Chapter 1

Early Markers for Cerebral Palsy

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Abstract

Cerebral palsy (CP) is a term referring to a nonprogressive disease of the brain originating during the antenatal, neonatal, or early postnatal period when brain neuronal connections are still evolving. Secondary effects of spasticity on growth may, however, be progressive. There may be additional disturbances of sensation, perception, cognition, communication, and behavior. Babies who are neurologically abnormal as newborns are at increased risk of neurologic abnormality in later months and years. Being born preterm (born <37 weeks of gestation) or with a very low birth weight (weighing <1500 g/<32 weeks of gestation) or extreme low birth weight (<1000 g/<28 weeks of gestation) is associated with significant motor impairment. Which specific signs in the neonate are of greatest predictive power, what long-term disability these signs predict, and how well they predict it remain unclear? Physician's major concern is to identify specific risk factors for severe impairment in early infancy so as to predict the developmental outcome of those children that may manifest later on with neurological deficit especially if they have perinatal insult. Parents on the other hand are also concerned about their growing infants, their development, and neurological outcome. Since cerebral palsy is a permanent disorder, early detection of signs of motor impairment is crucial to assist physicians to give close follow-up of those infants and to reassure parents whose children are normal. It has been shown that intervention may be most efficient when the plasticity of the brain is high, and an early detection of brain impairment is therefore crucial. An earlier follow-up and training program can have a positive effect of the motor development of the child with CP, in particular through prevention of limb contractions, and might make a difference in the child's ability to handle everyday challenges. In addition, an early detection of CP gives the parents more time for adjustment and preparation. Since clinical manifestations of cerebral palsy do not emerge before a child is at least 6 months, the general movement (GM) is considered the most reliable early markers for monitoring of fetal and infant movement. Abnormal General movements and absence of the so-called fidgety movements at 3-5 months post-term carries a high risk of developing cerebral palsy. Beside a high specificity (82–99%) and sensitivity (95–100%), the assessment of the general movements (GMs) is quick, nonintrusive, and easy to acquire.

Keywords: infant, cerebral palsy, early markers, general movement, neuroimaging

1. Introduction

Cerebral palsy (CP) is a permanent disorder in the development of movement and posture in the developing fetal or infant brain which usually manifests before 18 months of age [1]. Prematurity is a major risk factor for later motor impairment, and the prevalence of CP increases from 0.1% in term babies to 14.6% in those born preterm [2, 3].

The physical impairment is often accompanied by disturbances in cognition and perception [4]. Preterm birth, perinatal asphyxia and neonatal encephalopathy, genetic predisposition, white matter disease, deep gray matter lesion, cerebral infarction, and intraventricular hemorrhage are associated with increased risk of CP [5–7].

The ability to predict CP earlier than 2 years of age would have many advantages. Earlier recognition of infants at high risk for neurodevelopmental delay would also benefit families through individualized case management and interventions and may also lead to more focused follow-up and reassure the parents of those children who are unlikely to develop CP. One of the most challenging tasks for medical practitioners is to identify specific risk factors in early infancy and predict severe impairment that manifest later in development. Parents on the other hand still concerned about the developmental perspectives of their infant, especially if he has a perinatal insult. One should consider that overt clinical symptoms of CP usually do not manifest before the child is at least half year old [4]. In addition to that, identification of language and cognitive function delay requires long time follow-up for accurate detection [8]. Early recognition of neurodevelopmental delay needs a good tool for early diagnosis to predict the outcome and to enable early intervention as soon as possible. The plasticity of the brain is at its highest during the first 2 years and decreases gradually thereafter [9]. It has been shown that spontaneous motility is an excellent marker for neural dysfunction caused by brain impairment, which normally would not become evident and clinically manifested for years [10, 11]. The general movement assessment (GMA) developed by Prechtl is a known diagnostic tool for the functional assessment of the young nervous system and has shown good results in predicting CP at an early stage [12–15]. GMA is noninvasive, even nonintrusive, cost-efficient, and easy to learn [12]. During the last 15 years, considerable research has been devoted to GMs, whose quality has proven to be most indicative of functional integrity of the young nervous system, with specificity of 82–99% and a sensitivity of 95–100% [10, 16–17]. GMA conducted at 3 months of corrected age is useful in a clinical setting for predicting CP at 2 years of corrected age for children born <32 weeks of gestation [18]. In its predictive power, the GM assessment is superior to cranial ultrasound (US) or neurological examination and equivalent to MRI (white matter assessment) [19–21].

2. The aim of this chapter

The aim of this chapter is to discuss the early markers of cerebral palsy from the general movement assessment to the neurological examination and then neuroimgaing studies when indicated in assessing high-risk infants to provide opportunity for early detection of any poor motor performance and for early possible intervention.

3. General movements

General movement is a part of spontaneous movement activity that is generated by the developing nervous system; it appears from the 7th week postmenstrual until 3–5 months post-term. The beginning of early fetal movement at the 7th week is correlated with the development of synapsis in the spinal cord, the emergence of neuromuscular contacts, and before the development of spinal reflex pathway at 10–11 weeks postmenstrual [22–24]. It is characterized by a movement that involves the whole body in a variable sequence involving the arm, leg, neck, and trunk. They are complex in nature that wax and wane vary in intensity, speed, and range of motion and have a gradual onset and end. It has been proposed that GMs consist of rhythmic bursts of action potentials [16]. GMs are generated from a large neuronal generator network that extends from the brain stem to the spinal cord [25].

The variable nature of GM is explained by the presence of supraspinal projections that activate, inhibit, and modulate the central generator network [26]. Fetal and neonatal nervous system generates not only a variety of motor patterns such as simple startles or twitches but also more complex patterns such as stretching, yawning, or GM [12, 26]. General movements are movements which involve the entire body, rotations around the limb axes, and slight changes in the direction of movement that gives the GM its fluency and elegancy [10, 27]. The first-stage fetal movement that starts at the 7th week postmenstrual appears as movements that are restricted to the head and trunk, and then the second stage begins with the movement of all parts of the body as slow and simple movement of the arms and legs.

