Epidemiology of cerebral palsy in Southern Denmark

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ABSTRACT

INTRODUCTION: The aim of this study was to describe the prevalence, subtypes, severity and neuroimaging findings of cerebral palsy (CP) in a cohort of children born in Southern Denmark. Risk factors were analysed and aetiology considered.

METHODS: A population-based cohort study covering 17,580 live births from 2003 to 2008.

RESULTS: The study included 43 children diagnosed with CP. The overall prevalence of CP was 2.4 per 1,000 live births (95% confidence interval (CI): 1.8-3.2). The gestational age (GA)-specific prevalence ranged from 63.5 per 1,000 live births for GA < 32 weeks to 1.3 for GA ≥ 37 weeks. Almost half of the children were born preterm and 28% were from multiple pregnancies. The prevalence of CP was 1.8 per 1,000 in singletons and 15.4 per 1,000 in multiples. Low GA and birth weight were risk factors for CP, also after stratification for multiple births. Spastic CP was the predominating subtype of CP, and 24 children (56%) were able to walk independently. White-matter lesions were the most common magnetic resonance imaging finding, and the aetiology of CP was known in 37% of cases.

CONCLUSION: The overall prevalence of CP was slightly higher than that found in other Scandinavian studies due to its higher prevalence in the preterm group. Possible explanations include the high rate of multiple births in the background population. Neuroimaging findings were abnormal in the majority of children with CP, but aetiology could only be established in one third of the children. Primary prevention of CP is possible if the numbers of preterm births and multiple pregnancies can be reduced.

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Cerebral palsy (CP) is the most frequent and one of the most severe neurodevelopmental disorders in childhood. CP is described as an umbrella term referring to a group of disorders of movement and posture caused by a non-progressive interference, lesion or abnormality of the immature brain which is often accompanied by impairments of sensation, cognition and communication [1].

The prevalence of CP has been monitored since the 1960s. A collaborative network of registers was formed in 1998 (Surveillance of Cerebral Palsy in Europe (SCPE)), and consensus on important topics such as the definition and subtype classification of CP and the classification of magnetic resonance imaging (MRI) findings was reached [2, 3].

CP has various aetiologies and a wide spectrum of causal pathways. Established risk factors are preterm birth and a low birth weight [4, 5]. Neuroimaging techniques such as MRI have contributed to the description of the underlying pathology and understanding of the aetiology of CP [6, 7].

The aim of this study was to describe the prevalence, subtypes, severity and neuroimaging findings of cerebral palsy in children born between 2003 and 2008 in Southern Denmark. Risk factors were analysed and aetiology discussed.

METHODS

This was a population-based cohort study covering three communities in Southern Denmark. Included were all children living in the area, born between 1 January 2003 and 31 December 2008 and diagnosed with CP.

Denominator data from the background population were collected from the Danish Birth Registry. These data included gestational age (GA), birth weight (BW) and distribution for singletons and multiple pregnancies. The total number of live births in the area was 17,580 during the study period.

Data on children with CP were drawn from the database of the Danish Cerebral Palsy Follow-up Programme (CPOP). The programme was implemented in Denmark in 2009 and registers children with CP born after 1 January 2003 [8]. Epidemiological and clinical data are collected from standardised protocols. CPOP uses the definition and subtype classification of CP given by the SCPE [2, 3]. Severity is classified by the Gross Motor Classification System (GMFCS) and the Manual Ability Classification System (MACS) [9, 10].

Data from the CPOP database were crosschecked by a secretary and two paediatricians to ensure accurate data on place of birth and maternal address at birth as well as diagnosis and subtype classification.

Data from medical records were supplemented to elucidate clinical risk factors and aetiology. Severe birth asphyxia was defined according to the criteria of the Danish Paediatric Society [11].

ORIGINAL ARTICLE

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A complicated neonatal course in preterm infants was defined by combinations of multiple clinical risk factors like sepsis/infection, extended mechanical ventilation and hypotension requiring vasopressor therapy.

A neuroradiologist reviewed all MRIs and computed tomographies (CTs). The new SCPE classification system was used.

Exclusion criteria

All children not fulfilling the SCPE criteria of CP at four years of age. Children with CP admitted from other areas to a nursing home for disabled children wethin the study area. Children with CP dying before the age of two years (SCPE criteria). Children with post-neonatal CP.

Data analysis/statistics

To calculate a 95% confidence interval (CI) for population proportions, we used Wilson's confidence intervals. The χ^2-test was used to calculate p values when appropriate. Adjusted odds ratio (OR) and 95% Wald CI were computed by logistic regression using SAS 9.4 software.

