Brain & Development 41 (2019) 490–500

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

The association between brain morphological development and the quality of general movements

Tomoki Maeda *, Hajime Iwata, Kazuhito Sekiguchi, Mizuho Takahashi, Kenji Ihara

Department of Pediatrics, Oita University Faculty of Medicine, Oita, Japan

Received 3 November 2018; received in revised form 31 December 2018; accepted 23 January 2019

Abstract

Aim: To clarify the morphologic characteristics of the brain, which are the foundation of the emergence of general movements (GMs) in very-low-birth-weight infants.

Study design: Prospective cohort study. GMs were scored according to a semiquantitative scoring system: the GMs optimality score (GMOS) at preterm and term ages. Brain magnetic resonance imaging (MRI) at term-equivalent age was scored using a validated scoring system (MRI score). We examined the relationship between the two scores by multiple regression analysis with relevant clinical background.

Subjects: We included 50 very-low-birth-weight infants cared for at Oita University Hospital from August 2012 to August 2018 who underwent MRI and GMs assessment. Their median gestational age and birth weight were 29w2d and 1145 g, respectively.

Results: The MRI score and systemic steroid administration were related to preterm GMOS, and the MRI score was related to term GMOS. The component cerebellum score and cortical grey matter score of the MRI score were associated with preterm GMOS, and the cerebellum and the cerebral white matter scores were associated with term GMOS.

Conclusion: The quality of GMs was associated with brain morphological development. The co-evaluation of GMs and brain morphology leads to accurate developmental prediction.

Keywords: General movements; Magnetic resonance imaging; Cerebellum; Very-low-birth-weight infants

1. Introduction

The advancement of neonatal intensive care has improved the survival rate of very-low-birth-weight infants (VLBWI). In addition, there is an increasing number of VLBWI who develop cerebral palsy and intellectual and cognitive impairment. These are important issues for neonatal medicine. Early prediction is required for early intervention according to the character of impairment [1–3].

Abbreviations: GMs, general movements; MRI, magnetic resonance imaging; GMOS, GMs optimality score; VLBWI, very-low-birth-weight infants; TEA, term-equivalent age; NICU, neonatal intensive care unit; PR, poor repertoire; CS, cramped synchronised; WM, cerebral white matter; CGM, cortical grey matter; DGM, deep grey matter; BPD, biparietal diameter; IHD, interhemispheric distance; TCD, transcerebellar diameter; DGMA, deep grey matter area; HDC, hydrocortisone

* Corresponding author at: Department of Pediatrics, Oita University Faculty of Medicine, 1-1 Idaigaoka, Hasama, Yufu, Oita 879-5593, Japan.

E-mail address: tmaeda@oita-u.ac.jp (T. Maeda).

https://doi.org/10.1016/j.braindev.2019.01.007

The qualitative assessment of general movements (GMs) is a sensitive, noninvasive method to investigate the integrity of the young infant's brain [4]. Much evidence has accumulated regarding its usefulness for predicting cerebral palsy [5,6]. Recently, the number of studies reporting that GMs detailed assessments can predict intellectual and cognitive impairments has increased [7–9].

Brain magnetic resonance imaging (MRI) is also useful for predicting adverse neurological outcome. Cerebral MRI conducted at term-equivalent age (TEA) is a sensitive tool that can provide important information about the preterm infant's brain injury and structure, which is associated with long-term neurodevelopment, including motor and cognitive outcomes [10,11].

Regarding cerebral palsy, it is recommended that GMs assessments and brain MRI are combined for early diagnosis and early intervention [5]. Early detection of intellectual and cognitive impairment is also important. Understanding the relationship between both assessment methods leads to more accurate early prognostic prediction.

This study aims to clarify the morphologic characteristics of the immature brain, which is the foundation of GMs emergence by assessing the relationship between brain MRI and GMs in the neonatal period. Aiming for clinical application, both assessment methods can be practiced widely and generally. This enables early developmental prediction, leading to early intervention according to individual predicted developmental characteristics from the neonatal period.

2. Method

2.1. Participants

VLBWI were recruited from the neonatal intensive care unit (NICU) of Oita University Hospital, Japan, between August 2012 and August 2018. They were participants of the clinical research that investigated the association between GMs and long-term neurodevelopment. Brain MRI was routinely performed on all VLBWI for the clinical indication in our NICU. The subjects of this study were cases in whom MRI could be performed at the age of 37–43 postmenstrual weeks. Infants were enrolled after parental written consent for GMs assessment was obtained during their NICU stay. The ethics committee of Oita University approved this study. The authors (TM, MT, SK) obtained the informed consent for clinical research participation and collected the clinical data from medical records.

2.2. GMs assessment

GMs were recorded repeatedly in a standard way during the NICU stay [12]. We divided the recordings into two periods (preterm: 30–36 postmenstrual weeks; term: 37–43 postmenstrual weeks). When there were multiple records within the period, the GMs recording with the best quality was used for analysis, because the neonate's behaviour should be assessed by his or her best performance [13].

Normal GMs are characterized by complexity, variability, and fluency. In the neonatal period, the GMs are referred to as writhing movements. Typically, they are ellipsoid in form and are of small to moderate amplitude and speed. Abnormal GMs in the writhing period are divided into three main types, namely, poor repertoire (PR) GMs, cramped synchronised (CS) GMs, and chaotic GMs. PR GMs appear monotonous in their sequence of successive movement components. CS GMs appear rigid because all limb and trunk muscles contract and relax almost simultaneously. Chaotic GMs occur chaotically and lack any fluency or smoothness [4]. In addition, we assessed the GMs optimality score (GMOS) according to Prechtl's optimality concept for preterm GMs and writhing movements [14]. The optimality score is based on a detailed analysis of the quality of the GMs. Eight different aspects of the GMs are distinguished. The first item is the quality of the GMs, and it can be scored as normal, variable, and complex (4 points), PR GMs (2 points), chaotic GMs (1 point), or CS GMs (1 point). The other seven items are sequence, amplitude, speed, space, rotatory components, onset-offset, and tremulous movement. All can be scored as optimal (2 points) or non-optimal (1 point). The highest and therefore the most optimal score is 18, whereas the lowest score is 8. GMs assessments were conducted before MRI scoring by an author (TM) who had been repeatedly certified on a GM Trust advanced course.