More complex and variable GMs emerge at week 9–10 of postmenstrual age (PMA), where each phase has its own characteristics [28]. Complexity and variation of movements are brought about by the independent exploration of degrees of freedom in all body joints. The variable combinations of movement like flexion-extension, abduction-adduction, and endorotation-exorotation generate a series of changes in movement direction of the involved body parts. GMs are considered as the major tool of assessing fetal and infant brain integrity in which reduced modulation of the central neuronal generators results in less variable GM and may indicate fetal or neonatal motor compromise [25].

3.1. Fetal and preterm general movements

From week 9 up to term age, the GMs are referred to as fetal and preterm general movements. These movements have large amplitudes and fast speed in which the fetus develops the entire neonatal movement, which also includes arm and leg movements, startles, sucking, breathing, and stretching movements [12].

3.2. Writhing movements

From term age onward till the second month post-term, the GM is called "writhing movement" which is characterized by small-to-moderate amplitude and speed. In addition, trunk movements are smaller than previously [29].

3.3. Fidgety movements

At 6 to 9 weeks post-term, the writhing movement disappears where the so-called fidgety movement (FM) appears [10]. It consists of rounded tiny movements of the neck, trunk, and limbs. It is of moderate speed and variable acceleration; they disappear when the infant starts being fussy or cries and is drowsy or sleeps [12, 25]. FM disappear from 3 to 5 months post-term (**Figure 1**) [30].

General movements gradually disappear at 3–5 months post-term, when general movement activity is taken over by goal-directed movements of the arms. The latter consist, for instance, of mutual manipulation of the fingers or manipulation of clothes [10].

3.3.1. Clinical variants of fidgety movement

Prechtl had described a clinical interpretation for FMs into (**Table 1**) [12].

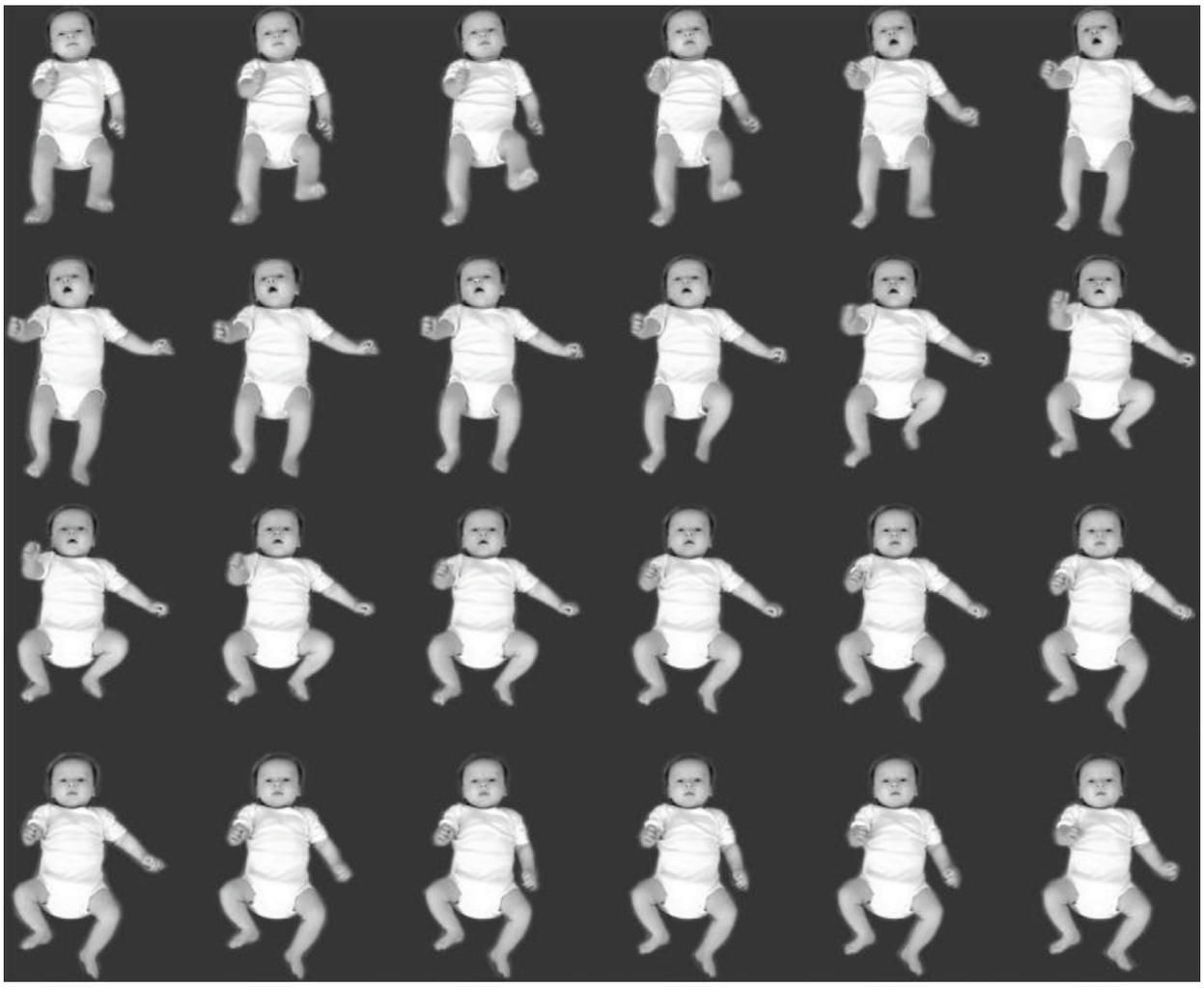

Figure 1. Video print of a 14-week-old infant showing fidgety movements as time evolves from left to right and from top to bottom. A frame rate of 12.5 Hz is used, yielding a total time of 1.92 s [30].

