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Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth year period 1991–94

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This 8th Swedish population-based cerebral palsy (CP) report comprises 241 children born 1991–94. The live birth prevalence was 2.12 per 1000. Excluding 7 postnatally-derived cases, the gestational age-specific prevalences were 86 for extremely preterm children, 60 for very preterm and 6 for moderately preterm, and 1.3 for term children per 1000. Spastic hemiplegic, diplegic and tetraplegic subtypes accounted for 33%, 44% and 6%, dyskinetic CP for 12% and simple ataxia for 4%. Neuroimaging had been performed in 90%. Probable aetiology was identified in 73% of preterm and 86% of term children. Among preterm children it was considered prenatal in 12%, peri/neonatal in 61% and unclassifiable in 27%, while it was 51%, 36% and 14% among term children.

Conclusion: The live birth prevalence for CP in the birth year period 1991–94 continued to decrease slightly. Gestational age-specific prevalences increased marginally in extremely and very preterm births, continued to decrease in moderately preterm births and decreased slightly in term births. Probable aetiology and timing of the brain insult could be revealed in 81%, birth asphyxia being the likely cause in 28% of term children.

Key words: *Aetiology, birth asphyxia, cerebral palsy, gestational age, prevalence*

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In recent years, the epidemiology of cerebral palsy (CP), particularly population-based, has become the subject of increasing international interest when it comes to improving our understanding of brain impairment patterns and considerations for future preventive efforts, as underlined by an EU project involving 14 centres from 8 countries (1). An impressive analysis and compilation of the vast body of CP epidemiology with special emphasis on causal pathways has also recently been published (2). In the western healthcare region of Sweden, we have continuously and systematically monitored CP since 1971. Our report from 1996 covers the birth years 1954–90 (3) and has now been supplemented with additional data from birth years 1991–94. During these four decades, dynamic developments globally have led to a successive decrease in perinatal mortality (PNM) and a parallel increase in the potential for survival at ever lower gestational ages (GAs). As a result, an increasing prevalence of CP, particularly in very and extremely preterm births, has occurred and an immense amount of research has focused on CP in these categories. Today, the brain pathology behind CP in very preterm births is shown to be predominantly periventricular leucomalacia (PVL) and/or intracranial haemorrhage (ICH) occurring neonatally, or late antenatally in a small proportion (3–5). The causes of CP in term births have been far more difficult to elucidate. In recent decades it has been postulated that they are predominantly prenatally derived with only a small proportion of around 10% originating around labour and birth (6). This, however, is even more than has been attributed to most other single groups of causes (2). We have repeatedly reported higher proportions of perinatally acquired CP in term births than given in most other studies (3). With still more access to neuroimaging and refined techniques, in the present series we have been able to elucidate and time-relate the aetiology of CP in the majority of children born at term. Our data again emphasize birth asphyxia as a fairly frequent cause of CP in term births, a cause of brain insult where research strategies for protective intervention have been presented (7).

Material and methods

The study comprised the western health care region of Sweden and, in addition, the closely located County of Jönköping, with a total population of 2.1 million

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inhabitants with a slightly positive net migration. The study covered the birth year period 1991–94, in which 113724 live births were recorded: 269 at <28 wk of gestation, 695 at 28–31 wk, 5500 at 32–36 wk and 107260 at >36 wk of gestation. Children with CP were included if they were born in Sweden and lived in the study area on 31 December, 1998. All the children were at least 4 y of age at diagnosis.

CP was defined as "an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of development" (8). The Swedish, and internationally accepted, classification of CP syndromes was applied (8). Extremely preterm birth was defined as birth occurring at a GA of <28 completed weeks, very preterm at a GA of 28–31 wk, moderately preterm at a GA of 32–36 wk and birth at term at a GA of ≥37 wk. Early ultrasound measurements were primarily used to estimate the GA and, when these measurements were not present, menstrual data were used. Low birthweight was defined as a birthweight of below 2500 g. Prenatal referred to the period of pregnancy until the onset of labour resulting in delivery; perinatal to the period from the onset of labour until the 7th day of life; neonatal to the first 28 d of life; and postnatal to the period from the 29th day of life up to 2 y of age. Small for gestational age (SGA) was defined as a birthweight for GA of ≤2 SD from the mean on a Swedish growth chart (9).

