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Changing panorama in risk factors of cerebral palsy

Promenljiva slika faktora rizika od cerebralne paralize

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Abstract

Background/Aim. The etiology of cerebral palsy (CP) is multifactorial and not yet fully understood. The aim of this study was to determine the changes in CP etiological factors over the past 30 years. **Methods.** A retrospective study analyzed a database of 296 individuals with CP. Risk factors (RFs) were divided into preconception, antenatal, intrapartum, and neonatal. Patients on the register were divided into three cohorts: those born before 2000, the ones born between 2000 and 2010, and those born after 2010. The changes in CP RFs were investigated at ten-year intervals. **Results.** The five RFs with the highest total frequency were low birth weight (46.62%), prematurity (44.25%), advanced maternal age – over 35 years (37.16%), emergency cesarean section (33.78%), and birth asphyxia (25.33%). The consanguineous marriage rate was 22.29%. **Conclusion.** Low birth weight and prematurity rates, which are the most frequently identified RFs, are gradually increasing. The rate of birth asphyxia has decreased in the last ten years. The rate of advanced maternal age is increasing, and consanguineous marriage is still an important RF in Turkey.

Key words:
birth weight; causality; cerebral palsy; infant, premature; risk factors.

Apstrakt

Uvod/Cilj. Etiologija cerebralne paralize (CP) je multifaktorijalna i još uvek nije potpuno razjašnjena. Cilj rada bio je da se utvrde promene u etiološkim faktorima CP tokom poslednjih 30 godina. **Metode.** Retrospektivnom studijom analizirana je baza podataka 296 bolesnika sa CP. Faktori rizika (FR) podeljeni su u prekonceptualne, antenatalne, intrapartalne i neonatalne. Bolesnici u registru podeljeni su u tri kohorte: na bolesnike rođene pre 2000. godine, one rođene između 2000. i 2010. godine i bolesnike rođene posle 2010. godine. Promene u FR od CP istraživane su u intervalima od po deset godina. **Rezultati.** Najveću učestalost imalo je sledećih pet FR: niska porođajna težina (46,62%), prevremenost (44,25%), životno doba majke iznad 35 godina starosti (37,16%), hitni carski rez (33,78%) i asfiksija pri porođaju (25,33%). Stopa brakova između srodnika iznosila je 22,29%. **Zaključak.** Stope niske porođajne težine i prevremenost, koji su najčešće označeni FR od CP, postepeno se poboljšavaju. Stopa asfiksije pri porođaju smanjena je u poslednjih deset godina. Stopa 'odmakla starost majke' raste, a brak između srodnika i dalje predstavlja važan FR u Turskoj.

Ključne reči:
telesna masa, rođenje; etiološki faktori; cerebralna paraliza; nedonošče; faktori rizika.

Introduction

Cerebral palsy (CP) is a group of permanent disorders affecting the development of movement and posture, causing a limitation of activity, attributed to nonprogressive disturbances that occur in the developing fetal or infant brain. The motor disorders of CP are often accompanied by disturbances of sensation, perception, cognition, communication, and behavior associated with epilepsy and secondary musculoskeletal problems [1].

The birth prevalence of CP has been calculated as 1.2–2.5/1,000 [2]. In a study conducted in Turkey, the prevalence of CP was found to be 4.4 *per* 1,000 live births [3]. The etiology of CP is multifactorial and not yet fully understood. While CP may be the result of exposure to a single etiological factor such as perinatal asphyxia, irreversible

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brain damage may also occur as a result of consecutive exposure to many factors [4]. Fahey et al. [5] reported that genetic mutations may be responsible for a substantial proportion of CP cases. At the same time, an environmental second hit those who suffer from a genetic susceptibility to CP may also be an important factor [6]. It has been reported that polymorphism in the catalase antioxidant gene is associated with decreased defense capacity against reactive oxygen species and causes higher susceptibility to CP in infants with perinatal hypoxic-ischemic encephalopathy [7]. Furthermore, no specific etiological factor can be currently identified in more than 50–75% of CP cases [8]. Foremost risk factors (RFs) are prematurity and low birth weight (LBW), but the precise etiology of most cases of CP remains obscure.

