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ORIGINAL ARTICLE

Movement, imaging and neurobehavioral assessment as predictors of cerebral palsy in preterm infants

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Objective: To study the relative efficacy of three early predictors of cerebral palsy.

Method: One Hundred and thirty infants with birth weight <1500 g were recruited. Video recordings of spontaneous general movements were made at 36 and 52 weeks postconceptional age. Magnetic resonance imaging and the neurobehavioral assessment of the preterm infant were done at 36 weeks postconceptional age. Follow-up neurological examination and Bayley assessments were made at 18 months corrected age to make early identification of cerebral palsy.

Results: Magnetic resonance imaging gave the best specificity and accuracy of 91 and 84% respectively. General movements at 52 weeks showed an improved specificity and accuracy over performance at 36 weeks postconceptional age. The negative predictive value for all methods tested was between 90 and 97%. Combining the results of magnetic resonance imaging and the neurobehavioral assessment improved the sensitivity of prediction to 80%, suggesting that a holistic approach to early detection of cerebral lesions is preferable to a single test.

Conclusions: The majority of infants who appeared to behave within normal limits and exhibit normal brain structure in the newborn period were classified as neurologically intact at follow-up.
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Introduction

Approximately 17% of extremely low birth weight (ELBW) preterm infants have cerebral palsy (CP),[1] a condition that frequently goes undiagnosed until the second year of life, thus delaying the possibility of early intervention. The success of rescuing ELBW is improving, but the rate of CP infants remains stable, so that the absolute numbers of CP infants is increasing. A literature review suggests that there is evidence that early detection and early intervention can help to ameliorate handicaps resulting from cerebral injury,[2] and indeed there is a US Federal Mandate to support early intervention for preterm infants shown to be at high risk (Public Law 99.457), so early accurate testing to identify at-risk infants is an important first step to establishing eligibility for services.

At a time of ever increasing demands on the limited health-care resources, a diagnostic method that is non invasive, ubiquitously available and relatively inexpensive to administer has many advantages. The analysis of video recordings of spontaneous general movements (GMs) as a method of early prediction of neurological deficits is such a method.[3–5] Initial development and testing of this method by Prechtl *et al*.[6] reported impressive results of sensitivity of 95% and specificity of 96% on a pre-selected population. More recently, Garcia *et al*.[7] presented relational results of GMs, serial cranial ultrasound and neurological testing of a preterm population as predictors of CP.

The optimal time for the most accurate analysis of general movements has been debated. Several investigators have recorded GMs longitudinally from birth,[8–10] and Cioni and Prechtl[11] and Maas[12] have reported that longitudinal recordings of preterm infants before term age are stable. Maas suggests that one observation before term age is representative of the preterm period. We compare the sensitivity, specificity, positive (PPV) and negative (NPV) predictive values for GMs recorded at 36 and 52 weeks postconceptional age (PCA) to detection of cerebral palsy by neurological examination at 18 months corrected age in a very low birth weight population <1500 g, a population that has been shown to be at highest risk for CP. For comparative purposes we evaluated magnetic resonance imaging (MRI), because we have shown that early brain MRI is more accurate than ultrasound in predicting cerebral palsy[13] and the neurobehavioral assessment of the preterm infant (NAPI); an assessment developed specifically to measure the relative maturity of infants in the preterm period.[14]

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Methods

This study was based on a longitudinal design to follow the neurobehavioral development of preterm infants of birth weight <1500 g and gestational age <32 weeks through 18 months corrected age. The study protocol was approved by the Administrative Panel on Human Subjects in Medical Research at Stanford University School of Medicine. Participants were recruited from consecutive newborn admissions to the Neonatal Intensive Care Unit at the Lucile Packard Children's Hospital at Stanford University between April 1996 and September 1999, who had birth weight <1500 g and gestational age <32 weeks. Exclusion criteria included congenital anomalies, families living more than 100 miles from the hospital, families who were not English speaking and for whom translators were not readily available on staff such as Arabic, Japanese and Chinese.

Spontaneous general movements of infants were recorded at 36 weeks PCA in the hospital and at 52 weeks PCA in the home. Video recordings were made for a period of 15 min with the infants in the supine position, free of the encumbrance of restrictive clothing and when possible in an under shirt and diaper. The optimum state for general movement analysis is active wakefulness and therefore infants were not distracted with pacifiers or human interaction.

