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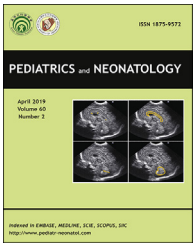

Original Article

Corpus callosum and cerebellar vermis size in very preterm infants: Relationship to long-term neurodevelopmental outcome

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Key Words
cerebellum;
cerebral palsy;
cranial ultrasound;
mental retardation;
preterm

Background: The neonatal changes of corpus callosum or cerebellar volume in preterm infants have been shown to link with abnormal mentality and motor disability in early childhood. This study aims to predict the long-term neurological outcomes by measuring these changes on neonatal brain ultrasound in preterm infants.
Methods: Our cohort consisted of infants aged below 32 weeks' gestation with very low birth body weights who completed neuro-assessments at 5 years of age. Corpus callosum or cerebellar vermis were measured at 28–30 weeks and at 37–40 weeks gestational age in premature infants with cerebral palsy (CP), mental retardation (MR) and normal control premature infants.
Results: There are 12 patients in MR group, 12 in CP group and 27 patients as controls for final analysis. There was no significant difference in other factors between study groups except lower gestational age ($P = 0.043$) in CP group. Respiratory distress syndrome was more common in MR group ($P = 0.037$) and cystic periventricular leukomalacia was more common in CP group ($P < 0.001$) than controls. After adjusting for sex and birth body weight, the MR group had smaller cerebellar vermis area at 37–40 gestational weeks ($P = 0.002$) than controls. They also reduced the growth of corpus callosum area (difference $= -0.12 \pm 0.16$, $P = 0.029$) and cerebellar vermis area (difference $= 1.10 \pm 0.44$, $P = 0.020$) from 28 to 30 gestational weeks to 37–40 gestational weeks compared with controls (difference $= 0.03 \pm 0.15$, 1.92 ± 0.70,

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respectively). In contrast, the CP group had reduced the growth of corpus callosum body (difference = −0.02 ± 0.18, $P = 0.034$) compared with controls (difference = 0.03 ± 0.04). They subsequently had smaller body thickness of corpus callosum (0.10 ± 0.02, $P = 0.015$) at 37–40 gestational weeks than controls (0.14 ± 0.04).
Conclusions: Serial monitoring corpus callosum and cerebellar vermis size in early life of very preterm babies may predict the motor or mentality neurological outcome at 5 years of age.
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1. Introduction

Premature birth is a global health problem and a major cause of neurological disability, especially in those with extremely premature birth (gestational age less than 28 weeks). Cognitive delay, i.e, mental retardation (MR) based on scores on standardized cognitive tests that are 2 standard deviation below the mean, is by far the most prevalent neurological sequela in children born extremely premature.[1,2] MR has been reported to be as high as 40% at school age among children born extremely premature.[1,2] The intelligence quotient (IQ) scores at school age of premature children without severe disability have consistently been found to be lower than those of their term control subjects and this is related to gestational age at birth.[1,2] In addition, cerebral Palsy (CP) which causes motor disability was present in around 14% of the survivors born extremely premature from the data of EPICure study.[3] With the improvement of neonatal intensive care, the survival rate of these high-risk infants increased in past decades.[3,4] Early predication of these neurological disability sequelae is crucial and will make early intervention possible to further improve the outcome.

Cranial ultrasonography (CUS) has been used widely in neonatal practice as it is a convenient, non-invasive, safe and quick imaging technique to visualize the neonatal brain parenchyma and ventricular system serially without disturbing or moving the patient.[5] Sequential CUS examinations are helpful for assessing the evolution of injury and particularly for defining the pattern of lesions and the timing of their onset in preterm infants.[5] CUS has also been shown to provide predictive information on the long-term neurodevelopmental outcome of preterm infants, and parenchymal cerebral lesions in particular are associated with poor outcome.[6] Among the brain structures, corpus callosum and cerebellum are the most identifiable structures on CUS. Corpus callosum represents the largest white matter structure in the brain, consisting of 200–250 million contralateral axonal projections, and it is the major commissural pathway connecting the hemispheres of the human brain.[7] Cerebellum constitutes about 10% of the total brain weight and has many nerve projections to cerebral cortex.[8] Both are known to be involved in motor developments and cognitive functions in children.[8–10] Thus, measuring the sizes and the growth difference of corpus callosum and cerebellum at early preterm and at term in children born extremely preterm might predict neurological disability sequelae in childhood.