	Normal FM	Abnormal FM
Old	+ +, +, + −	− −, Exagg
New	+ +, +	+ −, −, Exagg

Table 1. New and old Prechtl approach for classification of normal and abnormal FMs, where the FMs are categorized as continual (+ +), intermittent (+), sporadic (+ −), absent (−), and exaggerated (Exagg) [12].

3.3.1.1. Continual FMs

Continual FMs occur frequently with very short pauses (1–2 s). It scores (++). FMs involve the whole body, particularly the neck, shoulders, wrists, hips, and ankles. FMs may occur as asymmetrical movement depending on the position of the head. They are mainly displayed in the hips and ankles but not so much in the shoulders and wrists [31, 32].

3.3.1.2. Intermittent FMs

Intermittent FMs occur often but with longer pauses (up to 10 s) than continual movements, which may indicate that FMs are present only during half of the observation time [31, 32]. Intermittent FMs scores (+).

3.3.1.3. Sporadic FMs

The occurrence of FMs here is less frequent and sporadic with much longer pause up to 1 minute. Sporadic FMs are age-adequate from 6 to 8 weeks post-term until the 5th month when FMs start to wane [31, 32]. Sporadic FM is regarded as abnormal movement according to the new Prechtl approach of general movement assessment (**Table 1**).

The potential biological function of this tiny movement may be attributable to the postnatal calibration of the proprioceptive system [12, 33]. Children and adolescents with fine motor dysfunction had less pronounced or abnormal fidgety movement at infancy [34, 35]. Sporadic FMs score (+ −).

3.3.1.4. Abnormal FMs

Abnormal FMs (score: AF) look like normal FMs, but it occurs with greater amplitude, speed, and jerkiness (exaggerated) [10, 12, 19]. Abnormal FMs are rare; they occur more often in infants born preterm who show uncoordinated sucking [35]. Abnormal FMs have been described in infants with Down syndrome (trisomy 21) [36, 37] and infants who has intrauterine exposure to maternal opiate abuse and/or HIV [1, 38]. Infants with abnormal FMs may develop normally [19, 35, 39, 40] but may also develop CP [19, 32]. Some studies documented an association between abnormal FMs and coordination difficulties and/or fine manipulative disabilities [35, 40]. Recently, an exceedingly high rate of abnormal FMs was described in infants who were later diagnosed with autism spectrum disorder [41].

3.3.1.5. Absent FMs

Whenever FMs are missing altogether from 9 to 20 weeks of post-term age, this abnormality is called absent FMs (score: F−). Infants with absent FMs show other normal or abnormal movements [19]. Absent FMs are highly predictive of later neurological deficits [10], particularly of CP [10, 12, 19, 32, 38, 39]. Further observation allows for determination of the eventual type of CP as well as the anatomical distribution and severity of the activity limitation. Despite the absence of FMs, infants with an increased risk of non-spastic CP showed circular arm movements with or without spread fingers [42, 43]. Asymmetry of distal segmental movements may predict later development of unilateral CP [44, 45].

It has been shown that abnormal and absent FMs increase the risk of development of neurological impairment. Particularly, the absence of FMs has been shown to be highly predictive of CP, while normal FMs are associated with normal neurological outcome [10]. GMs during preterm and term age are considered abnormal if it lacks the variability in intensity, speed, and range of motion which may indicate a poor repertoire general movement. Another form of abnormal GMs that lacks the usual fluency and smoothness is described as cramped-synchronized GMs, a rigid movement of the limb and trunk muscles that contract simultaneously and relax almost simultaneously. Both the presence of cramped-synchronized GM and the absence of fidgety movements are highly predictive of CP [14, 21]. Chaotic movements on the other hand are also considered abnormal GMs in which it is abrupt and occurs with high speed and large amplitude and mostly observed in moderate preterm [10].

4. General movement assessment

Since long-time GMs regarded as standard tool for monitoring and predicting motor compromise like cerebral palsy [14]. It is an easy, noninvasive, and cost-effective method that consists of a video camera and a trained person who analyze the video record. The infant (should be silent, not crying) is monitored with video camera in supine position for 3–5 minutes [12]. There are several computer-based methods for assessing GM in infants with high risk of neurological impairment. The computerized video-based method is divided into two types: the motion capturing system and traditional color camera [46]. The motion capturing system has an advantage in separating healthy infants from the high-risk infants, but it is a costly and expensive and used only in research practice, while the traditional method is used outside the clinical and research practice like the infant's home that is called the GM tool box [47]. Adde et al. described that the GM tool box showed that the variability in displacement of spatial center of active pixels in the image had the highest sensitivity (81.5%) and specificity (70%) in classifying GMs [46]. Another study revealed that this type of computer-based analysis can reliably differentiate between normal (continual) and abnormal (intermittent) GMs [48]. The absence of fidgety movements was never specific for a particular subtype of CP. This fact indicates that intact corticospinal fibers and a normal output of the basal ganglia and cerebellum are necessary to generate normal fidgety movements [27].

Unilateral CP can be identified through GM assessment and application of Hammersmith Infant Neurological Examination (HINE) [49]. These results clearly lead to the conclusion that a 3- to 4-month-old infant with a normal neurological score but an absence of fidgety movements and asymmetric segmental movements is at a high risk of developing unilateral CP [45] (**Table 2**).

GMS during preterm age	Writhing GMs (at term until 8 weeks postterm)	Fidgety GMs (3–5 months)	Neurological outcome
Poor repertoire or normal GMs	Poor repertoire or abnormal GMs	Normal fidgety movements	Normal
Poor repertoire or cramped-synchronized GMs	cramped-synchronized GMs	Absence of fidgety movements; abnormal findings in neurological examination	Bilateral spastic CP
Poor repertoire or cramped-synchronized GMs	Poor repertoire or cramped-synchronized GMs	Absence of fidgety movements and asymmetrical segmental movements; normal or abnormal findings in neurological examination	Unilateral spastic CP
Poor repertoire GMs	Poor repertoire GMs; circular arm and finger spreading	Absence of fidgety movements; absence of foot-to-foot contact; circular arm movements and finger spreading	Dyskinetic CP

CP, cerebral palsy; GM, general movement.

