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Original Article

Risk factors and the occurrence of cerebral palsy in high risk infants

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Abstract

Background The incidence of cerebral palsy (CP) has increased due to better survival rates of high-risk babies. Early detection and time to the occurrence of CP in the first year of life is important in order to provide early intervention.

Objectives To determine the proportion of CP in high-risk babies, the time to the occurrence of CP in the first year, and assess possible associations between risk factors of CP and time to the occurrence of CP.

Methods A prospective cohort study was done on 150 high-risk babies up to the age of 12 months. We obtained history of motor ability and assessed primitive reflexes and postural reactions of subjects at the ages of 4 and 6 months. The diagnosis of CP was established at 6 and 12 months of age.

Results The proportion of CP was 26% at 6 months and 24% at 12 months of age. Significant risk factors associated with CP at 6 and 12 months of age were cerebral ultrasound abnormalities, hypoxic-ischemic encephalopathy, and intracranial hemorrhage. In 88.7% of subjects with CP, CP was detected in the first 6 months. Mean age at the occurrence of CP was 9.99 months (95%CI 9.46 to 10.53). Risk factors that significantly affected the time to the occurrence of CP by survival analysis were ultrasound abnormalities and hypoxic-ischemic encephalopathy.

Conclusions Cerebral palsy can be detected as early as the first 6 months of life. Cerebral ultrasound abnormalities and hypoxic ischemic encephalopathy are the risk factors associated with CP.

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Keywords: *early detection; cerebral palsy; proportion; risk factors; time to the occurrence of CP*

The incidence of cerebral palsy (CP) is 1.2 to 2.5 per 1,000 live births. Several factors, including prematurity, influence the occurrence of CP.[1] In Canada, the mortality of premature infants has declined from 256 per 1,000 live births in 1993 to 114 per 1,000 live births in 2002, accompanied by a rise in the rate of CP from 44.4 to 100 cases per 1,000 live births in the same period.[2] A similar trend has been observed in Sweden and Western Australia.[1]

Cerebral palsy is a static, non-progressive disorder of motor and postural function due to an insult on the developing brain, which results in motor delays as well as postural and motion abnormalities.[1] Some children with CP acquire various comorbidities and complications which may pose health threats and influence their quality of life.[3] Early detection of CP within the first year of life is essential to enable early intervention, which will affect the natural course of the disease.[4]

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Prematurity and low birth weight are risk factors for CP.[1,2] Theoretically, meningitis, intracranial hemorrhage (IC), and hypoxic ischemic encephalopathy (HIE) are also risk factors for CP due to brain injury.[4] Survival analysis on the time to the occurrence of CP in high-risk babies has yet to be established, despite the importance for early prediction of CP in high-risk babies. In Indonesia, the higher survival rate of premature and other high-risk babies has also led to an increase of CP cases. High-risk babies are at risk of developing CP at a later age, due to risk factors occurring in the pre-, peri-, and post-natal periods.

This study aimed to determine the proportion of CP in high-risk babies, the time to the occurrence of CP in the first year, as well as risk factors as they pertain to the time to the occurrence of CP.

Methods

The main design of this study was prospective. We followed a cohort of high-risk babies to the age of 12 months. The study was done in Cipto Mangunkusumo Hospital, Jakarta, from April 2010 to July 2012. During the follow-up period, we performed bi-monthly assessments comprising of motor development history and clinical-neurological examinations. A survival analysis was done using data obtained at each of these bi-monthly assessments, with the occurrence of CP as the endpoint.

Using the appropriate formula, the minimum number of subjects required was 180. Inclusion criteria were high-risk babies, as signified by prematurity (gestational age of ≤ 32 weeks), low birth weight (birth weight < 2,499 g) and very low birth weight (birth weight of ≤ 1,500 grams), full term or preterm neonates with meningitis, moderate or severe HIE, ICH, and >48 hours of mechanical ventilation. We excluded infants with central nervous system malformations, genetic, chromosomal, or metabolic anomalies, neuromuscular disorders, or congenital infections. The independent variables were (1) risk factors; (2) cerebral ultrasound results; (3) motor delays; (4) primitive reflexes (palmar grasp, fisting, withdrawal, crossed-extensor, and traction response); and (5) postural reactions (protective-extension reflex and parachute reaction). The dependent variable was the occurrence of CP as determined by the gold standard examination of muscle tone and increased physiological reflexes at the specified age.

