Early diagnosis of cerebral palsy

Leena Haataja

Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland Correspondence to: Leena Haataja, MD, PhD. Children's Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Puistosairaala, 2.krs, Stenbäckinkatu 11, 00029 HUS, Helsinki, Finland. Email: leena.haataja@hus.fi.

Abstract: Cerebral palsy (CP) is the most common severe motor disability in children, with prevalence estimates of 1.5–4 per 1,000 live births. Early diagnosis of CP is challenged by the fact that the CP phenotype is highly variable. Identifying the infants with a high risk of CP during the first months of life is based on a combination of detailed patient history, validated neurological examination or neuromotor assessment, and brain imaging. Based on research evidence, the best three tools to detect high risk of CP before the corrected age of 5 months old are neonatal magnetic resonance imaging (MRI), the Prechtl Qualitative Assessment of General Movements (GMs), and the Hammersmith Infant Neurological Examination (HINE). After the corrected age of 5 months old, the recommended tools are brain MRI, the HINE, and standardized motor assessment tools. The sequential cranial ultrasound is the method of choice if brain MRI is not feasible. Early identification of CP aims at timely awareness of this life-long disorder that has possible co-morbidities such as epilepsy, visual impairment and hearing deficit. Early identification of CP also promotes early exploration of available treatment options and early intervention that aim to enhance innate brain plasticity for improved functional outcome.

Keywords: Cerebral palsy (CP); neurological assessment; neuroimaging; early intervention

Received: 02 May 2020; Accepted: 20 May 2020; Published: 31 August 2020. doi: 10.21037/pm-20-53 **View this article at:** http://dx.doi.org/10.21037/pm-20-53

"Is my baby able to walk?" is one of the most common questions parents ask pediatric neurologists in the neonatal intensive care unit (NICU) and the NICU follow-up clinics. In the NICU context, this question refers to the risk of cerebral palsy (CP). Early detection of CP is clinically relevant to those infants who are at high risk of any developmental disorder based on the presently available research data. There is no consensus on how to precisely define the high-risk group, but internationally acknowledged recommendations are available. The very preterm infants (born under 32 weeks of gestation) and those who have one or more significant risk factors (e.g., abnormal neurological findings or symptoms at birth/ neonatal period, and/or who had abnormal neuroimaging findings) are known to be at highest risk for adverse outcomes (https://newborn-health-standards.org/).

It is often questioned whether early diagnosis of CP is possible, and if so, whether there is any evidence that

it is worthwhile. Emerging research data supports early intervention, mainly based on its effect on innate brain plasticity, which is at its most active phase during the early years of life. Animal research data has led to the main statement that without the active use of the motor cortex, there is a high risk of losing connections and selective function (1). Furthermore, clinical experience of late interventions that arise from delayed diagnosis suggests worse outcomes compared to active early intervention.

Early detection of high risk of CP relies on a combination of detailed patient history, developmental assessment, structured and validated neurological examination or neuromotor assessment, brain imaging, and further etiological investigations (e.g., neurophysiological or genetic investigations) when appropriate for differential diagnostics. The current overview focuses on CP and discusses its risk factors, clinical classification, and the present research evidence of available examinations aimed at

Page 2 of 7

early diagnosis of CP. In addition, the role of brain imaging in early diagnostics is also discussed.

СР

Definition

CP is defined as a group of disorders related to the development of movement and posture that cause activity limitation, and are attributed to non-progressive disturbances that occur in the developing fetal or infant brain (2). CP may present solely as a motor problem, but co-morbidities like disturbances of sensation, hearing and visual deficits, communication and learning problems, intellectual disability, epilepsy, behavioral and skeletal problems are common (2-4).

Prevalence

The prevalence of CP varies from country to country (5), but in high-income countries it occurs in roughly two cases per 1,000 live births (6). A male predominance has been shown (7). Even though the origin of CP is multifactorial, the risk of developing CP increases with lower gestational age at birth. Nevertheless, reports over the last decade have shown that the rate of CP in children born preterm is decreasing (8-10). In a database study that included 20 European population-based registers, Sellier et al. showed that the prevalence of CP declined from 70.9 to 35.9 per 1,000 live births in infants with very low birthweight (1,000 to 1,499 g) during 1980 to 1996 (10). Despite the increased risk of CP in preterm children, the absolute number of children with CP is reported to be higher (54.5%) among children carried to term (11). The incidence of CP in infants carried to term is higher in low-income countries due to the higher mortality of preterm infants.