Table 2. Developmental trajectories with a high predictive power for normal development and the development of cerebral palsy [42].

5. Value of neurological examination

Neurological assessment since long time is used as a monitoring system for development of the high-risk infants. The main goal of the high-risk infant follow-up programs is to monitor the development and to provide early identification and treatment of high-risk infants (preterm and those with perinatal insult). These programs are also considered as a referral centers for general providers who have identified delays on routine screenings. Neurological examination is considered a vital tool of neurodevelopmental assessment and follow-up, complemented by various developmental and medical assessments. There are several neurological examination methods available for high-risk infants used for both clinical care and research studies. The well-known methods are the Hammersmith Infant Neurological Examination (HINE) [50], the Touwen [51], the Amiel-Tison [52], the Bayley Scales of Infant and Toddler Development [53], and Dubowitz neonatal neurological examination [54]. These assessment methods have a high predictive value with sensitivity and specificity of 88 and 92%, respectively, in predicting CP [14]. The use of the above neuromotor and developmental assessment is to predict impairments as early as possible and to help physician provide guidance for families about their children development and help in discriminating between normally developing infants from those with abnormal development. It also enables prognostic information on the neurological and motor outcome and when to send those infants showing early impairment for rehabilitation programs.

The HINE is an easily performed and relatively brief standardized and scorable clinical neurological examination for infants between 2 and 24 months of age, accessible to all clinicians, with good interobserver reliability. It has no associated costs such as lengthy certifications or proprietary forms. It consists of 26 items that assess different aspects of neurological examinations such as cranial nerves, posture, movements, tone, and reflexes [53], with a questionnaire instructions and diagrams included on the scoring sheet, similar to Dubowitz neonatal neurological examinations [54]. Each item is scored individually (0, 1, 2, or 3), with a sum score of all individual items (range 0–78), Optimality scores for infants 3 to 18 months are based on the frequency of distribution of neurological findings in a typical infant population: it is considered optimal when an item is found in at least 90% of infants [53].

The sequential use of the HINE allows the identification of early signs of cerebral palsy and other neuromotor disorders, while individual items are predictive of motor outcomes. For example, in preterm infants assessed between 6 and 15 months of corrected age, scores above 64 predict independent walking with a walked sensitivity of 98% and specificity of 85%. Conversely, scores below 52 were highly predictive of cerebral palsy and severe motor impairments [55].

Neurological examination and tools that incorporate it are clinically influenced by the experience of an examiner and a child's state of rest. The neurological examination tools are mostly of value in term age, while general motor assessment has better predictive accuracy at preterm age. Signs that may appear transient during preterm period like jitteriness and dystonia that may be detected through neurological examination are misleading and have poor predictive accuracy of CP [56, 57]. Neurological examination is of value in the prediction of milder cases of CP, during which GMA is less sensitive [58]. The combination of both GMA and HINE at 3 months post-term is valuable in predicting infants at high risk of CP [49].

6. Neuroimaging studies

6.1. Cranial ultrasonography

Cranial imaging is the most well studied of the postnatal clinical findings correlated with CP. Serial cranial ultrasound has been used for nearly 30 years to evaluate CNS structure in infancy. Ultrasonography had been used for assessment of fetal well-being and behavior state in utero. Cranial ultrasound reliably detects germinal matrix and intraventricular hemorrhage, ventricular dilation, and periventricular leukomalacia (PVL). Although cystic white matter injury (WMI) and ventriculomegaly are highly associated with CP, premature infants with normal cranial ultrasound are also at risk for motor abnormalities [59]. Infants born after 28–30 weeks of gestation are not routinely examined with ultrasonography; this is partly due to the low sensitivity of cranial US (66–79%) [60]. Thus, a brain injury that does not present clear clinical signs can go undetected for a long period of time, resulting in an intervention being initiated late.

6.2. Magnetic resonance imaging

MRI, which is often used to reveal anatomic abnormalities, could offer a unique, noninvasive opportunity to predict neurological deficits, even as early as the newborn stage [61]. Also,

MRI has considerably higher sensitivity than cranial ultrasound (US) [62]. Its higher sensitivity is important to detect early damage occurring before reliable US imaging. In addition of hypoxia-ischemia, MRI can also show other patterns of injury, such as central cortico-subcortical damage, diffuse cortical involvement, bilateral parasagittal lesions, as well as brainstem, cerebella, and hippocampus lesions.

The patterns of MRI in children with cerebral palsy are:

1. White matter damage

According to the studies of pathological observations with patient phenotypes, white matter injury (WMI) is often observed in spastic diplegia and quadriplegia. The abnormalities of white matter are particularly frequent in children with CP born premature. Incidence of white matter damage, across all studies, was reported in nearly 30–40% of all subjects; also, myelin abnormalities are quite common in CP [63, 64].

2. Gray matter damage

The gray matter damage is defined as injuries to the basal ganglia, cortical defects, thalamic abnormalities, and diencephalic lesions. The hallmark of acute perinatal hypoxia-ischemia in term infants, central gray matter damage, is an important cause of death and cerebral palsy.

3. White and gray matter damage

The white and gray matter damage, most common among hemiplegics, infarcts are commonly found in both white and gray matter surrounding the middle cerebral artery among subjects with CP.

4. Ventriculomegaly, atrophy, and cerebrospinal fluid abnormalities

The ventriculomegaly, common subjects with CP, includes enlarged, dilated, or reduced ventricles (unilateral or bilateral), abnormalities of the atria, ventricular or occipital horns, and posterior fossa abnormalities [65, 60].

A significant relationship between white matter abnormalities on magnetic resonance imaging (MRI) and absent FMs in infants born at <30 weeks of gestation supports the idea that abnormal GMs reflect white matter injury [66].

