Mortality from 1- 18 Years in Bilateral Cerebral Palsy

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ABSTRACT
Objective: To ascertain mortality rates from 1 to 18 years, and predictors of mortality.
Design: Long term follow up of population cohort born 1989-92
Setting: Births in SE Thames Region
Patients: 346 children with bilateral cerebral palsy (CP)
Interventions: not applicable
Main outcome measures: Mortality rates; predictors of mortality.
Results: 98% of cohort traced. 61/340 (17.9%) had died by age 16-18 years at a steady mortality rate. The main predictive factor was severity of impairment of functional ability (hazard ratio 5.7, 95% confidence interval 2.1-15.0 for poor hand manipulation; 6.8 (1.9, 23.9).for severe communication problems).
Conclusions: Although there were deaths throughout the childhood and teenage years, the majority of children with bilateral CP are likely to survive to adulthood, especially if they do not have major functional impairment at 2 years. This confirms findings of other studies of children with CP.

BACKGROUND

Mortality in children with cerebral palsy (CP) is greatly increased compared with unaffected children.[1, 2, 3] Cohort studies suggest that severity of functional disability is the best predictor of mortality. They are based on CP registers and multiple clinicians' assessments, variably include post-neonatal causes and include children with unilateral CP, whose brain involvement may have a different functional impact from that of bilateral CP.

We therefore report the follow up to age 16-18 years of a cohort of children with bilateral CP alive at 12 months of age whose physical examination was made uniquely by one clinician (DS).

METHODS

The methods have been previously described.[4] Briefly, all children with movement impairment born to mothers resident in a geographically defined UK region in 1989-82 were physically examined by DS, and those with bilateral CP followed up. Intellectual and communicative ability was directly assessed by GB in approximately half the children and information obtained from local child development services for all. As the original study focused on the development of hips which lacked the influence of previous walking experience, only children diagnosed with CP by 15 months were included. Children who died before 12 months of age were excluded.

Between 2006 and 2008 the original cohort was followed up until death or censored at the latest date they were known to be alive. Death certificates were obtained from the Office of National Statistics. Factors (shown in Table 1) known by age two years (+/- 6 months) were used for the prediction of death. Children dying before 18 months were excluded.

Statistical analysis

Cox proportional hazard models were used to examine the association between survival and explanatory factors. In all initial analyses, the 5-point categorical scales and the categorised birthweight variable were treated as continuous measures; this approach was supported by tests for linear trend.

Following univariate analyses, multivariate analyses were carried out to consider the effect of several disabilities. In order to select the variables for the multivariate analysis, a full model on all explanatory variables was fitted, the least significant term was removed and the model re-estimated. This was repeated until all remaining variables were significant at the 5% level.

In order to allow comparison with other studies, we examined whether there was any difference in survival between early and late onset cases. Two approaches were used, firstly any acquired cause up to 28 days postnatally (as used by Hutton et al)[1] and secondly an acquired cause with onset later than 28 days postnatally (excluded by Hutton et al).[1]

Interaction tests were carried out between these two factors and the other univariate factors.

RESULTS

Mortality rates

Three hundred and forty six children were initially identified as alive from 1 year of age with bilateral CP (1.7/1000 live births). Only six (1.73%) could not be traced in 2006-08. Sixty one of the 340 children traced had died between the ages of one and 18 years – a rate of 17.94%.

The primary recorded cause of death in the majority was reported as respiratory: bronchopneumonia (19); respiratory infection (7); aspiration (6) (certificates for 2 of these cited gastro-oesophageal reflux contributing to aspiration and death); respiratory arrest (2) or respiratory failure (5). Eight died with epileptic seizure listed as the primary cause. The other primary causes were pancreatitis (1); diabetic ketoacidosis (1); hepatic failure (1); renal failure (1); and 4 gastrointestinal problems (3 peritonitis and septicaemia associated with complications with gastrostomy/PEG and one bowel infarction). In six cases, CP was given as the only cause of death, at ages ranging from 18 months to 13 years.

The survival of the cohort from the age of 1 year to 16-18 years is shown in fig 1. The mean age of death was 8.1 years (SD 5.2), but there were deaths throughout the period.

