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Cerebral palsy in preterm infants: a population-based case–control study of antenatal and intrapartal risk factors

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Previous studies have indicated that foetomaternal infection increases the risk of spastic cerebral palsy (CP) in term infants, whereas this association appears to be less evident in preterm infants. The aim of this study was to analyse infection-related risk factors for spastic CP in preterm infants. A population-based series of preterm infants with spastic CP, 91 very preterm (<32 wk) and 57 moderately preterm (32–36 wk), born in 1983–90, were included and matched with a control group ($n = 296$). In total, 154 maternal, antenatal and intrapartal variables were retrieved from obstetric records. In the entire group, histological chorioamnionitis/pyelonephritis, long interval between rupture of membranes and birth, admission–delivery interval <4 h and Apgar scores of <7 at 1 min just significantly increased the risk of CP, and Apgar scores of <7 at 5 and 10 min were strongly associated with an increased risk. Abruptio placentae, Apgar scores <7 at 1 min and pathological non-stress test (reason for delivery) were significant risk factors of CP only in the moderately preterm and hemiplegic groups, whereas fever before delivery was a significant risk factor in the very preterm and spastic diplegic groups. Antibiotics during pregnancy was associated with CP only in the spastic diplegic CP group.

Conclusion: Antenatal infections marginally increased the risk of CP. Low Apgar score and abruptio placentae were associated with CP, especially in moderately preterm infants with hemiplegic CP.

Key words: *Antenatal risk factors, case–control study, cerebral palsy, pregnancy complications, preterm infants*

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Preterm birth is the most important risk factor for cerebral palsy (CP). The risk of CP is inversely proportional to gestational age and the relative risk is 60 times higher at <28 wk of gestation than at term (1, 2). Only 6.1% of infants were born preterm (<37 wk of gestation) during the period 1983–1990 in western Sweden, but they accounted for 41.5% of that region's CP cases (1, 2). The number of preterm infants with CP has increased since 1970, mainly related to the parallel decrease in perinatal mortality (1, 2). Although perinatal and neonatal risk factors for CP appear to dominate in the preterm group, further investigation into antenatal and intrapartal risk factors is interesting, as they can act as antecedents to the brain damage resulting in CP. In previous analyses of antenatal risk factors for CP in preterm infants no single risk factor has been consistent across all or even most studies (3–16). Recent studies suggest that foetoplacental uterine infection/inflammation is important in the initiation of preterm labour and for the development of central nervous system injury and CP (16, 17). The western Swedish population is characterized by a low frequency of perinatal infections (18, 19) and a low rate of preterm birth. Testing the hypothesis that infection is a risk factor for CP in this population as part of the ongoing CP project (1, 2, 20), applying the uniform and internationally accepted definition of this condition (21), may thus be interesting from a pathophysiological standpoint.

The aim of this study was to evaluate maternal, antenatal and intrapartal risk factors for CP, especially those related to foetomaternal infections (1, 2). A case–control study was designed, based on the preterm cases of spastic CP from the birth cohorts 1983–1990 in the western Swedish CP project. The very preterm group (<32 wk) and the moderately preterm group (32–36 wk) were analysed separately, as infection is considered to be a more common cause of very preterm birth (22). Furthermore, the moderately preterm group

has usually not been investigated in previous studies (4–16), despite its comprising 44% of preterm CP and 18% of all CP (1, 2).

Material and methods

Selection of subjects

This study is part of the CP project in western Sweden; it is population-based and its geographical area consists of the western healthcare region of Sweden, with a total population of 1.7 million inhabitants. The total number of livebirths was 168 627 during the period 1983–1990. Of the births, 1063 occurred before 32 wk and 8829 occurred at 32–36 wk of gestation, which corresponds to a preterm birth rate (<37 wk) of 6.1%.

CP was defined as a group of non-progressive, but often changing, motor impairment syndromes, secondary to lesions or abnormalities of the brain arising in the early stages of development (21). The internationally accepted Swedish classification was used in this context (21). Owing to increasing interest in antecedents of preterm CP, especially the importance of inflammatory processes in the development of diplegic CP types (12), the study was restricted to the spastic type of CP in children born preterm (152 of 159 cases of CP in these cohorts).

