Long-term survival of children with cerebral palsy in Okinawa, Japan

MAYUMI TOUYAMA[1] | JUN TOUYAMA[1] | YASUO OCHIAI[2] | SATOSHI TOYOKAWA[3] | YASUKI KOBAYASHI[3]

1 Department of Paediatric Neurology, Okinawa Child Development Center, Okinawa; **2** Okinawa Children's Clinic, Okinawa; **3** Department of Public Health, Graduate School of Medicine, University of Tokyo, Tokyo, Japan.

Correspondence to Dr Mayumi Touyama at Department of Paediatric Neurology, Okinawa Child Development Center, 5-2-17 Hiyagon, Okinawa city, Okinawa 904-2173, Japan.
E-mail: mayumi@shoni.or.jp

This article is commented on by Day on pages 402–403 of this issue.

PUBLICATION DATA
Accepted for publication 13th July 2012.
Published online 9th February 2013.

AIM The aim of this study was to describe the survival prognosis of children with cerebral palsy (CP) in Okinawa, Japan.
METHOD A cohort study was conducted on all children with CP born between 1988 and 2005 in Okinawa, Japan. Survival proportions were determined with a life table and Kaplan–Meier survival curves were plotted. The effect of each predictor variable was estimated using Cox regression analysis.
RESULTS This study included 580 children with CP (332 males, 248 females). In the cohort, 119 (20.5%) children were classified in Gross Motor Function Classification System (GMFCS) level I, 65 (11.2%) were classified in level II, 40 (6.9%) in level III, 189 (32.6%) in level IV, 166 (28.6%) in level V and GMFCS level was unknown for one. Of the 34 children who died, 29 were classified in GMFCS level V and GMFCS level was unknown for one. Mean age at start of follow-up was 24.5 months (SD 2.6mo); mean length of follow-up was 8 years 8 months (standard error of the mean 0.214y). The 5 year- and 18-year survival percentages of the entire cohort were 98% and 89% respectively. In children with CP, significantly lower survival rates were associated with multiple factors, including a birthweight of at least 2500g (p=0.009), a gestational age of at least 37 weeks (p=0.004), and the most severe gross motor limitation, GMFCS level V (p<0.001). However, multivariate analysis showed GMFCS level V was the only significant predictor variable (p<0.001) for survival of CP.
INTERPRETATION This study is the first to describe survival of children with CP in Japan. Our results are similar to those previously reported in other countries. These results are important in planning adequate provision of social and medical services for individuals with CP.

Cerebral palsy (CP) is among the most common disabilities in childhood. A greater understanding of the pathophysiological and epidemiological characteristics of CP is necessary to provide the requisite obstetric and paediatric care and services. Moreover, investigation of long-term survival in children with CP provides a basis for the provision of adequate social and medical services for this population. This type of information is also valuable to physicians who counsel patients and their families.

The survival patterns of individuals with CP have been described previously for California,[1–3] Canada,[4] Australia,[5] and the UK.[6–13] These results suggest that most children with CP survive into adulthood, unless they have severe motor and/or cognitive impairments.

In Japan, there has been no report of long-term survival in children with CP based on population studies, and no evidence on the factors associated with survival. The aim of this study, therefore, was to describe the survival of children with CP born in the Okinawa Prefecture, Japan.

The Okinawa Prefecture is a chain of islands, comprising a main island and several smaller islands, which lie southwest of mainland of Japan. The current population is approximately 1.3 million, with about 16 000 to 17 000 live births per year. Most individuals reside on the main island, which is divided into three regions (south, central, and north). Okinawa is located far from mainland Japan; therefore, very few people who reside in Okinawa Prefecture move away from the chain of islands. Interestingly, the surnames of Okinawa natives are, for historical reasons, unique and can mostly be distinguished from those of residents of other prefectures in mainland Japan. These unique geographic and demographic features provide an ideal basis on which to conduct epidemiological studies in Japan.

