



Relationship between white matter pathology and performance on the General Movement Assessment and the Test of Infant Motor Performance in very preterm infants



Colleen Peyton^{a,*}, Edward Yang^{b,c}, Masha Kocherginsky^d, Lars Adde^{e,f}, Toril Fjørtoft^{e,f}, Ragnhild Støen^{e,g}, Arend F. Bos^h, Christa Einspielerⁱ, Michael D. Schreiber^{b,c}, Michael E. Msall^{b,c}

^a Department of Therapy Services, University of Chicago Medicine, 5841 S. Maryland Ave, Chicago, IL 60637, USA

^b Department of Pediatrics, University of Chicago Medicine, Comer Children's Hospital, Sections of Neonatology, Developmental Pediatrics, 5841 S. Maryland Ave, Chicago, IL 60637, USA

^c Kennedy Research Center on Intellectual and Neurodevelopmental Disabilities, 5841 S. Maryland Ave, Chicago, IL 60637, USA

^d Department of Health Studies, University of Chicago Medicine, 5841 S. Maryland Ave, Chicago, IL 60637, USA

^e Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Olav Kyrres gt. 11, 7491 Trondheim, Norway

^f Clinics of Clinical Services, St. Olav University Hospital, Box 3250, Sluppen, 7006 Trondheim, Norway

^g Department of Pediatrics, St. Olav University Hospital, Box 3250, Sluppen, 7006 Trondheim, Norway

^h Division of Neonatology, University of Groningen, 9712 CP Groningen, Netherlands

ⁱ Institute of Physiology, Center for Physiological Medicine, Medical University of Graz, Universitätsstraße 15, 8010 Graz, Austria

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ABSTRACT

Background: Cerebral Magnetic Resonance Imaging, the General Movement Assessment, and the Test of Infant Motor Performance are all tools that can predict neurodevelopmental outcome in preterm infants. However, how these tests relate to each other is unclear.

Aims: To examine the relationship between cerebral Magnetic Resonance Imaging measured at term age, and the General Movement Assessment and Test of Infant Motor Performance measured at 10–15 weeks post-term age.

Study design: Prospectively collected data in a sample of very preterm infants.

Subjects: Fifty-three infants (23 female, 30 male) with a median gestational age of 28 weeks (range: 23–30 weeks) and a median birth weight of 1000 g (range: 515–1465 g).

Outcome measures: Test of Infant Motor Performance, General Movement Assessment.

Results: Infants with abnormal white matter were significantly more likely to have both abnormal general movements ($p = 0.01$) and abnormal Test of Infant Motor Performance scores ($p = 0.001$). Infants with abnormal general movements were significantly more likely to have lower Test of Infant Motor Performance Scores ($p = 0.01$).

Conclusions: Abnormal white matter is related to motor deviations as measured by the General Movement Assessment and the Test of Infant Motor Performance as early as 3 months post-term age in a cohort of preterm infants.

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1. Introduction

Over the past four decades there have been dramatic improvements in survival of preterm infants across late, very, and extremely preterm epochs [1]. As a result there are increasing numbers of survivors at risk for neuromotor and neurodevelopmental impairments. There continues to be a graded response of risk across all preterm gestational ages with those infants at 22–26 weeks gestation at highest risk of death and neurodevelopmental disability [2]. Clinicians assessing high-risk preterm infants have a variety of assessments to choose from when

examining neurological and neuromotor development; however clinical assessment and correlation with brain pathology are not clear.

Magnetic Resonance Imaging (MRI) brain scans have significantly increased our ability to examine brain structure in the neonate. Abnormalities identified on cerebral MRI at term-equivalent age in preterm infants have been found to predict later neurodevelopmental outcomes [3]. Furthermore, moderate to severe white matter injury has been associated with neurosensory impairment, severe cognitive delay, and cerebral palsy [4].

Cerebral MRI has significantly enhanced our understanding of the preterm brain; however early neuroimaging does not replace the need for bedside clinical assessment. MRIs are not always available or used with preterm infants. As a result, it is important for clinicians who use clinical neurodevelopmental tests to understand the neurological

* Corresponding author at: 5841 S. Maryland Ave, MC1081, Chicago, IL 60637, USA.