Identifying a single and clear cause of CP is not always possible. Therefore, the terminology of RF is used to describe the etiology of the disease. Since the *per* pregnancy number for each etiological factor is not known, although the factors mentioned do not fully reflect RFs, these etiological factors will be referred to as RFs in this article as a generally accepted view. It would be accurate to evaluate RFs as a predisposition for the development of CP and the etiology of CP as a process that includes an integrated form of causal evidence [8]. Various RFs change over time, such as changes in pregnancy healthcare and neonatal care. Therefore, CP surveillance should be reviewed frequently in all countries.

In the last 30 years, there have been radical changes in etiological factors and our understanding of them. The factors shown in the etiology of CP will change over time due to the decrease in stillbirth and neonatal mortality rates and the increase in the survival rate of premature babies.

The aim of this study was to investigate the changes in CP RFs by screening individuals with CP who were followed up in a pediatric rehabilitation clinic in the last 30 years and to compare these RFs by CP subtype.

Methods

Participants

This retrospective study was carried out by reviewing the database of 296 individuals with CP followed in the university pediatric rehabilitation clinic. CP RFs and demographic information were obtained from the database. Twenty-two cases with missing information in the register were excluded. No parent declined to be involved in the study.

Research ethics approval was obtained from the Istanbul Medeniyet University Goztepe Ethics Committee (No. 2021/0006, from January 13, 2021). All patients' caregivers gave informed consent with the approval of the Ethics Committee.

Measures

CP subtypes are classified according to the Surveillance for Cerebral Palsy in Europe classification into four groups: spastic (unilateral and bilateral), dyskinetic (dystonic and choreoathetoic), ataxic, and non-classifiable [9].

CP RFs were divided into four groups: preconception, antenatal, intrapartum, and neonatal RFs with reference to the work of McIntyre et al. [10]. Then, RFs in the data were distributed to the appropriate RF group. Findings comprised four preconception, nine antenatal, eight intrapartum, and six neonatal RFs.

Risk factors

The RFs in the first, preconception group, are the following: consanguine marriage, blood incompatibility, maternal age, previous maternal miscarriage, and stillbirths. In the second, antenatal group, the following RFs are present: prematurity, LBW, plurality, prenatal infection, third-trimester hemorrhage, gestational diabetes, preeclampsia, maternal morbidity, and placental/amniotic abnormalities. In the intrapartum group, the RFs are as follows: birth asphyxia (BA), emergency cesarean section (C/S), home birth, premature rupture of membranes, vacuum and forceps, abnormal presentation, cord around neck, and meconium stained. In the final, neonatal group, these RFs are present: postnatal seizure, hypoglycemia, postnatal infection, metabolic and developmental diseases, postnatal cerebrovascular accident (CVA), and prolonged jaundice.

Babies born under 2,500 g were accepted as LBW, and babies born alive before the 37th gestational week were accepted as preterm [11]. Being over 35 years old was accepted as an advanced maternal age. Babies who were diagnosed with neonatal hypoglycemia by the neonatologist in the national health system were included as hypoglycemia. Miscarriage and stillbirths refer to miscarriage and stillbirths in the same woman who has given birth to a child with CP.

The data were classified according to date of birth and divided into three cohorts: those born before 2000, those born between 2000 and 2010, and those born after 2010. Changes in CP RFs were investigated at ten-year intervals. Secondly, the distribution and variation of RFs according to the CP subtype were investigated.

Data analysis

All statistical analyses were performed with SPSS version 25.0 software (IBM, Chicago, IL). Descriptive statistics were presented as frequencies with percentages, for categorical variables and mean ± standard deviation (minimum-maximum) for continuous variables. In order to investigate the relationship between two categorical variables, Pearson's Chi-square and Fisher's exact tests were used. Likewise, multinominal logistic regression was used to predict the prevalence of more than two categories. Statistical significance was determined as $p < 0.05$.

Results

The study included 296 patients, 135 (45.6%) female and 161 (54.4%) male. Their mean age was 11.85 ± 7.20 (min. =

1.00, max. = 38) years; 136 (45.9%) patients were born between 2010 and 2020, 126 (42.6%) were born between 2000 and 2010, and 34 (11.5%) patients were born before 2000.

The distribution according to CP subtypes is shown in Figure 1. The Chi-squared test result shows no significant difference in CP subtypes between cohorts [$\chi^2(6.\ 296) = 8.59$, $p = 0.20$].

Among the 296 patients, 277 (93.6%) had RFs, and the frequencies of RFs are presented in Table 1.

