Cerebral palsy of post-neonatal origin: characteristics and risk factors

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Summary

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We aimed to study the rates and trends over time of children with cerebral palsy (CP) of post-neonatal origin (arising more than 28 days after birth, and before the age of 25 months), to examine their aetiology and associated significant risk factors, and to compare them with other CP cases. Children with post-neonatal CP born 1976–90 were identified from a European database and seven registers were included (Surveillance of Cerebral Palsy in Europe collaboration). Using a previously published classification it was possible to allocate an aetiology to 99% of cases. The prevalence rate of post-neonatal CP was 1.26 per 10 000 live births and a significant decrease was observed over the period 1976–90 ($P = 0.011$). Infection accounted for 50%, vascular episodes for 20% and head injury for 18% of the cases. Although there has been little change in the profile of underlying causes in this period, within the infection group, a significant downward trend was observed for Reye's syndrome ($P < 0.001$) and non-central nervous system (non-CNS) infection ($P = 0.004$), but not for meningitis/encephalitis. There was evidence of some increased risk of post-neonatal CP among children with low birthweight (<2500 g) ($P < 0.001$). Overall children with CP of post-neonatal origin showed a more severe functional pattern than non-post-neonatal CP children. In order to ascertain the impact of public health and other preventive measures aimed at reducing the frequency of brain injury in the first 2 years after birth, it is necessary to continue to monitor the frequency and characteristics of children with post-neonatal CP into the 1990s.

Introduction

The term cerebral palsy (CP) is used to describe children with a cluster of clinical signs including abnormal muscle tone and movement, and associated loss of function presumed to be due to a non-progressive lesion or abnormality of the brain.[1] While a variety of antenatal and perinatal risk factors have been identified for CP, in many individual cases the precise aetiology may be difficult if not impossible to establish.[2] However, for 5–10% of children affected by CP, there is a clear identifiable cause in the post-neonatal period – that is 28 days or more after birth.[3–5] These post-neonatal cases of CP are of particular interest because the underlying causes are often preventable by public health interventions.[6] For example, meningitis-induced brain injury could be avoided by appropriate immunisation programmes

while accident prevention strategies could reduce the rate of road and water-based trauma.

Although CP is the commonest motor disorder in early childhood, the prevalence rate is only 2/1000 live births. Thus, most population-based CP registries include relatively few children with a post-neonatal aetiology. As a consequence, most reported series on the condition have either excluded post-neonatal cases[7,8] or have involved small numbers of such cases.[9,10] It has been difficult therefore to monitor any changes in the profile of underlying causes or to obtain reliable estimates of change in rate over time of post-neonatal CP cases. Similarly, there has been limited published research comparing the aetiological and clinical profiles of CP of prenatal/perinatal origin with that of post-neonatal onset.

A database of over 6000 children with CP has been compiled through the collaboration of 14 European registries and surveys.[1] This resource has provided an opportunity to study post-neonatal CP in some detail. In particular, it was possible to (1) examine its rate and specific aetiology over time, (2) investigate the influence, if any, of birthweight, and (3) compare post-neonatal and non-post-neonatal CP in terms of clinical signs and the extent of functional loss.

Methods

A collaborative network of CP registers and surveys, the Surveillance of Cerebral Palsy in Europe (SCPE), was formed across Europe and the centres were able to send anonymised data on children with CP to a co-ordinating centre. Details of the population base and case definition can be found elsewhere.[11] The birth years included were 1976–90.

Post-neonatal CP cases were identified by a recognised putative causal event occurring after the 28th day after birth. Not all centres collected post-neonatal cases; in one centre, CP cases were not included if an insult occurred after the first week of life and, in four centres, they were not included if an insult occurred after the fourth week of life. One further centre reported only two post-neonatal cases and was excluded, leaving seven centres providing data. On the database, morbidity information was coded using the ICD-10 taxonomy. Based on these, and according to a previously published classification,[2] it was possible to allocate cases to one of the following aetiological groups: *infection* such as meningitis, encephalitis, septicaemia, viral or bacterial other infection; *head injury* including all types of traumatic head injury whatever the origin of the injury (road or traffic accident, bullet injury, as well as non-accidental injury); *vascular episode* including cerebro-vascular accidents and surgical complications, e.g. cerebral haemorrhage, post-cardiac surgery or post-brain surgery; and a residual group was entitled *miscellaneous* to include all other known causes. The precise age at the time of brain insult, expressed in months, was recorded.