Two of the authors (MM and JCC), previously trained by the Prechtl team in both the introductory and advanced level of GM analysis, viewed the recordings and came to a consensus agreement. Both authors were masked to the MRI and NAPI results. Analysis of the recordings was made by means of Prechtl's Gestalt perception whereby GMs were classified as normal or abnormal.[15] At 52 weeks the presence of 'fidgety movements' as defined by Hopkins and Prechtl,[16] and Hadders-Algra and Prichtl[17] was used as a determinant of normality.

MRI was performed using a 1.5 Signa scanner with a quadrature head coil. Sagittal images were obtained with 5-mm-thick sections with 1 mm separation, and a repetition time of 600 to 800 ms. Axial images were obtained with 5-mm-thick sections with 2 to 2.5 mm separation, and repetition times of 600 to 800 msec. Images were captured at both T1 and T2 relaxation times. Infants were sedated before transportation to the imaging facility to keep them as calm and still as possible during the procedure. They were wrapped securely in a warm blanket and fitted with earmuffs to reduce the loud noise of the machine. The head was stabilized to maintain a midline position. Infants were monitored for oxygen saturation with a pulse oximeter during imaging. Images were read independently by two radiologists masked to the infants' medical history. The images were scored as normal or abnormal for three different types of brain injury. (1) The occurrence of intraventricular hemorrhagic injury (IVH). Infants with only minor hemorrhage scored as grade I were classified as normal. (2) The presence of ischemia, which is evidence of reduced blood supply and oxygenation. (3) Ventricular enlargement (VE).

The NAPI was performed according to the method described in the NAPI manual[14] at 36 weeks PCA by a certified NAPI examiner masked to the infants' medical history. The NAPI comprises of seven behavioral domains: three of these domains are made up of two or more item scores, the remaining domains are represented by a single item. It was hypothesized that the domains comprised of multiple items, which are (1) motor development and vigor, (2) alertness and orientation, and (3) irritability, conceptually would show better prediction than the single item domains of scarf sign, popliteal angle, cry quality and percent asleep ratings. To determine which of the NAPI cluster scores would be most predictive of later outcome we compared the NAPI scores of the CP subjects with the non-CP subjects in three major areas of behavioral functioning, motor, alertness and irritability. To calculate sensitivity and specificity NAPI results were classified as normal or abnormal based on the normative means, published in the NAPI manual. Abnormality was assigned when cluster scores fell more than 1 s.d. below the mean.

At 18 months corrected age the Amiel–Tison neurological assessment[18] was administered in the Lucile Packard Children's Hospital Mary L. Johnson Developmental and Behavioral Clinic by the attending physician and scored as normal, or abnormal based on evidence of neurologic injury. Those infants who were identified as having CP were classified according to the degree of severity of CP based on their functional skills according to a modified version of the Palisano assessment for CP.[19] Bayley Scales of Infant Development[20] were administered by one of a team of clinical psychologist trained to a high level of inter-rater reliability.

Results are reported as:

sensitivity – the percent of correctly identified CP cases
specificity – the percent of correctly identified non-CP cases
positive predictive value (PPV) – the percent of true CP out of all identified positive cases
negative predictive value (NPV) – the percent of true non-CP out of all identified negative cases
accuracy – the percent of true positives and negatives out of all infants tested.

Results

One hundred and thirty infants participated in the study: 56% were males and 41% were from multiple births. The racial distribution was White (44%), Hispanic (28%), Asian (13%), Black (11%) and Other (4%). Infant demographics of the original study group, the 18-month follow-up group, and those who were lost to follow-up are shown in Table 1. The highest Neonatal Medical Index (NMI)[21] score, which represents the greatest severity of illness, was experienced by 45% of the study population. Length of time on mechanical ventilation is the overarching determinant of severity of illness, but additional contributing factors are surgery for patent

Table 1 Infant demographics

	Initial study group, N = 130		*Follow-up group, N = 102*		*Lost to follow-up, N = 28*	
	Mean ± s.d.	*Range*	*Mean ± s.d.*	*Range*	*Mean ± s.d.*	*Range*
Birth weight (grams)	922.0 ± 203.1	502–1460	948.5 ± 237.4	502–1460	1077.0[a] ± 161.8	725–1399
GA (wks)	27.5 ± 1.8	23–32	27.3 ± 1.9	23–32	27.9 ± 1.2	26–31
Apgar 1 minute	5.0 ± 2.0	0–9	5.0 ± 3.0	0–9	6.0[a] ± 2.0	1–9
Apgar 5 minute	7.0 ± 2.0	1–9	7.0 ± 2.0	1–9	8.0 ± 2.0	1–9
NMI	4.0 ± 1.0	2–5	4.0 ± 1.0	2–5	3.0[a] ± 1.0	2–5
Days mech ventilation	26.3 ± 20.0	1–72	26.5 ± 18.7	2–84	13.9[a] ± 16.8	1–65
Length of stay (Days)	86.5 ± 28.6	34–207	90.3 ± 29.6	34–207	73.0[a] ± 20.1	37–106