According to Japanese law, each local government must have a registration system of births and deaths, including the cause of death for all citizens who have Japanese nationality. In addition, Japanese people have a duty to obtain official health insurance.

METHOD

Thirty years ago, the Okinawa Child Development Center, in collaboration with other clinics, hospitals, and health centres

in Okinawa Prefecture, established a regional care system for children with CP. Children with CP in Okinawa Prefecture receive treatment either at one of four rehabilitation hospitals (including the Okinawa Child Development Center) or at a care facility (Nahasiryouiku Center). Children with CP who live on small remote islands receive care at local medical institutions with full support from the four main rehabilitation hospitals.

Almost all children who were born in Okinawa Prefecture and diagnosed with CP by either a paediatrician or a paediatric neurologist were referred to one of the four rehabilitation hospitals or the care facility for their treatment. After attending those institutions, they were identified and registered on the database for children with CP. The data on children with CP were collected from their medical records at those institutions. Children with CP who underwent prolonged hospitalization in acute care hospitals because of severe complications associated with CP, and those who died before being referred to one of the institutions, were excluded from the registration database. Furthermore, an electronic database of children with CP was created in 1991 and updated every 4 to 5 years during an on-site visit by the researchers of the Okinawa Child Development Center. This was because children with CP received physical and/or occupational therapy or consulted certified physicians for the renewal of their disability benefits. Data on health and functioning status, such as feeding status, whether they had epilepsy, cognitive impairment level, and Gross Motor Function Classification System (GMFCS) level, were reviewed and updated every 4 to 5 years by the researchers.

For the present study, data were collected on individuals with CP from the CP database. Data from children with CP who were born in another prefecture and who moved to Okinawa after birth were not included in the present study. The study cohort consisted of all children with CP who were born between 1988 and 2005 in Okinawa.

Ethical approval for the present study was obtained from the institutional review board of the Graduate School of Medicine at the University of Tokyo.

Data collected from the CP database included date of birth, sex, gestational age, birthweight, date of initial clinical assessment, date of most recent clinical assessment, and GMFCS level. Data on GMFCS level were ascertained as closely as possible to the follow-up termination date of this study.

The definition of CP used in the present study was proposed at the International Consensus Meeting on CP in Bethesda, MD, USA.[14] CP was defined as a group of disorders of the development of movement and posture; these disorders cause activity limitation and are attributed to non-progressive disturbances that occur in the developing fetal or infant brain. CP is often accompanied by disturbance of sensation, cognition, communication, perception, or behaviour, and/or by a seizure disorder.[14] Individuals with CP-related brain injuries that occurred later than 28 days after birth were excluded from the present study. Children who died before their second birthday were not included, according to the CP definition.

Cerebral palsy could only be identified at age 2 years or older; therefore the start of follow-up for the survival analysis was at age 2 years or older for each child with CP. The date of 31 August 2008 was set as the follow-up termination date from the 1 January 1990 starting date of the study. Most death certificates were unavailable. Therefore, death or survival was confirmed through the CP database from medical records. The cause and date of death were described in many medical records but there were some for whom death or survival status could not be determined. The death certificate registry from the Ministry of Health, Labor, and Welfare was used for those children in whom survival was unknown from the CP database. Data on birth date, sex, and place of residence were matched with the data from the Ministry of Health, Labor, and Welfare registry to confirm death or survival.

Participant survival rates and survival curves were estimated using the Kaplan–Meier method. Differences in survival curves were determined using the log-rank test. Cox regression analysis was used to estimate the hazard ratios. Statistical analyses were conducted with SAS software (SAS Institute, Cary, NC, USA).

What this paper adds

- Survival prognosis of children with CP in Okinawa, Japan, is similar to that of other countries.
- Severe gross motor limitation is the only significant predictor for survival prognosis of children with CP.
- Children with CP born preterm/low birthweight have longer life expectancy as they are less likely to be in GMFCS level V.