Insert Figure 1 about here

Late onset cases show a non-significant increased mortality over early onset (p=0.16). The mortality rate for children with a postnatal cause is also not significantly different from those with presumed pre and perinatal causation (p=0.58).

Predictors of mortality

Four of the 61 children died before 18 months, thus analyses of predictive factors from 2 years +/- 6 months are based on 336 children (57 deaths and 279 surviving children).

Greater birth weight and a longer period of gestation were significantly associated with poorer survival (Table 1). Poorer survival was also significantly associated with greater severity of motor disorder, as classified by the GMFCS or characterised by delayed acquisition of motor milestones, feeding and swallowing problems (as measured by the presence of a

gastrostomy), and severe communication problems. All but 2 deaths were in the combined level IV and V group. These exceptions were due respectively to diabetic ketoacidosis and epileptic seizure.

Visual impairment, epilepsy (more than 6 seizures in a year) and poor intellectual ability were non-motor measures of severity of disability significantly associated with poorer survival. Factors examined which were not significantly associated with survival were gender, clinical type of CP, and respiratory infections indexed by reported wheeze and cough frequency at age 2 years.

Table 1 Univariate analysis of mortality predictors N (%)

	Alive n (%) N=279	Dead n (%) N=57	Hazard ratio (95% CI)
Early onset (insult prior to 28 days after birth)	258 (92.5)	50 (87.7)	
Late onset (onset 28 days to 15 months)	21 (7.5)	7 (12.3)	1.6 (0.7,3.6)
Any postnatal cause			
No	228 (81.7)	45 (79.0)	
Yes	51 (18.3)	12 (21.1)	1.2 (0.6,2.3)
Gender			
Male	170 (60.9)	28 (49.1)	
Female	109 (39.1)	29 (50.9)	0.7 (0.4,1.1)
Birth weight (g)			
=<1500	62 (22.2)	5 (8.8)	
1500-1999	48 (17.2)	7 (12.3)	
2000-2499	28 (10.0)	7 (12.3)	
>2500	140 (50.2)	38 (66.7)	1.4 (1.1,1.8) **
missing	1 (0.4)	0	
Gestational age (weeks)			
mean (sd)	34.9 (5.4)	37.3 (4.7)	1.1 (1.0,1.2) **
missing	1	0	
Multiple births			
1	247 (88.5)	55 (96.5)	
2	17 (6.1)	1 (1.8)	
3	10 (3.6)	1 (1.8)	
4	2 (0.7)	0	0.5 (0.2,1.3)
missing	3 (1.1)	0	

Table 1 continued

	Alive n (%) N=279	Dead n (%) N=57	Hazard ratio (95% CI)
Severity of non-motor functional disability			
Communication problems			
mean (sd)	1.6 (1.3)	3.5 (0.9)	4.4 (3.1,6.4) ***
no (score 0,1 or 2)	195 (69.9)	4 (7.0)	
yes (score 3 or 4) (severe & profound)	81 (29.0)	53 (93.0)	
missing	3 (1.1)	0	
Severe visual impairment (best eye)			
mean (sd)	0.5 (1.1)	2.0 (1.7)	1.8 (1.5,2.1)
no (score 0,1 or 2)	247 (88.5)	28 (49.1)	
yes (score 3 or 4)(<6/60)	28 (10.0)	26 (45.6)	
missing	4 (1.4)	3 (5.3)	
Severe hearing impairment (best ear)			
mean (sd)	0.1 (0.5)	0.2 (0.6)	1.1 (0.7,1.7)
no (score 0,1 or 2)	271 (97.1)	49 (86.0)	
yes (score 3 or 4) (<70Db aided)	5 (1.8) 3 (1.1)	1 (1.8) 7 (12.3)	
missing			
Hydrocephalus			
no	259 (92.8)	53 (93.0)	
yes	20 (7.2)	4 (7.0)	1.0 (0.4,2.8)
Shunt			
no	263 (94.3)	53 (93.0)	
yes	16 (5.7)	4 (7.0)	1.3 (0.5,3.5)
Intellectual ability			
Mean (sd)	1.5 (1.2)	3.2 (1.1)	3.2 (2.4,4.3)***
IQ?50 (score 0,1 or 2)	205 (73.5)	10 (17.5)	
IQ<50 (score 3 or 4)	72 (25.8)	47 (82.5)	
missing	2 (0.7)	0	

