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Assessment of neonatal brain volume and growth at different postmenstrual ages by conventional MRI

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Abstract

Data regarding neonatal brain volumes represent a basis for monitoring early brain development, and large sample of neonatal brain volume data has not been well described. This study was focused on neonatal brain volumes at different postmenstrual ages (PMA) and postnatal age (PNA).

A cohort of 415 neonates with PMA 30 to 43^{+4} weeks were recruited for the determination of brain volumes. Intracranial cavity (ICC), total brain tissue (TBT), and cerebrospinal fluid (CSF) were evaluated on the basis of T1-weighted sagittal plane magnetic resonance images. Brain magnetic resonance imaging was assessed using maturation scoring system and multiple linear regression analysis was conducted to forecast the effect factors of brain volumes.

TBT volume reached a peak growth at 39 to 40 weeks, ICC volume presented peak growth later at around 43 to 44 weeks, and CSF had a cliff fallen at 37 to 38 weeks PMA at scan. The maturation score increased along with PMA, and the TBT and CSF volumes were significantly different between higher and lower gestational age (GA) groups. The ICC and TBT volumes in higher GA group were larger than lower GA group. Most infants in higher GA group had higher TMS than those in lower GA group. Gender, PMA, PNA, and birth weight were predictors of TBT and ICC volumes.

Our results showed that premature volumes of ICC and TBT enlarged with the increasing PMA, while volumes of CSF decreased at 37 weeks. Premature earlier to leave the uterus can lead to brain mature retard although they had the same GA compared with those later birth neonates.

Abbreviations: CSF = cerebrospinal fluid, GA = gestational age, GM = germinal matrix, ICC = intracranial cavity, MRI = magnetic resonance imaging, NICU = neonatal intensive care unit, PMA = postmenstrual ages, PNA = postnatal age, TBT = total brain tissue, TEA = term-equivalent age.

Keywords: brain development, cerebrospinal fluid, intracranial cavity, MRI, neonate, postmenstrual age

1. Introduction

Cranial capacity is an indirect approach to evaluate the size of the brain.[1–3] Previous studies with limited samples have studied magnetic resonance imaging (MRI) of brain development in premature and term newborns.[4,5] Total brain tissue (TBT) volume accounts for 20% to 40% of the variance in cognitive and educational performance in extremely preterm adolescents as an important marker for neurodevelopmental deficits in preterm children.[6–8] Cross-sectional studies demonstrated that a linear increase of brain volume was observed between 25 and 40 weeks of gestation, with a difference in regional growth rates.[9] Total brain volume increases sharply, and the majority of sulcal and gyral formation takes place in the last 15 weeks of pregnancy.[10] Preterm undergoes a neonatal intensive care environment, in which it might possibly disturb their development.[11] Premature brain volumes at term-equivalent age (TEA) are influenced by various clinical factors, including brain injury, intrauterine growth retardation, chronic lung disease, and the use of corticosteriods.[12,13]

MRI is a noninvasive tool and provides high-resolution images of brain structures without ionizing radiation effects, and it has been used to assess brain volumes directly by means of tissue segmentation.[1,14] However, quantitative MRI examinations were not a practical option in routine clinical settings. Because of the small brain size and developing nature of the tissue, the quality of neonatal images is frequently poor with insufficient spatial resolution, low tissue contrast as a result of shorter scan times, and ambiguous tissue intensity,[15] which will hinder subsequent image processing such as image registration and tissue segmentation. Many studies have suffered from these problems.[16–18] The total brain volumes in newborns can be
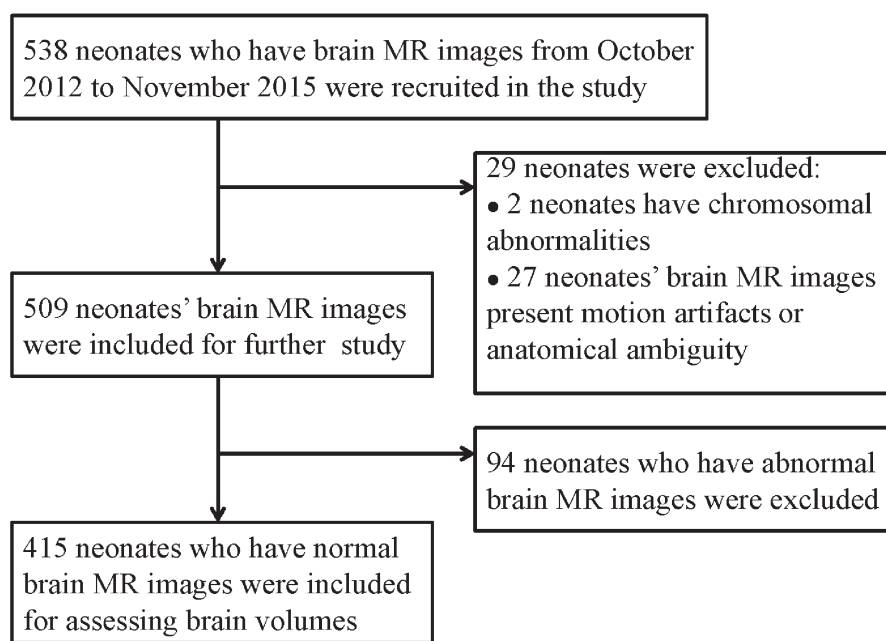
Figure 1. The flow chart of infants' selection.

obtained from T1-weighted sagittal conventional MR images using the Cavalieri principle of stereologic method.[19,20]

The purposes of this study were to calculate the neonatal brain volumes, evaluate the neonatal brain's development, and predict the influencing factors of brain volumes, which will provide important data of neonatal brain volumes for long-term complications and future clinical interventions.