RESULTS

Five hundred and eighty individuals were identified with CP for the present study (332 males, 248 females). In the cohort, 119 (20.5%) children were classified in Gross Motor Function Classification System (GMFCS) level I, 65 (11.2%) were classified in level II, 40 (6.9%) in level III, 189 (32.6%) in level IV, and 166 (28.6%) in level V; GMFCS level was unknown for one child. The mean age at the start of follow-up was 24.5 months (SD 2.6mo). The mean length of follow-up was 8 years 8 months (standard error of the mean [SEM] 0.214y). The total number of children born in Okinawa Prefecture from 1988 to 2005 was 307 021. The prevalence of CP was 1.88 per 1000 live births. The prevalence was calculated by taking the number of children diagnosed at age 2 years or older (mean age 24.5mo) who were born from 1988 to 2005 and dividing it by the total number of live births during the same period.

Of the 580 children with CP, 489 survived, 34 had died, and 57 were of unknown vital status including eight who had moved out of Okinawa Prefecture. Fifty-seven children in whom the vital status was unknown were included in this analysis until their most recent clinical assessment date. In the present cohort, birthweight data were unavailable for one child, gestational age was unknown for two, and the GMFCS level was unknown for one.

Within the present cohort, 158 (27%) of the children had a normal birthweight of at least 2500g, and 421 (73%) had birthweights of less than 2500g (low birthweight). The gestational age of 166 (29%) of the children was at least 37 weeks

Table I: Gross Motor Function Classification System (GMFCS) level, gestational age, birthweight, and death rate of study population

	Gestational age (wks)			Birthweight (g)				
GMFCS level	≥37, *n* (%)	<37, *n* (%)	Unknown, *n*	≥2500, *n* (%)	<2500, *n* (%)	Unknown, *n*	Total, *n* (%)	Deaths, *n* (%)
I	29 (17.5)	90 (21.8)		27 (17.1)	92 (22.1)		119 (20.5)	1 (2.9)
II	15 (9.0)	49 (12.0)	1	15 (9.5)	50 (11.9)		65 (11.2)	1 (2.9)
III	5 (3.0)	35 (8.5)		8 (5.0)	32 (7.6)		40 (6.9)	0 (0)
IV	42 (25.3)	147 (35.7)		37 (23.4)	152 (36.1)		189 (32.6)	2 (6.0)
V	75 (45.2)	90 (21.8)	1	71 (45.0)	94 (22.3)	1	166 (28.6)	29 (85.3)
Unknown							1 (0.2)	1 (2.9)
Total	166	412	2	158	421	1	580	34

Table II: Survival rates of the children with cerebral palsy according to different characteristics

Category	*n*	5 years (SEM)	18 years (SEM)	*p*[a]
Total	580	0.967 (0.008)	0.889 (0.023)	
Sex				
Male	332	0.966 (0.011)	0.910 (0.024)	0.636
Female	248	0.968 (0.012)	0.870 (0.038)	
Birthweight (g)				
<2500	421	0.971 (0.009)	0.924 (0.025)	0.009
≥2500	158	0.963 (0.016)	0.820 (0.046)	
Gestational age (wks)				
<37	412	0.972 (0.009)	0.927 (0.024)	0.004
≥37	166	0.960 (0.016)	0.818 (0.046)	
GMFCS level				
I–IV	413	0.997 (0.003)	0.966 (0.021)	<0.001
V	166	0.891 (0.026)	0.724 (0.051)	

[a]Log-rank test. SEM, standard error of the mean; GMFCS, Gross Motor Function Classification System.

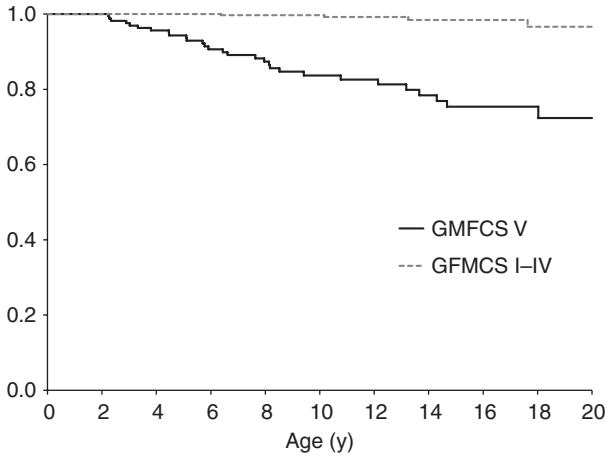

Figure 1: Relation of level of Gross Motor Function Classification System (GMFCS) to estimated proportion of surviving children with cerebral palsy.