2.3. Scoring of brain MRI

Infants were scanned at a median postmenstrual age of 39 weeks 4 days (range, 37w1d–43w5d). All infants were scanned while sedated using thiamylal sodium and were monitored by pulse oximetry. Images were obtained with a 1.5- or 3.0-Tesla MR scanner (1.5-T MRI system, EXCELART Vantage XGV PPP, TOSHIBA, Japan; 3T MRI system, MAGNETOM Verio, Siemens, Japan). Because MRI was examined by clinical indication, the scanned age and setting of sequence parameters were not constant. Axial T2-weighted MRI brain scans were acquired using the following sequence parameters median (range): echo time, 93 (80–115); repetition time, 4000 (2810–6000); and slice thickness, 4 mm (3–5).

Brain MRIs were assessed using a standardised scoring system that has been validated with very preterm infants [15]. This scoring system for conventional MRIs provides a comprehensive and objective characterisation of regional and global brain injury and brain growth.

This score consists of the sum of the scores at cerebral white matter (WM), cortical grey matter (CGM), deep grey matter (DGM), and cerebellum. The brain measurement values were one of the components of the score. The biparietal diameter (BPD) was a component of WM. The interhemispheric distance (IHD) was a component of CGM. The deep GM area (DGMA) was a component of DGM. The transcerebellar diameter (TCD) was a component of the cerebellum. A higher MRI score indicates that the brain injuries were strong and the brain growth was suppressed [15].

BPD and IHD were measured on an axial plane perpendicular to the cross-section through the bilateral cochlea. DGMA was measured on a single axial section at the level at which the caudate heads and the lentiform nuclei and the thalami are maximally visible. DGMA was manually segmented. TCD was measured using the maximum cerebellar diameters parallel to the line connecting the bilateral cochlea. Since there were differences depending on the scanned age, the brain measurement values were corrected according to the postmenstrual week at MRI scan. We applied a linear regression described in the article for the correction. A linear association was found between postmenstrual age at scan and BPD ($R = 0.41$; slope, 1.4 mm/week), DGMA ($R = 0.36$; slope, 0.26 cm^2/week), and TCD ($R = 0.35$; slope, 0.83 mm/week) [15]. The corrected values are expressed as cBPD, cDGMA, and cTCD, respectively. Where a significant association for age was not identified for IHD, ventricular diameter, and callosal thickness, we used the measured values for analysis.

One author (IH), who was unaware of the infant's clinical history, measured and scored the measurable values. Authors TM and KS scored the unmeasurable factors with reference to the radiologist's findings.

2.4. Statistics

The data were analysed using SPSS Statistics version 24 (IBM, Tokyo, Japan). We examined the difference between the normal GMs group and the abnormal group using Mann-Whitney *U* analysis for continuous variables (e.g., birth weight, height, MRI score) and Fisher's exact test for nominal variables. We used the Spearman rank correlation coefficient (*r*) to study the correlations among MRI score, the measured values of MRI score, and GMOS. Differences with $p < 0.05$ were considered statistically significant.

After confirming the correlation between GMOS and MRI score, we performed multiple regression analysis using the score of each part of the brain, constituting the MRI score and the GMs associating variables by univariate analysis. In addition, we examined associated brain measurement values and the optimal or nonoptimal elements of GMOS in Mann-Whitney *U* analysis.

3. Results

3.1. Participants

Within the study period, 65 VLBWI were admitted to our NICU. There were 3 deaths during the neonatal period, 1 case of chromosomal abnormality, and 1 case of congenital muscular dystrophy, which were excluded from the GMs clinical research assessment. Six cases did not give consent to participate in the clinical research. In addition, 4 cases were excluded from this study, as MRI could not be performed in TEA due to chronic respiratory failure. Eventually, 50 subjects were enrolled in this study. Their median gestational age was 29w2d, ranging from 24w0d to 37w4d. Their median birth weight, height, and head circumference were 1145 g, 37.1 cm, and 26.7 cm, respectively. Details of the body measurements at birth are listed in Table 1. Fetal growth restriction, defined as birth weight below the 10th percentile of the Japanese standard [16], was present in 36% of the subjects. Clinical background and candidate factors for the multivariate analysis are presented in Table 1.

3.2. General movements

We were able to assess GMs in 48 cases at preterm age and in 49 cases at term age. Abnormal GMs were found in 10 cases and normal GMs in 38 cases at preterm age. All abnormal patterns were PR GMs. At term age, abnormal GMs were found in 25 cases and normal GMs in 24 cases. In one case, CS GMs were observed, but another sequential record presented relatively good-quality PR GMs. Therefore, the PR GMs recording was used for examination. The median GMOS was 16 (range, 11–18) at preterm age and 14 (range, 9–18) at term age. The global qualitative assessments of GMs and the GMOS were significantly correlated in each period. The median GMOS in preterm age of PR GMs cases was 12 (range, 11–14) and of normal GMs cases was 16 (range, 13–18). The median GMOS in term age of PR GMs cases was 13 (range, 9–14) and of normal GMs cases was 16 (range, 13–18).

The trajectories of GMs through the preterm-term period showed PR-PR in 7 cases, PR-normal in 3 cases, normal-PR in 19 cases, and normal-normal in 18 cases.

3.3. MRI scoring

MRI was performed in all cases. The median MRI score was 5.0 (range, 0–18). The brain part subscores were 4.0 (0–12) for WM, 0.0 (0–5) for CGM, 0.0 (0–2) for DGM, and 0.0 (0–2) for cerebellum. The mean (standard deviation) of measured brain values were as follows: cBPD, 71.8 (3.8) mm; IHD, 3.6 (1.1) mm; cDGMA, 12.0 (0.8) cm^2; and cTCD, 50.1 (2.1) mm (Table 2).