The same methodology and classification as previously specified were used (3). The aetiological classification was based on given clinical criteria, combined with information from available neuroimaging documentation. Obstetric and peri/neonatal data were retracted from medical records. Results from ultrasound investigations were available in 42% of the children (102/241) and post-neonatal computed tomography (CT) and/or magnetic resonance imaging (MRI) in a total of 90% (161 CT, 17 MRI and 38 CT + MRI). The findings at CT/MRI were classified into six categories: maldevelopments, periventricular atrophy, cortical/subcortical atrophy, basal ganglia lesions, miscellaneous and normal. Cerebral/cerebellar maldevelopments were considered in the case of documented neural migration disorders, aplasia/hypopolasia and prenatal cysts. Intracranial haemorrhage (ICH) was graded according to Papile et al. (10). Hypoxic-ischaemic encephalopathy (HIE) was considered in the presence of at least two of the following symptoms/signs: Apgar score <5 at 1 or 5 min, resuscitation/ventilation, convulsions before day 3. Birth asphyxia severe enough to cause CP was considered when a series of the following four events were present: (a) intrauterine hypoxia (miscoloured amniotic fluid, fetal heart rate during labour < 100 or > 160 beats/min, silent pattern or dip 2 pattern on cardiotocography, cord prolapse or placental ablation); (b) Apgar score <5 at 1 or 5 min; (c) assisted ventilation or convulsions before day 3 and, when performed, (d) normal findings at early neuroimaging or evidence of acute cerebral abnormality. Birth asphyxia was considered to have started intrapartum when Apgar scores of 0–6 were documented for longer than 5 min.

The average PNM rate in 1991–94 was 5.7 per 1000 births and the average neonatal mortality rate 3.3 per 1000 live births, which did not differ from corresponding rates in 1987–90, 5.6 and 3. 3. The mean preterm rate was 5.7% and the mean low birthweight rate 4.1%.

The study was approved by the Ethics Committee at the Medical Faculty of the University of Göteborg. Seven parents did not give their consent to review the obstetric, neonatal and paediatric records. Their children will be reported only as to gender, GA, birthweight and CP subtype.

Results

The present CP series comprised 241 children born in 1991–94. The crude mean prevalence of CP was 2.12 per 1000 live births, 0.88 for preterm infants and 1.24 for term infants. The crude live birth prevalence from 1954 to 1994 is shown in Fig. 1. Preterm CP decreased significantly to the late 1960s, increased significantly to the mid-1980s and then stabilized. The prevalence of CP in term births did not show any temporal change. Seven of the 241 children (3%) had an obvious postnatal cause of CP and will be described separately.

Birth characteristics

Of the 234 children (postnatally acquired CP excluded), 23 (10%) were born extremely preterm, 42 (18%) very preterm, 34 (15%) moderately preterm and 135 (58%) at term. Thirteen children (6%) had a birthweight of

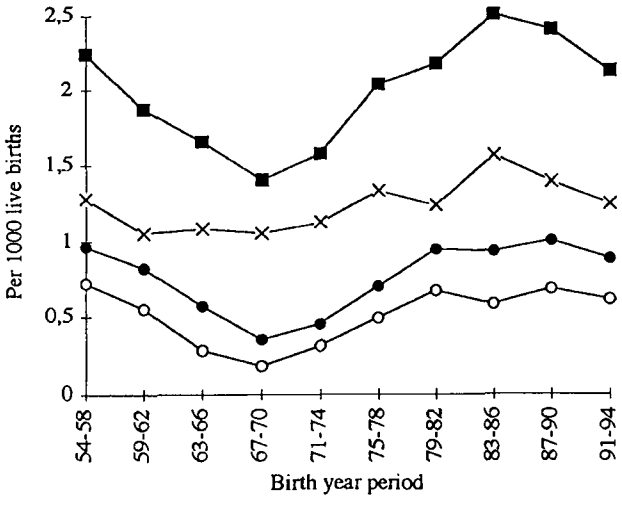

Fig. 1. Crude prevalence of CP per 1000 live births in 1954–94. —■— Total CP; —×— Term CP; —●— Preterm CP; —○— Preterm diplegia.