Trial registration: 2008-58-0034.

RESULTS

Prevalence

Neonatal CP was found in 43 children corresponding to a prevalence of 2.4 per 1,000 live births (95% CI: 1.8-3.2). A total of 27 were male (62.8%) and 16 female (37.2%). In all, 12 children (28%) were from multiple births compared with 4.4% in the background population.

The prevalence of CP in children born with GA < 32 weeks was 63.5 per 1,000 compared with 9.3 per 1,000 for children with GA = 32-36 weeks and 1.3 per 1,000 for children with GA 37 weeks or more (p < 0.0001). The prevalence of CP in children with BW < 1,500 g was 73.8 per 1,000 compared with 1.8 per 1,000 for children with BW of 2,500 g or more (p < 0.0001). The prevalence of CP was 1.8 per 1,000 in singletons and 15.4 per 1,000 in multiple births.

The distribution of GA and BW for children with and without CP is presented in **Table 1**. A total of 49% of children with CP were born with GA < 37 weeks compared with 7% in the background population. In singleton pregnancies, the numbers were 33% and 5%, respectively. In multiple pregnancies, the proportion of children born with GA < 37 weeks and with a birth weight below 2,500 g was 92% for both variables in the CP group compared with 48% with GA < 37 weeks for all children from multiple pregnancies and 42% for low birth weight in multiple births without CP.

ORs for CP related to preterm birth and low birth weight and stratified for singletons and multiple births are shown in **Table 2**. Both variables were significant predictors of CP in the whole group and in singletons. A very low birth weight < 1,500 g remained a significant predictor of CP in singletons after adjustment for GA. In multiple births, GA < 32 weeks and a very low birth weight were significant predictors of CP. Corrected for GA, only a borderline significant effect of very low birth weight could be shown in multiple births. Overall, the unadjusted odds ratio for CP for children from multiple pregnancies is 8.3 (95% CI: 4.5-17.3) compared with singleton pregnancies.

Subtype and functional impairment

Spastic CP was the predominating subtype, which was found in 88%. The proportion was 95% in the preterm

TABLE 1

Distribution of gestational age and birth weight in the population of children with cerebral palsy compared to the background population and prevalence of cerebral palsy per 1,000 births.

	Singletons					Multiples				
	no CP		CP			no CP		CP		
	n	% (95% CI)	n	% (95% CI)	CP/1,000 births, n	n	% (95% CI)	n	% (95% CI)	CP/1,000 births, n
Children, total	16,770	100.0	31	100.0	1.8	767	100.0	12	100.0	15.4
GA at birth, wks										
< 32	93	0.6 (0.5-0.7)	6	19.4 (9.2-36.3)	60.6	84	11.0 (8.9-13.4)	6	50.0 (25.4-74.6)	66.7
32-36	674	4.0 (3.7-4.3)	4	12.9 (5.1-28.9)	5.9	282	36.8 (33.4-40.2)	5	41.7 (19.3-68.1)	17.4
≥ 37	15,924	95.0 (94.6-95.3)	21	67.7 (50.1-81.4)	1.3	399	52.0 (48.5-55.5)	1	8.3 (1.5-35.4)	2.5
Unknown	79	0.5 (0.4-0.6)	0	–	0.0	2	0.3 (0.1-1.0)	0	–	–
Birth weight, g										
< 1,500	78	0.5 (0.4-0.6)	5	16.1 (7.1-32.6)	60.2	60	7.8 (6.1-9.9)	6	50.0 (25.4-74.6)	90.9
1,500-2,499	458	2.7 (2.5-3.0)	5	16.1 (7.1-32.6)	10.8	263	34.3 (31.0-37.3)	5	41.7 (19.3-68.1)	18.7
≥ 2,500	16,150	96.3 (96.0-96.6)	20	64.5 (47.0-78.9)	1.2	436	56.8 (53.3-60.3)	1	8.3 (1.5-35.4)	2.3
Unknown	84	0.5 (0.4-0.6)	1	3.2 (0.6-16.2)	11.8	8	1.0 (0.5-2.0)	0	–	–

CI = confidence interval; CP = cerebral palsy; GA = gestational age.

group (GA < 37 weeks) and 83% in the full-term group (GA ≥ 37 weeks).

Bilateral spastic CP had a prevalence of 1.3 per 1,000 live births. Unilateral CP had a prevalence of 0.8 per 1,000. Dyskinetic and ataxic CP had a prevalence of 0.1 and 0.2 per 1,000, respectively.