When subjects were 4 to 5 months of age, we performed the first motor development assessment and neurological examination comprising withdrawal reflex, palmar reflex, traction response, fisting, and crossed extensor reflex. At 6 months, motor development was again assessed, as well as all neurological examination items previously evaluated, with the addition of protective extension reflex. At 9 to 10 months, we again followed up the subjects' motor development and performed all neurological examination items evaluated previously, with the addition of parachute reaction. The presence of CP was officially determined at the ages of 6 and 12 months. We use the term 'officially' here so as to clarify that previous bi-monthly assessements were also done, as seen in the survival analysis in **Figure 1**. The diagnosis of CP was made by one of two experienced pediatric neurologists when abnormalities in muscle tone and increased physiological reflexes were found, without evidence of regression or progression.

Using assessment of CP based on clinical manifestation at 6, and 12 months of age, we determined the proportion of CP in high-risk babies at 6 and 12 months of age and determined the association between risk factors and CP. We used Kaplan-Meier survival analysis for the time of occurrence of CP in the first year of life, and the contribution of each risk factor. Significant risk factors were then subjected to multivariate Cox regression analysis. The study protocol was approved by the Medical Research Ethics Committee of the University of Indonesia.

Results

During the study period, 178 high-risk babies underwent screening for possible inclusion to the study. Out of these, 150 fulfilled the criteria for cohort analysis; 28 subjects were excluded (14 died and 14 were lost to follow-up due to undocumented address changes). At 6 months of age, 39/150 subjects (26%) had CP, and at 12 months of age 36/150 subjects (24%) had CP. For Kaplan Meiyer 14 died subjects have been participated for analysis. Subjects' characteristics are shown in **Table 1**.

On bivariate analysis, risk factors found to be associated with CP at the ages of 6 and 12 months

Table 1. Subjects' characteristics

Characteristics	(N=150)
Sex, n (%)	
Male	65 (43)
Female	85 (57)
Gestational age, n (%)	
≤32 weeks	120 (80)
>32 weeks	30 (20)
Birth weight, n (%)	
≤1,500 g	113 (75)
>1,500 g	37 (25)
Meningitis, n (%)	
Yes	5 (3)
No	145 (97)
Intracranial hemorrhage, n (%)	
Yes	19 (13)
No	131 (87)
Hypoxic-ischemic encephalopathy, n (%)	
Yes	7 (5)
No	143 (95)
Mechanical ventilation, n (%)	
Yes	30 (20)
No	120 (80)
Duration of mechanical ventilation, n (%)	
≥48 hours	24 (16)
<48 hours	6 (4)
Cerebral ultrasound, n (%)	
Abnormal	35 (23)
Normal	115 (77)

were cerebral ultrasound abnormalities, HIE, and ICH (**Table 2**). Sex, birth weight, meningitis, and duration of mechanical ventilation were not significantly associated with CP. Gestatational age was risk factor for CP at 12 months of age, but not at 6 months of age.

We performed a survival analysis on all subjects to determine the time of occurrence of CP during the 12 months of follow-up, as well as associated risk factors. Censored was a subject who has undergone effect (CP or died). The cumulative proportion surviving (CPS) was the sum of subjects without CP. **Figure 1** shows that the CPS at 6 months of age was 74% [standard error (SE) 3.5%], whereas CPS at 12 months of age was 70.7% (SE 3.7%). Mean age at the occurrence of CP was 9.99 months (95%CI 9.46 to 10.53).

Table 3 shows the survival analysis of the time to the occurrence of CP, based on risk factors. On bivariate analysis, factors significantly associated with survival, i.e., the time to the occurrence of CP, were gestational age of ≤32 weeks, cerebral ultrasound abnormalities, ICH, HIE, and meningitis. Cox regression analysis revealed that cerebral ultrasound abnormalities and HIE were significant risk factors for the occurrence of CP (**Table 4**).