Preterm children with spastic CP were included if they were born in Sweden and lived in the study region on 31 December 1990 (for the years 1983–1986) and 31 December 1994 (for the years 1987–1990) and lacked any obvious postnatal cause of CP. All children were at least 4 y old at the time of diagnosis (1, 2)

Using the Swedish National Birth Register each case was matched with two controls. The closest births occurring before and after the case birth were chosen. The controls were matched for gestational age, gender, multiple gestation and delivery ward. In most cases (97.1%), calculation of gestational age was based on ultrasound scans performed between gestational weeks 16 and 19. In cases that had not been dated by ultrasound, gestational age was estimated from the date of last menstrual period and clinical assessment of the child at birth.

The total number of spastic preterm CP cases was 152. Four cases with their respective controls were excluded: two cases had a proven perinatal cytomegalovirus infection and two cases had ultrasound-corrected gestational age exceeding 37 wk. Subsequently, analysis was performed on 148 CP cases and 296 matched controls. Matching was complete for gestational age, gender and multiple gestation. Matching with regard to delivery ward was complete in only 84.5%, as controls could not always be recruited from small units. In these cases, controls were recruited from another unit of similar level and size.

Subgroup analysis was performed with regard to the two major types of CP, spastic diplegia and hemiplegia, and the two gestational age groups, very preterm (<32 wk) and moderately preterm (32–36 wk).

Approval was obtained from the Ethics Committee in Göteborg.

Data collection

One investigator (BJ), unaware of the paediatric outcome, examined all 456 records, recording a total of 154 variables including maternal (40), antenatal (63), intrapartal and immediately postpartal (51) data. Clinical chorioamnionitis was defined as fever (≥38°C recorded on two occasions ≥4 h apart) and/or uterine tenderness and/or foetal tachycardia in the absence of other focus of infection. Fever before onset of delivery was defined as fever (≥38°C) prior to the occurrence of regular contractions and cervical dilation. Postpartum endometritis was defined as fever (≥38°C recorded on two occasions ≥4 h apart) and uterine tenderness or foul-smelling cervicovaginal discharge. Histological chorioamnionitis was defined as increased infiltration of polymorphonuclear white blood cells in the chorioamniotic membranes. Histopathological examination was performed in 73 of the 444 placentas (18.9% in cases, 15.2% in controls). Clinical chorioamnionitis and pyelonephritis were grouped together, as previous studies implied that severe infection in close relation to the genital tract may be associated with brain injury (23). Hypertensive disease was used as a compound diagnostic term including pre-eclampsia (≥140/90 and ≥0.3 g protein in urine), gestational hypertension (≥140/90 after 20 wk of gestation) and essential hypertension (≥140/90 before the pregnancy or <20 wk of gestation). Cervical insufficiency was defined as opening of the cervix without uterine contractions. The term "bad obstetric history" was used when one of following criteria was fulfilled: more than three subsequent spontaneous abortions, one spontaneous abortion after 20 wk of gestation, intrauterine foetal death or an earlier case of perinatal death. Maternal disease was defined as the presence of any of the following diseases at the onset of the pregnancy: diabetes, hypertension, severe psychiatric disease, asthma, active neoplasia, epilepsy and glomerulonephritis. Antenatal cardiotocographic (CTG) tracings were classified according to FIGO standards (24).

Standardization of birthweight according to gestational age and gender was performed using a recent study of ultrasonically estimated foetal weights to avoid underestimating the degree of size deviation in preterm infants (25). Growth restriction was defined as below −24% weight deviation compared with the mean birthweight for a given gestational age and gender (25), corresponding to below −2 standard deviations (SD) from the mean; the latter is a more common definition in paediatric contexts (25).

Table 1. Distribution of 148 preterm spastic cerebral palsy (CP) cases by type and gestational age group.

Type of CP	<32 wk[a]	32–36 wk[a]	Total
Spastic diplegia	60 (66)	28 (49)	88 (59.5)
Spastic hemiplegia	11 (12)	20 (35)	31 (21)
Ataxic–spastic diplegia	11 (12)	4 (7)	15 (10)
Spastic tetraplegia	9 (10)	5 (9)	14 (9.5)
Total	91	57	148

Data are *n* (%).
[a] Weeks of gestation.

Statistical methods

Univariate logistic regression was used to estimate the odds ratio (OR) with a 95% confidence interval (CI) for correlation between one factor and the outcome. Statistical significance was considered to exist if the 95% CI did not include 1.0.

Calculations were made using SAS (SAS Institute, Cary, NC, USA) and InStat 2.01 (Graph Pad Software, San Diego, CA, USA). Proportions were compared using Fisher's exact test. Wilcoxon's rank-sum test was used to test continuous variables for differences between two groups. A p-value <0.05 was considered to be statistically significant.