Table 1. Outcome of 31 multiple pregnancies with at least one child with CP.

	Twins	Triplets	Quadruplets	Total
Pregnancies	26	3	2	31
CP	28	3	2	33
Stillborn	4	1		5
Infant death	5		1	6
Not CP	15	5	5	25

<1000 g, 40 (17%) 1000–1499 g, 45 (19%) 1500–2499 g and 136 (58%) of ≥2500 g. Thirteen children (5.6%) were SGA, 2 of whom (3.2%) were born very preterm, 4 (11.8%) moderately preterm and 7 (5.2%) at term. There were 31 multiple pregnancies with a total of 33 children with CP (14%). The outcome of these pregnancies is given in Table 1. Assisted fertilization had occurred in 12 cases, 4 of which were born extremely preterm, 6 very preterm and 2 at term. Two represented quadruplets, 2 triplets and 5 twins, all of them originating from different pregnancies, while there were 3 singletons. There were 130 boys and 104 girls, giving a male excess ratio of 1.25:1, 1.68:1 for preterm births and 1.01:1 for term births.

Clinical characteristics

In all, diplegic (spastic/ataxic) and hemiplegic subtypes accounted for the vast majority, 44% and 33%. Spastic tetraplegia (massive total motor disability with all four limbs severely involved, the upper at least as much as the lower) was present in 6%, simple ataxia in 4% and dyskinetic CP in 12%. Diplegia was present in 83% of the extremely preterm group, 76% of the very preterm group, 56% of the moderately preterm group and 25% of the term group. In contrast, hemiplegia was present in 9% of the extremely preterm group, 10% of the very preterm group, 32% of the moderately preterm group and 44% of the term group.

Prevalence

The GA-specific mean prevalence was 85.5 per 1000 for a GA of <28 wk, 60.43 for a GA of 28–31 wk, 6.18 for a GA of 32–36 wk and 1.26 for a GA of >36 wk per 1000 live births. The birthweight-specific mean prevalence was 48.51 for a birthweight of <1000 g, 80.97 for a birthweight of 1000–1499 g, 11.42 for a birthweight of 1500–2499 g and 1.25 for a birthweight of ≥2500 g per 1000 live births.

Aetiology

Table 2 gives the distribution of aetiology in the 227 children for whom consent to the analysis was given. Seventy-eight of these 227 (34%) had an obvious

Table 2. Distribution of aetiology by gestational age group in 227 children with CP born in 1991–94. Seven postnatal cases and 7 children without parental consent to the study have been excluded. For definitions, see Hagberg et al. 1996 (3).

	Preterm <28w	28–31w	32–36w	Term >36 w	Total
Prenatal	*1*	*1*	*9*	*67*	*78*
Intrauterine infection	1		1	2	4
CNS maldevelopment					
Neuronal migration disorder				16	16
Cerebellar aplasia/hypoplasia				3	3
Cysts				1	1
Foetal lesions					
Hydrocephalus			1	3	4
Intracranial haemorrhage/infarction		1	4	2	7
Other prenatal CNS abnormalities			1	4	5
For children born at >34 wk gestation with normal pregnancy and delivery periventricular atrophy/porencephaly			2	36	38
Perinatal/neonatal	*21*	*29*	*8*	*47*	*105*
Most likely					
Intracranial haemorrhage/infarction/neonatal shock/brain oedema ± HIE	14	13	2	14[a]	43
Kernicterus			1		1
CNS infection and/or sepsis		1	1	4	6
For children born at >34 wk gestation: hypoxic-ischaemic encephalopathy only			1	29	30
For children born at ≤34 wk gestation: Periventricular leukomalacia and/or intracranial haemorrhage with normal initial ultrasound	6	13	3		22
Probable					
For children born at ≤34 wk gestation: Low Apgar and/or low pH/ mechanical ventilation >7 d or complicated by pneumothorax	1	2			3
Unclassifiable	*1*	*10*	*15*	*18*	*44*
Total	23	40	32	132	227

Items higher on the list took precedence over those lower on the list, with the exception of peri/neonatal intracerebral haemorrhage/infarction, neonatal shock and brain oedema (3).