Table 2. Bivariate association between risk factors and cerebral palsy at 6 and 12 months

Variables	CP at 6 months			CP at 12 months		
	OR	95%CI	P value	OR	95%CI	P value
Sex	1.04	0.60 to 1.82	0.87	1.22	0.68 to 2.17	0.5
Male	(reference)			(reference)		
Female						
Gestational age	0.64	0.36 to 1.13	0.14	0.5	0.29 to 0.88	0.022
≤32 weeks	(reference)			(reference)		
>32 weeks						
Birth weight	1.8	0.82 to 3.95	0.12	1.64	0.74 to 3.62	0.20
≤1500 g	(reference)			(reference)		
>1500 g						
Meningitis	0.76	0.13 to 4.49	0.76	0.83	0.14 to 4.89	0.83
Yes	(reference)			(reference)		
No						
Intracranial hemorrhage	4.31	2.8 to 6.6	<0.001	4.49	2.75 to 6.99	
Yes	(reference)			(reference)		<0.001
No						
Hypoxic-ischemic encephalopathy	4.47	3.29 to 6.1	<0.001	4.91	3.56 to 6.82	
Yes	(reference)			(reference)		<0.001
No						
Mechanical ventilation			0.85			0.84
>48 hours	1.12	0.32 to 3.9		1.12	0.32 to 3.92	
<48 hours	(reference)			(reference)		
Cerebral ultrasound	10.95	5.77 to 20.8	< 0.001	13.6	6.54 to 28.35	<0.001
Abnormal	(reference)			(reference)		
Normal						

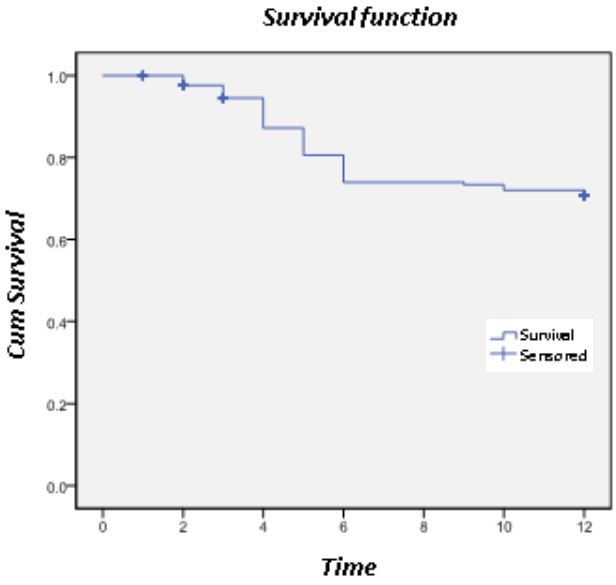

Figure 1. Survival analysis of the time to the occurrence of CP

Discussion

The limitations of this study were the recruitment of subjects in a tertiary referral hospital, possibly leading to a higher proportion of CP than would be found in the general population, and follow-up largely done by home visits by the principal investigator only. However, this study has the advantage of being the first to describe survival risk based on the time of occurrence of CP in the first year of life in high-risk babies, as well as differential survival based on risk factors.

The proportions of CP in our subjects were 26% at 6 months of age and 24% at 12 months of age. Similarly, Zafeiriou *et al.* obtained an incidence of 28.5% in 204 high-risk babies.[5] The difference between the incidence at 6 and 12 months of age may be explained by the normalization of neurological

Table 3. The time to the occurrence of CP based on risk factors

Variables	CPS, %	SE, %	Mean time to CP, months	95%CI	Log-rank P value
Gestational age					
≤32 weeks	73.7	4	10.27	9.71 to 10.82	0.047
>32 weeks	58.1	6.5	8.92	7.46 to 10.38	
Birth weight					
≤1500 grams	68.2	4.4	9.92	9.31 to 10.53	0.42
>1500 grams	78.3	6.5	10.24	9.17 to 11.31	
Meningitis					
Present	50	20.4	8.95	5.24 to 11.76	0.041
Absent	71.5	3.7	10.39	9.5 to 10.59	
ICH					
Present	60.5	7.5	8.95	7.81 to 10.09	0.052
Absent	74.7	4.1	10.39	9.82 to 10.97	
HIE					
Present	0	0	3.35	2.64 to 4.05	<0.001
Absent	74.4	3.61	10.35	9.85 to 10.85	
Mechanical ventilation					
>48 hours	61.6	9.7	9.14	7.62 to 10.67	0.932
≤48 hours	66.7	19.2	8.83	5.24 to 12.42	
Cerebral ultrasound					
Abnormal	11	5.2	5.44	4.51 to 6.36	<0.001
Normal	89.6	2.9	11.4	11.07 to 11.79	