Tel.: +1 773 795 7151; fax: +1 773 702 5340.

E-mail address: colleen.peyton@uchospitals.edu (C. Peyton).

implications of those tests and to document early signs of neurological dysfunction in order to identify children who need close monitoring and follow-up, and to direct and guide appropriate early rehabilitative interventions.

Traditional infant neurological assessments identify behavioral and neurodevelopmental repertoires, control of posture and movement, and other observable responses to external stimuli. These tools are based on responses to elicited stimuli, such as reflexes, and assessment of passive and active muscle tone; however clinical use can be limited by the infant's behavioral state and physiological status. The General Movement Assessment (GMA) is distinguished from traditional evaluations because the infant's spontaneous, endogenously generated movements are analyzed and used to identify neuromotor impairment [5]. The quality of general movements (GM) is thought to be modulated by cerebral functioning and is considered a reflection of neurological status [6]. Abnormal GMs have been associated with neuropathologies of the white matter [7], basal ganglia, thalamic [8], and cerebellar [9] brain regions.

The GMA [10] identifies a developmentally regulated pattern of spontaneous movements that emerge at 9–12 weeks post-conceptual age in the embryo and regress around 20 weeks post-term. At 10–15 weeks post-term, the predominant GMs are an identifiable pattern of continuous, small amplitude movements of the neck, trunk and limbs during wakefulness that disappear with agitation, termed fidgety movements. Absence of these fidgety movements at 10–15 weeks predicts the development of cerebral palsy with a high degree of accuracy [11]. Abnormal quality of the concurrent motor repertoire has been associated with minor neurologic dysfunction [12], intelligence at school age [13] and adaptive behavior in 10–11 year old children born preterm with a very low birth weight [14].

The Test of Infant Motor Performance (TIMP) has also been shown to be predictive of developmental delay in the infant tested at 12 weeks post-term age [15]. The TIMP is a norm-referenced measure designed to evaluate motor control and organization of posture and movement for functional activities in infants 32 weeks gestational age to 4 months post-term age and measures both spontaneous behaviors and elicited items [16]. While both the TIMP and the GMA tested at 12 weeks post-term age are predictive of future outcome, Snider et al. [17] found no concurrent validity between the two tests.

This study describes the relationship between the GMA, the TIMP, and neuropathologies detected on brain MRI scan at term age in a cohort of high-risk preterm infants. The aims of our study were (1) to elaborate on the relationship between the GMA and the TIMP at 3 months post-term age; (2) analyze the extent to which term-age MRI was related to performance on the GMA at 10–15 weeks post-term age; and (3) to analyze the relationship between term-age MRI and the TIMP scores at 10–15 weeks post-term age.

2. Methods

2.1. Participants

Infants born at ≤ 31 weeks gestational age, and a birth weight of ≤ 1500 g, who required oxygen at birth, were recruited prospectively between July 2011 and March 2013 from the XXXX Children's Hospital neonatal intensive care unit. Infants with congenital malformations, genetic syndromes, or who had respiratory distress that was severe enough that they were not expected to live (oxygenation index ≥ 20) were excluded from the study. Informed parental consent was obtained from each infant and ethical approval for the study was granted by the University's institutional review board.

2.2. MR image and data acquisition

MRI scans were performed at term equivalent age. Infants were fed an hour prior to the scan and gently restrained, without sedation,

using a MedVac immobilization bag (CFI Medical Solutions Inc., Fenton, MI, USA) [18]. Pulse oximetry was used to monitor heart rate and oxygenation throughout the study. Standard hearing protection was applied. MR imaging was performed on a 3 T Philips MRI scanner (Achieva, Best, the Netherlands) using a standard head 8-channel SENSE MRI coil array, designed for adult head imaging with high signal-to-noise ratio and optimum uniformity. Acquisition schema was as follows:

- i. 3D *T1-weighted TFE*: 1-mm isotropic spatial resolution, TI = 1100 ms, TR/TE = 8.0/2.9 ms, TFE factor 144.
- ii. 3D *T2-weighted, turbo spin echo*: 1-mm isotropic spatial resolution, matrix 192×132 TR/TE = 2500/264 ms, TSE factor 100.