[a] Hypoxic–ischaemic encephalopathy present in 8 cases.

prenatal aetiology of CP, 105 (46%) an indicated peri/neonatal one and 44 (19%) an unclassifiable one.

A *prenatal* aetiology was recorded in 51% of term births, 28% of moderately preterm births and 3% of very and extremely preterm births. The single most common prenatal aetiology was based on CT findings of periventricular atrophy in 26 children born at term or near term with uneventful peri/neonatal histories. The CT abnormalities that were revealed were compatible with PVL interpreted as having occurred early in the third trimester. In another 12 children, also with uneventful peri/neonatal histories, CT scans showed cortical/subcortical cavities interpreted as having occurred late in the third trimester. In 16 children, neuronal migration disorders of different kinds were diagnosed. Concomitant perinatal adverse events were few; in the 67 children born at term, Apgar scores of below 5 were recorded in one, neonatal seizures in one and the need for respirator treatment in none.

A *peri/neonatal aetiology* of CP was recorded in 36% of term births, 25% of moderately preterm births and 79% of very and extremely preterm births (Table 2). In term children, HIE was the single most common peri/neonatal aetiology, present in 37 of the 47 children (79%). In the remaining 10, the indicated cause was intracranial haemorrhage/infarction, neonatal shock or brain oedema but not HIE in 6 and CNS infection and/or sepsis in 4. In all 37 with HIE, birth asphyxia considered severe enough to have caused the CP was recorded. Predisposing prenatal factors had occurred in one-third (Table 3). The birth asphyxia was considered to have started intrapartum in 32 of the 37 children (86%). Among these 32, dyskinetic CP with or without additional but non-dominant lower limb spasticity was the most frequent clinical subtype, present in 19 (59%), 14 with severe and 5 with mild motor disability. The remaining 13 children had pure spastic CP subtypes; 2 tetraplegic, 2 severe diplegic, 6 mild diplegic and 3 hemiplegic in type. Neuroimaging had been performed at an early neonatal stage in 29 and later in 28 of the 32 children. Early neonatal findings revealed brain oedema or acute perinatal ICH/infarction in 10 and normal findings in 19. Brain pathology at neuroimaging performed later showed basal ganglia lesions with or without cortical/subcortical atrophy in 8, cortical/subcortical atrophy in 11 and normal findings in 9.

Table 3. Prenatal predisposing factors in 37 children born at term with birth asphyxia considered severe enough to cause CP. Intrapartum asphyxia required Apgar scores of 0–6 for longer than 5 min, early neonatal asphyxia Apgar scores of <5 at 1 or 5 min.

	Number	%
Intrapartum asphyxia, no predisposing factor	23	62
Intrapartum asphyxia, predisposing factor[a]	9	24
Early neonatal asphyxia, no predisposing factor	3	8
Early neonatal asphyxia, predisposing factor[b]	2	5
Total	37	100

[a] Maternal diabetes 4, drug abuse + small for gestational age 1, fever at partus 1, twin birth 1, pancreatitis + cleft palate 1, Weaver syndrome 1.
[b] Pre-eclampsia 2.

Four children fulfilled the criteria for both a pre- and a peri/neonatal aetiology. One girl (GA 35) with fetal hydrothorax and SGA sustained HIE, and one boy (GA 33) with intrauterine parvovirus infection had low Apgar scores and the need for a respirator. They were both referred to the prenatal category of aetiology because of congenital maldevelopment and infection, respectively. One boy (GA 37) with acute ICH had a Weaver syndrome and another boy (GA 39) with HIE and neonatal shock had an isolated cleft palate. They were both referred to the peri/neonatal group of aetiology because of ICH and neonatal shock, respectively.

