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Original Article

Early Identification of Cerebral Palsy Using Neonatal MRI and General Movements Assessment in a Cohort of High-Risk Term Neonates

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ABSTRACT

Background: Cerebral palsy (CP) is the most common motor disability of childhood. Its early identification is an important priority for parents and is critical for access to early intervention resources, which may optimize function.
Methods: A prospective cohort of term neonates at high risk for CP was assessed by neonatal magnetic resonance imaging (MRI) to determine myelination of the posterior limb of the internal capsule, General Movements Assessment to assess typical fidgety movements at age three months, and followed to at least age two years to determine diagnosis of CP based on neurological examination.
Results: Seven of 58 children developed CP (12%), two with moderate/severe CP. Sensitivity and specificity for abnormal myelination of the posterior limb of the internal capsule were (PLIC) was 29% and 94%, and for absent fidgety movements, 29% and 98%, respectively. Negative predictive value of both absent myelination of the PLIC and absent fidgety movements was 90% (79% to 96%) for any CP and 98% (90% to 100%) for moderate/severe CP cerebral palsy. None of the children with both normal PLIC and normal fidgety movements had moderate/severe CP.
Conclusion: Normal neonatal MRI and General Movements Assessment at age three months are reassuring that a high-risk term-born child is at low risk for moderate/severe CP. These results are important for counseling parents and individualizing therapy resources in the community.

Introduction

Cerebral palsy (CP) is the most common motor disability of childhood. It is widely understood to result from disruption to the developing brain in the antenatal or neonatal period.[1] CP can often be identified in early infancy; however, the diagnosis is usually not made until late in the second year of life.[2] There has been a long-standing call for, and more recent focus on, earlier diagnosis of CP,[3-5] especially in light of evidence that early intervention can positively impact neurodevelopment and functional attainment based on optimizing neuroplasticity of the developing brain as soon as possible after birth.[3,6,7] In addition, parents of high-risk children uniformly state that early diagnosis of CP is a top priority.[8] At the same time, parents may continue to worry throughout childhood that their child will develop CP. This anxiety has the potential to alter the developmental environment for the infant and family. Earlier parental guidance regarding the likelihood of a CP diagnosis may benefit family coping and mental health, encourage

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compliance with early intervention, and increase availability of and eligibility for support services.

Delays in CP diagnosis occur despite the fact that early injury to the central nervous system (the defining factor of CP) can often be detected within the first months of life. Two important tools that have been used to evaluate risk for CP in high-risk infants are neonatal magnetic resonance imaging (MRI) and the General Movements Assessment (GMA). Injury to the corticospinal tract can be identified on MRI as abnormal myelination of the posterior limb of the internal capsule (PLIC). This finding was first associated with neurodevelopmental impairment by Rutherford[9,10] and is a useful marker as early as the second or third day after birth, making it an important early tool for assessing the risk of CP.[11,12] General movements are spontaneous, complex movements that are present from early fetal life until age six months and are altered in the face of disabling brain injury.[13] The GMA is a standardized, noninvasive method of observation of these inherent developing movements to evaluate for typical maturation of the nervous system.[14] Multiple prior studies have shown high sensitivity and specificity of the GMA, in particular, the absence of a typical pattern of movements termed "fidgety" movements at age three months (corrected for preterm birth) to predict which low birth weight or preterm children are at the highest risk for developing CP.[15,16] Fidgety movements are spontaneous small movements of the neck, trunk, and limbs that are constant in an awake and calm infant.[14] Based on the strength of evidence in preterm neonates, health networks have successfully implemented widespread use of GMA.[17,18] However, relatively few studies have specifically examined term neonates whose patterns of injury and disability from CP are different than those of preterm-born infants.[19-22] Furthermore, whereas MRI and the GMA have been used individually to assess risk of CP, little is known about the role of MRI to improve the diagnostic accuracy of GMA and inform pattern and severity of disability, especially in term-born high-risk infants.

We evaluated a cohort of high-risk term infants with neonatal encephalopathy to determine the sensitivity and specificity of neonatal MRI and GMA at age three months to predict CP and to evaluate whether adding MRI assessment to GMA is better than GMA alone. We hypothesized that adding abnormal myelination of the PLIC to the observation of abnormal or absent fidgety movements would improve the ability to predict CP.

Methods

Study design

This was an observational prospective cohort of term neonates at high risk for CP due to encephalopathy from an acute cause (e.g., hypoxic-ischemic encephalopathy, stroke, intracranial hemorrhage) diagnosed at UCSF Benioff Children's Hospitals San Francisco and Oakland and born between February 2015 and October 2017. Children were screened and identified by the study team based on their clinical diagnoses and enrolled through informed and written parent consent. The institutional review board approved the study protocol.