2. Material and methods

2.1. Patients

A cohort of 538 Chinese Han neonates from the Neonatal Intensive Care Unit (NICU) at Zhongnan Hospital of Wuhan University was recruited in this study, from October 2012 to November 2015. Ninety-four infants were excluded due to abnormality, cystic periventricular leukomalacia, hemorrhagic parenchymal infarction, pseudocysts, and chromosomal abnormalities. Twenty-seven neonates were further excluded due to anatomical ambiguity (Fig. 1). Four hundred fifteen neonatal brain images were finally included in this study, which were born at median gestational age (GA) of 34^{+4} (27^{+3}–42^{+4}) weeks. The newborn is categorized based on its GA into preterm, full term, and post-term.[21,22] Apgar scores were recorded at 1, 5, and 10 minutes after delivery.[23] The postmenstrual age (PMA) at imaging was calculated as the GA-at-birth plus the time elapsed since birth and the postnatal age (PNA) at scan was defined as the interval time between birth and scan.[24] The median PMA at imaging was 36^{+4} (30–43^{+4}) weeks and PNA at scan 12 (2–74) days. The characteristics of the infants are presented in Table 1.

2.2. Ethics consent

This study was conducted after approval from the Zhongnan Hospital of Wuhan University Ethics Committee (clinical trial

Table 1

Characteristics of 415 neonates.

	Range	Number (%)	Median
Baseline factor (total number = 415)			
Gender—male		247 (60)	
Gestational age at birth, wk	27^{+3}–40^{+3}		34^{+4}
extremely preterm (< 28)		1	
very preterm (≥ 28, < 32)		52	
moderate to late preterm (≥ 32, < 37)		261	
full term (≥ 37, ≤ 42)		101	
post term (> 42)		1	
Birth weight, g	900–4400		2100
<1000		2 (0.5)	
1000–2500		286 (69)	
≥2500		127 (30.5)	
Births: Singleton		310 (75)	
Vaginal delivery		101 (24)	
Amniotic fluid			
Clear		352 (84.8)	
I° Faecal pollution		39 (9.4)	
II° Faecal pollution		7 (1.7)	
III° Faecal pollution		14 (3.4)	
Hemorrhagic		3 (0.7)	
Apgar scores	0–10		
One minute	2–9		8
Five minutes	3–10		9
Ten minutes	5–10		10
PNA at scan, d	2–74		12
PMA at imaging, wk	30–43^{+4}		36^{+4}
Acquired medical factors			
Confirmed sepsis		10 (2.4)	
Assisted ventilation		211 (51)	
Mechanical ventilation		59 (28)	
Continuous positive airway pressure		152 (72)	

PMA = postmenstrual age at time of MRI (wk), PNA = postnatal age at time of MRI (d).

registration No. ChiCTR-ORC-16008872). All parents or guardians signed an informed consent form.

2.3. MRI data acquisition

For the MRI examination, infants were unsedated, sleeping naturally after a feed, and wrapped in blankets and a deflated vacuum pillow. Data were acquired using a Siemens Magnetom Trio a Tim 3.0 T scanner (Siemens Medical Systems, Erlangen, Germany) with the following parameters for the calculation of brain volumes. T1-weighted images acquisition parameters were: slice number = 19, slice thickness = 3 mm, gap distance factor 30% interleaved (space between slice = 3.9 mm), field of view (FOV) read/phase = 140 mm/100%, repetition time (TR) = 400 ms, echo time (TE) = 2.7 ms, flip angle = 80°. T2-weighted images -turbo spin-echo acquisition parameters were: slice = 20 thickness mm, gap distance factor 30% interleaved (space between slice = 3.9 mm); FOV read/phase = 140 mm/100%, slice thickness = 3 mm, space between slices = 3.9 mm; TR = 4360 ms, TE = 98 ms, flip angle = 120°.

2.4. Calculation of neonatal brain volumes

Brain volumes were evaluated on the basis of T1-weighted sagittal plane MRI using Cavalier principle.[19,25,26] The slices sectioned the brain as a series of parallel plane with a constant distance of T=3.9 mm. Then an unbiased estimation of brain volume V is obtained by multiplying the area of all sections by the slice interval T, $V = T \times \sum_{i=1}^{n} A_i$, in which "n" is the number of slices and "A_i" denotes the section area of the slice. The area of the section was calculated with the pixel number occupied by the brain in the slice.

Each MRI slice was first preprocessed by a series of morphological operation based on brain shapes, such as removing neck, nose, etc. Then a sequence of intensity-based morphological operation was used to remove skull, scalp, fat, and background noise.[27] Subsequently a histogram of intensity is constructed and modeled with a Gaussian mixture model to obtain the gray levels of total brain tissue and cerebrospinal fluid

donated by I_{TBT} and I_{CSF}, then the threshold intensity is obtained by the average value, $I_{th} = (I_{TBT} + I_{CSF})/2$.[28,29] This procedure is repeated for 3 slices closest to the center of brain to obtain the mean of the threshold. Thus the TBT and CSF volumes are calculated from the brain volume in each slice by using the mean threshold.

Image was processed in 3 steps. Loading original MR image (Fig. 2A). The original image was transferred to a matrix (256 ×256 pixels) with pixel spacing = [0.5469, 0.5469]. Extraction of brain (Fig. 2B). Distinguishing cerebral parenchyma and CSF (Fig. 2C and D). Using the mean threshold from histograms, the brain is segmented into 2 parts of CSF and TBT (Fig. 2E).