Fig. 2 shows the GA-specific mean prevalences of CP from 1975 to 1994 by GA groups and indicated aetiology. In this 4-year period, 1991–94, the prevalence of CP in extremely preterm births, very preterm births and term births remained largely unchanged. The successive decline in CP in moderately preterm births continued. The proportions of the pre- and peri/neonatal groups of aetiology increased in all the GA groups at the expense of the unclassifiable group.

Postnatal CP

Six of the seven children assigned to the postnatal period were born at term and one was born moderately preterm. The damaging event was near sudden infant death syndrome in 1, ICH in 1, acute brain infarction in 2, severe asphyxia in 1, complication at heart surgery in 1 and septicaemia in 1.

Discussion

The most important message from the present study, the 4-y birth period 1991–1994, is the increasing proportion of time-related aetiology of CP in term births that was now possible to establish with high probability. This progress in understanding of the origin of CP was thought to be due to the increased access to neuroimaging techniques with their capacity to show the type of brain pathology, i.e. malformations originate in early fetal life not later than by 20–24 wk of gestation, periventricular atrophy relates predominantly to 24–34 wk and cortical-/subcortical atrophy after that. Early neonatal ultrasound had been performed in 42% and CT and/or MRI in 90% of cases, compared with 28% and 57% in the previous 4-y birth period, 1987–90 (3). The findings at neuroimaging were never contradictory to the clinical assessment. They either confirmed the clinically-based aetiological diagnosis or convincingly indicated time-related pathology in a number of cases otherwise regarded as unclassifiable. Strong support for the type of aetiology could thus be identified in 81% of children, 73% within the preterm group and 86% within the term group.