Inclusion and exclusion criteria

Enrollment criteria were (1) born ≥36 weeks' gestation, (2) neonatal encephalopathy due to an acute cause identified at ≤44 weeks postmenstrual age (neonatal encephalopathy with or without therapeutic hypothermia, seizure confirmed by electroencephalography, or brain injury identified on MRI), and (3) imaged with MRI with diffusion-weighted imaging at age less than two weeks. Children were excluded if they were diagnosed with a congenital brain malformation, inborn error of metabolism, or syndromic disorder (with or without genetic confirmation).

Measurements

Clinical data

Neonatal demographic and clinical data were determined by chart review. Neurological diagnosis was determined by a neonatal neurologist based on medical record and neonatal imaging review (H.C.G., M.G.).

MRI

MRI was performed on a General Electric MR 750 3T (65 infants) or a Philips Intera 1.5T (nine infants) at a median of four days (interquartile range [IQR] 4, 5) after birth. MRI myelination in the PLIC was scored as "normal," "abnormal" (absent or abnormal myelination on either the left or the right), or "cannot assess" using T1 images by a board-certified pediatric neuroradiologist who was unaware of the results of the GMA and CP evaluation (A.J.B./Y.L.). Exploratory MRI variables included pattern of injury (categorized as one of focal, multifocal, global, no injury, cannot assess, or other) and location of injury (to the cortex, white matter, deep gray nuclei, cerebellum, and other).

General Movements Assessment

Videos were acquired at a median of 15.4 weeks' (IQR 14.3, 17.3) corrected gestational age while the child was awake and calm. A study coordinator or the child's parents recorded for at least five minutes, with the child in a supine position, filmed from above, ensuring that the entire body was within the frame, and the child was dressed in lightweight clothing with hands and feet visible. Parents were instructed not to look at, talk to, or touch the baby; pacifiers, toys, and other distracting items were removed from the child for the duration of the recording. Videos were scored for the presence or absence of fidgety movements by an experienced investigator (I.N.) who was unaware of the clinical history and results of the MRI and CP evaluation. Fidgety movements were scored as "normal," "absent," "abnormal," or "cannot assess."

Outcome assessment

CP, defined as abnormalities in tone, posture, and reflexes leading to functional impairment, was evaluated at a median of 31 months (IQR 27, 35) in person by a pediatric neurologist or pediatrician, or by review of pediatric medical records. In all cases, the physician was unaware of the results of the MRI PLIC assessment and GMA. Motor function was assessed using the Gross Motor Function Classification System (GMFCS) as follows: GMFCS I: walks 10 steps independently with gait abnormalities (e.g., wide-based gait, frequent falling, tiptoe walking), GMFCS II: does not walk independently but crawls, pulls to stand, and cruises, GMFCS III: does not crawl, pull to stand, and cruise but can sit independently, GMFCS IV: cannot sit independently but has head control, and GMFCS V: cannot control head.[23] GMFCS has previously been used to simplify gross motor function assessment in large trials to objectively operationalize outcomes.[24,25] Children with GMFCS ≥II were considered to have moderate/severe CP.

Analysis

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and relative risk (with 95% confidence intervals) were assessed using Stata 14 (College Station, TX).

Results

Seventy-four infants were assessed at the UCSF Benioff Children's Hospital, San Francisco (62 infants), and at the UCSF Benioff Children's Hospital, Oakland (12 infants). Sixteen children were excluded from the final analysis for the following reasons: 12 infants did not have complete assessment (MRI low quality, two infants; GMA video not obtained, nine infants; GMA video low quality, one infant), one infant was diagnosed with a genetic epilepsy at follow-up (familial KCNQ2 epilepsy), and three infants did not have a follow-up neurological evaluation. Clinical characteristics of the 58 infants with complete evaluation are presented in Table 1.

Seven children (12%) were diagnosed with CP: five with GMFCS I, one with GMFCS III, and one with GMFCS V. Clinical characteristics of the children with CP are presented in Table 2.

MRI

Timing of MRI was at a median of four days after birth (IQR 4, 5). Imaging characteristics of children with and without CP are presented in Table 3.

Five infants had abnormal myelination of the PLIC, two of whom (two of five, 40%) were diagnosed with CP at follow-up, when compared with five of 53 children with normal myelination of the PLIC (9%). Both children with moderate/severe CP had abnormal PLIC. Sensitivity, specificity, PPV, and NPV are presented in Table 4. The relative risk of CP among children with abnormal myelination of the PLIC was 4.2 (95% confidence interval [CI] 1.1 to 16.5, $P = 0.04$).