Although the white matter damages are the most common abnormality [67, 68], but combined gray and white matter abnormalities are more common among children with hemiplegia. Isolated white matter abnormalities are more common with bilateral spasticity or athetosis and with ataxia. Isolated gray matter damage is the least common finding. In preterm-born infants, periventricular white matter lesions occurred more often than in term-born children (90% vs. 20%) [67]. It has been shown that both GMA and magnetic resonance imaging (MRI) had a sensitivity of 100% in predicting the development of CP by the age of 12 months in preterm infants [21].

The scientists had developed guidelines for early detection and intervention for cerebral palsy; they include recommendations for neurological examinations, neuroimaging, and motor assessments for infants between 5 months and 24 months of corrected age [13].

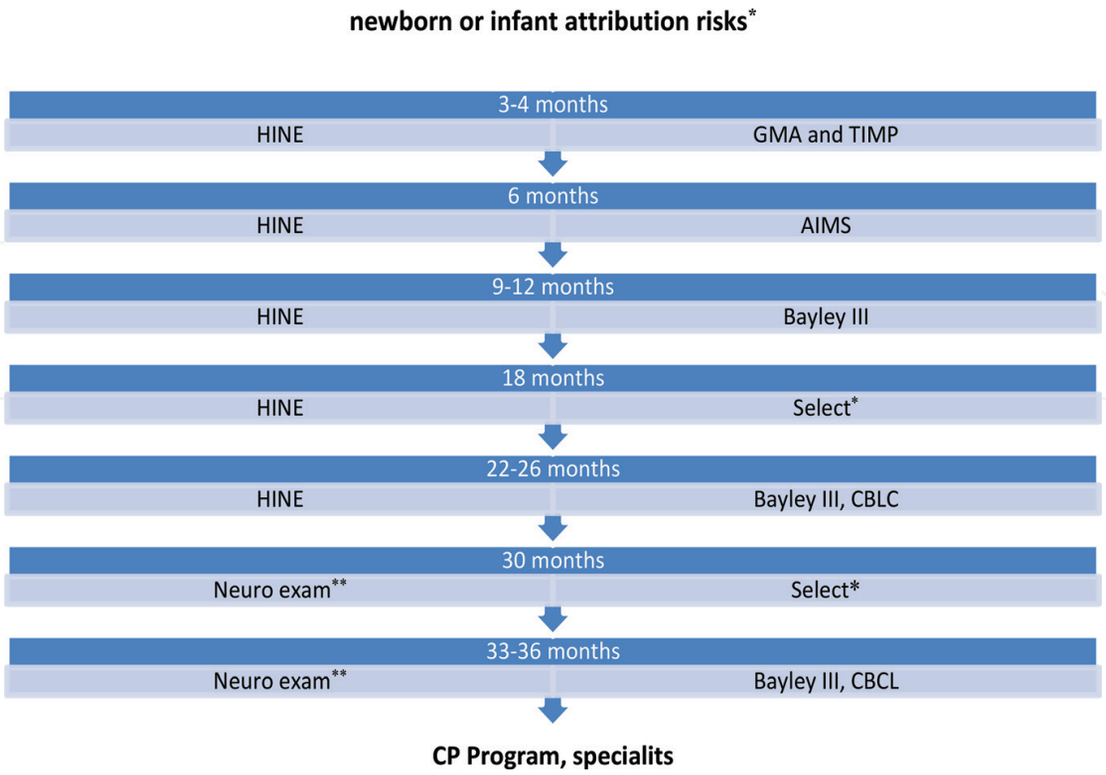

Figure 2. Translation of international guidelines into a clinical practice algorithm in a neonatal intensive care unit follow-up program. *Select examinations target developmental progression and represent the best feasible evidence for specific concern. **Neurological examination after a 2-year visit includes Amiel Tisonorother. Bayley-III, Bayley scales of infant and toddler development-third edition; CBCL, child behavior checklist; GMA, general movement assessment; HINE, Hammersmith infant neurological examination; TIMP, test of infant motor performance [69].

As shown in **Figure 2** [69], the guidelines can be translated into clinical practice by adapting core elements to suit individual clinical settings. As soon as the high-risk infants as a neonate (e.g., neuroimaging findings consistent with neonatal encephalopathy) are referred, they undergo surveillance according to the guidelines at the 3- to 4-month visits. In hospitalized extremely preterm infant with white matter injury, the surveillance occurs at the bedside according to the guidelines with a HINE, a Test of Infant Motor Performance, and a general movement assessment. Referred high-risk infant should start close to the point of the pathway, for example, a high-risk infant referred for the surveillance at 9 months due to inability to sit would start with a HINE and a Bayley Scales of Infant and Toddler Development.

7. Conclusion

This systematic review has shown that there is good evidence that GMA can accurately predict the development of CP. There is reasonable evidence to support the use of MRI at term corrected age, neurological examination in the older infant, and, to a lesser extent, ultrasound in infants of preterm age for early assessment. The great advantage of detecting an increased risk of CP at such an early stage consists of the possibility of intervention long before the emergence of obvious pathological features of CP.

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References

[1] Palchik AB, Einspieler C, Evstafeyeva IV, Talisa VB, Marschik PB. Intra-uterine exposure to maternal opiate abuse and HIV: The impact on the developing nervous system. Early Human Development. 2013;**89**(4):229-235. https://doi.org/10.1016/j.earlhumdev.2013.02.004

[2] Him pens E, van den Broeck C, Oostra A, Calders P, Vanhaesebrouck P. Prevalence, type, distribution, and severity of cerebral palsy in relation to gestational age: A meta-analytic review. Developmental Medicine and Child Neurology. 2008;**50**:334-340. DOI: 10.1111/j.1469-8749.2008.02047.x

[3] Andersen GL, Romundstad P, Cruz JD, et al. Cerebral palsy among children born moderately preterm or at a moderately low birthweight between 1980 and 1998: A European register-based study. Developmental Medicine and Child Neurology. 2011;**53**. DOI: 913-919. DOI: 10.1542/peds.2014-0945

[4] Bax M, Goldestein M, Rosenbaum P, Leviton A, Paneth N. Proposed definition and classification of cerebral palsy. Developmental Medicine and Child Neurology. 2005;**47**: 571-576. DOI: 10.1017/S001216220500112X