Results

The distribution of spastic CP types according to gestational age is shown in Table 1. Most antenatal/intrapartal factors were unrelated to CP, and the results are given for the more frequently reported factors and for variables with significant or borderline significant association to outcome. Maternal characteristics were comparable in CP and controls (Table 2). The birthweight, standardized for gestational age and gender, did not differ significantly between cases and controls (12% cases and 14% controls were below −2 SD). Infectious factors [clinical chorioamnionitis/pyelonephritis, histological chorioamnionitis and long duration of preterm prelabour rupture of membranes (pPROM)] were associated with an increased risk of CP, whereas treatment with anti-inflammatory corticosteroids was associated with a significantly lower risk (Table 3). There was a significant association between CP and an admission–delivery interval <4 h (Table 4). Hypertensive disease, cervical insufficiency and iatrogenic reasons for delivery were all associated with a lower occurrence of CP, whereas no difference was found between cases and controls with regard to spontaneous onset of labour [pPROM and preterm labour (PTL)] (Table 4). Decreased viability at birth (low Apgar scores at 1, 5 and 10 min) occurred more frequently in CP cases than in controls (Table 5).

Risk factors for CP were also analysed separately for very and moderately preterm infants, as well as for spastic diplegic and hemiplegic forms of CP (Table 6). Abruptio placentae and low Apgar scores were asso-

Table 2. Selected maternal factors in cerebral palsy (CP) cases and controls.

	CP cases (n = 148)	Controls (n = 296)	OR (95% CI) or p-value
Maternal age[a]	27 (24–33)	28 (24–33)	$p = 0.46$
Nulliparous	66 (45)	159 (54)	0.83 (0.67–1.02)
Infertility >1 y	13 (9)	32 (11)	0.78 (0.38–1.50)
Maternal disease	10 (7)	19 (6)	1.05 (0.50–2.21)
Bad obstetric history	17 (11)	19 (6)	1.89 (0.94–3.76)
Previous legal abortion	37 (25)	51 (17)	1.60 (0.99–2.58)

Data are a mean (interquartile range), or *n* (%).
OR: odds ratio; 95% CI: 95% confidence interval.

Table 3. Selected factors, related to infection and inflammation, in cerebral palsy (CP) cases and controls.

	CP cases (n = 148)	Control (n = 296)	OR (95% CI) for CP or p-value
Clinical chorioamnionitis or pyelonephritis	18 (12)	19 (6)	2.02 (1.02–3.99)
Clinical chorioamnionitis	16 (11)	19 (6)	1.77 (0.88–3.55)
Histological chorioamnionitis	10/28 (36)	6/45 (13)	3.61 (1.16–12.1)
Fever before onset of delivery	12/146 (26)	11/289 (4)	2.30 (0.99–5.17)
Fever during delivery	13/147 (9)	25/295 (8)	1.05 (0.52–2.12)
pPROM (h to delivery)[a]	63 h (28–252)	37 h (12–90)	$p = 0.01$
Postpartum endometritis	9 (6)	18 (12)	1.00 (0.44–2.28)
Antenatal corticosteroids	9 (6)	39 (13)	0.42 (0.20–0.90)

Data are a mean (interquartile range), or *n* (%).
OR: odds ratio; 95% CI: 95% confidence interval; pPROM: preterm prelabour rupture of membrane.

Table 4. Selected factors related to preterm birth and route of delivery in cerebral palsy (CP) cases and controls.

	CP cases (n = 148)	Controls (n = 296)	OR (95% CI)
pPROM	42 (28)	104 (35)	0.73 (0.48–1.09)
PTL	60 (41)	119 (40)	1.01 (0.68–1.52)
pPROM or PTL	102 (69)	223 (75)	0.91 (0.81–1.04)
Iatrogenic reason for delivery	14 (9)	48 (16)	0.54 (0.28–0.99)
Cervical insufficiency	2 (1)	16 (5)	0.85 (0.70–0.98)
Hypertensive disease	14 (9)	48 (16)	0.54 (0.28–0.99)
Pre-eclampsia	13 (9)	32 (11)	0.79 (0.40–1.56)
Caesarean section	99 (67)	169 (57)	1.11 (1.00–1.23)
<4 h from admission to delivery	34 (23)	42 (14)	1.80 (1.09–2.98)

Data are *n* (%).
OR: odds ratio; 95% CI: 95% confidence interval; pPROM: preterm premature rupture of membrane; PTL: preterm labour.

Table 5. Selected factors related to viability at birth and urgent delivery in cerebral palsy (CP) cases and controls.

