction in the severe CP form [3, 9].

The lower prevalence of quadriplegic and dyskinetic forms of CP (considered a consequence of HIE) in the first decade of the 21st century compared to the last decade of the 20th century is also associated with recent advances in ob-

stetric and neonatal care [9]. Mechanical ventilation is widely used when caring for extremely premature babies and contributes to an increased risk of CP [37]. HIE during the neonatal period is a strong predictor of CP and occurs mainly in children born at term [5, 38]. Neonatal convulsions are early manifestations of brain damage and can be mild, reversible, or severe, whereby the latter form results in long-term disability. Together with a low AS or the presence of HIE, neonatal convulsions are thought to be indicative of perinatal asphyxia. However, there is a possibility that brain damage occurred earlier during pregnancy and was not associated with ischemia or hypoxia at birth [33].

Identifying specific risk factors for CP contributes to a better understanding of the potential mechanisms of pathogenesis. As different CP subtypes exhibit different etiologic spectra, they will inform the measures that can potentially be taken to address the preventable causes of CP, as well as the most optimal preventive strategies in these patients. Targeting the preventable risk factors could be crucial in modifying the CP trends.

Conclusion

According to our findings, hormonally maintained pregnancy, twin pregnancy, premature birth with low birthweight, assisted delivery, need for treatment in the NICU, and assisted ventilation are the most common risk factors for CP. However, most factors that increase the likelihood of CP do not act in isolation but rather lead synergistically to damage in the affected children. Perinatal risk factors are most prevalent in preterm infants and spastic bilateral CP type. Premature birth poses the greatest risk for the occurrence of CP, and spastic bilateral CP type was most prevalent in the group of preterm-born children included in our study.

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