[a]Student *t*-test between initial study group and those lost to follow-up. $P < 0.05$.

Table 2 Temporal Stability of GMs at 36 and 52 wks PCA

	GMs 36 weeks PCA, N = 89	*GMs 52 weeks PCA, N = 99*
Normal	62 (70%)	78 (79%)
Abnormal	27 (30%)	21 (21%)
Normal at 36 weeks and 52 weeks	53 (60%)	
Abnormal at 36 weeks and 52 weeks	11 (12%)	
Abnormal at 36 weeks and normal at 52 weeks	16 (18%)	
Normal at 36 weeks and abnormal at 52 weeks	9 (10%)	

Table 3 MRI Findings In CP And NON-CP Subjects

MRI	*CP, N = 10*	*NON-CP, N = 85*	P-*value*[a]
Ischaemia	6 (60%)	7 (8%)	0.00001
IVH Grade II or higher	2 (20%)	12 (14%)	0.15
Ventricular enlargement	4 (40%)	11 (13%)	0.004
Normal MRI	3 (30%)	66 (78%)	0.001

[a]χ^2.

ductus arteriosus performed on 20% of the subjects, 13% had necrotizing enterocolitis, 45% had at least one episode of sepsis, 9% of the subjects had PVL and 9% had IVH Grade II, III or IV. The fragile medical condition of some infants, and scheduling conflicts, resulted in failure to assess all infants according to protocol. The number of subjects studied are documented in the tables. Table 1 shows that there were no significant differences between the 130 recruited study subjects and the 102 who returned at 18 months for follow-up examination, but there were many differences between the study group and the 28 subjects who failed to return for follow-up testing. On average, the subjects who returned to the clinic for follow-up testing had lower birth weight, lower 1 min Apgar scores and greater severity of illness calculated by the NMI, more days on mechanical ventilation and a longer initial hospital stay than the significantly more robust subjects who did not return.

Table 2 shows the temporal stability of the results of analysis of the GM video recordings from 36 and 52 weeks PCA. Sixty percent of subjects appeared normal on both recordings, 12% appeared to be abnormal on both recordings, 18% changed from abnormal to normal and 10% changed from normal to abnormal.

Table 3 shows the distribution of brain abnormalities detected with MRI at 36 weeks among those with and without CP at 18 months. Six of the 10 CP cases had evidence of ischemia and four of those six also had ventricular enlargement, one had IVH.

A χ^2 analysis confirms the obvious selection of ischemia as the best risk factor for prediction of CP. To explain some of the false-positive findings on MRI, Table 4 documents functional outcome at 18 months for subjects with abnormal MRI at 36 weeks who did not have CP. Approximately half (8/17 = 47%) of these participants are functioning within normal limits.

Fourteen of the 102 subjects who returned for follow-up examination at 18 months had CP. Table 5 compares the NAPI scores of the CP subjects with the non-CP subjects and indicates that only the domain of alertness and orientation show significant differences between the two groups; therefore, this domain score was used to determine NAPI prediction.

The calculations for sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) between the GMs, MRI ischemia and NAPI alertness and orientation tests can be seen in Table 6. Combining the results of the NAPI and MRI provided increased sensitivity of 80%, specificity of 81%, PPV of 36% and NPV 97% resulting in an accuracy of 80%.

