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Original Article

Early detection of cerebral palsy in high-risk infants: diagnostic value of primitive and developmental reflexes as well as ultrasound

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Abstract

Background The incidence of cerebral palsy (CP) has increased due to better survival of high-risk babies. A simple assessment method is needed for the early detection of CP, which can be performed by general practitioners and pediatricians in daily practice.

Objectives To assess motor delay, primitive and developmental reflexes, and cerebral ultrasound abnormalities as simple methods for early detection of CP in high-risk infants. We also aimed to evaluate the ease and consistency of the methods for use in daily practice, as well as determine risk factors associated with CP.

Methods A prospective cohort study was done on 150 high-risk babies starting from the age of 4 months up to 12 months. We obtained subjects' histories of motor ability and assessed primitive reflexes and postural reactions at the ages of 4, 6, 9 and 10 months. The diagnosis of CP was established at 6 and 12 months of age. We also determined Kappa test for inter-rater reliability between pediatric residents and the pediatric neurologist.

Results In 88.7% of subjects, CP was detected in the first 6 months. At 4 months, positive palmar reflex, head lag, and fisting were predictive of CP at 6 months of age. Motor delay, positive palmar grasp reflex, head lag, fisting, and absent protective extension reflex at 6 months were predictive of CP at 12 months. At 9 to 10 months, motor delays, absent protective extension reflex, and negative parachute reaction were predictive of CP at 12 months. Cerebral ultrasound abnormalities were predictive of CP at 6 and 12 months of age. Kappa test result was 0.9, indicating the ease and consistency of these methods for daily medical practice.

Conclusion Cerebral palsy can be detected as early as the first 6 months of life. Assessment for motor delays, physical examination for asssessing primitive and developmental reflexes, and cerebral ultrasound can be used for this purpose. **[Paediatr Indones. 2018;58:5-12 ; doi: http://dx.doi.org/10.14238/pi58.1.2018.5-12]**.

Keywords: *early detection; cerebral palsy; cerebral ultrasound; motor delay; postural reaction; primitive reflex*

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] 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

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occurring in the pre-, peri-, and post-natal periods.

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] Identification of CP in young infants is problematic due to the limited motor development in these infants, making it difficult to determine the types of motor delay that can be used to detect CP.4 Assessment of muscle tone and physiological reflexes, the cornerstones of CP diagnosis, are not always definitive.[4,5]

Several studies have reported methods for the early detection of CP before 3 to 6 months of age with reasonable predictive values, such as electroencephalography (EEG), cerebral function monitoring (CFM), brain magnetic resonance imaging (MRI) at 2 to 8 days of age, and spontaneous general movements (GMs) assessment at 2 to 4 months of age.[5-7] However, widespread use of such state-of-the-art methods is not feasible in developing countries such as Indonesia.

We aimed to determine the proportion of CP in high-risk babies, risk factors associated with CP, and the diagnostic performance of early detection methods using parameters of motor delay, physical examination, and cerebral ultrasound.

Methods

This prospective study followed a cohort of infants up 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 motor development assessments and clinical-neurological examinations.

Using the appropriate formula, the minimum number of subjects required was calculated to be 150. Inclusion criteria were high-risk babies as signified by prematurity (gestational age of ≤32 weeks), low birth weight (2,4999 grams) and very low birth weight (≤1,500 grams), term or preterm neonates with meningitis, moderate or severe hypoxic-ischemic encephalopathy, intracerebral hemorrhage (ICH), and/or >48 hours of mechanical ventilation. We excluded infants with genetic, chromosomal, or metabolic anomalies, central nervous system malformations, neuromuscular disorders, and congenital infections. The independent variables were (1) the risk factors present; (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 ages.

At 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 of age, motor development was again assessed, as well as all neurological examination items evaluated previously, with the addition of protective extension reflex. At 9 to 10 months of age, we 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 determined at the age of 6 and 12 months. 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.

To determine the contribution of each respective risk factor and the diagnostic value of these predictors, we used data obtained at 4, 6, 10, and 12 months of age. As such, we determined the proportion of CP in high-risk babies and performed bivariate analyses on the potential association between risk factors and CP. We also determined the diagnostic performance of cerebral ultrasound to predict CP at 6 and 12 months of age, as well as the diagnostic values of motor delay and various clinical examinations done at 4, 6, and 9-10 months of age to predict CP at 6 and 12 months of age, respectively. A P value of <0.05 was considered to be statistically significant. After the study, we performed a Kappa test between the pediatric neurologist and one of our pediatric residents to assess inter-rater reliability to determine ease of