Risk factors

The most important clinical advice regarding risk factors for CP is the concept of keeping risk factors and causes of CP development in any individual as separate entities. To date, several risk factors have been reported; a proportion of these are partly overlapping and interacting (12). In clinical practice, it is helpful to systematically screen all information on risk factors related to gestation period, i.e., prenatal, perinatal and postnatal factors. Prenatal factors include, e.g., genetic clotting problems in the family, signs of fetal distress, intrauterine growth restriction, multiple births, prematurity, maternal-fetal infections and placental injury. Among perinatal factors, the role of isolated birth asphyxia has been shown to be much less central than previously believed (13). Perinatal kernicterus, postnatal administration of steroids, sepsis and meningitis may also be part of the complex scenario of developing CP (12). Hydrocephalus and head traumas are examples of possible postnatal risk factors. The most common imaging findings related to CP are discussed later in this overview. If there are no identifiable risk factors in the patient history or in the course of clinical evolution, or if the brain imaging does not support the diagnosis of CP, thorough investigations of differential CP diagnosis is recommended.

Classification

The most common way to describe CP has been based on topographic features, i.e., the parts of the body involved in CP. In quadriplegia, all four limbs are involved; in diplegia, both legs show functional limitation; in hemiplegia, only one side of the body shows typical findings of CP. An alternative way to classify CP is provided by the Surveillance of Cerebral Palsy in Europe (SCPE), which classifies CP into a unilateral (one side of body) or bilateral (both sides of body) type. According to the Australian Cerebral Palsy Register Report, 38% of all children with CP have unilateral CP. Among those with bilateral CP, 37% have diplegia and 24% have quadriplegia (14).

The SCPE expert group has also provided a recommendation for how to define the CP sub-types into four main categories: spastic CP (including both unilateral and bilateral types), dyskinetic CP (including both dystonic and choreo-athetotic types), ataxic CP, and non-classifiable CP (15). The spastic types are the most common (86%), whereas the dyskinetic, ataxia and non-classified types cover 6%, 5%, and 3% of cases, respectively. The sub-type of CP can usually be reliably defined in all patients that are at least 2 years old.

Early diagnosis of CP

Early clinical signs of CP

Clinical signs of motor abnormalities that develop later are often very unspecific to CP in the neonatal period and early infancy. Instead, they are signs that are often seen in different injuries and disorders of the central nervous

Pediatric Medicine, 2020

Table 1 The common early signs and findings of CP

Invariable or poor attention and vigilance

Seizures

Poor head growth

Persisting primitive reflexes

Grasping reflex in fingers and toes

Asymmetric tonic neck reflex (ATNR)

Moro reflex

Cranial nerve dysfunction

Asymmetrical or poor facial movements

Poor or inconsistent visual attention and tracking

Strabismus or other abnormal eye movements

Hearing problems

Feeding problems

Abnormal quantity or quality of spontaneous movements

Passive or excessive movements

Monotonous or asymmetric movement pattern

Jerky, cramped, dystonic or other abnormal movements

Frequent or constant tremor

Asymmetric use of hands

Asymmetric weight bearing while supported in standing

Tiptoeing

Tone abnormalities

Poor head control

Increased extensor tone

Distal spasticity in limbs

Constant fisting of hands

Truncal hypotonia

Asymmetry of tone in limbs

Abnormal tendon reflexes

Exaggerated reflexes

Clonus

Positive Babinski sign

Delayed motor development

CP, cerebral palsy.

system. In fact, because the central nervous system rapidly develops in early infancy (i.e., before 2 years of age)—and hence the neurological findings are always changing—it has been debated if CP can even be diagnosed at all during this period. Moreover, the clinical pattern of how the early unspecific neurological findings change into specific signs of CP differs widely among infants. The characteristics of the wide spectrum of brain injuries related to CP also vary, and factors relating to the individual (e.g., neuroplasticity, general health status) and environment (e.g., family related factors, intervention) further modify the clinical outcome. The common early signs and findings of CP are listed in *Table 1*.