There was no significant difference in gross motor function between the full-term and the preterm group. A total of 24 children (56%) were able to walk independently (GMFCS I, II), while nine children (21%) had no gait function (GMFCS V); and ten children (23%) were dependent on walking aids (GMFCS III, IV)

In all, 29 children (67%) had independent hand function (MACS I, II). Five children (12%) had no usable hand function (MACS V), and nine children (21%) were dependent on support (MACS III, IV). More children were classified as MACS I in the preterm group (52%) than in the full-term group (14%). OR = 0.14 (95% CI: 0.03-0.64).

Neuroimaging

Neuroimaging information was available in 38 children (88%). Modalities were ultrasound in four (9%), CT in two (5%), and MRI in the remaining 32 children (74%).

White-matter (WM) lesions were the predominating pattern, which was found in 19 children (50%). WM lesions were seen in 14 preterm and in five full-term children. Most cases (n = 17) were classified as periventricular leucomalacia (PVL). Two children were found with sequelae after intraventricular haemorrhage/infarction.

Grey-matter (GM) lesions were seen in nine children (24%). GM lesions were found in two preterm and seven full-term children. Four children had middle cerebral artery (MCA) infarctions, three children watershed lesions and one child basal ganglia and cortical/subcortical haemorrhage, respectively. Malformations were found in one preterm and three full-term children (11%). Miscellaneous changes were seen in two full-term children (5%). MRI was normal in one preterm and in three full-term children (11%).

Aetiology

Aetiology could be established in 16 children (37%), and the aetiology remained uncertain or unknown in 27 children (63%) (**Table 3**). In the full-term group, 11 children (50%) had an identifiable cause of CP. Ten full-term children had an uneventful pre- and perinatal history without clinical risk factors.

In the preterm group, five children (24%) had an identifiable cause of CP. Eight preterm children had an uneventful neonatal course without identifiable clinical risk factors. MRI of these children showed no specific patterns.

TABLE 2

Odds ratios (95% confidence interval) for cerebral palsy related to preterm birth and low birth weight and stratified for singletons and multiples.

	All infants	Singletons	Multiples
Gestational age, wks			
< 32	54.8 (26.5-113.2)	51.9 (20.4-132.1)	30.7 (3.6-258.4)
32-36	7.3 (3.3-16.0)	4.7 (1.6-13.8)	7.1 (0.8-61.3)
≥ 37	1	1	1
Birth weight, g[a]			
< 1,500	13.9 (2.9-67.0)	9.4 (1.2-73.5)	17.8 (1.0-317.1)
1,500-2,499	4.9 (1.5-16.1)	4.4 (1.0-19.4)	4.5 (0.4-50.0)
≥ 2,500	1	1	1

a) Adjusted for gestational age.

TABLE 3

Aetiology and clinical risk factors for 43 children with cerebral palsy. The values are n.

	Gestational age		
	≥ 37 wks	32-36 wks	< 32 wks
Established aetiology			
Cerebral malformation	3	1	–
Birth asphyxia and encephalopatia	3	–	–
MCA infarction	4	–	–
Infection:			
Congenital, CMV	1	–	–
Enterovirus meningitis	–	1	–
Complicated neonatal course and GA < 28 wks	–	–	3
Uncertain aetiology with risk factors			
Neonatal sepsis	–	–	1
Chorioamnionitis	–	1	–
Other infections	–	–	1
Intracerebral haemorrhage	–	–	1
Apgar score ≤ 5/5	1	–	1
VSD with early surgery	–	1	1
Extended mechanical ventilation	–	–	1
Unknown aetiology without risk factors			
MRI: + WM changes	5	2	1
MRI: + GM changes	1	2	–
MRI normal	3	–	1
MRI not available	1	1	1
Patients, total	22	9	12

CMV = cytomegalovirus; GA = gestational age; GM = grey matter; MCA = middle cerebral artery; MRI = magnetic resonance imaging; VSD = ventricular septal defect; WM = white matter.

One full-term and eight preterm children had single clinical risk factors without a definite relationship to the development of CP.

DISCUSSION

The overall prevalence of neonatal CP in the study was 2.4 per 1,000 live births (95% CI: 1.8-3.2). This rate was

Visit by crown princess Mary on cerebral palsy day.

slightly higher than that reported in European registers where prevalence rates of CP between 2.08 and 2.18 are reported (1980s and 1990s) [12-15]. The prevalence in full-term children was slightly lower (1.3 per 1,000) than that reported in previous Scandinavian studies reporting rates between 1.4 and 1.47 per 1,000 [12-14].

