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ORYGINALNY ARTYKUŁ NAUKOWY

PRENATAL AND PERINATAL RISK FACTORS FOR CEREBRAL PALSY IN KURDISH CHILDREN: A CASE-CONTROL STUDY

PRENATALNE I OKOŁOPORODOWE CZYNNIKI RYZYKA PORAŻENIA MÓZGOWEGO U KURDYJSKICH DZIECI: BADANIE KLINICZNO-KONTROLNE

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Summary

Background. Cerebral palsy (CP) is the most frequent disease-causing physical disability in childhood. This study aimed to analyze prenatal and perinatal risk factors contributing to CP in Kurdish children.

Material and methods. A case-control study was conducted in Duhok, north of Iraq. The cases of CP children 0-10 years old, born between 2011 and 2021, were collected from primary health care centers and the rehabilitation center. The controls were age- and sex-matched with normal neurologic development. Maternal characteristics and prenatal and postnatal factors were studied.

Results. The study included 100 cases and 100 controls. Postnatal respiratory distress, infection acquired during labor, neonatal asphyxia, and maternal education were significantly different. The logistic regression showed the following variables as significant risk factors for CP: the use of drugs by mother, infections acquired during pregnancy and labor, intra uterine growth retardation, postnatal respiratory distress, asphyxia, consanguinity, a sibling with CP, maternal employment, maternal education, premature and prolonged rupture of membranes, parity,

multiple pregnancies, smoking by the mother, meconium aspiration, delivery by emergency Cesarean section, delayed first cry, hemorrhage during late pregnancy, neonatal seizures, birth defects, need for cardiopulmonary resuscitation during labor, hypocalcemia and use of antibiotics during neonatal period.

Conclusions. Various prenatal and perinatal factors were found to significantly predispose to CP.

Keywords: meconium, cerebral palsy, maternal health, seizure, cry

Streszczenie

Wprowadzenie. Mózgowe porażenie dziecięce (MPD) jest najczęstszą chorobą powodującą niepełnosprawność fizyczną w dzieciństwie. Niniejsze badanie miało na celu analizę prenatalnych i okołoporodowych czynników ryzyka przyczyniających się do wystąpienia MPD u kurdyjskich dzieci.

Materiał i metody. Badanie kliniczno-kontrolne przeprowadzono w Duhok, na północy Iraku. Przypadki dzieci z MPD w wieku 0-10 lat, urodzonych w latach 2011-2021, zostały zebrane z ośrodków podstawowej opieki zdrowotnej i ośrodka rehabilitacji. Grupy kontrolne z prawidłowym rozwojem neurologicznym zostały dobrane pod względem wieku i płci. Zbadano charakterystykę matki oraz czynniki prenatalne i postnatalne.

Wyniki. Badanie obejmowało 100 przypadków i 100 osób z grupy kontrolnej. Poporodowa niewydolność oddechowa, zakażenie nabyte podczas porodu, zamartwica urodzeniowa i wykształcenie matki różniły się w sposób istotny. Regresja logistyczna wykazała następujące zmienne jako istotne czynniki ryzyka wystąpienia MPD: stosowanie leków przez matkę, zakażenia nabyte podczas ciąży i porodu, wewnątrzmaciczne zahamowanie wzrastania płodu, poporodowe zaburzenia oddychania, zamartwica, pokrewieństwo, rodzeństwo z MPD, zatrudnienie matki, wykształcenie matki, przedwczesne i przedłużone pęknięcie błon

płodowych, liczba porodów, ciąża mnoga, palenie tytoniu przez matkę, aspiracja smółki, poród przez cesarskie cięcie w trybie nagłym, opóźnienie pierwszego płaczu, krwotok w późnym okresie ciąży, drgawki noworodkowe, wady wrodzone, potrzeba resuscytacji krążeniowo-oddechowej podczas porodu, hipokalcemia i stosowanie antybiotyków w okresie noworodkowym.