Since all premature babies had series CUS examinations during admission, we could retrospectively collect the CUS images in extremely premature patients with at 28–30weeks and 37–40 weeks of gestational age. In this study, we correlated the sizes and the growth difference of corpus callosum and cerebellum on CUS in patients born extremely premature with their long-term neurodevelopmental outcomes at 5 years old.

2. Methods

2.1. Study population

Very premature babies (birth weight < 1500 g and gestational age < 32 weeks) who were born between Jan 2006 and Dec 2010 and admitted to neonatal intensive care units in southern Taiwan were enrolled. Data on demographic background and medical complications in the prenatal, perinatal, and postnatal periods were collected after obtaining the parents' consent. During admission, CUS examinations were usually performed twice a week during the first week after birth, weekly from 2 to 4 weeks after birth, and monthly until gestational age of 40 weeks. After discharge, the follow-up clinic provided regular services at 1, 2 and 5 years old for these very premature survivors. At 5 years old, pediatric neurologists performed neuromotor examinations, while psychologists administered the Chinese version of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) to assess the verbal, performance, and full-scale intelligence quotients (VIQ, PIQ and FIQ).

In total, 423 very preterm infants were born from Jan 2006 to Dec 2010, but only 311 children born very prematurely had been regularly followed for 5 years. Among them, 2 patients who had chromosome abnormality and 1 patient who had brain malformation were excluded. Thus, 308 children born very premature were available for classification (Fig. 1). According to the neurological outcomes at 5 years old, patients whose VIQ and FIQ were all less than 70 and who did not have CP were classified as MR. Patients who had CP without impaired intelligence (both FIQ and VIQ > 70) were grouped as CP in our study. CP was diagnosed on the basis of abilities and limitations in gross motor function using the classification presented at an international symposium of cerebral palsy in 2008.[11] Patients whose FIQ, VIQ and PIQ were all more than 85 and who did not have motor disability were chosen as normal controls.

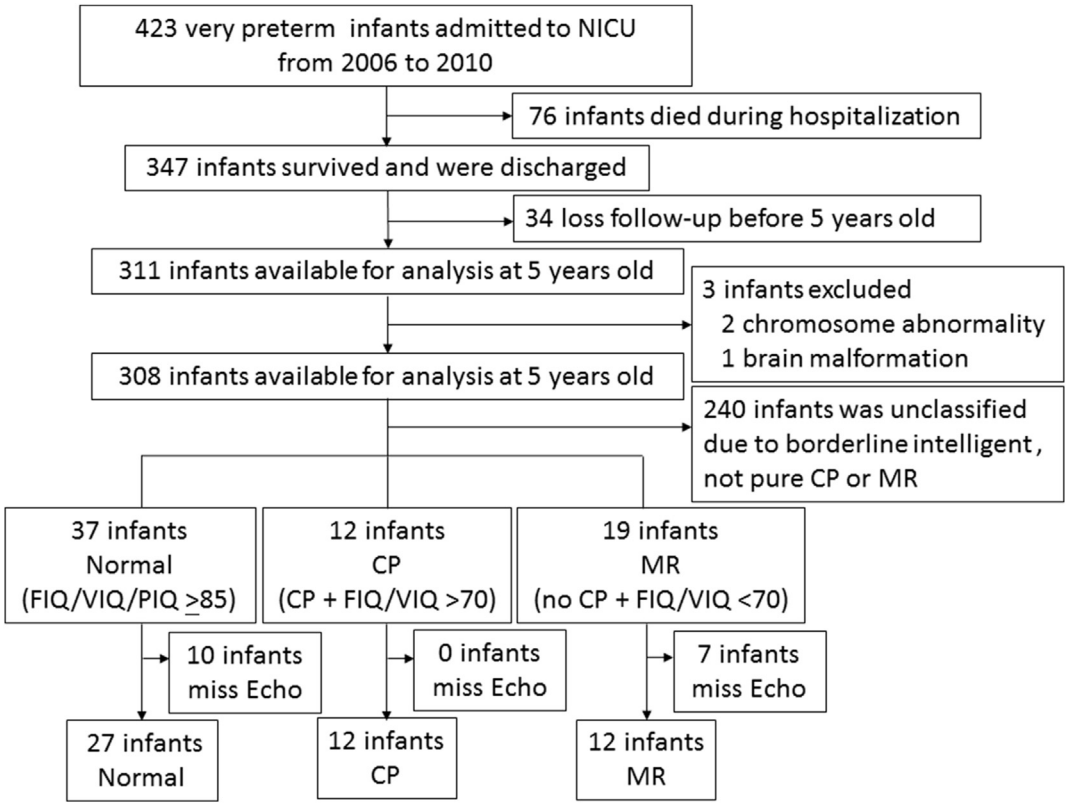

Figure 1 Flowchart of the inclusion process.