According to Hubermann *et al.* (16), children admitted to the NICU had been diagnosed with CP much earlier (mean 9.3 ± 10.2 months) than those infants who developed CP later but were not admitted to the NICU (mean 28.1 ± 24.9 months). Furthermore, there was a long delay in the diagnosis by the primary care providers (mean 28.8 ± 27.1 months), suggesting a lack of awareness of early signs and a need for further education at the primary level.

Evidence-based assessment tools in the clinics

In their systematic review, Novak *et al.* (17) identify the best three tools to detect high risk of CP before the corrected age of 5 months old: (I) neonatal magnetic resonance imaging (MRI) (86–89% sensitivity (18), (II) the Prechtl Qualitative Assessment of General Movements (GMs) (98% sensitivity) (19), and (III) the Hammersmith Infant Neurological Examination (HINE) (90% sensitivity) (20). After the corrected age of 5 months old, the best tools to recognize high risk of CP are brain MRI (86–89% sensitivity), the HINE (90% sensitivity), and the Developmental Assessment of Young Children (DAYC) (83% sensitivity) (21). The definition for high risk of CP is based on a combination of evident motor dysfunction and abnormal brain imaging findings known to relate to CP and/or clinical history indicating risk for CP.

The Prechtl Qualitative Assessment of GMs

GMs are the most frequent movement patterns in the first 3 months after term age. A characteristic of GMs is

that all parts of the body participate in these spontaneous movements. From 11 to 16 weeks post-term, GMs present as so-called fidgety movements that are described as being a continuous stream of small and fluent movements occurring irregularly over the body. The appearance of fidgety movements represents a phase in the re-organization of motor function that leads to the goal-directed motor activities (22). According to the vast research evidence, absent or abnormal fidgety movements are predictive of CP with 95–98% accuracy (17). Combining GMs with brain MRI has reportedly led to sensitivity and specificity of up to 100% in a cohort of extremely preterm infants (23).

In the clinics, GMs are easy to video record while the infant is fully awake, but not crying or fussing, and lying supine in a light bodysuit. A high-quality recording of 2-5 minutes is sufficient for confidently detecting the fidgety pattern. Outside of hospital settings, there is still little research data on the predictive value of GMs in a general population of newborn infants, which hinders its potential use in detecting high-risk infants within the low risk population (24,25).

HINE

The HINE method is a simple, quantifiable, neurologic examination for infants between 2 and 24 months of age (26). The aim of this neurological examination is to detect deviant neurological findings. The HINE has been proven to show a strong neuroanatomical correlation (i.e., good construct validity). The HINE method comprises three different components: neurological examination, developmental milestones, and behavior. The neurological component includes 26 items under the subsections of cranial nerve assessment, posture, movements, tone, and reflexes and reactions. The developmental milestone component is aimed at recording infants' motor development during the same appointment as the neurological examination. The milestones of head control, sitting, voluntary grasp, kicking, rolling, crawling, standing and walking are included. The behavior component is also an essential part of the examination, since the reliability of neurological findings is associated with emotional state and social orientation in young infants. The pattern of different clinical findings typical of CP is the key element of the utility of the HINE (e.g., increased tone in one of the upper limbs with fisted hand, combined with less tone in the trunk in the same side of the body that is affected).

The neurological component of the HINE (section 1)

can be scored (global score range 0-78). The related norm reference range of scores is also available at 3, 6, 9 and 12 months of age, separately from the term-born infants (gestational age 37 weeks or over), moderately preterm infants (gestational age of 33 to 36 weeks), and very preterm infants (gestational age of 32 weeks and under) (26,27). The HINE has been shown to have CP detection sensitivity of 96% and specificity of 87% already at 3 months of age (28). The predictive accuracy to detect a high risk of CP at a corrected age of over 5 months is 90% (20). Moreover, it has been shown that the integrated use of GMs and the HINE improves diagnostic accuracy (29). The HINE method is particularly effective because of the specific and clinically useful feature that its scores can predict the later ambulation of an infant with CP (27,30). The advantage of the HINE is that it can be used for sequential follow-up of an infant. In clinics, the persistence or increase of abnormal neurological findings is one of the cornerstones in the diagnostics of CP.