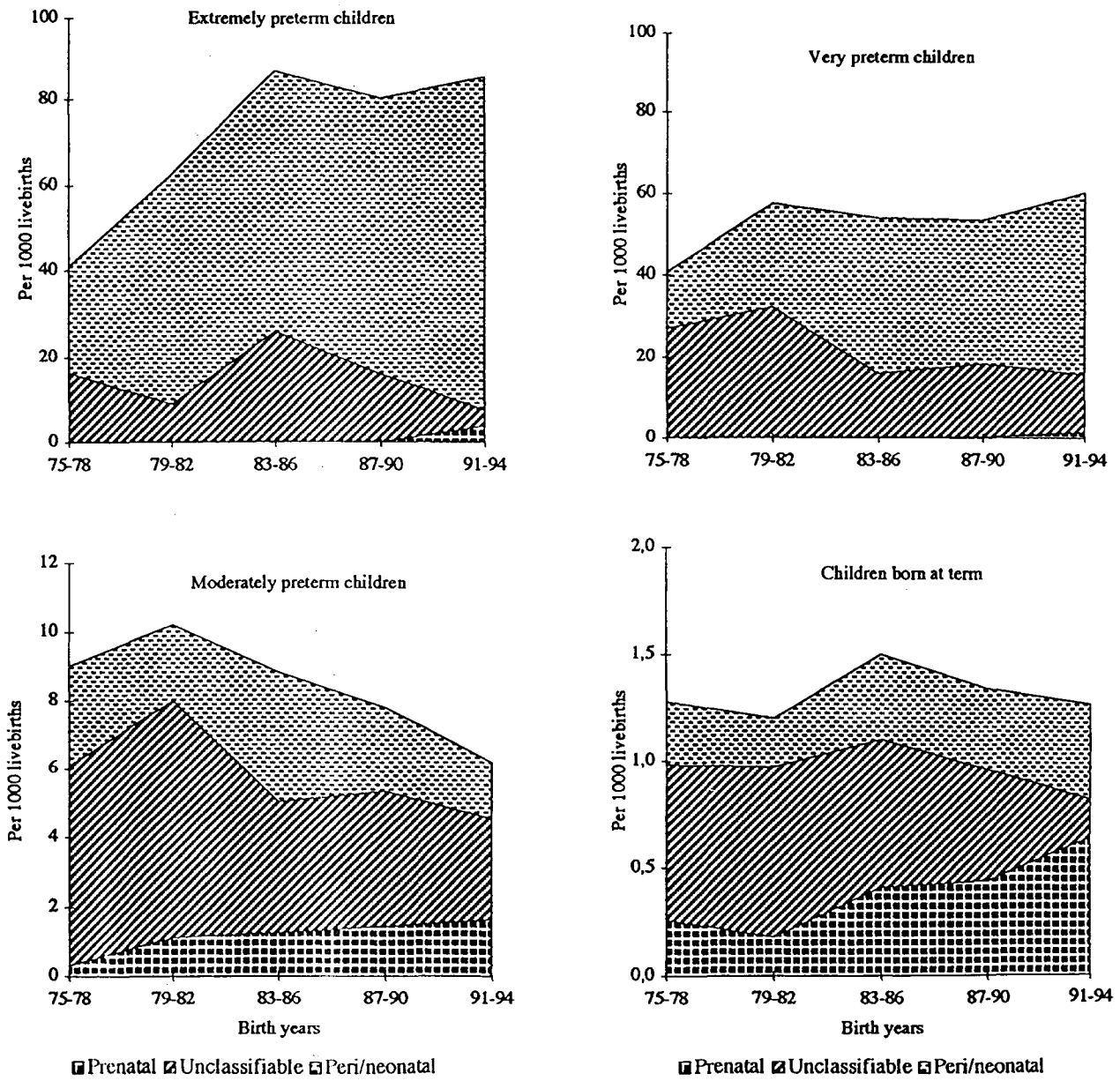

Fig. 2. Gestational age-specific prevalence of CP per 1000 live births by aetiology and gestational age group in 1975–94. Postnatal cases excluded.

In CP children born at term with a normal peri/neonatal history, our improved access to neuroimaging explains the increased proportion of cases with an obvious prenatal aetiology due to findings of periventricular atrophy or cortical/subcortical atrophy. Recent experience indicates that silent early third trimester intrauterine PVL lesions and late 3rd trimester cortical/subcortical lesions play a major role in CP in term births (12, 13). This is compatible with our identification of 36 such cases, i.e. 27% of all CP in term births and 54% of that acquired prenatally. Before diagnostic neuroimaging was generally available, the likely aetiology in such cases was only possible to identify on rare occasions. Cerebral maldevelopments, the second most common prenatal CP aetiology, were revealed in 15% of term children. In these cases, there had often been concomitant clinical indications of a prenatal origin of CP, but in some the type of brain pathology and the indicated timing of the brain compromise first became obvious at neuroimaging. Interestingly, in only two children born at term and assigned to the prenatal group were symptoms of perinatal hypoxia recorded. This contradicts the commonly stated opinion that perinatal hypoxic events are frequent in children with prenatally acquired CP (2).

The slight increase in a most probable peri/neonatal

aetiology in the term group, however, could not be explained simply by the successive increase in access to neuroimaging, as our aetiological classification in this category was based on purely clinical parameters, the neuroimaging was thus mainly used as a supporting tool. A most probable peri/neonatal origin of CP in term births was as high as 36% in the present 4-y period. A limited part of this was due to peri/neonatal infections or late neonatal hypoxic events, but in 37 children, i.e. in 28% of all CP in the term group, the CP was considered to be due to birth asphyxia severe enough to have caused the CP. Furthermore, the hypoxic events had most probably started intrapartum in 32 of these 37 newborns, i.e. in 24% of the term group. Such a large proportion is a controversial claim at the present time. The previous assumption, originating from Little (1862), that hypoxic events around birth are the most common cause of CP in term babies, is being increasingly refuted. Today, birth asphyxia is emphasized to be a most unusual cause of CP, while unspecified events before labour or in the newborn period are referred to as the main causes (14, 15).