[5] McIntyre S, Taitz D, Keogh J, Goldsmith S, Badawi N, Blair E. A systematic review of risk factors for cerebral palsy in children born at term in developed countries. Developmental Medicine and Child Neurology. 2013;**55**:499-508. DOI: 10.1111/dmcn

[6] Himpens E, Oostra A, Franki I, Vansteelandt S, Vanhaesebrouck P, den Broeck CV. Predictability of cerebral palsy in a high-risk NICU population. Early Human Development. 2010;**86**:413-417. DOI: 10.1016/j.earlhumdev.2010.05.019

[7] Moreno-De-Luca A, Ledbetter DH, Martin CL. Genetic insights into the causes and classification of cerebral palsies. Lancet Neurology. 2012;**11**:283-292. DOI: 10.1016/S1474-4422(11)70287-3

[8] Peyton C, Yang E, Msall ME, Adde L, Støen R, Fjørtoft T, Einspieler C, Zhou Y, Schreiber MD, Marks JD, Drobyshevsky A. White matter injury and general movements in high-risk preterm infants. American Journal of Neuroradiology. 2017;**38**:162-169. DOI: https://doi.org/10.3174/ajnr.A4955

[9] de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: What is happening when? Early Human Development. 2006;**82**(4):257-266. DOI: 10.1016/j.earlhumdev.2005.10.013

[10] Einspieler C, Prechtl HFR. Prechtl's assessment of general movements: A diagnostic tool for the functional assessment of the young nervous system. Mental Retardation and Developmental Disabilities Research Reviews. 2005;**11**(1):61-67. DOI: 10.1002/mrdd.20051

[11] Darsaklis, Snider L, Majnemer A, Mazer B. Predictive validity of prechtl's method on the qualitative assessment of general movements: A systematic review of the evidence. Developmental Medicine and Child Neurology. 2011;**53**(10):896-906. DOI: 10.1111/j.1469-8749.2011.04017.x. Epub 2011 Jun 17

[12] Einspieler C, Prechtl HFR, Bos AF, Ferrari F, Cioni G. Prechtl's Method on the Qualitative Assessment of General Movements in Preterm, Term and Young Infants. 1st ed. London: Mac Keith Press; 2008. DOI: 189868362X

[13] Novak I, Morgan C, Adde L, Blackman J, Boyd RN, Brunstrom-Hernandez J, et al. Early, accurate diagnosis and early intervention in cerebral palsy: Advances in diagnosis and treatment. JAMA Pediatrics. 2017;**171**:897-907. DOI: 10.1001/jamapediatrics.2017.1689

[14] Bosanquet M, Copeland L, Ware R, Boyd R. A systematic review of tests to predict cerebral palsy in young children. Developmental Medicine and Child Neurology. 2013; **55**:418-426. DOI: 10.1111/dmcn.12140

[15] De Bock F, Will H, Behrenbeck U, Marc NJ, Hadders-Algra M, Philippi H. Predictive value of general movement assessment for preterm infants' development at 2 years − implementation in clinical routine in a non-academic setting. Research in Developmental Disabilities. March 2017;**62**:69-80 https://doi.org/10.1016/j.ridd.2017.01.012

[16] Morgan C, Crowle C, Goyen TA, Hardman C, Jackman M, Novak I, et al. Sensitivity and specificity of general movements assessment for diagnostic accuracy of detecting cerebral palsy early in an Australian context. Journal of Paediatrics and Child Health. 2016;**52**(1):54-59. PubMed: PM26289780. DOI: 10.1111/jpc.12995 Epub 2015 Aug 19

[17] Oberg GK, Jacobsen BK, Jorgensen L. Predictive value of general movement assessment for cerebral palsy in routine clinical practice. Physical Therapy. 2015 Nov;**95**(11):1489-1495. PubMed: PM26023214. DOI: 10.2522/ptj.20140429 Epub 2015 May 28

[18] Datta AN, Furrer MA, Bernhardt I, Huppi PS, Borradori-Tolsa C, Bucher HU, Latal B, Grunt S, Natalucci G. Fidgety movements in infants born very preterm: Predictive value for cerebral palsy in a clinical multicentre setting. Developmental Medicine and Child Neurology. 2017;**59**:618-624. DOI: 10.1111/dmcn.13386 Epub 2017 Jan 19

[19] Prechtl HFR, Einspieler C, Cioni G, Bos AF, Ferrari F, Sontheimer D. An early marker for neurological deficits after perinatal brain lesions. Lancet. 1997;**349**:1361-1363. DOI: 10.1016/S0140-6736(96)10182-3

[20] Cioni G, Ferrari F, Einspieler C, Paolicellli PB, Brbani MT, Prechtl HFR. Comparison between observation of spontaneous movements and neurological examination in preterm infants. The Journal of Pediatrics. 1997;**130**:704-711. DOI: 10.1016/S0022-3476(97)80010-8

[21] Spittle AJ, Boyd RN, Inder TE, Doyle LW. Predicting motor development in very preterm infants at 12 months corrected age: The role of qualitative magnetic resonance imaging and general movement assessment. Pediatrics. 2009;**123**:512-517. DOI: 10.1542/peds.2008-0590

[22] Okado N. Development of the human cervical spinal cord with reference to synapse formation in the motor nucleus. The Journal of Comparative Neurology. 1980;**191**:495-513. DOI: 10.1002/cne.901910311

[23] Altman J, Bayer SA. Development of the Human Spinal Cord: An Interpretation Based on Experimental Studies in Animals. New York: Oxford University Press; 2001. ISBN-13: 978-0195144277

[24] Clowry GJ, Moss JA, Clough RL. An immunohistochemical study of the development of sensorimotor components of the early fetal human spinal cord. Journal of Anatomy. 2005;**207**:313-324. DOI: 10.1111/j.1469-7580.2005.00468.x

[25] Hadders-Algra M. Putative neural substrate of normal and abnormal general movements. Neuroscience and Biobehavioral Reviews. 2007;**31**:1181-1190. DOI: 10.1016/j.neubiorev.2007.04.009