Discussion

It is clear from the results presented in this paper that all the modalities tested have limitations as predictors of CP. It is apparent that the three assessments fail to give congruent information and the GM findings that changed between 36 and 52 weeks pose interesting questions. Those infants changing from abnormal to

Table 4 Participants With Abnormal MRI At 36 wks and No CP At 18 Months

ID No.	*IVH Grade I*	*IVH Grade II-IV*	*Ischaemia*	*Mild VE*[a]	*Severe VE*	*MDI*	*PDI*	*Function*
1	X					87	90	WNL[b]
2	X					103	98	WNL
3	X					49	63	Delayed
4	X					74	57	Delayed
5		X				58	78	Delayed
6		X				91	107	WNL
7		X				101	62	Motor delay
8		X				99	90	WNL
9	X			X		91	99	WNL
10	X			X		89	102	WNL
11			X			65	94	Mental delay
12			X			83	71	Motor delay
13	X		X	X		76	104	Mental delay
14		X	X		X	49	77	Delayed
15		X	X	X		60	98	Mental delay
16		X			X	87	98	WNL
17					X	91	94	WNL

[a]VE = Ventrical enlargement.
[b]WNL = Within normal limits defined as one s.d. from the mean.

Table 5 NAPI scores for CP and NON-CP Subjects

	CP, N = 14	*NON-CP, N = 54*	P-*value*[a]
Alertness and orientation	37.1 ± 21.4	51.4 ± 18.9	0.02
Motor development and vigor	61.7 ± 14.2	65.5 ± 13.1	0.37
Irritability	46.9 ± 25.1	47.6 ± 23.2	0.92

[a]Student *t*-test.

Table 6 Sensitivity, specificity, positive and negative predictive values of early assessments to CP at 18 months corrected age

	Sensitivity	*Specificity*	*PPV*	*NPV*	*Accuracy*
GMs 36 wks N = 78	62%	69%	29%	90%	66%
GMs 52 wks N = 84	50%	86%	41%	90%	78%
MRI ischaemia N = 74	60%	91%	50%	94%	84%
NAPI alertness N = 89	50%	84%	37%	90%	78%
GMs 36 wks+MRI	70%	76%	27%	95%	75%
GMs 36 wks+NAPI	75%	69%	28%	94%	70%
GMs 52 wks+MRI	70%	82%	35%	93%	80%
GMs 52 wks+NAPI	75%	77%	33%	95%	77%
NAPI+MRI	80%	81%	36%	97%	80%

normal may represent a normal process of healing, more puzzling are those who changed from normal to abnormal. One explanation for this change may be explained by late onset of brain injury. Serial ultrasound visualization to 40 weeks by de Vries[22] has shown that major cranial abnormalities can occur after 36 weeks. Such a situation could account for abnormalities at 52 weeks that were not detectable on the earlier recordings. MRI shows that similar brain abnormalities can result in very different outcomes at 18 months testifying to the plasticity of the brain and the potential to heal albeit in some cases with residual effects. It may be unrealistic to expect concordance from structural information given by MRI and behavior as assessed with the NAPI and GMs, because CP is known to emerge over time. Manifestations of structural changes appear to precede the emergence of behavioral changes. Prediction of outcome of preterm infants is fraught with confounding variables, most notably therapeutic interventions and socioeconomic conditions. Nevertheless, we can confirm with this study that in general infants who appear to behave within normal limits and exhibit normal brain structure in the neonatal period, continue to function within normal limits at 18 months of age. More discriminating tests may provide us with improved prediction and to this end a new method of quantitative analysis of GMs is being tested at our facility.[23]

The NAPI findings that indicate no differences in the motor maturity between CP and non-CP subjects at 36 weeks may be puzzling. It suggests that the primitive reflexes that make up the majority of the NAPI motor cluster items are not impacted by the injury that ultimately presents as CP. Irritability as determined by the frequency and extent of cry may be a measure of temperament as well as an expression of distress. The scope of this study did not allow us to tease out these differences and indeed CP may not confer more physical distress at 36 weeks. It suffices to say

irritability does not appear to be a distinguishing feature of CP infants. A shortcoming of this study is that not all infants received all of the initial measures; scheduling, MRI availability, medical stability of the infant and back transports were among the reasons for missed assessments. In addition, as a group, the infants who failed to return for follow-up assessment were significantly more robust at birth than those who were examined.

It is clear from this study and others that early abnormal MRI findings may not be associated with poor outcome and it is gratifying to note that half of the non-CP infants with abnormal MRI findings performed within normal limits at 18 months. However, all abnormalities that included ischaemia were associated with developmental delay and it could be argued that 18 months is still too soon to make a definitive diagnosis of CP.

In conclusion, the strong negative predictive value for the combined MRI and NAPI results give reassurance that infants who behave within normal limits and exhibit normal brain structure in the neonatal period, continue to function within normal limits at 18 months of age. These results point to the fact that a more holistic approach to early detection is preferable to a single test.

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