Our 32 term born with an intrapartum start of birth asphyxia considered severe enough to cause irreversible brain damage had presented all the necessary criteria as newborns: intrauterine hypoxia and prolonged low Apgar scores in all, multisystem organ involvement and/or severe respiratory problems in all but one, and early neonatal seizures in all but one. Predisposing or interacting prenatal factors had been present in nine cases but were not considered compatible with irreversible brain-damaging events. Maternal disease is a well-known risk factor making the fetus more vulnerable to develop brain damage resulting in CP (16) and was present in 6 of the 32 children born at term with intrapartum asphyxia, 4 of the 6 with diabetic mothers. Two children presented with non-cerebral maldevelopment syndromes not thought to be associated with CP; one boy with a Weaver syndrome sustained an acute perinatal ICH, and another boy with a cleft palate sustained HIE and neonatal shock where neuroimaging pathology supported a perinatal brain insult.

The criteria for considering birth asphyxia severe enough to cause brain pathology resulting in CP require a series of causal links. We generally choose the criteria suggested by Stanley et al. (2), supplemented by findings at neuroimaging. To consider an intrapartum start of the asphyxia, we also required prolonged low Apgar scores, as adapted from the Cerebral Palsy Task Force statement (11). Results from neuroimaging were available in 31 of our 32 CP children considered to have sustained brain damage from an intrapartum start of birth asphyxia and in all cases they supported the brain insult to be perinatally acquired. To be accepted as an intrapartum cause of CP, the Cerebral Palsy Task Force (11) also requires fetal acidosis of pH <7.00 and base deficit ≥ 12 mmol/l, a sentinel hypoxic event before or during labour and CP of the dyskinetic or quadriplegic type. We did not have data on the first of these requirements and the reliability of these measurements, when available, has been questioned (17). Potentially birth asphyxiating conditions, such as uterus rupture and placental ablation, have been shown not to be associated with CP (14), although 3 ruptures of the uterus and 1 placental ablation occurred among our 32 term children with intrapartum asphyxia. We also feel that the requirement that only dyskinetic and quadriplegic types of CP should be considered to have been caused by intrapartum hypoxic events is too conservative. Dyskinetic CP and spastic tetraplegic/severe diplegic subtypes certainly occurred in 59% of the children, but mild diplegic and hemiplegic subtypes comprised the remaining 41%. It is noteworthy that the infant with the most severe intrapartum asphyxia presented with slight diplegia was intellectually normal and MRI showed normal findings. This boy was born after a normal pregnancy at GA 42 with a BW of 5000 g, had Apgar scores of 0, 0, 0 at 1, 5 and 10 min, first heart beats after 30 min, need for a respirator treatment and early neonatal seizures.

Among CP in preterm births, increased access to neuroimaging explains the increase in our group of peri/neonatal aetiology in babies with normal ultrasound findings during the first days of life, along with findings of periventricular atrophy on postnatal CT/MRI, as found in 22 of our preterm children. In one very preterm child, early ultrasound showed ICH with indicated onset a few days before delivery.

Taken as a whole, the prevalence of CP in the period 1991–94 did not show any major changes when compared with the previous birth year period, 1987–1990. The crude live birth prevalence of CP verified the break in the increasing trend which started in the late 1980s. The GA-specific prevalences showed slightly increasing rates in our extremely and very preterm births and a significantly continuing decline in the group of moderately preterm births. Among term births, the prevalence declined slightly for the 2nd successive 4-y period, further supporting the hypothesis that the sharp rise reported for the period 1983–86 (3) was a random occurrence. A significant finding, however, was the increasing proportion of multiple births from 7% to 14%, in all probability owing to the increased use of assisted fertilization. This doubling of the multiple birth rate probably explains the small increase in the prevalence of CP in the extremely and very preterm groups.

In conclusion, stable prevalence rates for CP were reported for the birth year period 1991–94. The timing of the occurrence of brain damage could be established with great confidence in 73% of preterm births and in 86% of term births. The frequency of multiple births doubled compared with earlier periods. Assisted fertilization had occurred in 29% of multiple pregnancies. In term births, birth asphyxia considered severe enough to cause CP was recorded and documented in 28%, with

factors known to predispose for CP present in 30%. Additional potential predisposing factors such as genetic susceptibility to hypoxia or other fragility remain to be identified. Nevertheless, our main statement is: birth asphyxia cannot be regarded as a rare cause of CP in term births, particularly in dyskinetic types with severe acute compromise at delivery.

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