2.5. Reliability

Reliability analyses were performed using 40 randomly chosen subjects, ranging from 30 to 43 weeks' PMA. The intraclass correlation coefficient using a 2-way mixed effects model with absolute agreement on single measures was 0.970 (95% CI 0.771, 0.991; $P < .001$).

2.6. Maturation scoring system

According to the scoring system to assess cerebral maturation in preterm infants,[30] brain images were assessed using 4 parameters: levels of myelination (M), cortical infolding (C), germinal matrix (GM), and bands of migrating glial cells (B). Myelination leads to an increase in signal intensity on T1-weighted sequences and a decrease in signal intensity on T2-weighted sequences (scores 1–7 points with the appearance of myelination). The cortex is seen as having high signal intensity on T1-weighted images and low signal intensity on T2-weighted images (score 1–6 points with the depth of folding and sulci in frontal and occipital cortex). The germinal matrix shows high signal on T1-weighted images and low signal on T2-weighted images (score 1–4 points with the disappearance of germinal matrix). Bands of migrating glial cells present three bands of alternating signal intensity on T2-weighted sequences (score 1–4 points with the disappearance of migrating glial cells).
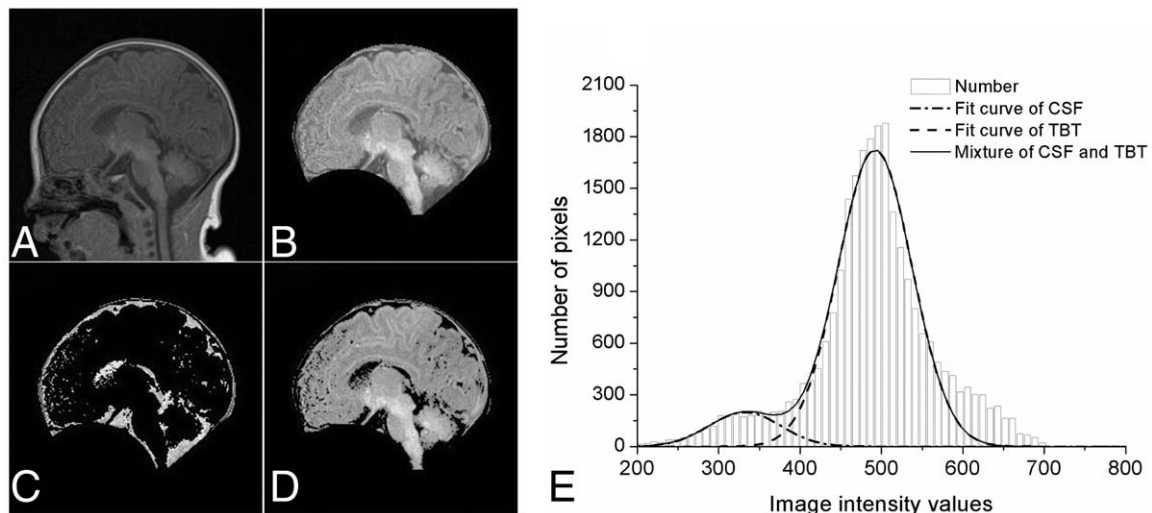

Figure 2. Image processing steps. A, Original T1-weighted brain MR image in sagittal plane. B, Edge of brain removing. C, Panorama of cerebrospinal fluid. D, Panorama of cerebral parenchyma. E, Gaussian mixture model for total brain tissue and cerebrospinal fluid.

2.7. Growth model for neonatal brain

Gompertz functions are sigmoid functions often used to model growth, where growth is initially low, then accelerates to reach peak growth, and then decelerates to low growth again at the end.[31] Gompertz-like function was used to model the relation of brain volumes with age: $f(t) = \beta_1 + \beta_2 e^{-e^{-\beta_3(t-\beta_4)}}$, in which β_1 is the initial value of f(t) and $\beta_1 + \beta_2$ is the ending value of f(t). β_3 and β4 are the parameters that adjust the growth rate and the t value is that f(t) reaches peak growth.[32]

2.8. Statistical analysis

Statistical analysis was performed by SPSS for Windows (version 20.0, IBM Corp, Armonk, NY). To investigate the differences in neonatal brain volume with different GA, 174 infants selected from 415 infants were divided into lower GA and higher GA groups, which have an equal-sized sample and equivalent PMA at scan. Each of group included 87 infants, ranged from 32^{+3} to 41 weeks PMA at scan. Every paired age at scan matched sample contained a relatively low GA infant and a relatively high GA infant. The lower GA group was defined as PNA < 14 days and the higher GA group was defined as PMA ≥ 14 days (PNA = PMA–GA, days). Independent samples t tests were used to determine the differences between the 2 groups. Multiple linear regression models were used to analyze the relation of perinatal factors and brain volumes. $P < .05$ was considerate significant difference.

3. Results

3.1. Brain volumes and growth rate of newborns

Table 2 shows intracranial cavity (ICC), TBT, and CSF volumes of 415 neonates aged from 30 to 43 weeks' PMA. The proportion of volume of TBT to volume of ICC gradually increased, while the fluctuating range of ratio of volume of CSF to volume of ICC decreased from 12% to 10% at 33 to 37 weeks' PMA and its proportion declined dramatically to 9% at 38 weeks' PMA.

The Gompertz function was used as the growth model of neonatal brain volumes with different PMA (Fig. 3A–C). Volumes of ICC and TBT enlarged with the increasing PMA, while CSF decreased with increasing PMA. The TBT volume reached a peak growth at around 39 to 40 weeks' PMA (β4 = 39.8, adjusted R^2 = 0.49), while the ICC volume present peak growth later at around 43 to 44weeks' PMA (β4 = 43.5, adjusted R^2 = 0.44). The CSF have a cliff fallen at around 37 to 38 weeks PMA at scan (β4 = 37.7, adjusted R^2 = 0.04).