Wnioski. Stwierdzono, że różne czynniki prenatalne i okołoporodowe w znaczącym stopniu predysponują do wystąpienia MPD.

Słowa kluczowe: smółka, mózgowe porażenie dziecięce, zdrowie matki, drgawki, płacz

Introduction

Cerebral palsy (CP) is the most frequent disease-causing physical disability in childhood. It includes different permanent deficiencies of movement and posture that interfere with activity. They are the result of non-progressive damages that involve fetal or infant brain development. This motor impairment accompanying CP may also be coupled with primary or secondary disorders of perception, sensation, communication, cognition, and behavior with epilepsy, as well as with secondary problems of the musculoskeletal system [1,2].

In developed countries, the known predisposing factors for CP in children who were born at full-term include low birth weight, placental abnormalities, meconium aspiration syndrome, congenital malformations, asphyxia during delivery, emergency Cesarean delivery, hypoglycemia, neonatal seizures, respiratory distress syndrome, and neonatal infections [1,3]. Low birth weight and small for gestational age (SGA) are possibly the main predisposing factors for CP [2,4]. The causes of CP may also be related to the quality of healthcare management [5]. In developing countries, the increased risk of CP is usually due to exposure to perinatal events [1].

Further clarification of the causes of CP can be obtained from large population-based data sets that include information from CP and birth defects registries. In one large, prospective, population-based study, 91.5% of term and near-term neonates who developed CP, did not have any potentially asphyxiating birth event, but intrauterine growth retardation and major birth defects were more frequent in CP infants as compared to controls [6,7]. Studies that involved placental disorders and genetic investigations point to prenatal processes being important for both CP and neonatal encephalopathy, which, in 20% of cases, precede CP in term and preterm children [7-9].

Since CP is highly prevalent in our society and exerts a high burden on the families of patients, as well as health authorities, in Kurdistan, this study is the first study carried out in this locality that may help us clarify the etiology and to find out factors significantly related to its occurrence so that avoiding such instances may hopefully help lower the frequency and lighten the burden of CP on our society.

Aim of the work

The aim of this study was to assess prenatal and perinatal risk factors that contribute to CP in Kurdish children.

Material and methods

A case-control study was conducted in Duhok, north of Iraq. The cases of CP were collected from primary healthcare centers and the rehabilitation center that is the referral center for all CP cases diagnosed in the city of Duhok. A questionnaire was filled out by the researcher through interviews with the parents. The controls were matched with cases in terms of age and

gender with normal neurologic development. They were chosen from children who visited healthcare centers with their parents. Maternal age, maternal education, number of children living, number of abortions, gestational age (preterm: ≤36 weeks; full-term: 37-42 weeks), single or multiple pregnancies, type of delivery, number of prenatal consultations, delayed first cry, child's gender, weight at birth (normal: ≥2,500 g; low: <2,500 g), and presence of congenital anomalies were all studied for both groups then statistically analyzed to find out the significance using Pearson's chi-squared test or Fisher's exact test, while Student's t-test was used to compare two independent samples of numerical variables. Univariate and multivariate logistic regression was applied to identify predictive factors. Children 0-10 years old, born between 2011 and 2021, living in Duhok, with a diagnosis of CP were included, while children diagnosed with progressive encephalopathies were excluded.

Results

The study included 100 cases and 100 controls. The children's background characteristics, as shown in Table 1 (infections acquired during labor, postnatal respiratory distress, and neonatal asphyxia), were significantly different between cases and controls (p=0.044, 0.002, and 0.013, respectively). The other characteristics did not differ significantly.