Overall, the five RFs with the highest total frequency were LBW (46.62%), prematurity (44.25%), advanced maternal age (37.16%), emergency C/S (33.78%), and BA (25.33%). The consanguineous marriage rate was 22.29%. When classified according to ten-year groups, the occurrence

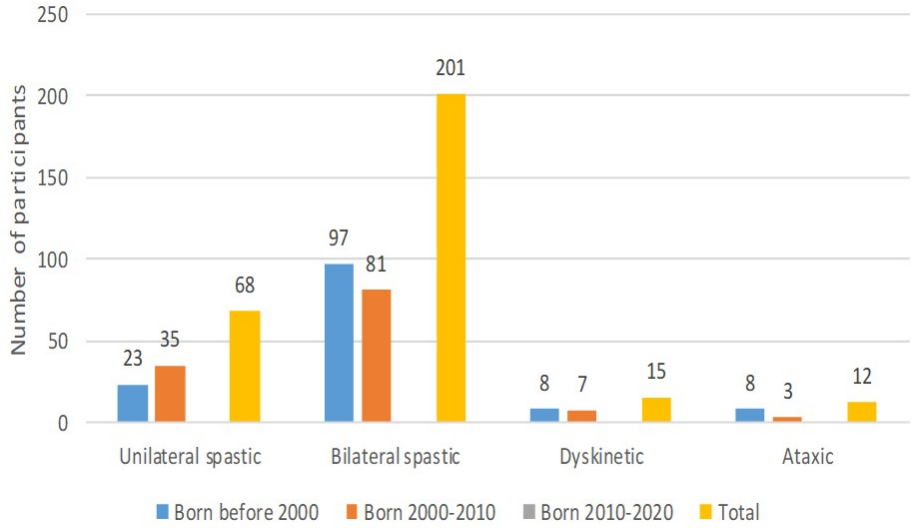

Fig. 1 – Distribution of cerebral palsy subtypes according to age groups.

Table 1

Frequencies of group/particular risk factors for cerebral palsy depending on the age group of patients

Risk factors	Born 2010–2020	Born 2000–2010	Born before 2000	Total
Preconception	79 (46.20)	71 (41.52)	21 (12.28)	171 (57.8)
consanguineous marriage	28 (42.42)	31 (46.97)	7 (10.61)	66 (38.6)
blood incompatibility	1 (8.33)	7 (58.33)	4 (33.33)	11 (6.4)
advanced maternal age	61 (55.45)	38 (34.54)	11 (10.00)	110 (64.3)
miscarriage and stillbirths	14 (27.45)	23 (45.10)	14 (27.45)	51 (29.8)
Antenatal	91 (50.00)	74 (40.66)	17 (9.34)	182 (61.5)
prematurity	77 (58.78)	45 (34.35)	9 (6.87)	131 (72.0)
low birth weight	82 (59.42)	46 (33.33)	10 (7.25)	138 (75.8)
plurality	10 (62.50)	5 (31.25)	1 (6.25)	16 (8.8)
prenatal infection	1 (11.11)	5 (55.56)	3 (33.33)	9 (4.9)
3rd trimester hemorrhage	12 (37.50)	17 (53.13)	3 (9.37)	32 (17.6)
gestational diabetes	2 (25.00)	5 (62.50)	1 (12.50)	8 (4.4)
preeclampsia	13 (41.94)	13 (41.94)	5 (16.12)	31 (17.0)
maternal morbidity	5 (62.5)	3 (37.5)	0 (0.00)	8 (4.4)
placental/amniotic abnormalities	5 (100.00)	0 (0.00)	0 (0.00)	3 (1.6)
Intrapartum	73 (51.05)	59 (41.26)	11 (7.69)	143 (48.3)
birth asphyxia	26 (34.67)	39 (52.00)	10 (13.33)	75 (52.4)
emergency C/S	67 (67.00)	32 (32.00)	1 (1.00)	100 (69.9)
home birth	2 (50.00)	0 (0.00)	2 (50.00)	4 (2.8)
premature rupture of membranes	1 (14.29)	6 (85.71)	0 (0.00)	7 (4.9)
vacuum and forceps	2 (50.00)	1 (25.00)	1 (25.00)	4 (2.8)
abnormal presentation	0 (0.00)	3 (75.00)	1 (25.00)	4 (2.8)
cord around neck	0 (0.00)	3 (60.00)	2 (40.00)	5 (3.5)
meconium stained	0 (0.00)	3 (75.00)	1 (25.00)	4 (2.8)
Neonatal	34 (37.78)	40 (44.44)	16 (17.78)	90 (30.4)
postnatal seizure	10 (27.78)	17 (47.22)	9 (25.00)	36 (40.0)
hypoglycemia	0 (0.00)	3 (75.00)	1 (25.00)	4 (4.4)
postnatal infection	8 (36.36)	11 (50.00)	3 (13.64)	22 (24.4)
metabolic and developmental diseases	9 (56.25)	5 (31.25)	2 (12.50)	16 (17.8)
postnatal CVA	4 (50.00)	3 (37.50)	1 (12.50)	8 (8.9)
prolonged jaundice	6 (46.15)	6 (46.15)	1 (7.70)	13 (14.4)