	CP cases ($n = 148$)	Controls ($n = 296$)	OR (95% CI)
Apgar <7 at 1 min	66/146	96/289	1.36 (1.06–1.74)
Apgar <7 at 5 min	38/145	30/288	2.52 (1.64–3.85)
Apgar <7 at 10 min	18/140	6/279	5.98 (2.72–13.2)
Maternal bleeding, reason for delivery	29/148	37/296	1.71 (1.00–2.90)

OR: odds ratio; 95% CI: 95% confidence interval.

ciated with a higher risk of CP, especially in the hemiplegic and moderately preterm (32–36 wk) group. Indicators of infection, such as antibiotics during pregnancy, were associated with diplegic CP. Fever before onset of delivery was an antecedent of CP in the very preterm (<32 wk) and the diplegic groups (Table 6).

Discussion

In studies of CP, there is an unavoidable delay of 4–5 y from birth before a reliable diagnosis can be established in all cases. In addition, a large number of cases is required if subgroups of CP types and different gestational age groups are to be analysed. The strengths of the present study are that virtually all cases of spastic CP in a geographically defined area (birth 1983–1990) were included, the size of the study and the fact that all children with CP were at least 4 y old at diagnosis. The problems encountered were some missing information in the records and, in both cases and controls, the limited number of histopathological examinations of the placentas (data available in only 73 of the 444 records).

The more frequently observed risk factors for CP in previous studies are clinical chorioamnionitis (3–5, 7, 11, 26), pPROM of long duration (3, 5, 8, 27), multiple pregnancy (4, 6), maternal antibiotics during pregnancy (11, 13), antepartum fever (11), rapid vaginal delivery lasting <4 h (6, 13), CTG abnormalities/low Apgar scores at birth (5, 13), vaginal bleeding (6, 13) and vaginal preterm delivery subsequent to PTL or pPROM (12). In contrast, delivery without labour (5, 13) and pre-eclampsia have been found to be associated with a reduced risk of CP (5, 13). The variable results obtained may relate to differences in study design, outcome (all CP or subgroups of CP), weight/gestational age groups included (most studies covered the <1500 g group), occurrence of risk factors in the population and data retrieval methods (records or birth registers).

In this study, there was an increased occurrence of CP in infants whose histories reported clinical chorioamnionitis/pyelonephritis or histological chorioamnionitis, and in cases with a delay between pPROM and delivery. Fever before onset of delivery was a significant antecedent of CP in the spastic diplegic and the very preterm (<32 wk) groups, and the use of antibiotics during pregnancy was correlated with diplegic CP. This is in agreement with previous reports demonstrating that infectious risk factors are, to some extent, associated with CP in preterm infants (3–5, 7, 8, 10, 11, 13). The present data support the general concept of foeto-placental infection as a possible pathogenic factor of both preterm birth and brain injury (16, 17), even in a population with a low occurrence of perinatal infections (18, 19). However, the association between CP and infectious factors was not particularly strong (Table 3) and these results differ from those of previous studies, which demonstrated a markedly increased risk of brain lesions (28) or a moderately increased risk of CP (12) in the PTL/pPROM group, compared with groups born preterm for other reasons. This may reflect the fact that infection was associated with spontaneous delivery (and CP) in only a minority of cases in the preterm population (see Table 3). It is important to point out that the associations found between infection-related factors and CP are not proof of direct causality; instead, infection/inflammation may play an intermediary role

Table 6. Risk of cerebral palsy (CP) for selected variables, given separately for the two major subgroups of CP (spastic diplegia and hemiplegia) and for the very preterm (<32 wk) and moderately preterm (32–36 wk) gestational groups. In the subgroup analyses, the cases are compared to their own matched controls.

	All patients	Spastic diplegia	Hemiplegia	<32 wk	32–36 wk
Abruptio placentae	1.64 (0.90–3.02)	1.05 (0.50–2.22)	7.20 (1.63–31.9)	1.31 (0.65–2.63)	4.31 (1.14–16.3)
Pre-eclampsia	0.79 (0.40–1.56)	0.94 (0.41–2.18)	0.17 (0.03–1.16)	1.32 (0.55–3.19)	0.40 (0.13–1.20)
Apgar <7 at 1 min	1.36 (1.06–1.74)	1.30 (0.77–2.21)	3.42 (1.40–8.36)	1.02 (0.61–1.70)	5.48 (2.61–11.5)
Apgar <7 at 5 min	2.52 (1.64–3.85)	2.44 (1.18–5.06)	4.58 (1.46–14.3)	2.30 (1.25–4.26)	7.90 (2.79–22.4)
Apgar <7 at 10 min	5.98 (2.72–13.2)	3.72 (1.06–13.1)	30.9 (1.7–568)	6.12 (2.34–16.0)	10.4 (1.74–62.0)
Antibiotics during pregnancy	1.18 (0.64–2.20)	2.39 (1.12–5.09)	0.47 (0.10–2.29)	1.35 (0.68–2.68)	0.65 (0.13–2.30)
Fever before onset of delivery	2.30 (0.99–5.17)	3.10 (1.14–8.44)	0.66 (0.07–6.56)	2.60 (1.06–6.36)	1.00 (0.09–11.3)
Pathological non-stress test (CTG), reason for delivery	2.89 (0.95–8.84)	2.04 (0.4–10.0)	4.20 (0.43–40.9)	1.01 (0.09–11.3)	4.3 (1.14–16.3)