[26] Einspieler C, Marschik PB, Prechtl HFR. Human motor behavior- prenatal origin and early postnatal development. Zeitschrift für Psychologie. 2008;**216**:147-153. DOI: 10.1027/0044-3409.216.3.147

[27] Prechtl HFR. Qualitative changes of spontaneous movements in fetus and preterm infants are a marker of neurological dysfunction. Early Human Development. 1990;**23**:151-158. DOI: 10.1016/0378-3782(90)90013-9

[28] Lüchinger AB, Hadders-Algra M, Van Kan CM, DeVries JIP. Fetal onset of general movements. Pediatric Research. 2008;**63**:191-195. DOI: 10.1203/PDR.0b013e31815ed03e

[29] Hopkins B, Prechtl HFR. Continuity of Neural Functions from Prenatal to Postnatal Life. Vol. 12. Spastics International Medical Pub; 1984. pp. 179-197

[30] Einspieler C, Peharz R, Mraschik PB. Fidgety movements- tiny in appearance, but huge in impact. The Journal of Pediatrics (Rio J). 2016;**92**(3 supp 1):64-70. DOI: 10.1016/j.jped.2015.12.003 Epub 2016 Mar 17

[31] Dibiasi J, Einspieler C. Spontaneous movements are not modulated by visual and acoustic stimulation in three months old infants. Early Human Development. 2002;**68**:27-37. DOI: 10.1016/S0378-3782(02)00010-5

[32] Einspieler C, Yang H, Bartl-Pokorny KD, Chi X, Zang FF, Marschik PB, et al. Are sporadic fidgety movements as clinically relevant as is their absence. Early Human Development. 2015;**91**:247-252. DOI: 10.1016/j.earlhumdev.2015.02.003

[33] Prechtl HF, Hopkins B. Developmental transformations of spontaneous movements in early infancy. Early Human Development. 1986;**14**:233-238. DOI: 10.1016/0378-3782(86)90184-2

[34] Groen SE, de Blécourt AC, Postema K, Hadders-Algra M. General movements in early infancy predict neuromotor development at 9 to 12 years of age. Developmental Medicine and Child Neurology. 2005;**47**:731-738. DOI: 10.1111/j.1469-8749.2005.tb01069.x

[35] Einspieler C, Marschik PB, Milioti S, Nakajima Y, Bos AF, Prechtl HF. Are abnormal fidgety movements an early marker for complex minor neurological dysfunction at puberty. Early Human Development. 2007;**83**:521-525. DOI: 10.1016/j.earlhumdev.2006.10.001

[36] Nieuwenhuis T, da Costa SP, Bilderbeek E, Geven WB, van der Schans CP, Bos AF. Uncoordinated sucking patterns in preterm infants are associated with abnormal general movements The Journal of Pediatrics 2012;**161**: 792-798. DOI: 10.1016/j.jpeds.2012.04.032. Epub 2012 May 26

[37] Herreroa D, Einspielerb C, Aizawac CYP, Mutlud A, Yange H, Nogolováf A, Pansyg J, Nielsen-Sainesh K, Marschik PB. The motor repertoire in 3- to 5-month old infants with down syndrome. Research in Developmental Disabilities. 2017;**67**:1-8. DOI: 10.1016/j.ridd.2017.05.006

[38] Yuge M, Marschik PB, Nakajima Y, Yamori Y, Kanda T, Hirota H, et al. Movements and postures of infants aged 3 to 5 months: To what extent is their optimality related to perinatal events and to the neurological outcome? Early Human Development. 2011;**87**:231-237. DOI: 10.1016/j.earlhumdev.2010.12.046

[39] Adde L, Rygg M, Lossius K, Oberg GK, Støen R. General movement assessment: Predicting cerebral palsy in clinical practice. Early Human Development. 2007;**83**:13-18. DOI: 10.1016/jearlhumdev.2006.03.005

[40] Brogna C, Romeo DM, Cervesi C, Scrofani L, Romeo MG, Mercuri E, et al. Prognostic value of the qualitative assessments of general movements in late-preterm infants. Early Human Development. 2013;**89**:1063-1066. DOI: 10.1016/j.earlhumdev.2013.08.008

[41] Zappella M, Einspieler C, BartlPokorny KD, Krieber M, Coleman M, Bölte S, et al. What do home videos tell us about early motor and socio-communicative behaviours in children with autistic features during the second year of life – An exploratory study. Early Human Development. 2015;**91**:569-575. DOI: 10.1016/j.earlhumdev.2015.07.006

[42] Einspieler C, Marschik PB, Bos AF, Ferrari F, Cioni G, Prechtl HF. Early markers for cerebral palsy: Insights from the assessment of general movements. Future Neurology. 2012;**7**:709-717. DOI: 10.2217/fnl.12.60

[43] Einspieler C, Cioni G, Paolicelli PB, Bos AF, Dressler A, Ferrari F, et al. The early markers for later dyskinetic cerebral palsy are different from those for spastic cerebral palsy. Neuropediatrics. 2002;**33**:73-78. DOI: 10.1055/s-2002-32368

[44] Cioni G, Bos AF, Einspieler C, Ferrari F, Martijn A, Paolicelli PB, et al. Early neurological signs in preterm infants with unilateral intraparenchymal echodensity. Neuropediatrics. 2000;**31**:240-251. DOI: 10.1055/s-2000-9233

[45] Einspieler C. Early markers for unilateral spastic cerebral palsy in premature infants. Nature Clinical Practice. Neurology. 2008;**4**:186-187. DOI: 10.1038/ncpneuro0831

[46] Adde L, Helbostad JL, Jensenius AR, Taraldsen G, Støen R. Using computer-based video analysis in the study of fidgety movements. Early Human Development. 2009;**85**(9): 541-547. DOI: 10.1016/j.earlhumdev.2009.05.003