C/S – cesarean section; CVA – cerebrovascular accident; Chi-square test used.
All values are given as numbers (percentages).

of premature birth in groups was 26.47%, 35.71%, and 56.61% (born between 2010 and 2020, born between 2000 and 2010, and born before 2000, respectively), and LBW in groups was 29.41%, 36.50%, and 60.30% (born between 2010 and 2020, born between 2000 and 2010, and born before 2000, respectively).

A Chi-square test for independence indicated no significant association between cohorts and RF groups of preconception, antenatal, and intrapartum, but a significant association was found between cohorts and neonatal RF group (Table 2).

Statistically significant associations for independence results between cohorts and RFs are shown in Table 3 (using a Chi-square test).

A Chi-square test for independence indicated no significant association between CP subtypes and RF groups of intrapartum and neonatal but a significant association between CP subtypes and preconception and antenatal RF groups (Table 4). *Post-hoc* analysis (adjusted residual analysis) was conducted to investigate which subtype of CP was significantly different. According to the Bonferroni adjustment, the critical *p*-value was determined as 0.006 (0.05/8 = 0.006). The association between antenatal RFs unilateral and bilateral spastic CP was statistically significant, $p < 0.006$.

Fisher's exact test results showed a significant association between preconception RFs and CP subtypes in patients born between 2010 and 2020, $p < 0.05$. Moreover, there was a significant association between antenatal RFs and CP subtypes in those born between 2000 and 2010, $p < 0.01$.

The association between placental/amniotic anomalies and ataxic CP was statistically significant, $p < 0.006$. For premature rupture of membranes, it was not possible to talk about a univariate significance.

Table 2

Frequency of group of risk factors for cerebral palsy, depending on the age group of patients

Risk factors	Born 2010–2020	Born 2000–2010	Born before 2000	*p*-values
Preconception	79 (26.7)	71 (24.0)	21 (7.1)	0.85
Antenatal	91 (30.7)	74 (25.0)	17 (5.7)	0.14
Intrapartum	73 (24.7)	59 (19.9)	11 (3.7)	0.08
Neonatal	34 (11.5)	40 (13.5)	16 (5.4)	0.04[a]

All values are given as numbers (percentages). [a]Statistically significant at level $p < 0.05$; Chi-square test used.

Table 3

Relation between the presence of particular/group cerebral palsy risk factors and age group of patients

Risk factors	Born 2010–2020		Born 2000–2010		Born before 2000		*p*-values
	present	absent	present	absent	present	absent	
Preconception							
blood incompatibility*	1 (0.3)	135 (45.6)	7 (2.4)	119 (40.2)	4 (1.4)	30 (10.1)	0.004[b]
advanced maternal age	61 (20.6)	75 (25.3)	38 (12.8)	88 (29.7)	11 (3.7)	23 (7.8)	0.04[a]
miscarriage and stillbirths	14 (4.7)	122 (41.2)	23 (7.8)	103 (34.8)	14 (4.7)	20 (6.8)	< 0.001[c]
Antenatal							
prematurity	77 (26.0)	59 (19.9)	45 (15.2)	81 (27.4)	9 (3.0)	25 (8.4)	< 0.001[c]
low birth weight	82 (27.7)	54 (18.2)	46 (15.5)	80 (27.0)	10 (3.4)	24 (8.1)	< 0.001[c]
prenatal infection*	1 (0.3)	135 (45.6)	5 (1.7)	121 (40.9)	3 (1.0)	31 (10.5)	0.04[a]
Intrapartum							
emergency C/S	67 (22.6)	69 (23.3)	32 (10.8)	94 (31.8)	1 (0.3)	33 (11.1)	< 0.001[c]
home birth*	2 (0.7)	134 (45.3)	0 (0.0)	126 (42.6)	2 (0.7)	32 (10.8)	0.04[a]
cord around neck*	0 (0.0)	136 (45.9)	3 (1.0)	123 (41.6)	2 (0.7)	32 (10.8)	0.02[a]
Neonatal							
postnatal seizure*	10 (3.4)	126 (42.6)	17 (5.7)	109 (36.8)	9 (3.0)	25 (8.4)	0.01[b]

C/S – cesarean section. All values are given as numbers (percentages).
Statistically significant at level: [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$; *Fisher's exact test.