After classification, CUS of all patients was retrospectively reviewed by Dr. WH Yu and Dr. LW Chen, who were blinded to the clinical classification. Enrolled patients whose CUS was available both at gestational age 28—30 and 37—40 weeks were selected for final analysis. This study was approved by the Institutional Review Board of National Cheng Kung University Hospital.

2.2. Definition of variables

The demographic factors included sex, gestational age, and birth weight. In the prenatal period, pregnancy-induced hypertension (PIH) was defined as arterial blood pressure more than 140/90 mm Hg during the second half of gestation. In the neonatal period, infants with respiratory distress syndrome (RDS) who received mechanical ventilation and infants with symptomatic patent ductus arteriosus who required indomethacin therapy or surgical ligation were recorded. Bronchopulmonary dysplasia (BPD) was defined as a supplemental oxygen requirement at 36 weeks of post-conception age.[12] Retinopathy of prematurity (ROP) was graded into five stages (I—V) according to the international classification.[13] Necrotizing enterocolitis (NEC) was characterized as an inflammatory disease of the newborn bowel and was staged according to Modified Bell Staging Criteria.[14] Intraventricular hemorrhage (IVH) was classified into four grades (I—IV), and high-grade intraventricular hemorrhage included grade III and grade IV.[15] Cystic periventricular leukomalacia (cPVL) was defined as periventricular echo-lucent cystic lesions according to ultrasonography.[16]

2.3. Corpus callosum and cerebellum measurement

Measurements of corpus callosum and cerebellum vermis were taken on CUS at gestational age 28—30 and 37—40 weeks using INFINITTI PACS ver 3.0.10.2 by two qualified pediatric neurologists (WH Yu, LW Chen), who worked separately and the inter-observer reliabilities from 10 scans were 0.84 in the qualitative assessment. The different parts of corpus callosum (genus, body, splenium) were identified using the natural indentation as boundaries and their thicknesses were measured in mm on mid-sagittal view. The total area of corpus callosum and cerebellar vermis were automatically calculated (cm^2) after manual outlining the areas with a (mouse-controlled) cursor. The length of cerebellar vermis was measured from the base of the fourth ventricle to the junction of folium and tuber vermis (Fig. 2).[17]

2.4. Statistical analysis

The differences in demographic factors and medical complications between control and MR or CP groups in very preterm children were compared using a Fisher exact test for categorical variables and the Mann—Whitney U test for numerical variables. The measurements on brain ultrasound were compared between control and MR or CP groups via Mann—Whitney Test. Where a significant association was demonstrated, it was adjusted for sex and birth body weight using linear regression. Statistical significance was set at a two-tailed $P < 0.05$. All analyses were done on SPSS statistical software (SPSS Version 17.0; SPSS Institute, Chicago, IL, USA).