[47] Philippi H, Karch D, Kang KS, Wochner K, Pietz J, Dickhaus H, et al. Computer-based analysis of general movements reveals stereotypies predicting cerebral palsy. Developmental Medicine and Child Neurology. 2014;**56**:960-967. DOI: 10.1111/dmcn.12528

[48] Valle SC, Støen R, Sæther R, Jensenius AR, Adde L. Test–retest reliability of computer-based video analysis of general movements in healthy term-born infants. Early Human Development. 2015;**91**(10):555-558. DOI: 10.1016/j.earlhumdev.2015.07.001

[49] Romeo DM, Guzzetta A, Scoto M, et al. Early neurological assessment in preterm infants: Integration of traditional neurological examination and observation of general movements. European Journal of Paediatric Neurology. 2008;**12**:183-189. DOI: 10.1016/j.ejpn.2007.07.008

[50] Haataja L, Mercuri E, Regev R, Cowan F, Rutherford M, Dubowitz V, et al. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. The Journal of Pediatrics. 1999;**135**:153-161. DOI: 10.1016/S0022-3476(99)70016-8

[51] Touwen B. Neurological development in infancy. [S.L.]: [S.N.]. In: Clinics in Developmental Medicine. Vol. 58. London: SIMP; 1976

[52] Amiel-Tison C. Update of the Amiel-Tison neurologic assessment for the term neonate or at 40 weeks corrected age. Pediatric Neurology. 2002;**27**:196-212. DOI: 10.1016/S0887-8994(02)00436-8

[53] Bayley N. Bayley Scale of Infant and Toddler Development. San Antonio, TX: The Psychological Corporation; 2006. DOI: 10.1177/073428906297199

[54] Dubowitz L, Ricciw D, Mercuri E. The Dubowitz neurological examination of the full-term newborn. Mental Retardation and Developmental Disabilities Research Reviews. 2005;**11**:52-60. DOI: 10.1002/mrdd.20048

[55] Maitre NL, Chorna O, Romeo DM, Guzzetta A. Implementation of the Hammersmith infant neurological exam in a high-risk infant follow-up program. Pediatric Neurology. 2016;**65**:31-38. DOI: 10.1016/j.pediatrneurol.2016.09.010

[56] Palmer F. Strategies for the early diagnosis of cerebral palsy. The Journal of Pediatrics. 2004;**145**(Suppl. 2):S8-S11. DOI: 10.1016/j.jpeds.2004.05.016

[57] De Vries LS, Van Haastert I-LC, Rademaker KJ, Koop man C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. The Journal of Pediatrics. 2004;**144**:815-820. DOI: 10.1016/j.jpeds.2004.03.034

[58] Margot B, Lisa C, Robert W, Roslyn B. A systematic review tests to predict cerebral palsy in young children. Developmental Medicine and Child Neurology. 2013;**55**:418-426. DOI: 10.1111/dmcn.12140

[59] Wood NS, Costeloe K, Gibson AT, Hennessy EM, Marlow N, Wilkinson AR, et al. EPICure study: Associations and antecedents of neurological and developmental disability at 30 months of age following extremely preterm birth. Archives of Disease in Childhood. Fetal and Neonatal Edition. 2005;**90**:F134-F140. DOI: 10.1136/adc.2004.052407

[60] Mirmiran M, Barnes PD, Keller K, et al. Neonatal brain magnetic resonance imaging before discharge is better than serial cranial ultrasound in predicting cerebral palsy in very low birth weight preterm infants. Pediatrics. 2004;**114**:992-998. DOI: 10.1542/peds.2003-0772-L

[61] Faria AV, Hoon A, Stashinko E, Li X, Jiang H, Mashayekh A, et al. Quantitative analysis of brain pathology based on MRI and brain atlases - applications for cerebral palsy. NeuroImage. 2011;**54**(3):1854-1861. DOI: 10.1016/j.neuroimage.2010.09.061

[62] Childs A, Cornette L, Ramenghi A, Tanner S, Arthure R, Martinez D, et al. Magnetic resonance and cranial ultrasound characteristics of periventricular white matter abnormalities in newborn infants. Clinical Radiology Journal. 2001;**56**:647-655. DOI: 10.1053/crad.2001.0754

[63] Robinson M, Peake L, Ditchfield M, Reid S, Lanigan A, Reddihough B. Magnetic resonance imaging findings in a population-based cohort of children with cerebral palsy. Developmental Medicine & Child Neurology. 2009;**51**(11):39-46. DOI: 10.1111/j.1469-8749.2008.03127.x

[64] Kwong K, Wong Y, Fong C, Wong S, Wong S, So K. Magnetic resonance imaging in 122 children with spastic cerebral palsy. Pediatric Neurology Journal. 2004;**31**(3):172-175. DOI: 10.1016/j.pediatrneurol.2004.02.005

[65] Bjorgaas H, Elgen I, Boe T, Hysing M. Mental health in children with cerebral palsy: Does screening capture the complexity? Hindawi Publishing Corporation. The Scientific World Journal. 2013;**4**:1-8. DOI: 10.1155/2013/468402

[66] Spittle AJ, Brown NC, Doyle LW, Boyd RN, Hunt RW, Bear M, et al. Quality of general movements is related to white matter pathology in very preterm infants. Pediatrics. 2008;**121**:e1184-e1189. DOI: 10.1542/peds.2007-1924

[67] Krageloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: A systematic review. Developmental Medicine & Child Neurology. 2007;**49**(2):144-145. DOI: 10.1111/j.1469-8749.2007.00144.x

[68] Glenn O, Barkovich A. Magnetic resonance imaging of the Fetal brain and spine: An increasingly important tool in prenatal diagnosis, part 1. American Journal of Neuroradiology. 2006;**27**(8):1604-1611. DOI: 10.1007/s00247-009-1459-3

[69] Byrne R, Noritz G, Maitre NL. Implementation of early diagnosis and intervention guidelines for cerebral palsy in a high-risk infant follow-up clinic. Pediatric Neurology. 2017;**76**:66-71. DOI: 10.1016/j.pediatrneurol.2017.08.002