replication in daily medical practice. Kappa test was done in another group of 40 high-risk infants. 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 visited our institution. Out of these, 150 fulfilled the criteria for analysis, while 28 infants were excluded (14 died and 14 were lost to follow-up due to undocumented address change). At 6 months of age, 39/150 subjects (26%) had CP, and at 12 months of age 36/150 subjects (24%) had CP. Diagnosis of CP was based on clinical manifestation. The majority of subjects were female (87%) and had gestational age <32 weeks (80%), birth weight <1,500 grams (75%), normal cerebral ultrasound (77%), as well as no history of meningitis (97%), intracranial hemorrhage (87%), or hypoxic-ischemic encephalopathy (HIE) (95%). On bivariate analysis, risk factors found to be associated with CP at the age of 6 and 12 months were cerebral ultrasound abnormalities, HIE, and ICH (**Table 1**). Gestational age was a significant predictor of CP at 12 months but not at 6 months of age. Sex, birth weight, meningitis, and duration of mechanical ventilation were not significantly associated with CP. Moderate and severe HIE were significant risk factors of CP, as were grade 3 and 4 IVH. Ultrasound abnormalities associated with CP included PVL, grade 3 and 4 IVH, encephalomalacia, meningitis, hydrocephalus, and ventriculomegaly.

The proportion of CP at 6 months of age was significantly higher in subjects with abnormal motor development and/or physical examination at 4 months of age than in those without. Odds ratios and diagnostic values of motor delay and other neurological examination parameters assessed at 4 months of age to predict CP at 6 months of age are presented in **Table 2**. Examination of palmar reflex, traction response (positive head lag) and fisting at 4 months had the best diagnostic value to predict CP at 6 months of age.

Subjects with motor delay and abnormalities on physical examination at 6 months of age had a

Table 1. Bivariate association between risk factors and cerebral palsy at 6 and 12 months

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

Table 2. Diagnostic values of parameters tested at 4 months to predict cerebral palsy at 6 months

Parameters	Cerebral palsy		Sensitivity, %	Specificity, %	OR	95%Ci	P value
	Yes	No					
Motor ability, n							
Abnormal	26	0	66.7	100			
Normal	13	113			9.6	9.43 to 10.2	<0.001
Withdrawal reflex, n							
Abnormal	25	0	64.1	100			
Normal	14	111			8.3	7.95 to 8.36	<0.001
Palmar reflex, n							
Abnormal	39	4	100	96.4			
Normal	0	107			0.03	0.01 to 0.09	<0.001
Traction response, n							
Abnormal	35	3	89.7	97.3			
Normal	4	108			12.21	4.12 to 36.2	<0.001
Fisting, n							
Abnormal	34	2	87.2	98.2			
Normal	5	109			26	9.10 to 50.92	<0.001
Crossed extensor reflex, n							
Abnormal	24	1	61.5	99			
Normal	15	110			7.4	4.94 to 12.95	<0.001

significantly higher proportion of CP at 12 months of age than normal subjects. Subjects with motor delay or abnormalities in primitive reflexes and protective extension reflex had higher risk of CP than those without. Motor delay and abnormal palmar reflex, fisting, traction response and protective extension had the best diagnostic value to predict CP at 12 months of age. Odds ratios and diagnostic values of motor delay and other neurological examination parameters assessed at 6 months of age to predict CP at 12 months of age are presented in **Table 3**.

We found a higher proportion of CP at 12 months of age in subjects who had motor delay or

Table 3. Diagnostic values of parameters tested at 6 months to predict cerebral palsy at 12 months

Parameters	Cerebral palsy		Sensitivity, %	Specificity, %	OR	95%Ci	P value
	Yes	No					
Motor ability, n							
Abnormal	35	7	97.2	93.8			
Normal	1	107			89	12.7 to 636	<0.001
Withdrawal reflex, n							
Abnormal	8	0	22.2	100			
Normal	28	114			4.2	3.64 to 7.1	<0.001
Palmar reflex, n							
Abnormal	33	2	91.6	98.2			
Normal	3	112			31.33	11.8 to 110.7	<0.001
Traction response, n							
Abnormal	25	1	69.4	99.1			
Normal	11	113			60	6.13 to 19.15	<0.001
Fisting, n							
Abnormal	34	2	94.4	98.2			
Normal	2	112			55.3	50.5 to 58.6	<0.001
Crossed extensor reflex, n							
Abnormal	13	113	36.1	8	0.1		
Normal	23	1				0.06 to 0.18	<0.001
Protective extension reflex, n							
Abnormal	35	8	97.2	92.9			
Normal	1	106			90	12.3 to 611.64	<0.001

abnormalities traction response, fisting, protective extension reaction, and parachute reaction at 9 to 10 months of age. Abnormalities in motor delay, primitive reflexes and postural reaction were associated with an increased risk of CP. Motor delay and postural reaction had the best diagnostic value to predict CP at 12 months of age. Odds ratios and diagnostic values of parameters assessed at 9 to 10 months of age to predict CP at 12 months of age are presented in **Table 4**.