(term), whereas 412 (71%) were born before 37 weeks' gestation (preterm; Table I).

In the present cohort, 119 (20.5%) children were classified in GMFCS level I, 65 (11.2%) were classified in level II, 40 (6.9%) in level III, 189 (32.6%) in level IV, and 166 (28.6%) in level V (Table I). All Children in GMFCS level V at first assessment have remained level V till last ascertainment. Only 8 children became GMFCS level V at the last assessment from level IV at first assessment, and all of them were alive at the termination of this study. No child in GMFCS level I to III at first assessment become level V at the last ascertainment.

Twenty-two per cent (94/421) of children with low birthweight, 45% (71/158) of children with normal birthweight, 21.8% (90/412) of children who were born preterm, and 45.2% (75/166) of children who were born at term were classified in GMFCS level V (Table I). Of the 34 children who died, 29 were classified in GMFCS level V (Table I).

Five-year and 18-year survival rates of the cohort were 0.967 (SEM 0.008) and 0.889 (SEM 0.023) respectively. No significant difference in the rates of survival between males and females were noted (p=0.636; Table II). Individuals with normal birthweight had significantly lower rates of survival than those with low birthweight (p=0.009; Table II). Individuals born at term had significantly lower rates of survival than individuals born preterm (p=0.004; Table II). Significantly lower survival rates were noted in the groups in GMFCS level V (transported in a manual wheelchair) than those in GMFCS levels I to IV (p<0.001; Table II and Fig. 1).

Table III: Hazard ratios for survival of children with cerebral palsy

	Hazard ratio[a]	95% CI	*p*
Sex	1.152	0.571–2.322	0.693
Gestational age ≥37wks	0.622	0.192–2.016	0.429
Birthweight ≥2500g	1.102	0.340–3.570	0.871
GMFCS level V	16.281	5.612–47.236	<0.001

[a]Multivariate analysis included all variables listed in the table. CI, confidence interval; GMFCS, Gross Motor Function Classification System.

Table III shows the hazard ratios resulting from Cox regression analysis of the survival of children with CP. Multivariate analysis included all variables listed in the table. Severe gross motor limitation (GMFCS level V) was the only significant risk factor (p<0.001) for survival of CP in the present study. Other factors such a birthweight of at least 2500g and a gestational age of at least 37 weeks were not significant factors.

According to the CP database and death certificates, cause of death was reported as diseases related to CP with no further information in 11 children, pneumonia in five, respiratory distress (e.g. lung hemosiderosis, acute bronchitis) in three, acute upper airway obstruction due to food aspiration in two, sepsis in five, acute lymphoblastic leukemia in one, malnutrition due to neglect in one, ileus in one, and unknown in six.

DISCUSSION

The survival patterns of individuals with CP have previously been described.[1–13] The results of previous studies have suggested that most children with CP survive into adulthood, unless they have severe motor and cognitive impairments. The results of the present study revealed that children with CP in Japan have an 89% chance of survival to 20 years of age. These results are consistent with those previously reported from the UK.[6,7,9,12] Previous reports[7,12] have shown that children with CP who had low birthweight and those born preterm had longer life expectancies than children with CP who had normal birthweight and those born at term because the former group had a lower proportion of severe disability. Similarly, the present study also suggested that both the low birthweight and preterm groups had a higher survival rate because both groups had a lower proportion of severe gross motor limitation.