3.2. Maturation determination of neonatal brain at different PMA

Figure 4A and B display a set of axial T1- and T2-weighted neonatal brain images aged from 31 to 43 weeks' PMA. The maturation score (TMS) increased along with PMA. Myelination can be seen in the posterior limb of the internal capsule from 36 weeks' PMA (M = 3 or 4) (Fig. 4A), and there was a dramatic increase in cortical folding, which transforms a relatively smooth surface at 41 weeks' PMA at imaging to a highly folded structure by 43 weeks' PMA (Fig. 4B). After 39 weeks' PMA at imaging, the frontal and occipital cortex was more folded and rich in sulci and the insula are completely infolded (C = 5). The distribution of the germinal matrix is not evident after 40 weeks' PMA (GM = 4). Similarly, bands of migrating glial cells tend to disappear after 39 weeks' PMA at imaging (B = 4). Previous data have shown that the full TMS is 21 points (GM4, B4, M7, C6) and an infant of 52 weeks' PMA can get full scores.[33] The TMS at 43 weeks' PMA

Table 2

Descriptive statistics of neonatal brain volumes at different PMA.

Brain volume (cm³)	PMA (wk)	N	Mean	Std. deviation	Max.	Min.	95% Confidence interval for mean	
							Lower bound	Upper bound
V.ICC	30–33	36	356.01	42.14	445.51	268.30	341.75	370.27
	34	31	370.19	34.85	445.66	312.88	357.41	382.97
	35	73	392.17	36.17	489.52	298.14	383.73	400.61
	36	101	400.70	33.54	486.99	314.19	394.08	407.33
	37	49	411.07	37.26	499.92	322.87	400.37	421.78
	38	33	419.73	36.97	505.38	350.43	406.62	432.84
	39	36	441.12	49.14	536.43	304.60	424.49	457.75
	≥40	56	474.73	42.67	566.22	331.94	463.30	486.16
	Total	415	409.28	50.57	566.22	268.30	404.40	414.16
V.TBT (%)	30–33	36	312.61 (88)	36.90	401.73	232.87	300.12	325.09
	34	31	332.96 (90)	32.81	405.98	276.06	320.92	344.99
	35	73	348.90 (89)	32.51	452.62	264.37	341.31	356.49
	36	101	359.08 (90)	32.47	438.41	287.65	352.67	365.49
	37	49	364.73 (89)	33.71	430.98	271.65	355.05	374.42
	38	33	382.90 (91)	33.99	456.40	322.18	370.84	394.95
	39	36	406.69 (92)	48.37	500.95	288.82	390.33	423.06
	≥40	56	433.41 (91)	40.62	531.36	291.35	422.53	444.29
	Total	415	368.03 (90)	49.40	531.36	232.87	363.26	372.79
V.CSF (%)	30–33	36	43.40 (12)	12.17	75.80	20.58	39.29	47.52
	34	31	37.23 (10)	10.78	57.43	20.01	33.28	41.19
	35	73	43.58 (11)	10.41	75.18	24.57	41.15	46.01
	36	101	41.87 (10)	9.14	70.39	20.46	40.07	43.68
	37	49	46.34 (11)	12.84	84.30	21.98	42.65	50.03
	38	33	36.83 (9)	16.94	95.36	12.21	30.82	42.84
	39	36	34.43 (8)	12.66	70.85	8.75	30.14	38.71
	≥40	56	41.32 (9)	16.55	92.52	18.53	36.89	45.75
	Total	415	41.37 (10)	12.75	95.36	8.75	40.14	42.60

%: Percentage of volume of TBT (V.TBT)/volume of ICC (V.ICC) or volume of CSF (V.CSF)/V.ICC.