Table 1
The clinical backgrounds of the subjects.

	n = 50			Preterm GMs n = 48			Term GMs n = 49		
	median	min	max	normal n = 38	abnormal n = 10	p	normal n = 24	abnormal n = 25	p
Birth gestation	29w2d	24w0d	37w4d	29w5d	27w3d	0.05**	30w0d	29w0d	n.s.
Birth weight (g)	1145	536	1478	1179	890	n.s.	1113	1150	n.s.
Height (cm)	37.1	28.5	42	37.6	34.8	n.s.	37.2	37.1	n.s.
Head circumference (cm)	26.7	21.2	29.5	27	24.7	n.s.	27.1	26.7	n.s.
Period of intubated ventilation (day)	3.5	0	52	2	26.5	0.03**	2.5	4	n.s.
				normal	abnormal	p	normal	abnormal	p
Male/Female	26/24			20/18	5/5	n.s.	13/11	13/12	n.s.
Singleton/Twin	27/23			22/16	4/6	n.s.	13/11	13/12	n.s.
FGR (+/−)	18/32			13/25	4/6	n.s.	8/16	10/15	n.s.
	+/−		N.E						
Chorioamnionitis	9/39		2	7/30	2/8	n.s.	4/19	4/20	n.s.
Sepsis	4/46			3/25	1/9	n.s.	0/24	3/23	n.s.
Catecholamine admin.	11/39			7/31	4/6	n.s.	5/19	6/19	n.s.
Systemic steroid admin.	10/40			5/33	5/5	0.02**	4/20	6/19	n.s.
Indomethacin admin.	17/33			10/28	7/3	0.02**	10/14	7/18	n.s.
Xanthine admin.	33/17			26/12	7/3	n.s.	13/11	19/6	n.s.

Median value and number of cases were presented.
FGR; fetal growth restriction, admin.; administration, N.E. not examined, n.s. not significant $^{**}p < 0.05$.

Table 2
The comparison of the MRI scores and measurement value for each brain parts between GMs normal group in preterm and term age.

	Preterm GMs (n = 48)										Term GMs (n = 49)						
				normal (n = 38)			abnormal (n = 10)				normal (n = 24)			abnormal (n = 25)			
	med	min	max	med	min	max	med	min	max	p	med	min	max	med	min	max	p
MRI score	5	0	18	4	0	10	7.5	5	18	<0.01*	4	0	8	5	2	18	<0.01*
WM	4	0	12	4	0	7	5	3	12	<0.01*	4	0	5	4	2	12	0.02**
CGM	0	0	5	0	0	2	1	0	5	<0.01*	0	0	2	0	0	5	0.05**
DGM	0	0	2	0	0	1	0	0	2	n.s.	0	0	1	0	0	2	n.s.
Cerebellum	0	0	2	0	0	2	1	0	2	<0.01*	0	0	2	1	0	2	n.s.

Measured value			normal		abnormal			normal		abnormal		
	mean	SD	mean	SD	mean	SD	p	mean	SD	mean	SD	p
cBPD (mm)	71.8	3.8	71.4	3.8	71.2	3.5	n.s.	72.0	3.6	70.8	3.5	0.03**
IHD (mm)	3.6	1.1	3.3	0.6	4.2	1.7	<0.01*	3.5	0.8	3.3	1.3	n.s.
cDGMA (cm^2)	12.0	0.8	12.1	0.7	12.1	1.0	n.s.	12.2	0.8	12.0	0.7	n.s.
cTCD (mm)	50.1	2.1	50.5	1.9	48.8	1.8	<0.01*	50.5	2.0	50.8	2.1	n.s.

cBPD; corrected biparietal diameter, IHD; Interhemispheric distance, cDGMA; corrected deep gray matter area.
cTCD; corrected transcerebellar diameter, med; median, n.s; not significant. SD; standard deviation, $^{*}p < 0.01$, $^{**}p < 0.05$.

3.4. Correlation between GMs and MRI scores

The MRI scores were significantly higher in the abnormal GMs group than in the normal GMs group at both preterm and term age ($p < 0.01$; Fig. 1a, b). The GMOS at preterm and term ages were correlated with the MRI score ($p < 0.01$; Fig. 1c, d).

The GMOS also correlated with the measured values of each brain part that are elements of the MRI score. The preterm GMOS correlated with IHD, cTCD ($p < 0.01$), and cBPD ($p < 0.05$). The term GMOS correlated with cBPD ($p < 0.01$), IHD, cDGMA, and cTCD ($p < 0.05$) (Fig. 2).

3.5. Relationship with clinical background

We examined the differences in clinical background between the GMs normal group and the GMs abnormal group (Table 1). Abnormal GMs in the preterm age group were associated with significantly earlier birth gestational age and a longer period of intubated ventilation ($p < 0.05$) and many cases of systemic steroid administration and indomethacin administration ($p < 0.05$) than in the normal GMs group. There was no significant related factor other than MRI score between the term GMs normal and abnormal groups.