The life expectancy of adults with CP in California was reported by Strauss and Shavelle,[3] and by Hemming et al.[13] for the UK. These reports indicated that the overall outlook of survival in adults with CP was good. However, it was lower than the survival rates in the general population[15] and was affected by numerous variables. Moreover, a group of high-functioning adults with CP had a life expectancy close to that of general population.[15] The life expectancy in adults with CP could not be determined in the present study, and further investigation is needed.

Our study revealed that the group with the most severe gross motor limitation (GMFCS level V) had significantly poorer survival, and that GMFCS level V was the only predictor variable for survival with CP in multivariate analyses. Most of the recent studies of CP survival agree that survival rates were significantly poorer in those who have severe disabilities.[1–13] Indeed, severe cognitive and motor disabilities are strong predictors of mortality in children with CP.[4–6,9] Moreover, severe visual disabilities have been shown to have a significant effect on the probability of survival.[10–13] In this study, we could not have estimated the effect of cognitive and visual disabilities on the probability of survival, therefore further investigation is needed. An estimation of the probability of survival based on the severity of functional disabilities requires specific defining criteria. The GMFCS is a standardized system to measure the severity of movement disability in children with CP[16] and we suggest that it is good for defining the severity of movement disability. Westbom et al.[17] in Sweden reported that fragile children with CP (i.e. those in GMFCS level V), had the lowest chance of surviving childhood; the estimated survival at 19 years of age was 60%. Similarly, our study revealed that the estimated survival at 20 years of age was 72% in children in GMFCS level V and that they had the lowest chance of surviving childhood.

Respiratory disease is a leading cause of death in individuals with CP,[5,8,13,18] particularly in those who die before age 40, compared with the general population.[13,18] Deaths due to cancer and circulatory diseases are more frequent in adults with CP over the age of 30 in the USA and the UK.[12,18] In the present study, half of deceased children had identified causes of death. Respiratory disease accounted for many identified causes of death. An unfortunate case in our study was one child whose cause of death was malnutrition due to neglect. This may serve as a reminder of the importance of adequate social support for children with CP and their families.

Blair et al.[5] in Western Australia, and Hutton and Pharoah[10] in the UK, reported no improvement in the rates of survival over a study period of 1958 to 1994 and 1966 to 1989 respectively. In contrast, Strauss et al.[15,19] in California reported that individuals with CP and severe disabilities demonstrated an increase in their life expectancy over a study period of 1983 to 2002. These findings encourage further investigation to elucidate possible improvements in the survival prognosis of children with CP in Japan and elsewhere.

There has been significant debate on whether the life expectancy of individuals with CP is similar across different regions and countries. Regional variation was reported[20] in a study in the UK; however, no significant differences were noted after adjustments for birthweight and socio-economic status. A previous study[21] compared information from databases in California, Australia, and the UK, and reported similar rates of survival in children with CP from those areas. Large comparison studies between regions are difficult because of the lack of information in the databases.

The main limitations of the present study are that the size of the cohort was relatively small and the duration was short compared with previous studies.[2–5,9] An official registration system for CP does not exist for Japan. Therefore, the population-based Okinawa CP database was used in the study. Again, this database has many unique features because of the historical and geographical variables associated with Okinawa.

The results of the present study provide practical information for health service and social welfare providers of children with CP in Japan. Moreover, these results are beneficial to the Obstetric Compensation System for Cerebral Palsy[22] in Japan. This programme was established in 2009 to provide financial support for children with CP and their guardians. The rate of low birthweight in Okinawa has nearly doubled over the past three decades.[23] Therefore, future studies are necessary to determine the factors that influence preterm birth and affect the survival of children with CP.

ACKNOWLEDGEMENTS

We thank all the staff members at the rehabilitation hospitals and the care facility in Okinawa for their assistance with the present study. We also gratefully acknowledge the support of the No-Fault Compensation System Division of Obstetrical Adverse Events, which is associated with the Japanese Council for Quality Health Care (JCQHC).