$$f(t) = 317.00 + 528.46 \times e^{-e^{-0.09 \times (t-43.45)}}$$

$$f(t) = 287.36 + 337.22 \times e^{-e^{-0.13 \times (t-39.80)}}$$

$$f(t) = 42.37 + 5.08 \times e^{-e^{-84.99 \times (t-37.67)}}$$
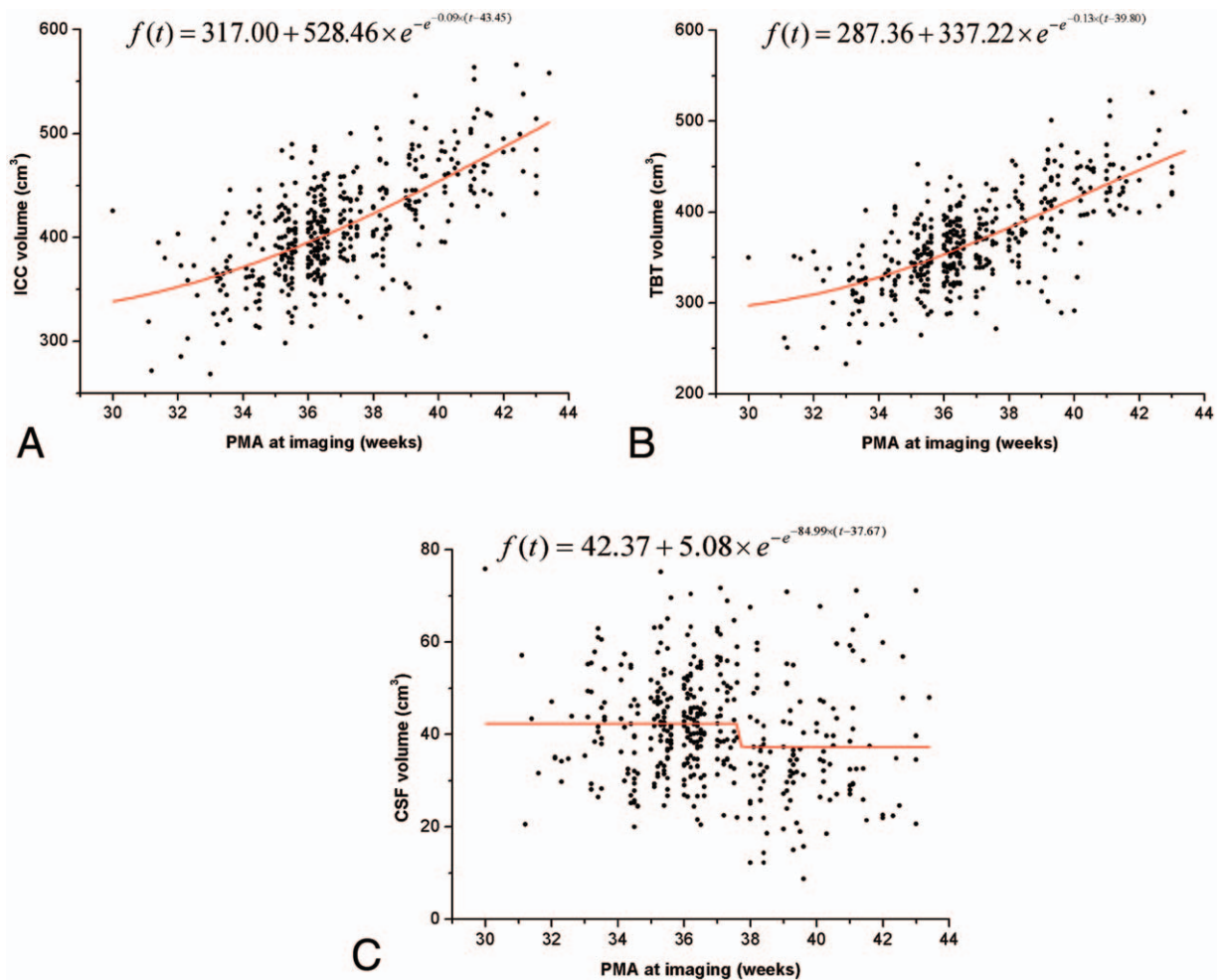
Figure 3. Neonatal brain volumes (ICC, TBT, and CSF) increased with PMA at imaging. The red line represents the fitting curve of the data.

was 17 points, which illustrates that the neonatal brain will continue experiencing a long period of development to achieve complete maturation outside of the uterus.

3.3. The impact of leaving uterus earlier on premature brain development

To evaluate the effect of different GA and PNA on the neonatal brain development, the growth rate and maturation scores between lower GA group and higher GA group were analyzed. There was no significant difference in ICC between the 2 groups, but significant differences in volume of TBT and CSF. Figure 5A to C shows the growth of brain volumes with increasing PMA for the 2 groups. The ICC and TBT volumes in higher GA group were larger than lower GA group at the equivalent PMA. This phenomenon was obvious between 33 weeks to 44 weeks' PMA. The ICC and TBT volumes in lower GA group have a trend to catch up with higher GA group at 44 weeks' PMA. However, the CSF volume in higher GA group dramatically fell at around 37 to 38 weeks' PMA. And the CSF volume in lower GA group was not well fitted by the Gompertz function curve (adjusted $R^2 = -0.03$).

Thirteen pairs of infants were selected from the 87-paired age-matched infants at different PMA at scan. And their brain volumes and total maturation scores were displayed in Table 3. Most of the infants in higher GA group had higher TMS than those in lower GA group, with the exception of infants with 31, 32 weeks' PMA. In these 4 subgroups, infants with higher GA had the same TMS as those with lower GA. These results imply that premature earlier to leave the uterus can lead to brain mature development retard although they had the same GA compared with those later birth neonates.

3.4. Perinatal factors and neonatal brain volumes

Multiple linear regression analysis was conducted using a stepwise procedure to forecast the factors that affect the brain volume. Regression models were set up for TBT, CSF, and ICC volumes, respectively. And independent variables included PNA, PMA, birth weight, births (singleton or multiple birth), gender, Apgar scores, pattern of assisted ventilation, and GA.