At the age of 6 months, cerebral ultrasound had a sensitivity of 76.9%, specificity of 95.5%, positive predictive value of 85.7%, and negative predictive value of 92.2% for CP. At the age of 12 months, the abovementioned values for cerebral ultrasound were 74.3%, 94.6%, 82.8%, and 91.3%, respectively.

Kappa test was done between the pediatric neurologist and pediatric residents to assess inter-rater reliability for predicting CP at 6 and 12 months of age (with regards to exams for motor ability as well as primitive and developmental reflexes). Kappa test result was 0.9, indicating the ease and consistency of the methods for daily medical practice. The mean time taken to examine subjects' primitive reflexes at 4 months of age was 2 minutes and 37 seconds (SD 32.3 seconds), and the mean time taken to examine subjects' developmental reflexes at 9 months of age was 5 minutes and 18 (SD 53 seconds) seconds.

Discussion

The limitations of this study include 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 only the principal investigator. However, this study has the advantage of being the first in Indonesia to determine the diagnostic value of clinical assessment results (motor ability as well as primitive and developmental reflexes) and cerebral ultrasound to predict CP in the first year of life.

The proportion of CP in our study was 26% at 6 months of age and 24% at 12 months of age.

Table 4. Diagnostic values of parameters tested at 9 to 10 months to predict cerebral palsy at 12 months

Parameters	Cerebral palsy		Sensitivity, %	Specificity, %	OR	95%Ci	P value
	Yes	No					
Motor ability, n							
Abnormal	36	7	100	93.8			
Normal	0	107			6.14	3.12 to 12.1	<0.001
Withdrawal reflex, n							
Abnormal	1	0	2.7	100			
Normal	35	114			3.2	2.18 to 9.23	0.074
Palmar reflex, n							
Abnormal	0	0					
Normal	36	114					
Traction response, n							
Abnormal	5	1	13.8	99.1			
Normal	31	113			3.9	2.8 to 4.6	0.001
Fisting, n							
Abnormal	3	1	8.3	99.1			
Normal	33	113			3.41	1.75 to 6.3	0.015
Crossed extensor reflex, n							
Abnormal	1	0	2.7	100			
Normal	35	114			3.33	3.18 to 5.68	0.074
Protective extension reflex, n							
Abnormal	25	2	69.4	98.2			
Normal	11	112			11.25	10.4 to 15.2	<0.001
Parachute reaction, n							
Abnormal	26	0	72.2	100			
Normal	10	114			12.5	11.4 to 14.15	<0.001

Our results were similar to those of Zafeiriou *et al.* who obtained an incidence of 28.5% in 204 high-risk babies.[8] The difference between the incidence at 6 and 12 months of age may be explained by the normalization of neurological features over time, possibly due to intervention, CNS maturation, or by improvement 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.[9]

We did not find a significant birth-weight- or gestational-age-specific difference in the incidence of CP. Our findings were in disagreement with literature stating that prematurity and low birth weight were risk factors for 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 gestational age of 28-32 weeks.[10] Only 30/150 subjects (20%) needed mechanical ventilation. Cools *et al.* reported that 90% of infants born at gestational age of <30 weeks required mechanical ventilation.[11] This difference may have been due to different gestational ages in the inclusion criteria or 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.[12]

Cerebral ultrasound abnormalities were found in 35 subjects (23.3%). Six of these 35 subjects developed CP. There was a significant difference in the proportion of CP in infants with abnormal ultrasound compared to those with normal ultrasound ($P<0.001$). This result concurs with previous studies reporting that ultrasound abnormalities, especially grade 3 and 4 intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and ventriculomegaly were associated with CP or other abnormalities of motor development.[13-15] All subjects with moderate and severe HIE (n=7) had CP, a significant difference from the proportion of CP in subjects with no or mild HIE ($P<0.001$). Similarly, previous studies reported that HIE, particularly in term infants, causes tissue damage in the form of PVL, focal and multifocal ischemia, and cerebral tissue necrosis.[16,17] Term infants made up the majority of subjects with HIE in our study (5/7). Forty-three out of 150 subjects (28.6%) had ICH; of these, 39.5% 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.[18]