Table 4

Relation between particular/group cerebral palsy risk factors and subtypes

Parameters	US	BS	D	A	*p*-values
Preconception	43 (14.5)	110 (37.2)	7 (2.4)	11 (3.7)	0.04[a]
Antenatal*	32 (10.8)	136 (45.9)	7 (2.4)	7 (2.4)	0.01[b]
prematurity	18 (6.1)	105 (35.5)	3 (1.0)	5 (1.7)	< 0.001[c]
low birth weight	21 (7.1)	105 (35.5)	5 (1.7)	7 (2.4)	0.01[b]
placental/amniotic abnormalities*	1 (0.3)	2 (0.7)	0 (0.0)	2 (0.7)	0.03[a]
Intrapartum	33 (11.1)	99 (33.4)	4 (1.4)	7 (2.4)	0.34
premature rupture of membranes	3 (1.0)	2 (0.7)	1 (0.3)	1 (0.3)	0.04[a]
Neonatal*	19 (6.4)	64 (21.6)	5 (1.7)	2 (0.7)	0.71

US – unilateral spastic; BS – bilateral spastic; D – dyskinetic; A – ataxic.
All values are given as numbers (percentages).
Statistically significant at level: [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$; *Fisher's exact test; Chi-square test used.

Regarding the association between CP subtypes and listed RFs investigated by cohorts, it was found that Fisher's exact test results showed that there was a significant association between prematurity and CP subtypes in cohorts born between 2000 and 2010, $p < 0.01$. Furthermore, there was a significant association between LBW and CP subtypes in cohorts born between 2000 and 2010, $p < 0.05$.

Discussion

This study is the most recent on CS RFs in Turkey. In this study, the changes in CS RFs were investigated at ten-year intervals. The distribution of CP subtypes is compatible with the literature [2, 12]. The foremost RFs were found to be LBW, prematurity, advanced maternal age, emergency C/S, and BA.

No significant change was detected in the distribution of preconception, antenatal, and intrapartum RFs at ten-year intervals. However, neonatal RFs were found to be significantly higher in the group born before 2000. Among the neonatal RFs, the postnatal seizure rate has decreased significantly. There was no patient with a history of cord around the neck among patients born within the last ten years. These findings can be explained by the fact that neonatal RFs are now better controlled.

In literature, preterm delivery is still one of the main RFs for CP [13, 14], with more than 40% of individuals with CP born preterm [15]. The prematurity rate was found to be 45% in the United States of America and 24.8% to 48.4% in studies in Turkey [3, 16–18]. In the study by Tosun et al. [17], the LBW rate was found to be approximately 30%. In the literature, intrauterine growth restriction, which results in LBW, is one of the most important RFs in term babies [19, 20]. Premature birth in groups 26.47%, 35.71%, 56.61%, and LBW in groups 29.41%, 36.50%, and 60.30%, respectively, gradually, increase with each decade in accordance with the literature [19, 20]. However, rates of prematurity and LBW in the literature found in the last ten years were even much higher than the data in older literature. In other words, in addition to the increase reported in the literature, the rates continue to increase. This may be the result of increasing technology and intensive care services and keeping premature and LBW babies alive.

Although prematurity is the most frequently accused etiology when the most common RFs in term babies were investigated, babies with neonatal encephalopathy and perinatal stroke were reported as high risk, and babies with congenital disabilities, septicemia, meningitis, and small for gestational age were reported as moderate risk [20]. In our study, according to the total number of cases, the frequency of postnatal factors such as septicemia, meningitis, and perinatal stroke was much less than antenatal and intrapartum causes. This can be attributed to several factors. Firstly, antenatal and intrapartum factors are often more controllable and preventable through medical interventions during pregnancy and childbirth. This includes timely detection and treatment of prenatal bacterial infections or complications during labor and delivery. Additionally, advancements in postnatal care and medical technology have significantly reduced the impact of postnatal complications. Modern neonatal intensive care units and perinatology expertise allow for prompt diagnosis and management of postnatal issues. Moreover, underreporting or challenges in diagnosing and recording postnatal factors may contribute to their seemingly lower frequency in the study. Lastly, genetic or biological factors could also play a role, with postnatal effects being less pronounced or identifiable compared to pre-existing conditions. These combined factors underscore the importance of a comprehensive assessment and interpretation of study findings regarding the frequency of different causal factors in CP.