Among the exploratory MRI variables, global pattern of injury (relative risk [RR] 3.5, 95% CI 0.9 to 14.1, $P = 0.09$ for any CP and RR 8.9, 95% CI 0.6 to 121.4, $P = 0.06$ for moderate/severe CP) and injury to the cerebellum (RR 9.5, 95% CI 4.5 to 20.2, $P = 0.007$ for any CP and RR 57, 95% CI 8.2 to 397.7 for moderate/severe CP, $P < 0.0005$) were associated with CP.

General Movements Assessment

Three infants had absent fidgety movements, two of whom (two of three, 67%) were diagnosed with CP (both with moderate/severe CP) at follow-up, when compared with five of 55 children with normal fidgety movements (9%). Sensitivity, specificity, PPV, and NPV are presented in Table 4. The relative risk of CP among children with absent fidgety movements was 7.3 (95% CI 2.3 to 23.3, $P = 0.003$) and 18.3 (95% CI 1.5 to 227.1, $P = 004$) for moderate/severe CP.

TABLE 1.
Clinical Characteristics of 58 Children at Risk for Cerebral Palsy due to Neonatal Encephalopathy

Clinical Characteristic	Total N = 58
Male	27 (47%)
Gestational age at birth (weeks)	39.55 (±1.58)
Birth weight (g)	3428 (±594)
1-minute Apgar score	2 (1, 4)
5-minute Apgar score	4 (2, 6)
Primary neurological diagnosis	
Hypoxic-ischemic encephalopathy	42 (71%)
Ischemic stroke	8 (14%)
Intracranial hemorrhage	4 (8%)
Other	4 (7%)
Received therapeutic hypothermia	40 (68%)

Abbreviation:
IQR = Interquartile range
Data are presented as n (%), mean (S.D.), or median (IQR).

Combined MRI and GMA

One child had *both* abnormal myelination of the PLIC and absent fidgety movements, and that child was diagnosed with moderate/severe CP at follow-up (100%), when compared with six of 57 children without both risk factors (10%). Sensitivity, specificity, PPV, and NPV are presented in Table 4. The relative risk of CP among children with both abnormal myelination of the PLIC and absent fidgety movements was 9.5 (95% CI 4.5 to 20.3, $P = 0.007$) and 57 (95% CI 8.2 to 397.7, $P < 0.0005$) for moderate/severe CP. NPV of both absent myelination of the PLIC and absent fidgety movements was 90% (79% to 96%) and 98% (95% CI 90% to 100%) for moderate/severe CP. There was minimal improvement in the area under the curve after adding abnormal myelination of the PLIC plus absent fidgety movements for predicting moderate/severe CP (0.75, 95% CI 0.26 to 1.0) when compared with absent fidgety movements alone (0.73, 95% CI 0.24 to 1.0), and the difference was not significant ($P = 0.15$).

Discussion

In this cohort of term infants at risk for CP due to a diagnosis of neonatal encephalopathy, abnormal myelination of the PLIC on neonatal MRI and absent fidgety movements on the GMA provided similar low sensitivity (29%) and high specificity (94% to 98%) for CP. Combining both imaging and assessment of general movements yielded high NPV for CP when both assessments were normal. Furthermore, none of the children with normal PLIC and GMA had a diagnosis of CP with moderate or severe functional impairment. Based on these results, when used together, neonatal MRI assessment of myelination of the PLIC and GMA at age three months can be used to assess the risk of CP in high-risk term neonates.

These findings have important clinical relevance, because having a child with CP increases psychosocial distress and decreases the quality of life in the family.[26,27] Early communication of risk for and diagnosis of CP has been identified as a priority by parents.[8] Accurate and clearly communicated risk information has the potential to mitigate familial stress, as well as increase access to financial and other resources to meet functional needs such as early intervention, transportation, and equipment that may improve quality of life. Access to comprehensive early intervention services in many regions is also dependent on having a diagnosis to secure eligibility, thus providing a clear incentive to utilize all available tools to diagnose CP as early as possible. At the same time, normal early markers like normal MRI and GMA can help ensure that comprehensive services are distributed in a precise nature to the children and families who are at the highest risk and will benefit most from early intervention.