Results of multiple linear regression analysis are shown in Table 4. Gender, PMA, PNA, birth weight, and births were predictors of TBT and ICC volumes. However, PNA and pattern of assisted ventilation were predictors of CSF volume. This showed that the TBT and ICC volumes have a significant correlation of gender, birth weight, births, PNA, and PMA. These predictors have positive correlation of ICC and TBT volumes
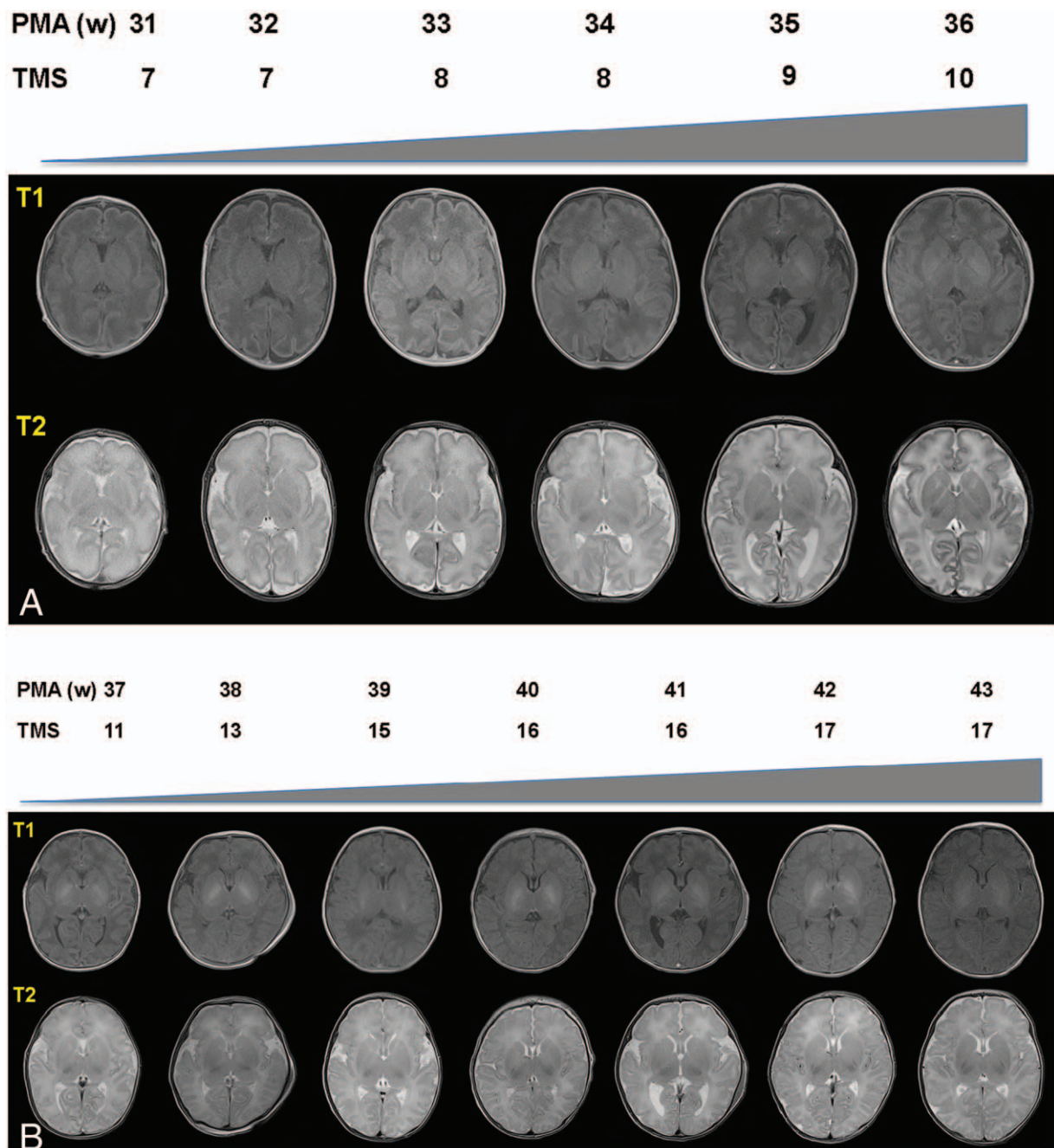
Figure 4. Neonatal brain MR images and total maturation scores with different PMA. A, It displayed T1 and T2-weighted transverse section images of 31 weeks' to 36 weeks' PMA. B, It displayed T1 and T2-weighted transverse section images of 37 weeks' to 43 weeks' PMA.

with the exception of gender. Gender was negatively correlated of ICC and TBT volumes, which indicated that the TBT and ICC volumes of male infants were larger than female infants. The primary predictor of ICC and TBT volumes was PMA (standardized coefficients $\beta = 0.49$ and 0.52, respectively). Birth weight was the second vital predictor of ICC and TBT volume (standardized coefficients $\beta = 0.36$ and 0.37). PNA was positively related with CSF volume. Pattern of assisted ventilation had significant correlation of CSF volume, which indicated that infants who acquired mechanical ventilation had larger CSF volume.

4. Discussion

To our knowledge, no published, in vivo conventional MR imaging studies of China's Han newborns brain changes in the neonatal life span from premature to term neonates with large sample sizes exist. Brain volumes' calculation and its growth rate's determination for neonates from 30 weeks to 43 weeks' PMA would benefit to clinical evaluation and intervention for premature babies.

In the present study, we show that the TBT, and CSF volumes were smaller than those previous reports,[34] and larger in ICC

Table 3

The total maturation score of lower and higher GA groups.

PMA (wk)	GA (wk)	BW (g)	V.ICC (cm³)	V.TBT (cm³)	V.CSF (cm³)	M (1–7)	C (1–6)	GM (1–4)	B (1–4)	TMS
31	30	1920	394.61	351.23	43.38	2	2	2	1	7
31	28	1380	318.51	261.34	57.17	2	2	2	1	7
32	30	1760	372.57	337.47	35.09	2	2	2	1	7
32	27	1110	358.63	324.44	34.19	2	2	2	1	7
33	32	1830	398.08	342.87	55.22	2	3	2	1	8
33	30	1720	372.67	337.94	34.73	2	2	2	1	7
34	33	1800	445.51	401.73	43.78	2	3	2	1	8
34	29	1550	381.30	327.13	54.17	2	2	2	1	7
35	34	2500	416.24	377.10	39.14	2	3	2	2	9
35	28	1230	391.94	344.05	47.89	2	3	2	2	8
36	35	2180	423.26	396.39	26.88	3	3	2	2	10
36	33	2000	390.60	352.50	38.10	2	3	1	2	8
37	36	2460	425.60	372.57	53.03	3	4	2	2	11
37	32	1770	405.24	350.14	55.11	2	3	2	2	9
38	37	2850	405.48	380.40	25.08	4	3	3	3	13
38	28	1150	447.25	352.09	95.36	2	3	2	3	10
39	38	3000	444.67	425.11	19.56	3	5	3	4	15
39	36	2360	473.72	416.71	57.01	3	4	3	4	14
40	39	3400	474.49	432.07	42.42	3	5	4	4	16
40	37	2800	459.29	450.53	8.75	3	4	4	2	15
41	40	3530	503.30	474.40	28.90	4	5	4	3	16
41	39	3700	500.59	462.04	38.55	4	5	4	3	16
42	41	3500	482.06	459.50	22.57	4	5	4	4	17
42	39	3150	421.66	399.68	21.98	3	5	4	4	16
43	42	3370	463.27	406.39	56.88	4	5	4	4	17
43	40	3500	484.44	449.87	34.57	3	5	4	4	16