There is no official certification system required for the use of the HINE method. The methodological teaching videos and main references, as well as examination proformas translated into multiple languages are available at www.hammersmith-neuro-exam.com. In principle, as a neurological examination the detection rate of neurological abnormalities using the HINE method is not bound to hospital settings.

Standardized motor assessments

The Developmental Assessment of Young Infants (DAYC) is a standardized interactive questionnaire with milestones achieved as reported by parents. Maitre et al. (21) have shown that when DAYC was used to assess former preterm and term-born NICU patients who were later diagnosed with CP, a decrease in the scores was seen between the ages of 6 and 12 months. This pattern was not observed in patients without CP. The motor delay quantified by the DAYC is reportedly 89% predictive of CP (17). Another standardized assessment, the Alberta Infant Motor Scale (AIMS), has been shown to be 86% predictive of an abnormal motor outcome (17). The AIMS was designed to be an observational tool to identify atypical motor development up to 18 months of age (31). The strength of the AIMS is that it is quick and easy to administer in clinical situations; according to the author's experience, it also functions well if scored by physiotherapists in the community neonatal clinics.

Clinical neuroimaging

The diagnosis of CP is based on clinical criteria. Accordingly, by definition, brain imaging is not obligatory for diagnosis if it cannot be done safely or its arrangement is not feasible due to technical or financial resources. Brain imaging is highly recommended for understanding the possible pathogenic mechanism(s) related to the development of CP and the clinical phenotype. Brain MRI is preferred over other imaging modalities (17). Computed tomography (CT) should not be used due to its radiation load and moderate resolution. Instead, cranial ultrasound (cUS) is recommended either as combined with a brain MRI, or as the method of choice if MRI is not feasible (32,33).

The most common injury type is white matter injury (19–45%); grey matter injury is dominant in 21% of the findings, while focal vascular insults and malformations cover about 10% and 11%, respectively (34).

Major cUS abnormalities show high specificity and sensitivity for CP. For example, in two different cohorts (≤32 weeks of gestation, and 33–36 weeks of gestation) of high-risk preterm infants, grade III hemorrhage, venous infarction, cystic periventricular leukomalacia and focal infarctions showed 95% and 99% specificity, and 76% and 86% sensitivity, respectively, for CP (32). It is essential that cUS are performed sequentially during the first 4–6 weeks after birth, and that the last cUS in the sequence is timed between 36 to 40 weeks post-menstrual age due to the variable evolution time for clinically significant cysts (32).

Brain MRIs have been reported to detect abnormal findings in about 85–86% of children with CP (34,35). Subtle white matter lesions, myelination of the posterior limb of internal capsule (PLIC), and cerebellar lesions are findings for which brain MRI is superior to cUS (33). Mercuri *et al.* (36,37) have reported that the myelination of PLIC is a good predictor of motor outcome. They have shown that in term-born infants with middle cerebral artery infarction, the involvement of the parenchymal white matter, basal ganglia and thalamus, and the PLIC predicted hemiplegia.

Differential diagnosis of CP

For differential diagnosis, one should consider the child's overall development, since cognitive impairment often presents together with motor delay. Dissociative motor development (i.e., gross motor development that only transiently lacks behind other aspects of development) and bottom shuffling are common benign variants of early motor performance. Mild ligament laxity is also a common constitutional characteristic in families.

It has been recommended that brain imaging should be performed on children with CP of unknown etiology (18). If there are no brain findings typical of CP, or if there are atypical features in the patient history (e.g., family history of CP), one should consider targeted genetic tests (e.g., hereditary spastic paraplegia, spinocerebellar ataxia, microdeletions/duplications, or other chromosomal aberrations), metabolic investigations (e.g., mitochondrial disorders, biotinidase deficiency) or neurophysiological investigations (e.g., brachial nerve palsy) (38).

Conclusions

There has been a longstanding debate about whether early identification of CP before two years of age is possible. Despite the various doubts, the accumulated research evidence convincingly shows that the high risk of CP can be detected already before 6 months of age. Early identification is important from the child's, parent's and society's point of view. Recent reports provide data that methods such as systematic parental coaching as a means of early intervention can have positive effects on the overall functional outcome of high-risk infants (39,40). Determining the most effective means of early intervention is still under intensive research, but methods that include both motor and sensory stimuli, as well as those that activate children themselves in their everyday functions in their home environment hold at present the best promise (25, 41).