Our findings align with previous studies that have also suggested lower sensitivity of the GMA in term-born children when compared with preterm-born children.[16,19] The reported sensitivity of abnormal fidgety movements for CP is very high (97%)[16]; however, this is based largely on studies of *preterm* infants. The sensitivity is much lower in studies that examine the predictive ability of GMA for CP in *term* infants.[19] It is not certain whether the difference in sensitivity for preterm and term infants is related to the prevalence of CP in the at-risk population, due to differences in expression of general movements among preterm versus term-born children, or due to differences in outcome among children with abnormal GMA. Prior studies also have shown that the predictive value of the GMA for CP in the general population is much lower than in high-risk populations, which helps to support the

TABLE 2.
Clinical Characteristics, Imaging, and GMA Results for Seven Children With Cerebral Palsy

Sex	Gestational Age at Birth (Weeks)	Birth Weight (g)	Apgars at 1 and 5 Minutes	Hypothermia	Neurological Diagnoses	DOL MRI	MRI Pattern	MRI PLIC	Fidgety Movements	Age at GMFCS Evaluation (Months)	Cerebral Palsy
F	39 1/7	4720	2/4	Yes	HIE	6	No injury	Normal	Normal	28	Spastic diplegia, GMFCS I
M	42	4060	5/6	No	Intracranial hemorrhage	8	Multifocal injury	Abnormal	Normal	38	Spastic quadriplegia, GMFCS III
F	36 5/7	4700	0/0	Yes	HIE	6	Multifocal injury	Normal	Normal	31	Spastic hemiplegia, GMFCS I
F	36	2660	1/2	No	HIE	4	Multifocal injury	Normal	Normal	34	Spastic hemiplegia, GMFCS I
F	40 6/7	2680	1/3	No	Arterial ischemic stroke	5	Multifocal injury	Normal	Normal	36	Spastic diplegia, GMFCS I
F	38 6/7	3075	1/2	Yes	HIE	4	Global injury	Normal	Absent	26	Spastic diplegia, GMFCS I
F	40 1/7	3340	4/6	No	HIE	2	Global injury	Abnormal	Absent	28	Spastic quadriplegia, GMFCS V

Abbreviations:
DOL = Day of life
GMA = General Movements Assessment
GMFCS = Gross Motor Function Classification System
HIE = Hypoxic-ischemic encephalopathy
MRI = Magnetic resonance imaging
PLIC = Posterior limb of the internal capsule

importance of prevalence.[28] Also, one large study in a population of low- to medium-risk term-born children found that although the GMA is associated with CP, it may also predict milder forms of neurodevelopmental impairment among those study infants who did not develop CP.[22]

There were four children in our cohort with both normal MRI and normal fidgety movements on GMA who received a diagnosis of CP (Table 2). Importantly, these children had GMFCS I, indicating ambulation with gait abnormalities assessed in early childhood, and are known to be harder to detect early. Older children with GMFCS I are highly functional: they can walk independently in all settings (home, school, and in the community), climb stairs without the use of a handrail, as well as perform gross motor skills such as running and jumping. However, speed, balance, and coordination may be limited in children and adults with CP functioning in GMFCS I.[23] Longer-term follow-up will be needed to assess the function of these children with early, mild, gait impairment.

Although we present a cohort of term neonates assessed with gold-standard neonatal MRI and GMA scored by a qualified assessor at age three months, our data are not without limitations. First, the number of children diagnosed with CP in this cohort was low (seven of 58, 12%, and only two with moderate/severe CP), which limited the power of our results. Second, in-person evaluation could not be standardized and performed by a single examiner for the purpose of this study; however, in all cases the neurological examination was performed by a blinded physician with experience in diagnosis of CP. Third, GMFCS is a simplified assessment designed to estimate motor function in children with CP. Children with GMFCS I at 24 to 36 months may have minor motor impairment that continues to improve and is not disabling, or ultimately not diagnosed as CP. Conversely, mild CP may not be diagnosed by 24 to 36 months, and subtler, non-CP motor impairments may also become evident after this time. Longitudinal assessment will be needed to determine whether more children develop CP or non-CP

TABLE 3.
MRI Findings in 58 Children With and Without Cerebral Palsy Following Neonatal Encephalopathy

MRI Feature	Total N = 58	Cerebral Palsy N = 7	No Cerebral Palsy N = 51	*P* Value
MRI age (days)	4 (4, 5)	5 (4, 6)	4 (4, 5)	0.3
Normal MRI	20 (34%)	2 (28%)	18 (35%)	0.7
MRI pattern of injury				0.3
No injury	20 (34%)	2 (28%)	18 (35%)	
Focal	9 (15%)	0	9 (18%)	
Multifocal	20 (34%)	3 (43%)	17 (33%)	
Global	6 (10%)	2 (29%)	4 (8%)	
Other	3 (5%)	0	3 (6%)	
MRI location of injury				
Cortex	25 (43%)	4 (57%)	21 (41%)	0.4
White matter	29 (50%)	5 (71%)	24 (47%)	0.2
Deep gray	6 (10%)	2 (29%)	4 (8%)	0.09
Cerebellum	1 (2%)	1 (14%)	0	0.006
PLIC myelination abnormal	5 (9%)	2 (29%)	3 (6%)	0.045

Abbreviations:
MRI = Magnetic resonance imaging
PLIC = Posterior limb of the internal capsule
Data are presented as n (%).