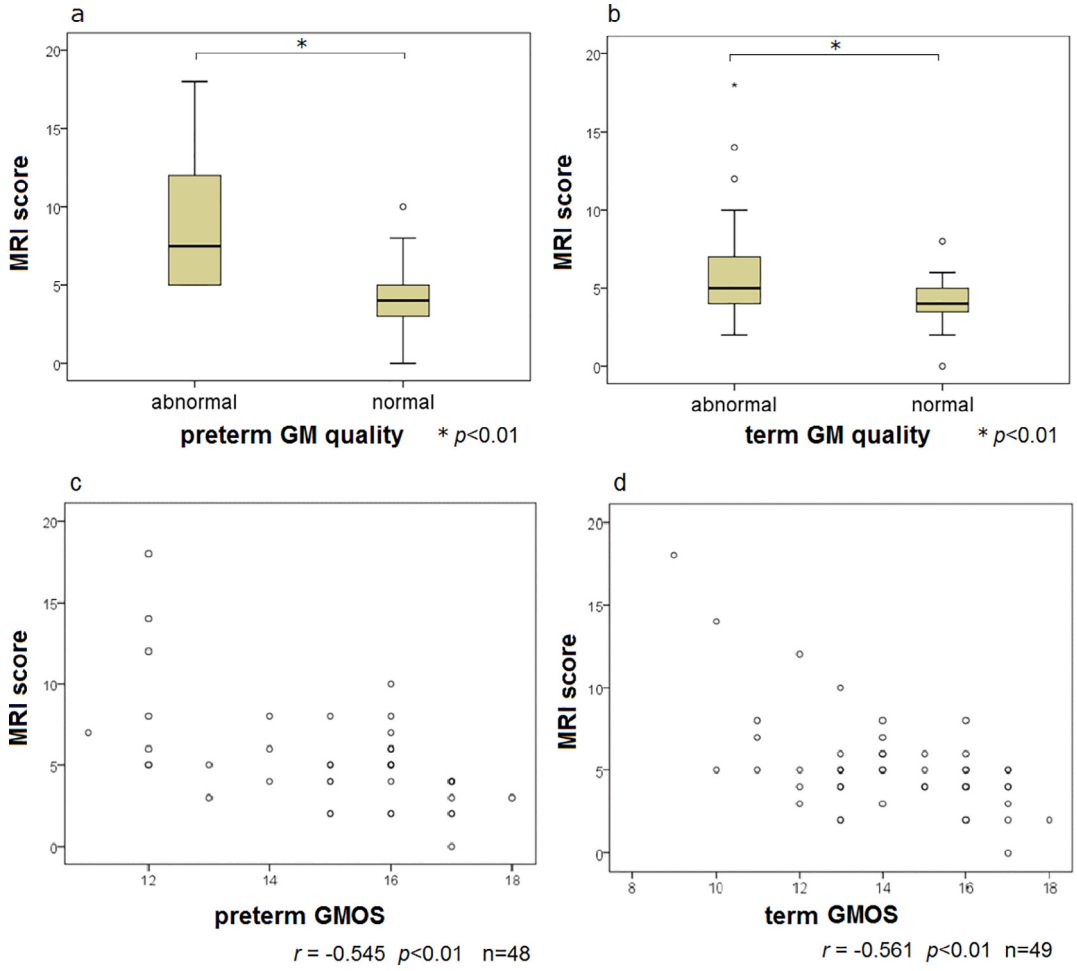

Fig. 1. The correlation between GMs and MRI scores. (a, b) The comparison of MRI scores between GMs abnormal and normal group in preterm age (a) and term age (b). ($p < 0.01$) The MRI scores were significantly higher in the abnormal GMs group than in the normal GMs group at both ages. ($p < 0.01$). (c, d) The correlation between GMOS in preterm age (c) and term age (d) and MRI score. The GMOS at both ages were correlated with the MRI score ($p < 0.01$).

There were significant differences in WM, CGM, and cerebellum scores between the normal and abnormal GMs groups of preterm age and in WM and CGM scores between the normal GMs and abnormal groups of term age. Comparison of the mean measurement values of each brain part presented significant differences in IHD and cTCD between the preterm normal and abnormal GMs groups ($p < 0.01$) and in cBPD between the term normal and abnormal GMs groups ($p < 0.05$). The abnormal GMs group of preterm age presented longer IHD and shorter cTCD than the preterm normal GMs group. The term abnormal GMs group presented shorter cBPD than the term normal GMs group (Table 2).

3.6. Multiple regression analysis

We performed multiple linear regression analysis with the GMOS as a dependent variable using the stepwise variable increase/decrease method. The MRI score and the related background factors were introduced as independent variables. In the preterm GMOS, MRI score and systemic steroid administration were recognised as related factors. The normality of the residual was confirmed: R^2 was 0.40, and the Durbin-Watson ratio was 1.697. When analysing by the score of each part of the brain instead of using the MRI score, the cerebellum score and the CGM score remained relevant. R^2 was 0.366, and the Durbin-Watson ratio was 1.942.

With regard to the term GMOS, because no relevant factors other than the MRI score were observed, the score of each part of the brain was examined as an independent variable. The WM score and cerebellum score remained relevant. The normality of the residual was confirmed. R^2 was 0.339, and the Durbin-Watson ratio was 1.759 (Table 3).

3.7. Relation between brain metrics and characteristics of GMs

Since multiple regression analysis showed the relation between the GMOS and the MRI score of each part of