It was observed that preconception and antenatal RFs were associated with subtypes. In further analysis, only antenatal RFs were found to be significantly associated with unilateral and bilateral CP. It can be concluded that antenatal RFs (among which prematurity and LBW are the most common) are still the most important RFs. Managing antenatal RFs, mainly by preventing preterm births, becomes important in the prevention of spastic CP, which is the most common subtype.

The maternal age at first birth has increased significantly both in Europe and America, as in Turkey [21, 22]. In many countries, women postpone their first pregnancy to older ages. Advanced maternal age, which is one of the preconception RFs, was found to be statistically significantly higher in CP cases born in the last ten years. However, advanced maternal age brings with it many pregnancy risks [23]. Wu et al. [19] reported that independent RFs for CP include maternal age over 35, black race, and intrauterine growth restriction. Among the intrapartum RFs, the rate of emergency C/S was found to be significantly higher in the last decade. This may be due to the increase in older-age pregnancies.

The consanguineous marriage rate was found to be 22.29% in this study, and there was no significant difference between the groups. In their study, Tosun et al. [17] compared RFs of individuals with CP followed in the period of 1972–1994 and 1995–2006 and determined consanguineous marriage rates as 16.4% and 10.4%, respectively. Consanguineous marriage was reported as 21.4% in the study by Yılmaz Yalcinkaya et al. [24] and 23.8% in the study by Erkin et al. [18]. Consanguineous marriage rate is still very high in Turkey.

The rate of BA, which is one of the most accused factors in CP etiology in the past years, was found to be 25.33% in this study. McIntyre et al. [10] reported BA strongest and the most consistent intrapartum RF in children born at term in developed countries in their systematic review. Likewise, in Turkey, the perinatal asphyxia rate was reported as 66.3% and 71% in the studies by Tosun et al. [17] and 34.6% in the studies by Erkin et al. [18], much higher than in this study. BA ratio seems to be stable in the first two decades in this study, but a significant decrease is observed in the last ten years. With it still counting among the top-ranked five RFs, it is promising that it tends to decrease gradually.

In this study, ataxic CP was found to be associated with placental anomalies. The relationship of subtypes with BA has been specifically looked into. Although the relationship between BA and CP types was not significant, in addition to the placental anomalies, BA was the most associated RF for ataxic CP. In the studies by Erkin et al. [18], in accordance with this study, BA was observed at a much higher rate in hypoxic and dyskinetic CP compared to the spastic type.

Stillbirth history and blood incompatibility are decreasing RFs. Maternal history of stillbirth was defined as RF for all CP cases [10]. However, the causes of stillbirths are not fully understood. Stillbirths after 24 weeks of pregnancy are primarily due to pregnancy/delivery-related causes such as placental abnormalities, birth defects, and infection [25].

Limitations of the study

One of the limitations of this study is that the results could not be generalized since this was a single-center study. Moreover, since the study was conducted with patients followed up in the university rehabilitation unit, mild cases that were not followed up by a doctor may have been overlooked. One of the limitations is the fact that the study is retrospective and the database analysis structure may have caused many methodological issues, such as recording errors and missings and subjective assessments of different recorders. Although the small sample size in the third cohort (n = 34) may impact the statistical power and generalizability of the results, the observed trends provide valuable insights into the changes in CP RFs over time. Future studies with larger sample sizes across all cohorts are needed to confirm these findings. In addition, since the decrease of some RFs may be the reason for the increase of some, individual evaluation of RFs may not always give accurate results. For instance, the decrease in neonatal mortality is associated with an increase in LBW and premature babies, which may be the most important determinant of CP.

Conclusion

Cerebral palsy is a heterogeneous disability. Although it is expected that many different causal pathways play a role in its etiology, it is important to evaluate these etiological risk factors both individually and interrelated and, more importantly, at regular intervals at the national level. The right intervention should be done at the right time to ensure prevention. Therefore, we need to continuously monitor and report changes in the frequency of these specific risk factors.

Conflict of interest

The authors declare no conflict of interest.

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