In contrast, the GA-specific prevalence rates for preterm children were slightly higher (63.5 for GA < 32 weeks and 9.3 per 1,000 for GA 32-36 weeks) than reported previously: prevalence rates in Eastern Denmark (1995-1998) were found to be 47.9 per 1,000 for GA < 32 weeks and 6.2 per 1,000 for GA 32-36 weeks [13]. Similar rates were found in Sweden in the periods 1999-2002 and 2003-2006 [11, 12]. The Danish Cerebral Palsy Register has shown a continuous decline in CP prevalence since the 1980s owing to a decreasing prevalence in the preterm group [14]. New data from Sweden show that this trend has ceased in the 2003-2006 period. The authors attribute this finding to the increasing number of ever more preterm children [13]. This finding is supported by our data for the birth year period 2003-2008.

The higher prevalence of CP found in our study may be related to the high rate of children from multiple births. The proportion of multiple births in the background population (4.4%) was similar to data for the entire Danish population [16], but high compared with previous European studies which report a rate of 2.4% for multiple births in 1990 [17]. The higher proportion of multiple births in the Danish population would explain an additional five cases in a population of this size (95% CI: 1-10) calculated based on CP prevalence rates of 1.8 and 15.6 per 1,000 in singletons and multiple births, respectively. This is comparable to 0.29 extra cases per 1,000 births. This calculation may explain the higher CP prevalence of 2.4 per 1,000 births and the high proportion of children with CP from multiple births (28%) in our study compared with a CP prevalence of 2.18 per 1,000 births in Sweden in the 2003-2006 period which included only 9% multiple births [13]. However, our data showed a significant difference in the prevalence of CP in singletons of 1.8 per 1,000 as compared with 15.4 per 1,000 in multiple births, which runs contrary to the findings in a large Danish study reporting a CP prevalence of 1.8 per 1,000 in singletons, but only 5.9 per 1,000 in multiple births for children born in 1995-2003 period [16].

Several studies have tried to elucidate whether multiple birth is an independent risk factor for CP, but the results have been inconclusive [15-17]. Our study shows consistently higher GA- and birth weight-specific CP rates for multiple births than for singletons. This may indicate that other factors contribute to the development of CP to a higher degree in multiple birthss than in singletons. Conclusions have to be drawn with caution because of the small sample size. Furthermore, a low GA and birth weight are risk factors for CP even after stratification for multiple births, and a low birth weight is a risk factor after adjustment for GA.

It has been shown that in vitro fertilisation IVF and other fertilisation techniques increase the risk of preterm delivery, low BW, and multiple birth and thereby the risk of CP [16]. A meta-analysis from 2009 including 19,462 IVF children showed a summary OR of 2.18 for the risk of CP in IVF children (95% CI: 1.71-2.77) [18]. In Denmark, the access to assisted conception is more liberal than in other countries, which presumably leads to an increased number of children conceived with IVF. Data on fertilisation treatments are not registered in the CPOP database, but would be of great interest for further research.

The high prevalence of bilateral spastic CP (1.3 per 1,000 births) may be related to the high proportion of children born preterm. Bilateral spastic CP is known to be the most frequent subtype in this group. The Danish Cerebral Palsy Register reported a prevalence of 0.96 per 1,000 for children born in the 1986-1998 period [13, 14]. The prevalence data for unilateral CP were similar to previous data from Denmark [14].

Functional data on GMFCS and MACS were comparable to reports from other studies [8, 12]. Preterm children were more likely to be classified as MACS I than full-term children. This finding reflects the higher proportion of diplegia in the preterm group [19].

Neuroimaging has contributed to the definition of a time frame for pre- and perinatal insults [20]. Malformations are thought to indicate a first-trimester origin, WM lesions are attributed to insults in the late second and early third trimester and GM lesions to insults in the late third trimester. The distribution of neuroimaging findings was similar to results from other studies [6, 7]. PVL was the predominating pattern in preterm children and supported a perinatal aetiology. PVL occurred in a small

group of full-term children with uneventful pre- and perinatal history, indicating a prenatal origin.

Neuroimaging findings were abnormal in the majority of children with CP (79%), but aetiology could only be established in 16 children (37%). Eighteen children had an uneventful neonatal course, and the aetiology remains unknown. Nine children had relevant clinical risk factors, but their impact on the development of CP remains uncertain.

CONCLUSION

The overall prevalence of CP in the study area was slightly higher than that found in other Scandinavian studies due to a higher GA-specific prevalence in the preterm group. A possible explanation is the high rate of multiple births in the background population. Neuroimaging findings were abnormal in the majority of children with CP, but the aetiology could only be established in 37%.

Primary prevention of CP is possible if the numbers of preterm births and multiple pregnancies can be reduced.

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