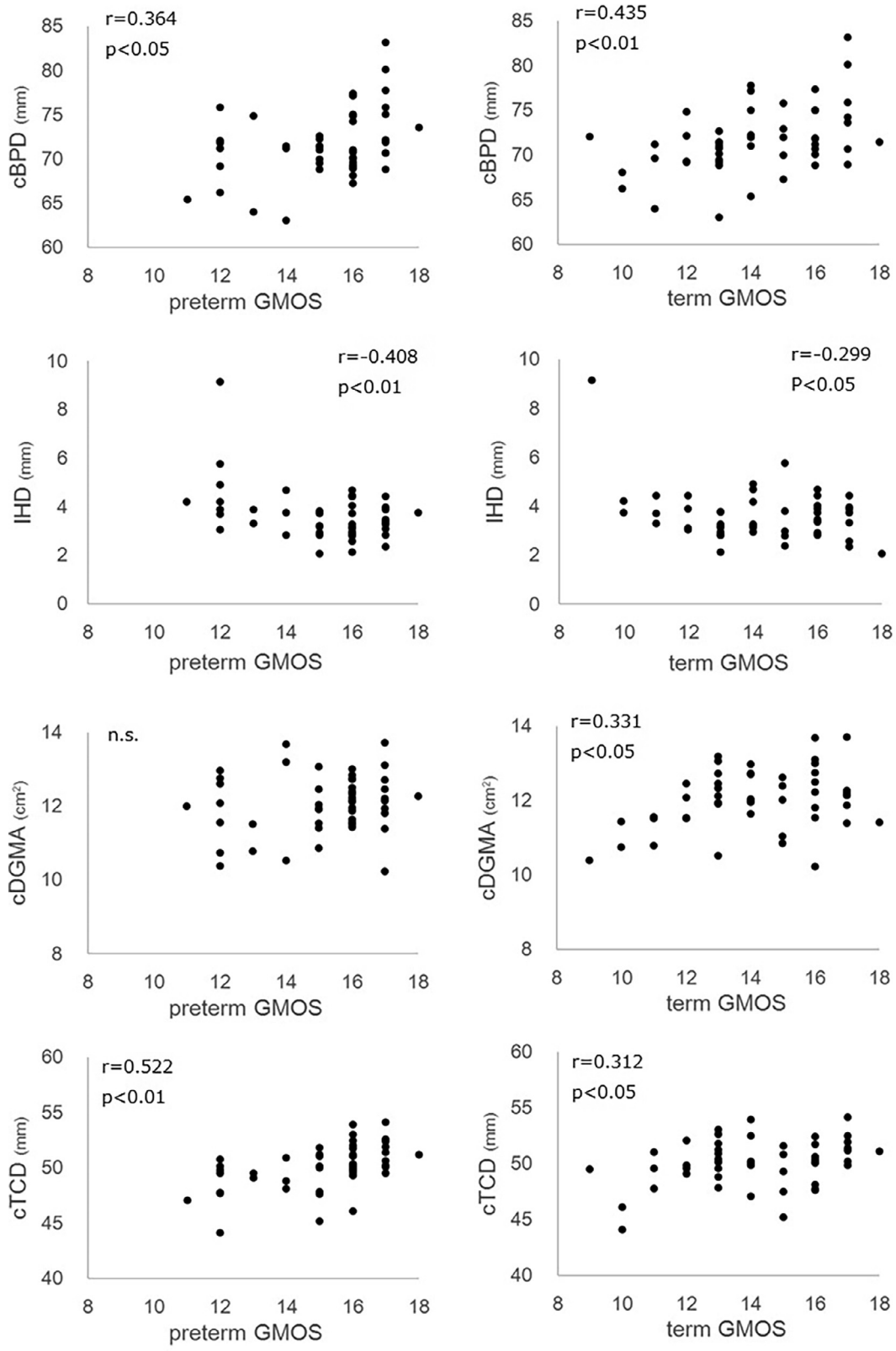

Fig. 2. The correlation between GMOS and measured values of MRI scores. The scatterplot on the left represents preterm GMOS and on the right represents term GMOS. The preterm GMOS were correlated with cBPD ($p < 0.05$), IHD, and cTCD ($p < 0.01$). The term GMOS were correlated with cBPD ($p < 0.01$), IHD, cDGMA, and cTCD ($p < 0.05$).

Table 3
Multivariate linear regression models. The related variables to GMOS.

GMOS preterm (30-36w)	B	Std. Error	Beta	p	95%CI of B	
Constant	17.10	0.42		<0.01		
MRI score	-0.31	0.07	-0.54	<0.01	-0.44	-0.18
Steroid administration	-1.42	0.51	-0.32	<0.01	-2.45	-0.40

Excluded variables (stepwise): Birth gestation, Period of intubated ventilation, Indomethacin use

R= 0.633,
R^2=0.41,
Adj. R^2=0.401

GMOS preterm (30-36w)	B	Std. Error	Beta	p	95%CI of B	
Constant	16.21	0.29		<0.01		
Cerebellum score	-1.38	0.34	-0.47	<0.01	-2.07	-0.70
CGM score	-0.71	0.22	-0.38	<0.01	-1.15	-0.27

Excluded variables (stepwise): WM score, Deep GM score, systemic steroid use

R= 0.627,
R^2=0.393,
Adj. R^2=0.366

GMOS term (37-43w)	B	Std. Error	Beta	p	95%CI of B	
Constant	16.66	0.58		<0.01		
WM score	-0.50	0.13	-0.46	<0.01	-0.77	-0.23
Cerebellum score	-0.96	0.44	-0.27	0.03	-1.84	-0.07

Excluded variables (stepwise): Gray matter score, Deep GM score
Std. Error; standard error, CI; confidence intervals.

R= 0.605
R^2=0.367,
Adj. R^2=0.339

the brain, we compared the measured values of each brain part to items on the GMs optimality list to examine the characteristics of GMs by brain morphologic change. The relevance was recognised between preterm GMOS and CGM and cerebellum score and between term GMOS and WM and cerebellum score. We compared the difference in IHD and cTCD values between the preterm optimal GMs group and the nonoptimal group and the difference in cBPD and cTCD values between the term GMs optimal group and nonoptimal group. Because the "quality of the GMs" item on the GMOS is the same as the global qualitative assessment of GMs, we compared the other items of GMOS. In the preterm GMs groups, the space score of the nonoptimal group was associated with a significantly longer IHD ($p < 0.05$), and sequence, space ($p < 0.01$), and tremorous movements ($p < 0.05$) of the nonoptimal group were associated with a significantly longer cTCD. With regard to the GMs of the term group, there were no significant differences in any item, except for quality score (Table 4).

Fig. 3 presents a boxplot diagram of the comparison of the cTCD values of each item on the preterm GMOS optimality list. The GMs of infants with small cTCD were characterised by poor sequence, lack of use of full space, and prominent tremulous movements.

4. Discussion

This study demonstrated the association between the quality of GMs and the MRI assessment scale, which reflects both injury and brain growth. The clinical background factors that may influence the quality of GMs can also be examined by multiple regression analysis. For preterm GMs, MRI score and systemic steroid administration were associated factors. For term GMs, the MRI score was the only associated factor. The association between the GMOS and the component score of each brain part were observed in the CGM and cerebellum for preterm GMs and in the WM and cerebellum for term GMs. With the exception of systemic steroid administration, clinical background was not recognised as a factor of GMs quality. There are reports that the quality of GMs in the preterm period deteriorates because of acute illness and systemic steroid administration [17,18]. Abnormal GMs are common in the first 14 days of life in extremely-low-birth-weight infants because of physiologic instability. Septicaemia and artificial ventilation are associated with deterioration of GMs [19]. In the present study, GMs recording was conducted when the patients were in a stable condition after acute illness. In addition, cases in which MRI could not be performed at TEA because of chronic respiratory failure were excluded from this study. Therefore, this study was conducted in subjects with a good general condition, which allows for less influence of clinical background factors. Our results suggested that hydrocortisone (HDC) was associated with a decrease in the GMOS in the preterm period. Hitzert reported that HDC treatment did not present a statistically significant difference of GMOS between the HDC treated group and the control group [17]. However, their subjects were few in number; there was a possibility of type 2 error. In their report the HDC group showed a tendency to lower GMOS on day 1 of HDC therapy. In addition, in all three cases of normal GMs before therapy, the GMs quality decreased on day 7 of therapy; two cases changed to PR, and one case changed to chaotic. We use

Table 4
The comparison of measured value and the items of GMs optimality list.