The prevalence rates were calculated per 10 000 live births born to mothers resident in the area of study at the time of delivery, with one exception in the Isère centre. In this centre there was a high level of migration of the population, both in and out of the area and the population 'currently resident in the area' was used instead.

Prevalence rates were presented with exact 95% confidence intervals. Logistic regression was used to investigate possible between-centre rate differences, and trends over time. Fisher's exact test was used when necessary, and the ANOVA procedure for comparing the age of onset within different subgroups.

Results

There were 347 CP cases of putative post-neonatal origin born between 1976 and 1990 reported to the SCPE common database by seven different centres. These

Table 1. Proportion and rate of post-neonatal CP cases in seven centres 1976–90

Centre	Birth years	All CP cases *n*	Post-neonatal cases *n*	Proportion %	Post-neonatal cases born in the area and with an age of onset <25 months	Rate per 10 000	Live births
Isère, France	1980–89	301	40	13.29	30[a]	2.05	146 379[a]
Scotland, UK	1984–90	814	31	3.81	21	0.46	454 312
Cork, Eire	1976–90	260	28	10.77	22	1.55	142 139
Belfast, UK	1981–90	711	58	8.16	41	1.51	272 198
Göteborg, Sweden	1976–90	686	37	5.39	36	1.20	300 795
Oxford, UK	1984–90	729	61	8.37	37	1.54	240 691
Mersey, UK	1976–89	1011	92	9.10	65	1.46	444 171
Total [95%, CI]		4512	347	7.69 [6.93, 8.50]	252	1.26 [1.11, 1.43]	2 000 685

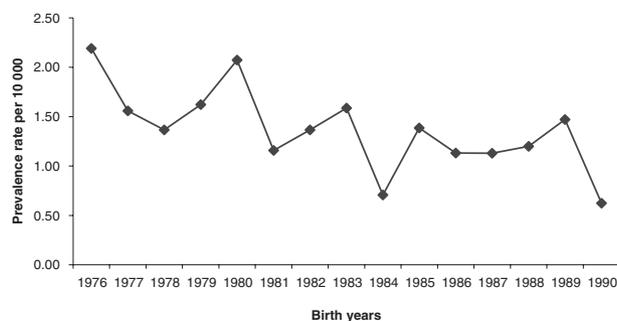[a]Children resident at 7 years old in the area.
CP, cerebral palsy.

Figure 1. Trend over time of post-neonatal cerebral palsy cases with an age of onset <25 months (*n* = 252 cases) seven centres.
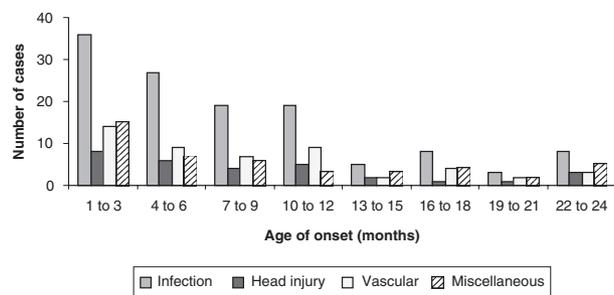

Figure 2. Age of onset and aetiological groups in 250 cerebral palsy cases.

represented 7.7% (347/4512) of the total CP cases from the seven centres (Table 1). The proportion of CP children with a post-neonatal origin varied from 4% to 13%. There were more males (59.4% or 206/347) than females; the relative risk for males being 1.16 [1.06,1.26].

The age at onset of CP was known for 94% (325/347) of cases; it ranged widely from 1 to 132 months with a mean value of 16 months, reflecting the variation of registration practices in relation to an upper age limit between centres. The post-neonatal cases with an age of onset above 24 months (*n* = 53), and the cases not born in the area (*n* = 20) were both excluded from further analysis. Among the remaining 252 cases having an age at onset below 25 months, 77.0% had their onset during the first year after birth (range 67.6% to 84.6% in the different centres). The mean prevalence rate was 1.26 per 10 000 [1.11,1.43], ranging from 0.46 to 2.05 per 10 000; the only register to differ significantly from the mean rate was the Scottish centre which reported the lowest level (*P* < 0.001).

Trend over time

As there was no significant interaction between years and centres it was possible to study the trend over time: there was evidence of a significant downward trend in the rate of post-neonatal CP over the period 1976–90 (*P* = 0.011), from 2.19 per 10 000 for 1976 birth cohort to 0.62 per 10 000 for the 1990 birth cohort (Fig. 1).