CPS: cumulative proportion surviving without CP; SE=standard error; ICH=intracranial hemorrhage; HIE= hypoxic-ischemic encephalopathy

Table 4. Risk factors significantly associated with the time to the occurrence of CP

Variables	β	SE	Wald	df	Sign	Exp(β)	95%CI
Cerabral ultrasound	2.799	0.380	54.206	1	0.000	16.421	7.796 to 34.590
HIE	1.332	0.475	7.852	1	0.005	3.785	1.492 to 9.620
Mechanical ventilation	0.057	0.389	0.021	1	0.884	1.085	0.494 to 2.268
ICH	-0.071	0.042	0.042	1	0.838	0.932	0.473 to 1,834
Prematurity	-0.488	0.396	1.516	1	0.218	0.614	0.282 to 1,335
Meningitis	1.298	0.635	4.176	1	0.041	3.662	1.054 to 12,717

SE=standard error; HIE= hypoxic-ischemic encephalopathy;ICH=intracranial hemorrhage;

features over time, possibly due to intervention or CNS maturation, or by the worsening of such features over time. Our results support the notion that clinical manifestations of CP can change with increasing age, particularly in the first year of life.[6]

We did not find a significant birth weight or gestational age differences in the incidence of CP. In contrast, other studies stated that prematurity and low birth weight were risk factors of CP.[1,2] This finding may be due to improved perinatal health services and medical technology, enabling better hemodynamic monitoring leading to prevention of extreme fluctuations of cerebral blood flow, thus reducing the rate of complications such as ICH in infants born with a birth weight of 1,000-1,500 grams and infants born at 28-32 weeks' gestational age.[7] Only 30/150 subjects (20%) needed mechanical ventilation. Cools *et al.* reported that 90% of infants born at <30 weeks' gestation required mechanical ventilation.[8] This difference may be caused by the difference in gestational age in the inclusion criteria, or due to advances in the management of premature babies, including surfactant therapy and the use of continuous positive airway pressure (CPAP), thereby reducing the need for mechanical ventilation.[9]

Cerebral ultrasound abnormalities were found in 35 subjects (23.3%). Six out of these 35 subjects developed CP. There was a significant difference in the proportion of CP in infants with abnormal ultrasound results compared to those with normal ultrasound results ($P<0.001$). This result concurred with previous reports that ultrasound abnormalities, especially grade 3 and 4 intraventricular hemorrhage (IVH), PVL, and ventriculomegaly are associated with CP or other abnormalities of motor development.[10-12] All subjects with moderate or severe HIE (n=7) had CP, a significant difference from the proportion of CP in subjects with no or mild HIE ($P< 0.001$). Our result was in agreement with previous studies that reported HIE, particularly in term infants, causing tissue damage in the form of PVL, focal and multifocal ischemia, and cerebral tissue necrosis.[13,14] Full term infants made up the majority of the infants with HIE in this study (5/7). Forty-three out of 150 subjects (28.6%) had ICH; 39.5% of these had CP. There was a significant difference in CP incidence in the ICH group compared to the non-ICH group, possibly due to the large proportion of grade 3 and 4 IVH found in the ICH group, which potentially develops into PVL cysts.[15]

On bivariate analysis, HIE, ICH, and ultrasound abnormalities showed significant associationS with CP ($P<0.001$) at 6 and 12 months. Moderate and severe HIE were significant risk factors of CP, as were grade 3 and 4 IVH. Ultrasound abnormalities associated with CP include PVL, grade 3 and 4 IVH, encephalomalacia, meningitis, hydrocephalus, and ventriculomegaly. Our results agree with current literature.[10-12]

We performed a survival analysis to determine the time to the occurrence of CP. Most subjects who had CP were diagnosed by the age of 6 months. Our findings suggest that the first 6 months is an important window for clinicians and parents to closely observe infants for signs of CP to enable early intervention for better outcomes. Multivariate Cox regression analysis showed that only cerebral ultrasound abnormalities, HIE, and meningitis significantly affected occurrence of CP.

In conclusion, the proportions of CP in our subjects are 26% at 6 months and 24% at 12 months. In 88.7% of subjects, CP is detected in the first 6 months. Significant risk factors related to the occurrence of CP and survival analysis are cerebral ultrasound abnormalities, hypoxic-ischemic encephalopathy, and intracranial hemorrhage.

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Conflict of interest

None declared

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