	IHD (mm)			cTCD (mm)		
Preterm GMOS	non-optimal	optimal	*p*	non-optimal	optimal	*p*
quality	4.7	3.4	<0.01*	48.5	50.6	<0.01*
sequence	4.1	3.4	n.s.	49.0	50.7	<0.01**
amplitude	3.8	3.6	n.s.	48.4	50.3	n.s.
speed	3.5	3.7	n.s.	49.9	50.2	n.s.
space	3.9	3.2	0.03**	49.2	51.6	<0.01*
rotation	4.2	3.6	n.s.	47.1	50.2	n.s.
onset-offset	3.7	3.5	n.s.	50.5	49.6	n.s.
tremor	3.7	3.6	n.s.	49.7	50.6	0.03**
	cBPD (mm)			cTCD (mm)		
Term GMOS	non-optimal	optimal	*p*	non-optimal	optimal	*p*
quality	68.0	70.2	0.04**	48.1	48.4	n.s.
sequence	67.6	70.2	n.s.	47.6	48.7	n.s.
amplitude	61.5	70.3	n.s.	42.7	49.2	n.s.
speed	67.8	69.6	n.s.	46.6	49.0	n.s.
space	68.6	69.4	n.s.	48.2	48.1	n.s.
rotation	61.2	70.4	n.s.	43.1	49.1	n.s.
onset-offset	67.6	70.1	n.s.	47.6	48.6	n.s.
tremor	69.0	68.8	n.s.	48.4	47.8	n.s.

Mean values and *p* values were presented.
cBPD; corrected biparietal diameter, IHD; Interhemispheric distance, cTCD; corrected transcerebellar diameter.
n.s; not significant. $^{*}p < 0.01$, $^{**}p < 0.05$.

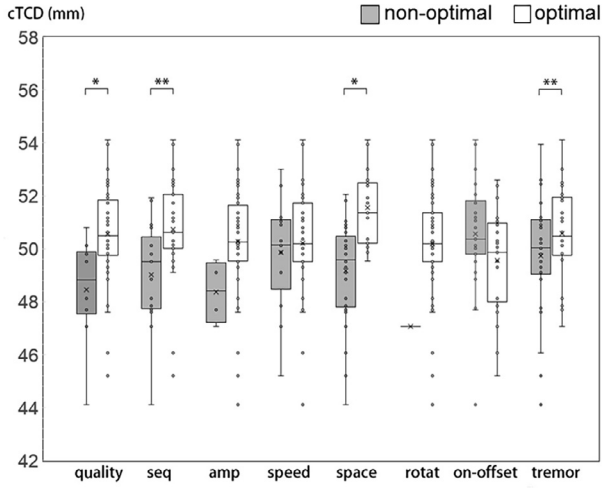

Fig. 3. The comparison of the cTCD values of each item on the preterm GMOS non-optimal and optimal groups. seq: sequence, amp; amplitude, rotat; rotatory components, on-offset; onset-offset of movements, tremor; tremulous movements $^{*}p < 0.01$, $^{**}p < 0.05$.

HDC to prevent late-onset circulatory collapse after the acute illness phase. The GMs recording and steroid administration period overlapped. Therefore, the quality of the GMs might have been decreasing in association with systemic steroid administration.

Regarding the trajectory of GMs, preterm infants often show abnormal GMs before term, which may normalise at TEA [20]. Contrary to this, there were many subjects in the present study whose GMs in the preterm period were normal, but changed to PR at TEA. De Vries reported that abnormal GMs at TEA are common in extremely low-birth-weight infants. Their GMs often appear stiff and cramped with extended legs [21]. Our subjects often presented the same character of GMs at TEA, which might have caused the decreasing GMs quality. Another possibility was an influence of neonatal care. The infants were swaddled during the preterm period. We loosened the swaddling surrounding the baby in the incubator and recorded the GMs. Ferrari reported that swaddling promotes a flexed posture of the limbs with adduction of shoulders, facilitates elegant wrist movements and movements toward and across the midline, and reduces abrupt movements [22]. After infants are out of the incubator at TEA, we record the GMs of the infants wearing only a nappy without swaddling. Many VLBWI tend to present posture and state instability if they are not swaddled or wearing clothing. The infants in nappies only began to cry soon after awakening, accompanied by jerky, fast, and large GMs or reflexes such as startle.

There are several reports regarding the association between term GMs and brain MRI at TEA [23,24]; however, the association between preterm GMs and brain MRI remains largely unexplored [25]. In the present study, we found a significant correlation between the GMOS for both age and the MRI score in TEA using semiquantitative detailed scoring. In consideration of the quality of GMs and related parts of the brain, it was reported that abnormal GMs at 1 and 3 months' corrected age were associated with WM abnormalities

on MRI at TEA [23,26]. In the present study, we also found a significant association between the GMOS at term age and WM score. However, the association was not found between GMOS at preterm age and WM score by multiple regression analysis. This might be due to low incidence of cystic periventricular leukomalacia, which is major disorder leading to WM lesions and abnormal GMs in preterm period [6]. There was only one case of cystic periventricular leukomalacia in this study subject.

Regarding the CGM score, Olsen reported that abnormal GMs at both preterm and term age were associated with larger IHD and higher CGM abnormality on MRI at TEA [25]. These findings were consistent with our results by univariate comparisons. However, no association was found between term GMs and CGM score by multiple regression analysis. Olsen analysed the quality of GMs with binary value: categorised as normal and abnormal by generalised estimating equations; whereas, we applied GMOS as a continuous variable that made the multiple regression analysis possible with a small number of subjects. Since the degree of GMs normality or abnormality is variable, it would be more beneficial to assess the GMs quality as continuous variables in multivariate analysis.

From the results of the present study, IHD, which was the main component of the CGM score, correlates with cerebrospinal fluid volume, and a larger IHD is thought to reflect an impairment in brain growth [11]. The GMs in the term period might reflect WM injury rather than brain growth impairment.