Aetiology

The aetiology was known in 99% of the cases (250/252). Half of cases were attributed to infection and 20% to some type of vascular episode (Table 2). The distri-

Table 2. Aetiology of post-neonatal CP in 250 cases with an age of onset known below 25 months. Aetiology not known in two cases

	n	%	Median age of onset (months)
Infection	125	50.0	6
Meningitis/encephalitis[a]	48		6
Reye's syndrome	30		6
Severe dehydration following gastro-enteritis	22		7
Other[b]	25		5.5
Head injury	30	12.0	7.5
Road traffic accident	7		7
Other traumatic injury	10		10.5
Non-accidental injury	13		5
Vascular episode	50	20.0	7
Post-heart surgery	20		6.5
Post-other surgery	9		4
Assoc. with congenital heart disease	5		12
Other (cerebrovascular accident)	16		7.5
Miscellaneous	45	18.0	7
Drowning	6		20
Near-miss cot death	15		3
Other[c]	24		7.5
Total	250	100.0	7

[a]Among the 48 meningitis/encephalitis, the identified infectious agents responsible were: Herpes virus (*n* = 8), Haemophilus influenzae (*n* = 7), pneumococcus (*n* = 5), meningococcus (*n* = 3), E Coli (*n* = 2), other virus (*n* = 4), proteus (*n* = 1) streptococcus (*n* = 1), unknown (*n* = 17).
[b]Among the other infections there were cases of bronchiolitis, endocarditis, septicaemia, and other not well defined infections (viral, febrile convulsion, acute epiglottitis …).
[c]Among the other 'miscellaneous' aetiologies, 'post seizures' disorders were the most frequently observed, and then brain tumour sequelae, burns/CO poisoning, unknown encephalopathy….
CP, cerebral palsy.

bution of aetiology by age of onset is shown in Fig. 2. Some examples of such vascular episodes are: complications post-cardiac surgery or post-catheterisation, intra-cerebral haemorrhage due to malformation of cerebral blood vessels, cerebro-vascular accident post-sickle cell anaemia. Head injury accounted for 12% of the post-neonatal CP cases and a broad residual group, including near cot death and near drowning events, accounted for the remaining 18% of cases. Prominent specific causal factors within these main categories include 30 of the 125 cases within the infection group which are attributed to Reye's syndrome; almost half (13 of 30) of head injuries were of a non-accidental nature, while 40% (20 of 50) of vascular episode-related post-neonatal CP was due to post-heart surgery sequelae. Aetiology was independent of sex ($P = 0.62$), birthweight ($P = 0.46$), gestational age ($P = 0.09$) and age of onset of CP ($P = 0.84$). Children with CP following head injury tended to have a lower gestational age than post-neonatal cases of other aetiological groups, but this did not reach statistical significance.

During the study period, the prevalence rate of infection-induced post-neonatal CP tended to decrease from 0.80 per 10 000 during 1976–78 to 0.42 per 10 000 for the period 1988–90 ($P = 0.015$). Reye's syndrome prevalence rate decreased from 0.34 per 10 000 live-births in 76–78 to 0.04 per 10 000 livebirths in 88–90 ($P < 0.001$), and other non-CNS infection prevalence rate decreased, respectively, from 0.40 to 0.14 per 10 000 livebirths ($P = 0.004$). For meningitis/encephalitis subgroup and in the other three aetiological main groups, i.e. head injury, vascular episode and miscellaneous groups, the prevalence rates remained remarkably stable throughout.

Perinatal characteristics

In the Isère centre data on live births per birthweight were not available. In the six other centres data on

birthweight of live births were available, and birthweight was known in 95% of the post-neonatal CP cases (212/222) in these six centres. The birthweight profiles of (1) the post-neonatal CP cases, (2) non-post-neonatal CP cases, and (3) all live births are compared in Table 3. There is evidence of some increased risk of post-neonatal CP with low birthweight (<2500 g) when compared with all live births ($P < 0.001$). However, the proportion of low-birthweight children among the post-neonatal CP group (11.3%) is far lower than the proportion in the non-post-neonatal CP group (46.5%).

Population information on gestational age was only available for three of the seven centres. Based on 91 post-neonatal CP cases, there was no statistically significant evidence of a lower average gestational age for CP cases of post-neonatal origin ($P = 0.39$). The proportion of preterms among the post-neonatal group was 8.8% compared with 46.1% among the non-post-neonatal CP cases.