Data are odds ratio (95% confidence interval).
CTG: cardiotocography.

between CP and some other, yet unknown, factor (29). To investigate this further, more detailed information regarding the presence of microbes and inflammatory mediators in the membranes, amniotic fluid and blood of the newborn is required.

The use of antenatal corticosteroids (betamethasone) was associated with a decreased risk of CP, which is in agreement with a recent report indicating that betamethasone (but not dexamethasone) reduces periventricular leukomalacia in preterm infants (30), possibly through its beneficial effects on respiration during the neonatal period, anti-inflammatory actions or neuroprotective properties. Alternatively, there may have been a selection bias among cases receiving treatment towards those delivered for iatrogenic reasons and with a longer latency between admission and delivery, and this group may therefore have been at lower risk even without corticosteroids. This issue is of great importance and must be addressed in prospective randomized controlled trials.

Traditionally, preterm birth has been subdivided into a very preterm (<32 wk) and a moderately preterm (32–36 wk) group. Periventricular leukomalacia, known to be strongly correlated with spastic diplegic CP in preterm children, predominantly occurs in the 24th to 32–34th wk of gestation, whereas cortical/subcortical insults (which correlate with moderate–severe neonatal encephalopathy) occur after that time (20). Hence, the observed rate of CP in low-birthweight infants with low Apgar at 10–20 min is relatively low, whereas the CP rate in term babies with low Apgar at 10–20 min is very high, probably reflecting that the immaturity of the nervous system of preterm infants confers cerebral resistance to asphyxia, whereas the brain of term infants is more vulnerable (31). Accordingly, from an aetiological point of view, the moderately preterm group is an intermediate group between the very preterm and term groups, which is, to some extent, illustrated in this study. In the very preterm group, fever before delivery and low Apgar scores at 5 and 10 min were significant risk factors for CP, as in the spastic diplegic group that dominated the very preterm group. In the moderately preterm group, abruptio placentae, low Apgar scores at 1, 5 and 10 min and pathological non-stress test (reason for delivery) were significant risk factors, as in the hemiplegic group (Table 4).

These results indicate that foetal distress and precipitous delivery constitute a risk for CP, not a consistent finding in previous studies, which may be explained by the exclusion of moderately preterm cases in most studies (4–14). However, the present data are in agreement with Cooke, who found an association between CTG abnormalities and preterm CP (4). Although the data may indicate that intrapartal distress is contributory in the aetiology of spastic CP in preterm infants, drawing a firm conclusion is complicated by the fact that infants born with low Apgar scores at birth (or delivered after abruptio) are probably more likely to have suffered from other adverse events antenatally and/or neonatally as well. Since adjustment for all of these possible confounders was not made, the results must be interpreted with caution.

The risk of CP was lower in infants born to mothers with hypertensive disease (but not significantly for pre-eclampsia as a separate group). Pre-eclampsia appears to be associated with a reduced risk, irrespective of whether $MgSO_4$ was used or not (5, 6, 13). It has been suggested that pre-eclampsia does not decrease the risk in itself but rather represents a group delivered preterm in the absence of adverse infectious/inflammatory factors, as opposed to the PTL–pPROM group (5, 12). As mentioned previously (Table 5), no higher risk of CP in the PTL/pPROM group was found compared with the pre-eclamptic group, suggesting that other mechanisms may be in play.

In summary, among the antenatal variables studied, infectious factors were significantly, but weakly, associated with CP. Low Apgar scores and abruptio placentae correlated with hemiplegic CP in moderately preterm infants, whereas a similar relationship was less evident in the very preterm diplegic cases. Postpartal and neonatal variables were not studied, but are known to be associated with brain damage resulting in CP in preterm births (1, 26).

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