Table 1 continued

	Alive n (%) N=279	Dead n (%) N=57	Hazard ratio (95% CI)
Severity of motor disorder hand manipulation (best hand) (0-4, 4 worst) mean (sd)	1.5 (1.1)	3.3 (1.0)	
score 0,1 or 2	218 (78.1)	7 (12.3)	
score 3 or 4	57 (20.4)	49 (86.0)	3.7 (2.7,5.0) ***
missing	4 (1.4)	1 (1.8)	
Able to sit by 24 m1			
yes	131 (47.0)	1 (1.8)	
no	144 (51.6)	56 (98.3)	44.4 (6.1,320.8) ***
missing	4 (1.4)	0	
Able to cruise by 24 m2			
yes	102 (36.6)	2 (3.5)	
no	176 (63.1)	55 (96.5)	14.4 (3.5,59.2) ***
missing	1 (0.4)	0	
Disability predominantly in:			
upper limb	14 (5.0)	2 (3.5)	
lower limb	131 (47.0)	2 (3.5)	0.04 (0.0,0.2)
equal	125 (44.8)	51 (89.5)	0.4 (0.1,1.6) ***
missing	9 (3.2)	2 (3.5)	
Type of CP predominantly:			
Spastic	250 (89.6)	50 (87.7)	
Ataxic	10 (3.6)	0	
Dyskinetic	12 (4.3)	6 (10.5)	2.3 (1.0,5.4)
Mixed	7 (2.5)	1 (1.8)	0.7 (0.1,4.9)
Bulbar involvement			
no	131 (47.0)	49 (85.0)	
yes	136 (48.8)	7 (12.3)	6.3 (2.8,13.9) ***
missing	12 (4.3)	1 (1.8)	
Gastrostomy			
no	275 (98.6)	49 (86.0)	
yes	4 (1.4)	7 (12.3)	5.1 (2.3,11.3) ***
Fixed spinal curve			
no	265 (95.0)	53 (93.0)	
yes	1 (0.4)	3 (5.3)	8.3 (2.6,26.6)***
missing	13 (4.7)	1 (1.8)	
GMFCS score3			
I walks without limitations	39 (14.0)	0	
II walks with limitations;	85 (30.5)	2 (3.5)	
III walks using a hand-held mobility device;	34 (12.2)	0	
IV & V self-mobility with limitations, may use powered mobility; level V - transported in a manual wheelchair.	121 (43.3)	55 (96.5)	6.2 (2.8,14.0)

Table 1 continued

	Alive n (%) N=279	Dead n (%) N=57	Hazard ratio (95% CI)
Epilepsy			
Seizures in the last year			
none	193 (69.2)	14 (24.6)	
1-2	29 (10.4)	6 (10.5)	
3-6	23 (8.2)	3 (5.3)	
>6	24 (8.6)	30 (52.6)	2.2 (1.8,2.7) ***
missing	10 (3.6)	4 (7.0)	

* <0.05
** <0.01
*** <0.001

[1] Getting to any sitting position from any lying position on the floor and then sitting without propping with either arm for 15 seconds.

[2]Cruising along furniture or a wall, even if placed in standing, for at least two steps sideways in either direction (not necessarily both).

[3] The Gross Motor Function Classification System (GMFCS) [5] retrospectively assigned at age 2 to allow comparability to current studies. Levels IV and V combined due to insufficient data at the age of 2 years to confidently distinguish them.

The conclusions from these univariate analyses were not changed when taking into account age of onset (interaction tests p>0.05).

The results from the multivariate analysis suggest that survival can be predicted by severely impaired hand function and/or communicative ability, and fixed spinal curvature. Removing the 4 participants affected by fixed spinal curvature at age 2 years from the analysis did not change this conclusion. Following Hutton et al,[1] we recoded both communication and hand manipulation problems into severe (scores 3 or 4) *vs* not severe (scores 0, 1 or 2). The hazard ratios and 95% confidence intervals for severe communication problems and for severe hand manipulation problems were highly significant (6.8 (1.9, to 23.9) and 5.7 (2.1 to 15.0) respectively).