Cerebral palsy subtypes

Cerebral Palsy subtype and aetiology were known in 94% of cases (238/252). Spasticity was the predominant CP condition (88.4%); these were equally distributed between unilateral and bilateral sub-groups (Table 4). The latter finding contrasts with the non-post-neonatal CP group where the unilateral : bilateral ratio was 0.62 : 1 ($P < 0.001$).

Within the post-neonatal CP cases there was a significant association between CP type and aetiology ($P = 0.014$). In particular, children in the infection and miscellaneous group were more likely to have a spastic bilateral manifestation, whereas the children with vascular lesions or head injuries were more likely to have a unilateral manifestation. While instances of dyskinesia (6.6%) and ataxia (5.0%) were relatively uncommon, these conditions were also more likely

Birthweight	Post-neonatal CP cases n (%)	Non-post-neonatal CP cases n (%)	Live births n (%)
<1000 g	0 (0)	175 (4.9)	4 192 (0.2)
1000–1499 g	4 (1.9)	536 (15.0)	8 348 (0.5)
1500–2499 g	20 (9.4)	946 (26.6)	84 595 (5.0)
≥2500 g	188 (88.7)	1906 (53.5)	1 589 958 (94.2)
Total	212 (100.0)	3563 (100.0)	1 687 093 (100.0)

Table 3. Birthweight profile of post-neonatal CP in 212 cases with an age of onset below 25 months. Birthweight not known in 10 cases among 222 cases of six centres

CP, cerebral palsy.

Table 4. Cerebral palsy (CP) sub-types of post-neonatal CP in 238 cases with an age of onset below 25 months. Cerebral palsy sub-type or aetiology not known in 14 cases

	Post-neonatal CP cases					Non-post-neonatal cases
	Infection n (%)	Head injury n (%)	Vascular episode n (%)	Miscellaneous n (%)	Total n (%)	%
Spastic unilateral	50 (42.7)	18 (60)	27 (56.3)	10 (23.3)	105 (44.2)	34.3
Spastic bilateral	53 (45.3)	12 (40)	17 (35.4)	23 (53.5)	105 (44.2)	54.9
Dyskinetic	5 (4.2)	0 (0)	4 (8.3)	7 (15.9)	16 (6.6)	5.6
Ataxia	9 (7.6)	0 (0)	0 (0)	3 (6.8)	12 (5.0)	5.1
Total	117 (100)	30 (100)	48 (100)	43 (100)	238 (100)	100

within the infection and miscellaneous aetiological categories.

Severity of disability

Four indicators of severity of disability – walking, intellectual impairment [intelligence quotient (IQ) < 50], active seizures, and visual impairment – were compared across the aetiological groups (Table 5). While little variation was apparent in terms of the intellectual and visual impairment profiles, there was evidence of a higher level of walking disability and active seizure pattern among the infection and miscellaneous groups.

For each severity indicator there was a significantly higher overall level of disability among post-neonatal CP cases when compared with the corresponding non-post-neonatal CP children –

unable to walk ($P = 0.002$), IQ below 50 ($P < 0.001$), active seizures ($P < 0.001$) and severe visual impairment ($P < 0.001$).

Discussion

This study estimates that post-neonatal origin accounts for 7.7% [6.9,8.5] of all cases of CP, and that the prevalence rate of post-neonatal CP with an age of onset below 25 months is 1.3 per 10 000 live births. These findings are similar to those already reported.[2] There was a significant decrease in prevalence rate over the period 1976–90 ($P = 0.011$), but this trend was heavily influenced by an exceptionally low rate for the final study year, 1990. This was possibly due to under-ascertainment and the ongoing collection of cases on the SCPE database will help to clarify the significance of these trends over time.

Table 5. Pattern of severity of disability according to aetiology of post-neonatal CP in 238 cases with an age of onset below 25 months. Severity of disability or aetiology not known in 14 cases

	Post-neonatal cases						Non-post-neonatal cases
Severity of disability	Infection %	Head injury %	Vascular episode %	Miscellaneous %	Total %	P-value[a]	
Unable to walk	40.5	21.4	38.3	54.8	40.3	0.05	30.6
IQ < 50[b]	58.5	54.2	50.0	66.7	57.8	0.51	29.5
Active seizures[c]	41.7	21.4	16.7	29.4	30.3	0.06	16.7
Severe visual impairment[d]	21.6	23.3	22.0	26.7	22.8	0.92	9.6
Number of cases	117	30	48	43	238		

Percentages are estimated after exclusion of cases with unknown information.
[a]Comparison between aetiological groups among post-neonatal CP cases.
[b]Without Scottish centre.
[c]Without Belfast and Mersey centre.
[d]Blind or visual acuity <3/10.
CP, cerebral palsy.