2.3. Assessments

2.3.1. General Movement Assessment

Fidgety movements were assessed according to the Prechtl method [6]. In this study, fidgety movements were classified as normal if present (intermittent or continual), and as aberrant if abnormal (exaggerated with respect to speed and amplitude), sporadic (interspersed with long pauses) or absent.

Video recordings were made using a standardized observation system, with the baby in a state of active wakefulness. The recordings were made at 10–15 weeks post term age. Two raters who are general movement assessment certified and blinded to the imaging and outcome data classified the video recordings according to the Prechtl methodology [10]. An additional GMA certified rater from a second institution also rated the cases using the same method (Kappa = .21). If there was a discrepancy between assessments, the videos were sent to a third (tie-breaking) reader who was blind to what the previous readers reported. There were 16 cases of discrepancy. The tie-breaking reader agreed with the first raters in 4 cases and with the second rater in 12 cases. The consensus or the tie-breaking reader's scores were used for analysis.

2.4. TIMP

The TIMP consists of 42 test items: 13 observed items and 29 elicited items, which test the infant's postural and motor control. Each item has its own scale; the number of points varies from 0 to 6. A total raw score is summed from item scores (maximum 142) and results of scores are categorized as "average" (within -0.5 to $+1.0$ standard deviations (SD) of age mean), "low average" (-0.5 to -1.0 SD below age mean), "below average" (-1.0 to -2.0 SD below age mean), and "far below average" (> -2.0 below age mean).

Infants were assessed with the TIMP at 10–15 weeks post-term age. The TIMP was performed by an experienced and reliable tester blinded to imaging data.

2.5. MRI qualitative scoring

A pediatric neuroradiologist independently scored the scans and was blinded to neonatal morbidities and scores on other assessments. A standardized scoring system [4] was used to grade gray and white matter (WM) pathology. The WM was scored on a scale from 1 to 3 for the following five areas: nature and extent of WM signal abnormality, periventricular white matter volume loss, thinning of the corpus callosum, ventricular dilation, and presence of any cystic abnormalities.

The WM pathology scores for the individual items were totaled and classified into four groups: normal (score: 5–6), mild (score: 7–9), moderate (score: 10–12), and severe (score: 13–15). Gray matter was scored similarly with a scale from 1 to 3 for the following: size of the subarachnoid space, gyral maturation, and cortical gray matter signal abnormality. The gray matter pathology scores for the individual items

were totaled and classified into two groups: normal (score: 3–5) and abnormal (score: 6–9).

2.6. Statistical analysis

Demographic and clinical characteristics are summarized in Table 1. Association between two categorical variables was assessed using Fisher's exact test. Relative risk (RR) and its confidence intervals are reported. The Wilcoxon rank sum test was used to compare continuous or ordinal outcomes between two groups. A nonparametric trend test was used to examine whether there was a trend in TIMP-z scores across ordered GM categories. Throughout the analyses, $p < 0.05$ was considered to be statistically significant. Analyses were performed using Stata 14 [19].

3. Results

3.1. Sample characteristics

A total of 68 families were approached for recruitment for MRI scans at term-age equivalent. Of these, eight declined to participate. Sixty infants received MRI scans at a median postmenstrual age of 38.5 weeks (range of 35–45 weeks).

Six infants who received MRI did not return for follow-up visit at 10–15 weeks, and one child could not complete the TIMP due to irritability. Accordingly, 53 infants were analyzed (Fig. 1). The descriptions of clinical and demographic variables are listed in Table 1.

3.2. Clinical MRI scores

All participants had normal gray matter scores. Forty-one infants (77%) had normal WM scores. Twelve infants (23%) had abnormal WM scores. Of these infants 9 (75%) had mildly abnormal WM, 2 (16.7%) had moderately abnormal WM and 1 (8.3%) had severely abnormal WM (Table 2).

3.3. General Movement Assessment

Forty-two infants (79%) had normal fidgety movements and 11 infants (21%) had aberrant fidgety movements. Of the aberrant fidgety movements, seven (63.6%) infants were classified as sporadic, one (9%) as abnormal, and three as absent (27%) (Table 2).