Table 1. Distribution of respondents according to the children's background characteristics

Characteristics		Group status				*p*-value
		Case		Control		
		N	%	N	%	
Gender	Male	54	54	58	58	0.569
	Female	46	46	42	42	
Drugs taken by the mother during labor and delivery	Analgesics	1	1	1	1	0.600
	Anti-hypertensive drugs	5	5	7	7	
	Folic acid	30	30	35	35	
	No	49	49	39	39	

	Prostaglandin tab	1	1	4	4	
	Tonics, antibiotics	14	14	14	14	
Infections acquired during pregnancy and labor	**Yes**	29	29	17	17	0.044
	No	71	71	83	83	
Gestational age at delivery	**Term**	68	68	75	75	0.273
	Preterm	32	32	25	25	
Birth weight	**Low birth weight**	19	19	10	10	0.084
	Normal	76	76	88	88	
	Overweight	5	5	2	2	
First initial crying	**Immediate**	60	60	72	72	0.073
	Delayed	40	40	28	28	
Intrauterine growth retardation	**Yes**	19	19	13	13	0.274
	No	81	81	87	87	
Postnatal respiratory distress	**Yes**	35	35	16	16	0.002
	No	65	65	84	84	
Hypoglycemia after delivery	**Yes**	9	9	3	3	0.074
	No	91	91	97	97	
Hypocalcemia	**Yes**	2	2	2	2	1
	No	98	98	98	98	
Intracranial hemorrhage	**Yes**	2	2	3	3	0.651
	No	98	98	97	97	
Neonatal sepsis	**Yes**	27	27	19	19	0.179
	No	73	73	81	81	
Neonatal asphyxia	**Yes**	37	37	21	21	0.013
	No	63	63	79	79	

The mothers' characteristics did not differ between cases and controls except for the mother's educational level, where being illiterate was more commonly associated with CP (p=0.016), as shown in Table 2.

Table 2. Distribution of respondents according to mothers' background characteristics

Characteristics		Group status				*p*-value
		Case		**Control**		
		N	**%**	**N**	**%**	
Consanguinity	**First cousin**	42	42	38	38	0.377
	No	41	41	50	50	
	Others	17	17	12	12	
Employment	**Yes**	9	9	11	11	0.637
	No	91	91	89	89	

Education	**Illiterate**	28	28	14	14	0.016
	Primary	37	37	36	36	
	Intermediate	16	16	16	16	
	Preparatory	14	14	16	16	
	University	5	5	18	18	
Diabetes mellitus	**No**	93	93	95	95	0.834
	Gestational diabetes mellitus	4	4	3	3	
	Known diabetes mellitus	3	3	2	2	
Premature rupture of membrane	**Yes**	16	16	10	10	0.207
	No	84	84	90	90	
Hypertension	**No**	89	89	93	93	0.540
	Gestational	9	9	5	5	
	Permanent	2	2	2	2	
Parity	**Primiparous**	16	16	20	20	0.462
	Multiparous	84	84	80	80	
Number of pregnancies	**Single**	99	99	98	98	0.561
	Twin	1	1	2	2	
Smoking during pregnancy	**Yes**	6	6	4	4	0.516
	No	94	94	96	96	
Placental abnormalities	**Yes**	4	4	2	2	0.407
	No	96	96	98	98	

Logistic regression analysis, as shown in Table 3, reveals that there is a significant association between CP and use of drugs by the mother, infections acquired during pregnancy and labor, intrauterine growth retardation, postnatal respiratory distress, asphyxia, consanguinity, a sibling with CP, maternal employment, maternal education, premature and prolonged rupture of membranes, parity, number of pregnancies, smoking by the mother, meconium aspiration, delivery by emergency Cesarean section, delayed first cry, hemorrhage during late pregnancy, neonatal seizures, birth defects, need for cardiopulmonary resuscitation during labor, hypocalcemia, and use of antibiotics during the neonatal period.