The first year after conception is characterised by high developmental activity in the brain, especially in the cortical subplate and cerebellum. As the complexity and variation of GMs emergence and the synaptic activity in the cortical subplate emergence coincide, Hadders-Alga speculated that the cortical subplate is the neural substrate of GMs complexity and variation [27]. The subplate is a transient structure that gradually dissolves between 3 months before term and 3 months' corrected age, when the cortical plate takes over. The subplate itself is not evaluated in MRI score; it would be related to CGM and WM scores.

Regarding the cerebellum score, in the present study, the GMs scores for both the preterm and term periods were associated with the cerebellum score. The relationship between infantile GMs and cerebellar size has been reported. Decreased cerebellar diameter at TEA was related to abnormal GMs at 3 months postterm age [28]. Abnormal GMs at term age were associated with a smaller TCD [25]. There has been no report showing the association between cerebellar size and the quality of GMs in the preterm period. It seems that this relevance was also found in preterm GMs and cerebellar size by applying the semiquantitative scoring of GMs quality. The normal value of the TCD at TEA in the preterm infant cohort was reported as mean 50.8 mm, standard deviation 3.3 mm [29]. In the present study, the mean cTCD of the preterm normal GMs group was 50.5 mm and that of the preterm abnormal GMs group was 48.8 mm. This showed that those with sufficient cerebellar growth had good-quality GMs.

The cerebellar volumetric growth impairment is prevalent in preterm infants even in the absence of destructive cerebellar injury [30]. The mechanism for impaired cerebellar development has been presumed to be the presence of severe supratentorial injury, that is, through the cerebro-cerebellar diaschisis [31]. However, in the present study, the cTCD was significantly small in the abnormal GMs group independently of the CGM or WM scores. It is unclear whether sufficient cerebellar growth created good-quality GMs or whether good-quality GMs promoted cerebellar growth. We speculated that motor and sensory feedback stimulus that was accompanied by GMs under in the extrauterine environment might be related to cerebellar growth. The cerebellar neurons receive excitatory inputs from the precerebellar nuclei outside the cerebellum. The Purkinje cells receive these inputs and send their axons to neurons in the deep cerebellar nuclei. The deep cerebellar nuclei neurons send their axons to other regions of the brain [32]. The anatomy and development of the cerebellum is conserved between mammals and bony fish. In zebrafish, it is reported that afferent sensory stimulation develops rapidly with the emergence of Purkinje cell excitability [33], which is also correlated with the anatomic development of the cerebellum [34].

With respect to the relation between cerebellar size and development, Shah reported that cerebellar volume reduction was correlated with cognitive and motor development at 2 years of age [35]. In view of the role of the cerebellum in motor learning and cognitive functioning, impaired cerebellar development in preterm infants may contribute to the motor impairments and cognitive deficits commonly experienced by preterm infants [36]. In the present study, when comparing the score for each GMOS item and the cTCD, the cTCD was significantly larger in cases with optimal sequence, space, and tremulous movement. These elements of GMs might be related to the cerebellar development.

The MRI assessment scale, which reflects both injury and brain growth, can be applied easily to MRI scans used for clinical purposes. The measurable components of the score of IHD, BPW, and TCD can be repeatedly obtained by brain ultrasonography in the NICU. By evaluating those measurements together with the assessments of GMs over time, more detailed relationships between GMs and brain morphologic development will be found.

In the present study, the association between the quality of GMs and brain morphologic development was confirmed. Both GM quality and brain morphologic development have been reported to be associated

with motor and cognitive prognosis [8,11]. It is important to evaluate them in combination to make an early accurate prediction of cognitive and intellectual impairments, which are currently difficult to predict in the neonatal period. This will lead to early intervention with family support, depending on the characteristics of the individual predicted impairment from the neonatal period.

We recognise several limitations of this study. First, the number of subjects was relatively small. There are possibilities of type 2 errors in the multiple regression analysis. GMs reflect the integrity and development of the central nervous system. Therefore, the development of any part of the brain may be somewhat related to GMs. We believe we have been able to clarify the predominant part of the brain that is strongly related to GMs quality. Second, the MRI scanned age and the setting of the scanning sequence parameters were not constant. On the other hand, this means that the scoring system can be applied to MRI scans that are done for clinical purposes. Therefore, general versatility of the MRI score is a high and promising indicator for the assessment of morphological character of the developing brain. Third, this study was an examination from a single facility. The GMs assessments and the MRI score are methods that can be generally performed in many facilities, and it is desirable that the results of the present study will be re-verified in multicentre study. Fourth, we have not presented the relationship in terms of prognosis of the subjects. Further prospective studies will be needed to confirm the association with long-term prognosis.

In conclusion, the developmental brain morphological characteristics that are the foundation of the emergence of GMs were clarified. Coevaluation of the GMs assessments and brain morphological assessments from the neonatal period leads to an accurate understanding of the developing brain and would be useful for the early prediction of various developmental impairments.

Acknowledgement

This work was supported by JSPS KAKENHI Grant Number 15K11705.