3.4. TIMP

Forty-seven infants (89%) had normal TIMP scores with 6 of these infants in the “low average” range (0.5–1 SD below the mean). Six infants had abnormal TIMP scores with four in the below average range (1–2 SD

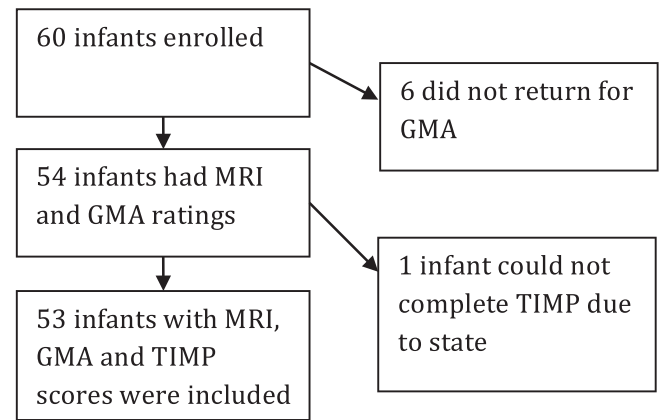


Fig. 1. Patients included in the study.

below the mean) and two in the “far below average” range (>2 SD below the mean) (Table 2).

3.5. Comparison between tests

Infants with abnormal WM scores were significantly more likely (RR = 4.1, 95%CI: 1.5–11.1; $p = 0.01$, Fisher's exact test) to have aberrant fidgety movements (50%) compared to normal fidgety movements (12%). Infants with abnormal WM scores also had lower TIMP z-scores (-0.68 ± 1.28) compared to those with normal WM scores (0.16 ± 0.63), although this did not reach statistical significance ($p = 0.06$). However, 45% of infants with an abnormal WM score had a TIMP z-score in the below average range (>1 SD below the mean), compared to only 2% of infants with a normal WM score (RR = 18.6, 95%CI: 2.4–143.5; $p = 0.001$ Fisher's exact test) (Table 3).

TIMP z-scores increased as the general movements improved from aberrant to normal fidgety movements ($p = 0.01$, nonparametric trend test), and infants with aberrant fidgety movements had significantly lower TIMP z-scores compared to infants with normal fidgety movements ($p = 0.01$ Wilcoxon ranksum test).

4. Discussion

We identified a relationship between below average TIMP scores (>1 SD below the mean) and abnormal WM pathology. Additionally, we confirmed a significant relationship between WM abnormality and GMs tested at 3 months post-term age [7]. The lack of association between GMs, TIMP, and gray matter pathology, may reflect the relative vulnerability of WM in a cohort of preterm infants.

Previous authors were not able to establish a correlation between the TIMP and the general movement assessment [17], suggesting that the two tests may measure different constructs. In contrast, our findings demonstrate that infants with aberrant fidgety movements had significantly lower TIMP scores when tested at 10–15 weeks post-term age and a trend was established between aberrant fidgety movements and TIMP z-scores.

Notably, the majority (65%) of our infants with aberrant fidgety movements were classified as sporadic. While several studies have described the relationship between GMs and neuropathologies [7–9], none have specifically examined the structural correlates of sporadic fidgety movements with MRI. In our sample 45% of patients with sporadic fidgety movements had abnormal WM. Hamer et al. [20] found sporadic fidgety movements in ten out of 44 high-risk infants; one of these children with sporadic fidgety movements developed cerebral palsy. In another study, sporadic fidgety movements were noted in 61 children who developed cerebral palsy, but they were not prognostic of level of impairment at age 3–5 [21]. The clinical relevance of sporadic

Table 1
Clinical and demographic characteristics of the cohort (n = 53).

Variable	Mean (SD)	Range
Birthweight (grams)	998 (264)	505–1465
Gestational age (weeks)	27.3 (1.6)	23.4–30.3
Age at MRI (weeks postmenstrual age)	37.6 (2.8)	35.0–45.4
Age at GMA and TIMP (weeks)	12 (1)	10–15
Variable	Frequency	%
Females	23	43%
Chorioamnionitis	3	6%
Bronchopulmonary dysplasia (BPD)	22	42%
ELBW (<1000 g)	25	47%
VLBW (1000–1500 g)	28	53%
Intraventricular hemorrhage (grade I 9, grade II 1, grade III 1, grade IV 2)	13	25%
NEC with laparotomy or drain	3	6%
Treated ROP	7	13%

Table 2
Relationship between GMA and TIMP at 10–15 weeks post-term age and specific white matter pathology at term.