Table 3. Correlation of different variables with CP by logistic regression

Group status	*p*-value	Odds ratio	95% CI	
			Lower bound	Upper bound
Gender	0.682	0.311	0.001	82.386
Drugs taken by the mother during labor and delivery	0.266	1.891	0.615	5.811
Infections acquired during pregnancy and labor	0.211	1.832	0.709	4.730
Gestational age at delivery	0.269	0.602	0.244	1.480
Birth weight	0.074	0.127	0.013	1.221
Intrauterine growth retardation	0.215	1.973	0.675	5.768
Postnatal respiratory distress	0.100	2.227	0.858	5.782
Intracranial hemorrhage	0.502	0.464	0.049	4.366
Neonatal sepsis	0.957	0.970	0.319	2.948
Neonatal asphyxia	0.427	1.440	0.585	3.547
Consanguinity	0.918	1.063	0.333	3.397
A sibling with CP	0.011	4.095	1.388	12.082
Employment	0.960	1.038	0.244	4.412
Education	0.025	5.802	1.241	27.131
Diabetes mellitus	0.228	0.140	0.006	3.419
Premature rupture of membranes	0.072	3.371	0.898	12.650
Prolonged rupture of membranes	0.146	3.342	0.656	17.014
Hypertension	0.786	0.663	0.034	12.816
Parity	0.238	1.858	0.664	5.203
Number of pregnancies	0.421	3.384	0.174	65.674
Smoking during pregnancy	0.373	2.192	0.390	12.314
Placental abnormalities	0.818	0.770	0.083	7.149
Meconium aspiration	0.351	2.075	0.448	9.614
Instrumental emergency Cesarean section delivery	0.536	1.325	0.543	3.232
First initial crying	0.42	1.35	0.65	2.79
Hemorrhage in late pregnancy	0.22	3.45	0.47	25.09
Neonatal seizures	0.084	5.630	0.792	40.036
Birth defects	0.87	1.18	0.15	9.05
Need for CPR	0.54	1.32	0.55	3.16
Hypocalcemia	0.84	1.28	0.11	14.28
Hyperbilirubinemia	0.184	0.539	0.216	1.342
Antibiotics during the neonatal period	0.020	3.186	1.203	8.440

Discussion

This study demonstrated that a significant risk factor for CP was infections the newborn got after birth. This is in line with other studies [10-14]. Infection leads to the release of cytokines that produce inflammatory changes in the brain, leading to damage and CP [10-14].

Intrauterine growth retardation was found to be a risk factor for CP in this study. It is often assumed that fetuses with growth restriction are especially at risk of asphyxia at birth, and birth asphyxia explains the link between growth restriction and CP [6,15-17]. This is reiterated in literature, which indicates that low birth weight is a risk factor in several studies [1,10,12,18-21].

Postnatal respiratory distress has been proven to be significantly associated with CP. Hypoxia in the early hours of life due to different causes can produce brain damage, leading to CP. This is in line with a meta-analysis of observational studies by Mc Intyre et al. [10].

In this study, we found that asphyxia at birth significantly predisposes one to CP. The similar results were obtained in other studies [1,10,21-24]. There has been some evidence indicating that birth asphyxia is not necessarily the main cause of CP [25]. A study by Victora et al. [26] revealed that 41% of fetal deaths are caused by intrapartum asphyxia, even in hospital deliveries.

The parents' consanguinity was demonstrated to be related to CP in this study, which raises the possibility of a hereditary risk. This is in line with a study conducted in Palestine [21] and a study from Türkiye [27]. Some authors suggest that consanguinity increases susceptibility to multifactorial diseases and increases risks for autosomal recessive disorders when compared to the general population [28].

Having a sibling with CP strongly increases the risk of CP, as found in our study. This supports the idea of the role of genetic disorders. Until recently, causative mutations have been

linked to 1-2% of cases of CP. Recent genetic studies of exome sequencing show that 14% of cases were linked to single-gene mutations, while up to 31% had clinically relevant copy number variations [14]. This has also been found in other studies [6,29,30].