TABLE 4.
Sensitivity, Specificity, PPV, and NPV for PLIC Myelination and GMA for Predicting Cerebral Palsy (GMFCS ≥ I) and Moderate/Severe Cerebral Palsy (GMFCS ≥ II)

Factor	Cerebral Palsy N = 7	No Cerebral Palsy N = 51	Sensitivity	Specificity	PPV	NPV
PLIC myelination						
Normal	5 (71%)	48 (94%)	29% (4%-71%)	94% (84%-99%)	40 (5%-85%)	91% (79%-96%)
Abnormal	2 (29%)	3 (6%)				
Fidgety movements						
Normal	5 (71%)	50 (98%)	29% (4%-71%)	98% (90%-100%)	67% (9%-99%)	91% (80%-97%)
Abnormal	2 (29%)	1 (2%)				
PLIC myelination or Fidgety movements						
Either one normal	6 (86%)	51 (100%)	14% (0–58%)	100% (93%–100%)	100% (3%–100%)	90% (79%–96%)
Both abnormal	1 (14%)	0				
PLIC myelination and fidgety movements						
Both normal	4 (57%)	47 (92%)	43% (10-82%)	92% (81-98%)	43% (10-82%)	92% (81-98%)
Either one abnormal	3 (43%)	4 (8%)				
	Moderate/ Severe Cerebral Palsy N = 2	No Moderate/ Severe Cerebral Palsy N = 56	Sensitivity	Specificity	PPV	NPV
PLIC myelination						
Normal	0	53 (94%)	100% (16%-100%)	95% (84%-98%)	40% (5%-85%)	100% (93%-100%)
Abnormal	2 (100%)	3 (5%)				
Fidgety movements						
Normal	1 (50%)	54 (96%)	50% (1%-99%)	96% (89%-100%)	33% (1%-91%)	98% (90%-100%)
Abnormal	1 (50%)	2 (4%)				
PLIC myelination or fidgety movements						
Either one normal	1 (50%)	56 (100%)	50% (1%-99%)	100% (94%-100%)	100% (3%-100%)	98% (90%-100%)
Both abnormal	1 (50%)	0				
PLIC myelination and fidgety movements						
Both normal	0	51 (91%)	100% (16%-100%)	1% (80%-97%)	29% (4%-71%)	100% (93%-100%)
Either one abnormal	2 (100%)	5 (9%)				

Abbreviations:
GMA = General Movements Assessment
GMFCS = Gross Motor Function Classification System
HIE = Hypoxic-ischemic encephalopathy
MRI = Magnetic resonance imaging
NPV = Negative predictive value
PLIC = Posterior limb of the internal capsule
PPV = Positive predictive value

motor impairments. Fourth, it is important to note that PLIC myelination should be assessed after the second day after birth and optimally on or after day four, as early scans may miss abnormal myelination of the PLIC.[10] In addition, the corticospinal tract, including the PLIC, is not the only source of brain injury giving rise to CP; other motor areas such as basal ganglia and genetic predisposition are also important.[29] Fifth, more recent work published since we initiated this study shows that a combination of three tools (MRI plus GMA plus the Hammersmith Infant Neurological Examination) has even greater accuracy for early detection of CP.[30] Finally, we were unable to measure the impact of early intervention services such as physical and occupational therapy. Training-based interventions take advantage of and induce neuroplasticity to improve outcomes.[31] In spite of these limitations, our results are important for detecting functionally impairing CP, which is most amenable to early intervention and presents before the second birthday.

Conclusion

Normal PLIC on neonatal MRI and normal assessment on the GMA at age three months are reassuring that a child is at low risk for moderate/severe CP. These results are important for counseling parents and individualizing therapy resources in the community, both to promote neuroplasticity and improve functional outcomes in the infant as well as for the family's well-being. For children living in areas where there is limited access to specialists, or where specialists have limited experience with CP, evaluation of the PLIC and GMA may provide an important layer of added support. Larger, multicenter studies are needed to investigate early biomarkers of neurodevelopmental impairments, not only motor impairment and CP but also sensory, communication, and manual impairments. Evidence supports the benefits of an enriched environment for all high-risk infants,[32-35] and therefore clinicians should continue to encourage parents to provide exposure to developmentally appropriate activities to optimize outcomes for all infants.

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