	WMSA			WMVL			CA			VD			CC			Total WM score	
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	Normal	Abnormal
GMA	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3	Normal	Abnormal
Normal	35	2	3	38	3	0	41	0	0	31	10	0	34	7	0	36	5
Abnormal FM	1	0	0	1	0	0	1	0	0	1	0	0	5	2	0	1	0
Sporadic FM	3	3	1	7	0	0	7	0	0	4	3	0	1	0	0	4	3
Absent FM	1	0	2	1	1	1	3	0	0	1	1	1	0	2	1	0	3
TIMP score																	
Normal	33	4	2	37	2	0	39	0	0	29	10	0	34	5	0	33	6
Normal low average	7	0	0	7	0	0	7	0	0	6	1	0	5	2	0	7	0
Below average	0	2	2	3	1	0	4	0	0	2	2	0	1	3	0	1	3
Far below average	0	0	2	0	1	1	2	0	0	0	1	1	0	1	1	0	2

WMSA indicates white matter signal abnormality; WMVL, periventricular white matter volume loss; CA, presence of any cystic abnormalities; VD, ventricular dilatation; CC, thinning of the corpus callosum; Normal TIMP score (>0.5 SD below mean), normal low average (between 0.5 and -1 SD below mean), below average (score between -1 SD and -2 SD below the mean), below average (more than -2 SD below the mean); FM, fidgety movements.

fidgety movements may be related to WM abnormality in preterm infants at post-term age, but the long-term outcomes are not yet clear.

Interestingly, although the MRI and GMA showed a similar proportion of abnormal results, 23% and 21% respectively, only six infants (11/3%) were classified as abnormal by both methods. The TIMP (11%) detected slightly less abnormality, and only three infants were classified as abnormal by all three tests. These findings suggest that each test provides a unique contribution to the identification of high-risk infants and may be used together in the clinic setting to generate referrals to early intervention services. Notably, in the infant with the most extreme case of brain injury, all three tests detected abnormality (severe WM score, absent fidgety movements, TIMP score > 2 SD below the mean).

It is well known that WM abnormality seen on MRI is predictive of neuromotor impairment at later ages [4]. Notably, the three infants with absent fidgety movements all had abnormal WM, confirming previously reported associations between absent fidgety movements and WM pathologies [7,22]. The findings from our study confirm that deviations in motor behavior, both spontaneous (GMs) and elicited (TIMP), begin as early as 3 months post-term age.

Spittle and colleagues [7] examined the relationship between GMs and MRI in preterm infants. Our cohort of preterm infants was, by contrast, smaller and relatively healthier with less incidence of WM abnormality. However the results were replicated with significant relationships seen between abnormal GMs and abnormal WM. Importantly, only short-term outcomes, assessed at 3 months, were investigated in this study. Future research directions include detailed motor assessments and correlation with long-term gross, fine, and oral motor, communicative, social-emotional and adaptive competencies.

5. Conclusion

This study demonstrates that abnormal WM is related to motor deviations as measured by the TIMP and the GMA at 3 months post-term age. Infants born preterm may benefit from both MRI and clinical assessments such as the GMA and the TIMP to delineate differing forms of cerebral development in early motor abilities and their adaptive correlates. Understanding the relationship between MRI findings and

Table 3
Relationship between GMA and TIMP at 10–15 weeks post-term age and white matter pathology at term.

	Total white matter-normal	Total white matter abnormal	Fischer's exact test p-value
Normal fidgety movements	36	6	p = 0.01
Aberrant fidgety movements	5	6	
Average TIMP Score	40	1	p = 0.001
Below average TIMP scores (>1 SD below mean)	6	5	

neurodevelopmental tests may be useful to clinicians assessing high-risk preterm infants.

Conflicts of interest

None declared.

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