As for the socio-demographic factors, maternal employment was linked to CP in our study. This agrees with a study conducted in Iraq that proved a strong association of CP with maternal employment [22,31]. This association is probably due to the stress and workload pressure that the mother is exposed to, which would have a higher adverse effect on her pregnancy compared to the benefits received from the better income from her employment, eventually resulting in having a baby with CP.

The educational level of the mother showed a significant association with CP, with illiterate mothers having the highest risk of having a child with CP, which corresponds with other studies [32-34]. The underlying causal pathway is unknown, but it is well known that mothers with higher education have better health behavior, leading to less risk of CP.

In this study, it was concluded that each prolonged and premature rupture of the membrane can increase the possibility of sepsis, which can lead to CP. This is also in line with other studies [21].

Multiparity was found in our study to be significantly associated with CP, which is similar to the results from a study by Saadi et al. [22], but at the same time contrary to other studies that identified multiparity to be more likely associated with CP [21].

Multiple pregnancy is high risk and frequently leads to low birth weight and prematurity, which in turn predisposes one to CP. This result has been proven by our study and is in agreement with other studies [11,13,14,21,34].

In this study, smoking by the mother during pregnancy was a risk factor for CP. This is supposedly related to fact that smoking causes hypoxemia in the fetal brain cells, leading to their damage and, consequently, to CP. Smoking may also lead to placental infarction and

microinfarctions, interrupting blood supply to parts of the placenta. This leads to reduced blood and oxygen supply to the fetus, causing brain maldevelopment.

Meconium-stained liquor usually indicates fetal distress and hypoxemia of the fetus, which may lead to brain damage. It may also be aspirated, leading to obstruction and various pulmonary complications that consequently potentiate hypoxemia and brain injury. In this way, meconium-stained liquor is a predisposing factor for CP. Our study reached this result and was in agreement with other studies [10,21].

The delivery by emergency Cesarean section was also significantly associated with CP, similar to what was found by other studies [10,12]. This type of delivery may be associated with potentially fatal breathing problems that in turn lead to brain injury.

As concluded by our study and a study by Hirvonen et al. [24], a delayed first cry is a manifestation of hypoxic-ischemic encephalopathy, which is a predisposing factor for CP.

Bleeding in late pregnancy may also increase the risk of prematurity, which by itself leads to brain leukomalacia and then CP, as found by this study and a study by O'Callaghan et al. [13].

A significant association between neonatal seizures and CP was identified in this study and other studies [10,21], which denotes a brain anomaly or brain damage that leads to the seizure and CP.

The presence of birth defects and congenital anomalies are significantly associated with CP, which is in line with other studies [1,6,10,12,14]. Either the association between brain anomalies and this malformation or the fact that these anomalies increase the risk of prematurity can explain this.

In this study, neonates who needed cardiopulmonary resuscitation at birth were significantly at risk of CP, similar to the results of study by Hirvonen et al. [24].

Cardiopulmonary instability can lead to hypoxia and ischemia and, as a result, hypoxic ischemic encephalopathy.

Hypocalcemia in neonatal life was found to be significantly associated with CP in our study, as well in other studies [24]. It is well known to be present in hypoxic ischemic encephalopathy.

In this study, the exposure to antibiotics in neonatal life increased the risk of CP, which was also confirmed in a study by Saadi et al. [22]. The use of antibiotics potentiates the development of persistent periventricular leukomalacia, which may lead to CP.

There were some limitations to this study. Some factors that are known risk factors, as found in literature and which are related to the prenatal and perinatal periods, could not be assessed because they were not remembered by the mothers and birth records were not accessible.

Conclusions

The two largest risk factors for CP were maternal education and neonatal seizures. Having a sibling with CP, hemorrhage in late pregnancy, premature and prolonged rupture of membranes, multiple gestations, and respiratory distress in the neonatal period are also significantly associated with CP. The presented risk factors may be considered as indicators to identify children at risk of developing CP and to target individuals for early intervention.

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