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 included PVL, grade 3 and 4 IVH, encephalomalacia, meningitis, hydrocephalus, and ventriculomegaly, which were similar to previous findings in the published literature.[13-15]

The diagnosis of CP is straightforward in cases of severe CP or in older children. It is difficult to accurately diagnose CP in the first 6 months of life, in milder cases, or in cases of isolated motor delay. Motor delay is the first sign of CP and has a good sensitivity and specificity to detect CP after the age of 6 months, whereas neurological examination of primitive reflexes, postural reactions, and muscle tone as been reported to have a poor predictive value in the first months of life.[5]

In our study, when the subjects were evaluated at 4 months of age, all independent variables were significantly associated with the presence of CP at the age of 6 months. The most significant neurological features were palmar grasp reflex, traction response, and fisting. These results were in agreement with those reported by Morgan *et al.*[19] and the principal investigator's clinical experience. Motor delay did not yield a high OR, possibly due to infants' limited motor ability at 4 months of age. Variables measured during the evaluation at 4 months of age, especially palmar reflex, traction response, and fisting, had good sensitivity, specificity, and positive and negative predictive values in the range of 88 to 100%.

The evaluations done at the age of 6 months to predict CP at 12 months of age included all variables evaluated at 4 months and the protective extension reaction was added. All variables showed significant associations with later CP, with protective-extension reflex having the highest OR, followed by motor ability, traction response, fisting, and palmar grasp reflex. Motor ability and the protective-extension

reflex also had the highest ORs, as well as good sensitivity, specificity, and positive and negative predictive values. These two features can, therefore, be used as hallmarks for predicting CP at 12 months of age. Previous reports were in agreement with our results.[20] Infants who show poor postural control at 6 months of age need special attention and early intervention, as this skill is a prerequisite for sitting, standing, and walking.[20-22]

When a subject had a normal examination at 6 months of age, the child was re-evaluated at the age of 9 to 10 months. We found a higher risk of CP in subjects with abnormal protective-extension reflex, abnormal traction response, motor delay, fisting, and abnormal parachute reaction, compared to normal subjects. The primitive reflexes showed smaller ORs at 6 months than at 4 months. Motor delay showed lower ORs than were found at 4 and 6 months, but two examinations (motor delay and postural reaction showed superior sensitivity, specificity, when assessed at 9 to 10 months of age. As subjects progressed in age, the sensitivity of primitive reflexes tended to decline, although specificity remained high. After 6 months of age, primitive reflexes are no longer a sensitive tool and are rarely seen except in severe CP cases. Therefore, positive primitive reflexes at this age had high specificity for the diagnosis of CP. In mild cases, components of motor delay and postural examination can be used to diagnose CP. Results of this study confirmed the theory that postural reactions are a continuation of primitive reflexes, which reflect CNS maturation.[23] In practice, assessment of motor ability and postural reactions can be used to diagnose CP in infants older than 6 months.

All abnormalities found on cerebral ultrasound showed non-progressive anatomical lesions. Our results were in agreement with reports stating that causative insults produced static lesions in the brain.[12] However, the clinical manifestations of CP may change with advancing age, reflecting brain maturation and plasticity.[12] Cerebral ultrasound also had good sensitivity, specificity, and positive and negative predictive values, hence, it can be used in the early detection of CP.

In our study, neurological examinations such as for primitive and developmental reflexes were found to be simple, quick tests with high diagnostic value as tools to detect CP in the first year of life.

In conclusion, the proportion of subjects with CP at 6 months of age is 26% and at 12 months of age is 24%. In 88.7% of subjects, CP is detected in the first 6 months. Risk factors associated with CP at the age of 6 and 12 months are cerebral ultrasound abnormalities, HIE, and ICH. At 4 months of age, positive palmar grasp reflex, head lag, and fisting are predictive of CP at 6 months of age. Motor delay, positive palmar grasp reflex, positive head lag, fisting, and absent protective extension reflex at 6 months of age are predictive of CP at 12 months of age. At 9 to 10 months of age, motor delays, absent protective extension reflex, and negative parachute reaction were predictive of CP at 12 months of age. Cerebral ultrasound abnormalities were predictive of CP at 6 and 12 months of age. Kappa test result was 0.9 indicating the ease and consistency of the methods for daily medical practice.