Early detection of CP relies on a basic clinical principle; the combination of detailed patient history, especially known risk factors of CP, developmental assessment, and validated neurological examination or neuromotor assessment. The available evidence-based assessment tools, GMs and HINE, are relatively easy to integrate in clinics after appropriate training. Brain imaging is highly recommended as an integral part of the clinical diagnostic process.

Acknowledgments

Funding: None.

Pediatric Medicine, 2020

Page 6 of 7

Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at https://pm.amegroups. com/article/view/10.21037/pm-20-53/coif). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

- Martin JH, Chakrabarty S, Friel KM. Harnessing activitydependent plasticity to repair the damaged corticospinal tract in an animal model of cerebral palsy. Dev Med Child Neurol 2011;53:9-13.
- Rosenbaum P, Paneth N, Leviton A, et al. A Report: The Definition and Classification of Cerebral Palsy April 2006. Dev Med Child Neurol Suppl 2007;109:8-14.
- Ricci D, Romeo DM, Gallini F, et al. Early visual assessment in preterm infants with and without brain lesions: correlation with visual and neurodevelopmental outcome at 12 months. Early Hum Dev 2011;87:177-82.
- Novak I. Evidence-based diagnosis, health care, and rehabilitation for children with cerebral palsy. J Child Neurol 2014;29:1141-56.
- Donald KA, Samia P, Kakooza-Mwesige A, et al. Pediatric cerebral palsy in Africa: a systematic review. Semin Pediatr Neurol 2014;21:30-5.
- 6. Himmelmann K, Uvebrant P. The panorama of cerebral palsy in Sweden. XI. Changing patterns in the birth-year period 2003-2006. Acta Paediatr 2014;103:618-24.
- Chounti A, Hägglund G, Wagner P, et al. Sex differences in cerebral palsy incidence and functional ability: a total population study. Acta Paediatr 2013;102:712-7.
- 8. Hack M, Costello DW. Trends in the rates of cerebral

palsy associated with neonatal intensive care of preterm children. Clin Obstet Gynecol 2008;51:763-74.

- van Haastert IC, Groenendaal F, Uiterwaal CSJ, et al. Decreasing incidence and severity of cerebral palsy in prematurely born children. J Pediatr 2011;159:86-91.e1.
- Sellier E, Platt MJ, Andersen GL, et al. Decreasing prevalence in cerebral palsy: a multi-site European population-based study, 1980 to 2003. Dev Med Child Neurol 2016;58:85-92.
- Bax M, Tydeman C, Flodmark O. Clinical and MRI correlates of cerebral palsy: the European Cerebral Palsy Study. JAMA 2006;296:1602-8.
- Korzeniewski SJ, Slaughter J, Lenski M, et al. The complex aetiology of cerebral palsy. Nat Rev Neurol 2018;14:528-43.
- Nelson KB, Ellenberg JH. Antecedents of cerebral palsy. Multivariate analysis of risk. N Engl J Med 1986;315:81-6.
- ACPR Group (2013), Australian Cerebral Palsy Register Report, Sydney, Cerebral Palsy Alliance. Available online: https://cpregister.com/wp-content/uploads/2018/05/ ACPR-Report_Web_2013.pdf [Accessed 6 April 2019]
- Surveillance of Cerebral Palsy in Europe. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). Dev Med Child Neurol 2000;42:816-24.
- Hubermann L, Boychuck Z, Shevell M, et al. Age at Referral of Children for Initial Diagnosis of Cerebral Palsy and Rehabilitation: Current Practices. J Child Neurol 2016;31:364-9.
- Novak I, Morgan C, Adde L, et al. Early, Accurate Diagnosis and Early Intervention in Cerebral Palsy: Advances in Diagnosis and Treatment. JAMA Pediatr 2017;171:897-907.
- Ashwal S, Russman BS, Blasco PA, et al. Practice parameter: diagnostic assessment of the child with cerebral palsy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2004;62:851-63.
- Bosanquet M, Copeland L, Ware R, et al. A systematic review of tests to predict cerebral palsy in young children. Dev Med Child Neurol 2013;55:418-26.
- Romeo DM, Ricci D, Brogna C, et al. Use of the Hammersmith Infant Neurological Examination in infants with cerebral palsy: a critical review of the literature. Dev Med Child Neurol 2016;58:240-5.
- 21. Maitre NL, Slaughter JC, Aschner JL. Early prediction of cerebral palsy after neonatal intensive care using motor