REFERENCES

1. Singer RB, Strauss D, Shavelle R. Comparative mortality of cerebral palsy patients in California, 1908-1996. *J Insur Med* 1998; **30:** 240–6.
2. Strauss D, Shavelle RM, Anderson TW. Life expectancy of children with cerebral palsy. *Pediatr Neurol* 1988; **18:** 143–9.
3. Strauss D, Shavelle R. Life expectancy of adults with cerebral palsy. *Dev Med Child Neurol* 1988; **40:** 369–75.
4. Crichton JU, Mackinnon M, White CP. The life expectancy of persons with cerebral palsy. *Dev Med Child Neurol* 1995; **37:** 567–76.
5. Blair E, Watson L, Badwai N, Stanley FJ. Life expectancy among people with cerebral palsy in Western Austraria. *Dev Med Child Neurol* 2001; **43:** 508–15.
6. Evans PM, Evans SJW, Alberman E. Cerebral palsy: why we must plan for survival. *Arch Dis Child* 1990; **65:** 1329–33.
7. Hutton JL, Cooke T, Pharoah POD. Life expectancy in children with cerebral palsy. *BMJ* 1994; **309:** 431–5.
8. Williams K, Alberman E. Survival in cerebral palsy: the role of severity and diagnostic labels. *Dev Med Child Neurol* 1998; **40:** 376–9.
9. Hutton JL, Colver AF, Mackie PC. Effect of severity of disability on survival in north east England cerebral palsy cohort. *Arch Dis Child* 2000; **83:** 468–74.
10. Hutton JL, Pharoah POD. Effect of cognitive, motor, and sensory disabilities on survival in cerebral palsy. *Arch Dis Child* 2002; **86:** 84–90.
11. Hutton JL, Pharoah POD. Life expectancy in severe cerebral palsy. *Arch Dis Child* 2006; **91:** 254–8.
12. Hutton JL. Cerebral palsy life expectancy. *Clin Perinatol* 2006; **33:** 545–55.
13. Hemming K, Hutton JL, Pharoah POD. Long-term survival for a cohort of adults with cerebral palsy. *Dev Med Child Neurol* 2006; **48:** 90–5.
14. Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N. Proposed definition and classification of cerebral palsy, April 2005. *Dev Med Child Neurol* 2005; **47:** 571–6.
15. Strauss D, Brooks J, Rosenbloom L, Shavelle R. Life expectancy in cerebral palsy: an update. *Dev Med Child Neurol* 2008; **50:** 487–93.
16. Morris C, Bartlett D. Gross Motor Function Classification System: impact and duty. *Dev Med Child Neurol* 2004; **46:** 60–5.
17. Westbom L, Bergstrand L, Wagner P, Nordmark E. Survival at 19 years of age in total population of children and young people with cerebral palsy. *Dev Med Child Neurol* 2011; **53:** 808–14.
18. Strauss D, Cable W, Shavelle R. Cause of excess mortality in cerebral palsy. *Dev Med Child Neurol* 1999; **41:** 580–5.
19. Strauss D, Shavelle R, Reynolds R, Rosenbloom L, Day S. Survival in cerebral palsy in the last 20 years: signs of improvement? *Dev Med Child Neurol* 2007; **49:** 86–92.
20. Hemming K, Hutton JL, Colver A, Platt MJ. Regional variation in survival people with cerebral palsy in the United Kingdom. *Pediatrics* 2005; **116:** 1383–90.
21. Shavelle R, Strauss D. Comparison of survival in cerebral palsy between countries. *Dev Med Child Neurol* 2001; **43:** 574–6.
22. Japan Council for Quality Health Care. Guide to the Japanese Obstetric Compensation System for Cerebral Palsy, explanatory leaflet. Japan Council for Quality Health Care; 2011 Sep. Available from: http://www.sanka-hp.jcqhc.or.jp/pdf/bira_english_color201109.pdf. (accessed 20 September 2011).
23. Hokama T, Binns C. Trends in the prevalence of low birth weight in Okinawa, Japan: a public health perspective. *Acta Paediatr* 2009; **98:** 242–6.