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Conflict of interest

None declared

References

1. Oskoui M, Shevell MI, Swaiman KF. Cerebral palsy. In: Swaimann KF, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, Pearl PL, Shevell MI, editors. Pediatric neurology principles and practice. 6th ed. Philadelphia: Mosby Elsevier; 2017. p. 734-4.
2. Vincer MJ, Allen AC, Joseph KS, Stinson DA, Scott H, Wood E. Increasing prevalence of cerebral palsy among very preterm infants: a population based study. Pediatrics. 2006;118:e1621-6.
3. Cooley WC, American Academy of Pediatrics Committee on Children with Disabilities. Providing a primary care medical home for children and youth with cerebral palsy. Pediatrics. 2004;114:1106-13.
4. Illingworth RS. The diagnosis of cerebral palsy in the first

year of life. Dev Med Child Neurol. 1966;8:178-94.
5. Palmer FB. Strategies for the early diagnosis of cerebral palsy. J Pediatr. 2004;145:S8-11.
6. Hadders-Algra M. General movements: a window for early identification of children at high risk for developmental disorders. J Pediatr. 2004;145:S12-S8.
7. Toet MC, Hellstrom-Westas L, Groenendaal F, Eken P, de Vries LS. Amplitude-integrated EEG 3 and 6 hours after birth in full term neonates with hypoxic-ischaemic encephalopathy. Arch Dis Child Fetal Neonatal Ed. 1999;81:F19-23.
8. Zafeiriou DI, Tsikoulas IG, Kremenepoulos GM. Prospective follow-up of primitive reflex profiles in high-risk infants: clues to an early diagnosis of cerebral palsy. Pediatr Neurol. 1995;13:148-52.
9. Shapiro BK. Cerebral palsy: a reconceptualization of the spectrum. J Pediatr. 2004;145:S3-7.
10. Volpe JJ. Intracranial hemorrhage: Germinal matrix-intraventricular hemorrhage of the premature infant. In: Volpe JJ, editor. Neurology of the newborn. 5th ed. Philadelphia: Saunders Elsevier; 2008. p. 517-73.
11. Cools F, Askie LM, Offringa M. Elective high-frequency oscillatory ventilation in preterm infants with respiratory distress syndrome: an individual patient data meta-analysis. BMC Pediatr. 2009;9:33-9.
12. Dani C, Bertini G, Pezzati M, Cecchi A, Caviglioli C, Rubaltelli FF. Early extubation and nasal continuous positive airway pressure after surfactant treatment for respiratory distress syndrome among preterm infants <30 weeks' gestation. Pediatrics. 2004;113:e560-3.
13. Ito T, Hashomoto K, Kadowaki K, Nagata N, Makio A, Takahashi H, *et al.* Ultrasonographic findings in the periventricular region in premature newborns with antenatal periventricular leukomalacia. J Perinat Med. 1997;25:180-3.
14. Boal DK, Watterberg KL, Miles S, Gifford KL. Optimal cost-effective timing of cranial ultrasound screening in low-birth-weight infants. Pediatr Radiol. 1995;25:425-8.
15. Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial ultrasound prediction of disabling and nondisabling cerebral palsy at age two in low birth weight population. Pediatrics. 1995;95:249-54.
16. Volpe JJ. Hypoxic-ischemic encephalopathy: clinical aspects. In: Volpe JJ, editor. Neurology of the newborn. 5th ed. Philadelphia: Saunders Elsevier; 2008. p. 517-73.
17. Miller SP, Ramaswamy V, Michelson D, Barkovich AJ, Holshouser B, Wycliffe N, *et al.* Patterns of brain injury in term neonatal encephalopathy. J Pediatr. 2005;146:453-60.
18. Accardo J, Kammann H, Hoon AH. Neuroimaging in cerebral palsy. J Pediatr. 2004;145:S19-27.
19. Morgan AM, Aldag JC. Early identification of cerebral palsy usiang a profile of abnormal motor patterns. Pediatrics. 1996;98:692-7.
20. Zafeiriou DJ, Tsikoulas IG, Kremenepoulos GM, Kontopoulos EE. Using postural reactions as a screening test to identify high-risk infants for cerebral palsy: a prospective study. Brain Dev. 1998;20:307-11.
21. Georgieff MK, Bernbaum JC, Hoffman-Williamson M, Daft A. Abnormal truncal muscle tone as a useful early marker for developmental delay in low birth weight infants. Pediatrics. 1986;77:659-63.
22. Hadders-Algra M. Development of postural control. In: Hadders-Algra M, Carlberg EB, editors. Postural control: a key issue in developmental disorders. 1st ed. London: McKeith Press; 2008. p. 22-73.
23. Swaimann KF. Neurologic examination after the newborn period until 2 years of age. In: Swaimann KF, Ashwal S, Ferriero DM, Schor NF, Finkel RS, Gropman AL, Pearl PL, Shevell MI, editors. Pediatric neurology principles and practice. 6th ed. Philadelphia: Mosby Elsevier; 2017. p. 37-46.