Again following Hutton and colleagues,[1] we re-coded these predictors into four categories: (i) severe communication *and* hand manipulation problems (n=98); (ii) a severe communication problem but not a severe hand manipulation problem (n=35); (iii) a severe hand manipulation problem but not a severe communication problem (n=7); or (iv) *neither* a severe communication problem *nor* a severe hand manipulation problem (n=189). As expected, the survival was highest in those in category (iv) and lowest in category (i) (fig 2). Of those children who had both severe manipulation and

communication impairment, 42.7% survived to 18 years. However, when only one of either manipulation or communication function was severely impaired, there was 88% survival to 18 years.

Insert Figure 2 about here

DISCUSSION

This study has reported mortality from a complete population cohort of children with bilateral CP, who were all examined by one experienced clinician. Based on children who were alive at one year of age, the study had 98% ascertainment of deaths to age 16-18 years; 82% were still alive at age 16-18 years.

Important findings are that there is a steady mortality throughout childhood and adolescence; and that death is associated with severity of impairment from inferred bilateral brain damage affecting particularly the upper limbs and the bulbar region, with respiratory causes of death being most common.

Management of cerebral palsy has changed over time, principally the use of gastrostomy in those with severe feeding problems and reflux. Strauss and colleagues have shown [6, 7] that survival for children who are largely immobile and fed by others (ie the severely disabled group) has improved, possibly due to earlier gastrostomy. The present cohort study cannot address this point.

Brain insult may also give rise to cortical visual impairment and epilepsy. Both severe visual impairment and epilepsy were univariately associated with increased mortality in this study and a seizure was recorded as the primary cause of death in eight children. Spinal curvature already fixed at age 2 years, a likely indicator of severity of motor involvement, was also a risk factor. Hearing loss, thought at one time to be an additional mortality risk factor, was not a significant risk factor in this study.

The mortality rate we report is likely to be an underestimate of the birth cohort mortality rate of children with bilateral cerebral palsy, as children who died before 12 months of age were never seen to confirm diagnosis and thus never included in the study. Variation in inclusion criteria may have an impact on results. This cohort mortality rate is a little higher than the Hutton et al study [1], which described mortality in a birth cohort of CP registered from 1 month of age, whereas our study comprised those alive at 12 months; excluded onset after 28 days post birth; and had a mix of unilateral and bilateral CP, and where the 20 year survival was 89.3% for females and 86.9% for males.

Of the other factors noted previously, we found that the hazard ratio for female gender was also reduced,[1] although this reduction did not reach conventional statistical significance; and

that larger birth weight and greater gestational age were also factors relevant to survival,[1] although less predictive than functional impairment. This latter could be due to a greater infant death rate in those born prematurely and of low birth weight. Another factor may be that those with a post neonatal brain insult have increased mortality (and greater functional impairment) but are more likely to have been of larger birth weight and greater gestational age.

We have shown that easily ascertainable measures are relevant to prognosis and are presented here in a way that enables their use in conversations with parents. In children with bilateral CP, parents and clinicians can confidently expect most children with bilateral CP who at the age of 2 years have good or mildly impaired communication and manipulation skills with no bulbar problems, and who can cruise and can get to sit, will live to 18 years and - according to data from UK and USA studies [8] - well beyond.

Ethical approval was granted by the South-East MREC, reference number 06/MRE01/18

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What is already known on this topic

Most children with cerebral palsy (CP) live to adulthood.

Severity of functional disability is the best predictor of mortality.

What this study adds

Even among the category of children with bilateral CP, most live to adulthood but there is an 18% mortality rate from those alive at 1 year with deaths occurring steadily to 16/18 years.

Based on factors known at age 2 years, the main independent predictor of mortality is the severity of motor impairment affecting communication and manual function.

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Figure 1: Survival of the cohort from the age of 1 year

Figure 2: Survival of cohort from 18 months split by presence/absence of communication and manipulation problems