B = bands of migrating glial cells, BW = birth weight, C = cortical infolding, G = germinal matrix, M = myelination, TMS = Total Maturation Score.

volume than recent published data.[32] The discrepancy in neonatal brain volume may be the reason of different PMA distribution in cohort study sample, method of estimation brain volume, as well as the racial difference. Although real brain volume can be estimated by fluid displacement technique,[35] it showed the living brain volume was larger than that for the postmortem brain.[36] The inferred reason is that the postmortem brain might shrink during fixing, producing a different measurement from that in living brain. Some cohort studies have established the influence of preterm birth on brain tissue volumes [10,37] and its reductions appeared to be most prominent in more immature infants. It was demonstrated that brain tissue

volumes of preterm infants at term were reduced primarily in cortical gray matter, subcortical gray matter, myelinated white matter, and cerebellum, with a corresponding increase in CSF compared with healthy term controls.[13] CSF volume will change with regional brain tissue alteration, and regional tissue volumes usually reduce in preterm infants; thus the CSF volume will increase reciprocally. In our study, the TBT volume reached a peak growth at around 39 to 40 weeks' PMA, while the ICC volume presents peak growth later at 43 to 44 weeks' PMA. The CSF volume has a cliff fallen at around 37 to 38 weeks PMA at scan. It has been reported that the brain, particularly the microstructure, grows rapidly at near-term age, the brain

Table 4

Predictors of brain volume of neonates.

Dependent variable	Adjusted R²	Model		Standardized coefficients	Unstandardized coefficients	
		Constant	Predictors	B	β	P
V.ICC	0.50	−47.87	PMA	10.39	0.49	.00*
			PNA	0.82	0.16	.00*
			Birth weight	0.03	0.36	.00*
			Births	14.18	0.12	.00*
			Gender	−9.57	−0.09	.01*
V.TBT	0.56	−91.68	PMA	10.62	0.52	.00*
			PNA	0.56	0.11	.01*
			Birth weight	0.03	0.37	.00*
			Births	12.92	0.11	.00*
			Gender	−10.20	−0.10	.00*
V.CSF	0.06	37.02	PNA	0.16	0.20	.00*
			Assisted ventilation	0.13	2.34	.01*

Volume of ICC (V.ICC), volume of TBT (V.TBT), volume of CSF (V.CSF).
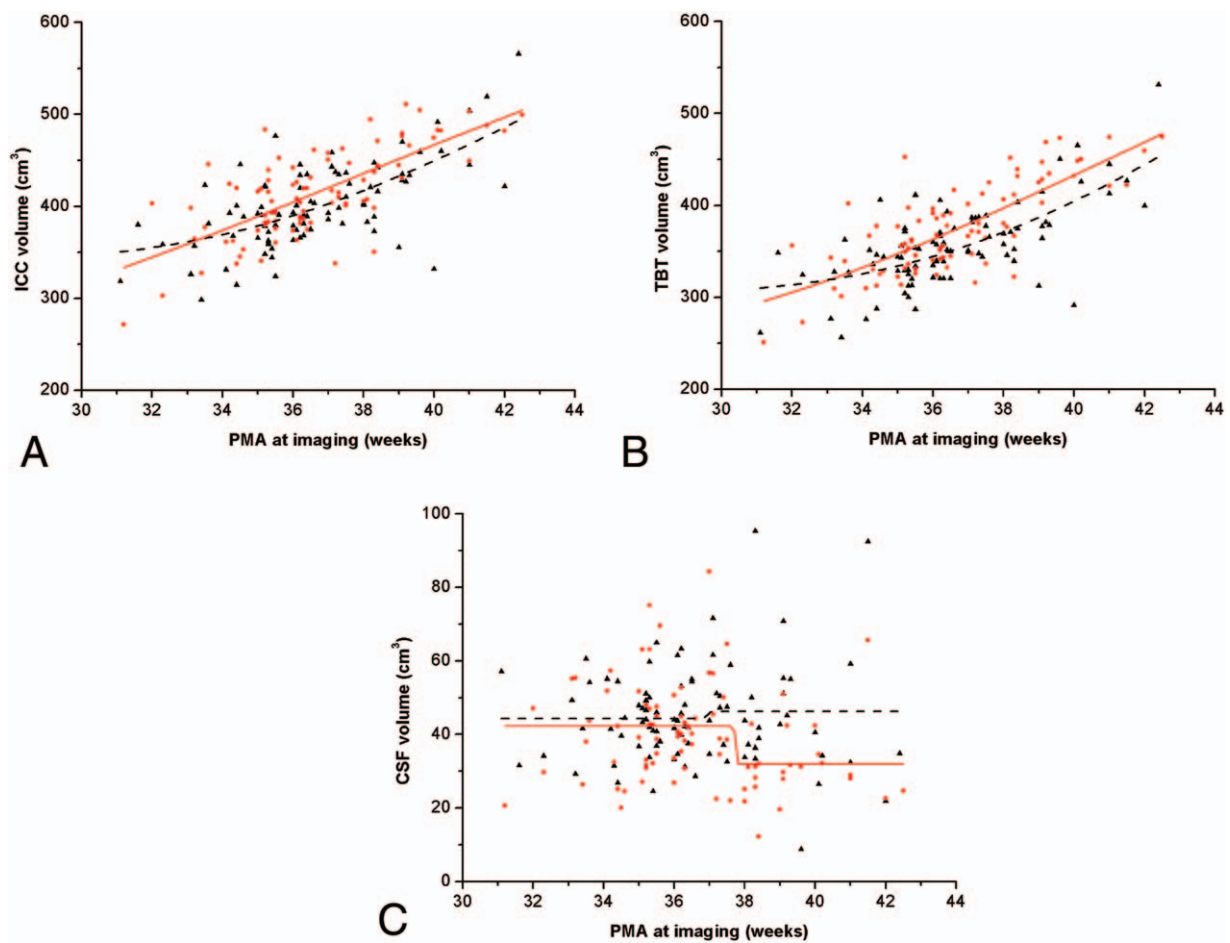* P value is significant at the .05 level.