References

[1] Jarjour IT. Neurodevelopmental outcome after extreme prematurity: a review of the literature. Pediatr Neurol 2015;52:143–52.
[2] Brydges CR, Landes JK, Reid CL, Campbell C, French N, Anderson M. Cognitive outcomes in children and adolescents born very preterm: a meta-analysis. Dev Med Child Neurol 2018;60:452–68.
[3] Hadders-Algra M. Early diagnosis and early intervention in cerebral palsy. Front Neurol 2014;5:185. https://doi.org/10.3389/fneur.2014.00185.
[4] Einspieler C, Prechtl HF. Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system. Ment Retard Dev Disabil Res Rev 2005;11:61–7.
[5] 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 Pediatr 2017;171:897–907.
[6] Ferrari F, Cioni G, Einspieler C, Roversi MF, Bos AF, Paolicelli PB, et al. Cramped synchronized general movements in preterm infants as an early marker for cerebral palsy. Arch Pediatr Adolesc Med 2002;156:460–7.
[7] Beccaria E, Martino M, Briatore E, Podesta B, Pomero G, Micciolo R, et al. Poor repertoire general movements predict some aspects of development outcome at 2 years in very preterm infants. Early Hum Dev 2012;88:393–6.
[8] Hitzert MM, Roze E, Van Braeckel KN, Bos AF. Motor development in 3-month-old healthy term-born infants is associated with cognitive and behavioural outcomes at early school age. Dev Med Child Neurol 2014;56:869–76.
[9] Bruggink JL, Van Braeckel KN, Bos AF. The early motor repertoire of children born preterm is associated with intelligence at school age. Pediatrics 2010;125:e1356–63.
[10] Woodward LJ, Anderson PJ, Austin NC, Howard K, Inder TE. Neonatal MRI to predict neurodevelopmental outcomes in preterm infants. N Engl J Med 2006;355:685–94.
[11] Kidokoro H, Anderson PJ, Doyle LW, Woodward LJ, Neil JJ, Inder TE. Brain injury and altered brain growth in preterm infants: predictors and prognosis. Pediatrics 2014;134:e444–53.
[12] Einspieler C, Prechtl HF, Ferrari F, Cioni G, Bos AF. The qualitative assessment of general movements in preterm, term and young infants–review of the methodology. Early Hum Dev 1997;50:47–60.
[13] Als H, Tronick E, Lester BM, Brazelton TB. The brazelton neonatal behavioral assessment scale (BNBAS). J Abnorm Child Psychol 1977;5:215–31.
[14] Ferrari F, Cioni G, Prechtl HF. Qualitative changes of general movements in preterm infants with brain lesions. Early Hum Dev 1990;23:193–231.
[15] Kidokoro H, Neil JJ, Inder TE. New MR imaging assessment tool to define brain abnormalities in very preterm infants at term. AJNR Am J Neuroradiol 2013;34:2208–14.
[16] Itabashi K, Miura F, Uehara R, Nakamura Y. New Japanese neonatal anthropometric charts for gestational age at birth. Pediatr Int 2014;56:702–8.
[17] Hitzert MM, Benders MJ, Roescher AM, van Bel F, de Vries LS, Bos AF. Hydrocortisone vs. dexamethasone treatment for bronchopulmonary dysplasia and their effects on general movements in preterm infants. Pediatr Res 2012;71:100–6.
[18] Bos AF, Dibiasi J, Tiessen AH, Bergman KA. Treating preterm infants at risk for chronic lung disease with dexamethasone leads to an impaired quality of general movements. Biol Neonate 2002;82:155–8.
[19] De Vries NK, Erwich JJ, Bos AF. General movements in the first fourteen days of life in extremely low birth weight (ELBW) infants. Early Hum Dev 2008;84:763–8.
[20] Olsen JE, Brown NC, Eeles AL, Lee KJ, Anderson PJ, Cheong JL, et al. Trajectories of general movements from birth to term-equivalent age in infants born <30 weeks' gestation. Early Hum Dev 2015;91:683–8.
[21] De Vries N, Bos A. The motor repertoire of extremely low-birthweight infants at term in relation to their neurological outcome. Dev Med Child Neurol 2011;53:933–7.
[22] Ferrari F, Bertoncelli N, Gallo C, Roversi MF, Guerra MP, Ranzi A, et al. Posture and movement in healthy preterm infants in supine position in and outside the nest. Arch Dis Child Fetal Neonatal Ed 2007;92:F386–90.

[23] 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:e1184–9.
[24] Skiold B, Eriksson C, Eliasson AC, Aden U, Vollmer B. General movements and magnetic resonance imaging in the prediction of neuromotor outcome in children born extremely preterm. Early Hum Dev 2013;89:467–72.
[25] Olsen JE, Brown NC, Eeles AL, Einspieler C, Lee KJ, Thompson DK, et al. Early general movements and brain magnetic resonance imaging at term-equivalent age in infants born <30weeks' gestation. Early Hum Dev 2016;101:63–8.
[26] Peyton C, Yang E, Kocherginsky M, Adde L, Fjortoft T, Stoen R, et al. Relationship between white matter pathology and performance on the general movement assessment and the test of infant motor performance in very preterm infants. Early Hum Dev 2016;95:23–7.
[27] Hadders-Algra M. Neural substrate and clinical significance of general movements: an update. Dev Med Child Neurol 2018;60:39–46.
[28] Spittle AJ, Doyle LW, Anderson PJ, Inder TE, Lee KJ, Boyd RN, et al. Reduced cerebellar diameter in very preterm infants with abnormal general movements. Early Hum Dev 2010;86:1–5.
[29] Nguyen The Tich S, Anderson PJ, Shimony JS, Hunt RW, Doyle LW, Inder TE. A novel quantitative simple brain metric using MR imaging for preterm infants. AJNR Am J Neuroradiol 2009;30:125–31.
[30] Limperopoulos C, Soul JS, Gauvreau K, Huppi PS, Warfield SK, Bassan H, et al. Late gestation cerebellar growth is rapid and impeded by premature birth. Pediatrics 2005;115:688–95.
[31] Tam EW, Ferriero DM, Xu D, Berman JI, Vigneron DB, Barkovich AJ, et al. Cerebellar development in the preterm neonate: effect of supratentorial brain injury. Pediatr Res 2009;66:102–6.
[32] Hashimoto M, Hibi M. Development and evolution of cerebellar neural circuits. Dev Growth Differ 2012;54:373–89.
[33] Hsieh JY, Ulrich B, Issa FA, Wan J, Papazian DM. Rapid development of Purkinje cell excitability, functional cerebellar circuit, and afferent sensory input to cerebellum in zebrafish. Front Neural Circuits 2014;8:147.
[34] Bae YK, Kani S, Shimizu T, Tanabe K, Nojima H, Kimura Y, et al. Anatomy of zebrafish cerebellum and screen for mutations affecting its development. Dev Biol 2009;330:406–26.
[35] Shah DK, Anderson PJ, Carlin JB, Pavlovic M, Howard K, Thompson DK, et al. Reduction in cerebellar volumes in preterm infants: relationship to white matter injury and neurodevelopment at two years of age. Pediatr Res 2006;60:97–102.
[36] Allin M, Matsumoto H, Santhouse AM, Nosarti C, AlAsady MH, Stewart AL, et al. Cognitive and motor function and the size of the cerebellum in adolescents born very pre-term. Brain 2001;124:60–6.