The dominant role of infection as an aetiological factor in post-neonatal CP identified in this study is consistent with other published findings[2,6] and the decrease in prevalence rates due specifically to infection has also been described by the Australian group.[2] A study based on hemiplegic post-neonatal cases, has identified haemophilus influenzae as the most frequently observed agent responsible for cerebral infection.[12] Since infection was the main diagnosed cause of post-neonatal CP, one might speculate that the reduction in the rate of such lesions over the study period might be at least partially due to the introduction of public health measures to reduce the frequency of meningitis. However, the significant downward trend was observed for Reye's syndrome and non-CNS infection, but not for meningitis/encephalitis. The decrease in the prevalence of post-neonatal CP attributed to Reye's syndrome almost certainly reflects the withdrawal of aspirin treatment in children since 1980.[13,14] Our study period predated the widespread introduction of vaccination programmes aimed at reducing the frequency of meningitis, such programmes starting only in 1992 in UK and 1993 in France.

As reported previously[6] children with a low birthweight (<2500 g) appear to have a twofold higher risk of developing post-neonatal CP than children of normal birthweight. One reason for this finding might be that low-birthweight babies, particularly if also preterm, may have a higher probability of a serious infection during infancy. However, our data suggested that it was the group with head injury which had the highest proportion of birthweight <2500 g (22% of cases vs. <10% in the other groups). Among CP children with head injury and low birthweight, non-accidental head injury was the most frequently reported cause. This raises the question as to whether low-birthweight infants are more at risk of non-accidental injury, or even whether there is a common risk factor, i.e. those babies that are more at risk of low birthweight (e.g. due to family circumstances) may also be more at risk of non-accidental injury, and thus to post-neonatal CP.[15,16]

The higher proportion of hemiplegia among post-neonatal CP cases has been reported previously.[2] Surprisingly, this does not seem to lead to a less severe overall pattern of disability. The fact that post-neonatal cases with an age of onset below 25 months have a more severe clinical pattern than other CP cases of antenatal or perinatal origin might be explained in part by the fact that, since the brain lesion occurred late in the infant period (median age 7 months), post-neonatal CP cases are similar to 'at term' or normal-birthweight CP children. However, this relationship between severity and birthweight is not constant over time and between studies.[17]

The impact of vascular episodes on post-neonatal CP is particularly noteworthy as it affects one in every five such cases. However, it must be kept in mind that such morbidity may be due to pre-operative neurodevelopmental abnormality (hypoxic-ischaemic postnatal lesion) as well as peri-operative adverse events. It has been reported that up to 3% of children undergoing surgery for congenital heart disease will have neurological complications[18] and strategies for preventing such accidents have been outlined recently.[19]

Post-neonatal CP with onset in the first 2 years after birth is rare with 13 affected infants for every 100 000 livebirths. However, half of these post-neonatal CP cases are due to infection, and head injury and surgery-related vascular episodes are also significant risk factors. It is likely that a high proportion of these are potentially preventable by more recently implemented public health and other measures. It will be important therefore to continue to monitor the frequency and characteristics of post-neonatal CP into the 1990s. The ongoing SCPE database will be able to do this.

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Appendix.

Post-neonatal CP cases with an age of onset above 24 months

Fifty-three post-neonatal CP cases from six centres of the SCPE common database had an age of onset ranging from 25 months to 132 months, of whom 86% had an age of onset below 60 months. For these 53 cases, head injury was the most common aetiology (56.6%) followed by infection (20.8%). While the majority were again spastic (92.5%), unilateral lesions were more common (63.3%). The severity of their disability seemed less pronounced than that observed for post-neonatal CP cases with onset up to 2 years of age; 25.5% of the group could not walk, 31.7% had a severe intellectual impairment, 24% had active seizures while 7.5% had a severe visual impairment.

When the age of onset of post-neonatal CP exceeds 2 years the severity levels are seen to diminish. Within this small subgroup of post-neonatal cases, CP was more often unilateral ($P = 0.02$) and less severe, i.e. more children able to walk ($P = 0.03$), less children with IQ < 50 ($P < 0.001$), and less blind children ($P = 0.01$), except for the presence of active seizures ($P = 0.41$) than in post-neonatal cases with an age of onset below 25 months. In view of these differences in the characteristics of this group compared with the group with an earlier onset, and in order to avoid ascertainment bias between centres, the defined cut-off of 24 months seems justified.