Figure 5. Comparison in brain volumes of lower GA and higher GA groups by Gompertz model. Red dots and solid line represented brain volume and fitting curve of higher GA group, respectively. Black triangle points and dash line represented brain volume and fitting curve of lower GA group, respectively. The fitting functions of ICC, TBT, and CSF for lower GA group were $f(t) = 339.65 + 502.61 \times e^{-e^{-0.10 \times (t-44.02)}}$, $f(t) = 301.87 + 659.96 \times e^{-e^{-0.10 \times (t-46.41)}}$ and $f(t) = 44.28 + 1.95 \times e^{-e^{-21.40 \times (t-36.91)}}$ respectively. The corresponding functions for higher GA group were $f(t) = 220.99 + 555.39 \times e^{-e^{-0.08 \times (t-37.33)}}$, $f(t) = 235.87 + 588.71 \times e^{-e^{-0.08 \times (t-41.10)}}$ and $f(t) = 42.25 + 10.22 \times e^{-e^{-75.97 \times (t-37.72)}}$.

volumetric growth peaks at 35 weeks and the CSF present peak growth later at around 38 to 39 weeks.[32,38] The difference of findings may be accounted for different range of age.

To explore the influence of GA-at-birth, we compared brain volumes between lower GA and higher GA groups at the same PMA at scan. There was no significant difference in volume of ICC at the equivalent PMA at scan of the 2 groups, but significant differences in volume of TBT and CSF. The ICC and TBT volumes in higher GA group were larger than lower GA group at the equivalent PMA. This implies that GA as an internal impact of immaturity plays a role in brain development.[13] After 44 weeks' PMA at scan, the ICC and TBT volumes in lower GA group have a trend to catch up with higher GA group in our study. Some brain regions in infants with lower GA may undergo an accelerated growth after birth and some treatments of neonates with lower GA may benefit regional development.[39] Until full-term-equivalent age, premature infants still have reduced cerebral volume, increased CSF volume compared with age-matched term controls.[13,32,40] Even without major central nervous system lesions, some premature infants still have smaller brains at TEA than do full-term controls.[41] And smaller brain volumes at TEA may not only be a direct consequence of

prematurity itself, but also correlated with some postnatal complications, such as prolonged oxygen requirement.[42]

Myelination begins at 32 weeks' PMA, emerges in the posterior limb of the internal capsule (PLIC) at 36 to 38 weeks' PMA, and achieves full myelination by 46 weeks' PMA.[43] At the beginning of 36 weeks' PMA, infants born near term showed evidence of myelination in PLIC, while prematurely born infants did not show myelination in this region in our study. Comparing lower GA and higher GA groups, lower GA infants fell behind in TMS, even in the case of similar brain volumes. This demonstrated that premature left the mother earlier might delay the myelination development. Due to more volume of CSF, infants with lower GA have larger ICC and TBT volumes than those with higher GA at 38 and 39 weeks' PMA. The infants with lower GA had lower TMS, but larger brain volumes than infants with higher GA at 38, 39, and 43 weeks' PMA, which indicated that the degree of neonatal brain maturation is not always synchronized with the pace of growth of brain volumes.

Our data show that PMA and PNA rather than GA were positively associated with brain volumes. PNA and pattern of mechanical ventilation were 2 predictors of CSF volume. Intubation, as a basic step in mechanical ventilation, is associated

with improper brain development in infants born preterm.[44,45] Furthermore, data suggest that ICC and TBT are larger in male infants than in female infants. It has been found that male infants have an approximately 12% greater ICC than female infants in a sample aged.[46] Premature male infants have greater cortical and white matter volumes, but identical cortical sulcation compared with premature female infants.[47] In preterm infants, there were differences in global and regional cortical sulcation indices between the sexes.[10] These differences between male and female preterm infants persist to the age of 5 years.[48] We acknowledge several limitations of the present study. First, the number of extremely preterm and very early preterm infants ($\leq$30 weeks' PMA) was few, and had only a Chinese population could be a limitation for the study. Second, considerable growth differences were observed in PMA at imaging because of different GA. This heterogeneity in neonates at different PMA at scan may lead to biases. Finally, deficiency of following up of brain MRI data may lead to an incomplete display of dynamic alteration of brain volumes.

In conclusion, our results showed premature volumes of ICC and TBT enlarged with the increasing PMA, while volumes of CSF decreased. Premature earlier to leave the uterus can lead to brain mature retard although they had the same GA compared to those later birth neonates.

Author contributions

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