Pediatric Medicine, 2020

- 22. Ritterband-Rosenbaum A, Herskind A, Li X, et al. A critical period of corticomuscular and EMG-EMG coherence detection in healthy infants aged 9-25 weeks. J Physiol 2017;595:2699-713.
- 23. Skiöld B, Eriksson C, Åden U, et al. General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm. Early Hum Dev 2013;89:467-72.
- Bouwstra H, Dijk-Stigter GR, Grooten HM, et al. Predictive value of definitely abnormal general movements in the general population. Dev Med Child Neurol 2010;52:456-61.
- Herskind A, Greisen G, Nielsen J. Early identification and intervention in cerebral palsy. Dev Med Child Neurol 2015;57:29-36.
- Haataja L, Mercuri E, Regev R, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr 1999;135:153-61.
- Romeo DM, Cioni M, Palermo F, et al. Neurological assessment in infants discharged from a neonatal intensive care unit. Eur J Paediatr Neurol 2013;17:192-8.
- Romeo DM, Cioni M, Scoto M, et al. Prognostic value of a scorable neurological examination from 3 to 12 months post-term age in very preterm infants: a longitudinal study. Early Hum Dev 2009;85:405-8.
- Romeo DM, Guzzetta A, Scoto M, et al. Early neurologic assessment in preterm-infants: integration of traditional neurologic examination and observation of general movements. Eur J Paediatr Neurol 2008;12:183-9.
- Haataja L, Mercuri E, Guzzetta A, et al. Neurologic examination in infants with hypoxic-ischemic encephalopathy at age 9 to 14 months: use of optimality scores and correlation with magnetic resonance imaging findings. J Pediatr 2001;138:332-7.
- 31. Piper M, Darrah J. Motor Assessment of the Developing

doi: 10.21037/pm-20-53

Cite this article as: Haataja L. Early diagnosis of cerebral palsy. Pediatr Med 2020;3:9.

Infant. Philadelphia: WB Saunders, 1994.

- 32. de Vries LS, van Haastert IC, Benders MJ, et al. Myth: cerebral palsy cannot be predicted by neonatal brain imaging. Semin Fetal Neonatal Med 2011;16:279-87.
- De Vries LS, Van Haastert IL, Rademaker KJ, et al. Ultrasound abnormalities preceding cerebral palsy in highrisk preterm infants. J Pediatr 2004;144:815-20.
- Reid SM, Dagia CD, Ditchfield MR, et al. Populationbased studies of brain imaging patterns in cerebral palsy. Dev Med Child Neurol 2014;56:222-32.
- 35. Krägeloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. Dev Med Child Neurol 2007;49:144-51.
- 36. Mercuri E, Rutherford M, Cowan F. Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram, and magnetic resonance imaging study. Pediatrics 1999;103:39-46.
- Mercuri E, Barnett A, Rutherford M, et al. Neonatal cerebral infarction and neuromotor outcome at school age. Pediatrics 2004;113:95-100.
- Mayston M. Intervention, planning, implementation, and evaluation. In: Dan B, Mayston M, Paneth N, et al. editors. Cerebral Palsy: Science and Clinical Practice. London: Mac Keith Press, 2014:329-60.
- 39. Dirks T, Blauw-Hospers CH, Hulshof LJ, et al. Differences between the family-centered "COPCA" program and traditional infant physical therapy based on neurodevelopmental treatment principles. Phys Ther 2011;91:1303-22.
- Dirks T, Hadders-Algra M. The role of the family in intervention of infants at high risk of cerebral palsy: a systematic analysis. Dev Med Child Neurol 2011;53 Suppl 4:62-7.
- 41. Morgan C, Novak I, Badawi N. Enriched environments and motor outcomes in cerebral palsy: systematic review and meta-analysis. Pediatrics 2013;132:e735-46.