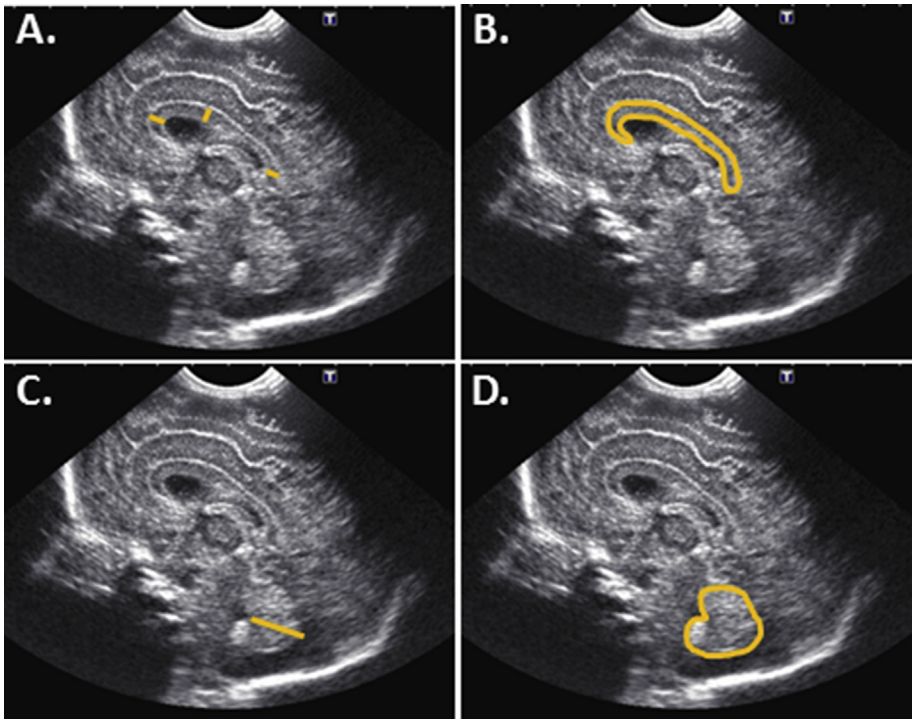

Figure 2 Corpus callosum and cerebellum measurements. (A) Genu, body, splenium thickness and (B) area of corpus callosum, and (C) length and (D) area of cerebellar vermis were measured in mid-sagittal view. The body thickness was measured in the middle segment of corpus callosum body.

3. Results

Among the 308 available children, we excluded 240 patients because they failed to meet our strict criteria for inclusion into the study groups. The birth weight was 1093.0 ± 246.2 g and the gestational age was 28.5 ± 2.4 weeks in this excluded population. Totally, we had 12 very premature patients with MR, 12 very premature patients

Table 1 Demographic and perinatal factors between normal and mental retardation group.

Perinatal factor	Control n = 27	MR n = 12	P value[a]	CP n = 12	P value[b]
Demographic data					
GA	29 ± 2.7	28 ± 2.5	0.141	27 ± 2.4	0.043
BBW	1072 ± 255	945 ± 212	0.144	907 ± 189	0.053
sex	14 (52%)	9 (75%)	0.291	7 (58%)	0.742
Prenatal factors					
PIH	7 (26%)	1 (8%)	0.394	3 (25%)	1.000
Prenatal steroid	19 (70%)	10 (83%)	0.693	5 (42%)	0.153
Postnatal comorbidities					
RDS	16 (59%)	11 (92%)	0.037	9 (75%)	0.447
NEC ≥ grade 3	1 (4%)	0 (0%)	1.000	0 (0%)	1.000
ROP ≥ grade 3	2 (7%)	3 (25%)	0.301	2 (17%)	0.577
PDA	11 (40%)	7 (58%)	0.488	6 (50%)	0.730
Sepsis	8 (30%)	3 (25%)	1.000	3 (25%)	1.000
IVH ≥ grade 3	1 (4%)	0 (0%)	1.000	3 (25%)	0.078
PHH	0 (0%)	1 (8%)	0.308	0 (0%)	—
cPVL	0 (0%)	2 (17%)	0.089	7 (58%)	<0.001

GA and BBW were presented as mean ± standard deviation. The others were presented as number (%).
BBW: birth body weight; cPVL: cystic periventricular leukomalacia; GA: gestational age; IVH: intraventricular hemorrhage; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; PHH: posthemorrhagic hydrocephalus; PIH: pregnancy-induced hypertension; RDS: respiratory distress syndrome; ROP: retinopathy of prematurity.
[a] Compare mental retardation (MR) with control.
[b] Compare cerebral palsy (CP) with control.

Table 2 Measurements in very premature with MR.

Echo parameter	Control n = 27 (mean ± SD)	MR n = 12 (mean ± SD)	P value	Adjusted P value
At 28–30wks				
Genu	0.12 ± 0.03	0.11 ± 0.03	0.175	–
Body	0.12 ± 0.03	0.14 ± 0.02	0.068	–
Splenium	0.17 ± 0.06	0.15 ± 0.04	0.840	–
Corpus callosum area	0.71 ± 0.16	0.65 ± 0.12	0.240	–
Cerebellar vermis area	2.70 ± 0.58	2.55 ± 0.52	0.481	–
At 37–40wks				
Genu	0.14 ± 0.04	0.12 ± 0.02	0.240	–
Body	0.14 ± 0.04	0.15 ± 0.02	0.338	–
Splenium	0.17 ± 0.06	0.14 ± 0.26	0.249	–
Corpus callosum area	0.71 ± 0.22	0.55 ± 0.15	0.041	0.067
Cerebellar vermis area	4.57 ± 0.79	3.57 ± 0.64	0.002	0.019
Difference				
Genu	0.02 ± 0.04	0.01 ± 0.04	0.408	–
Body	0.03 ± 0.04	0.01 ± 0.03	0.268	–
Splenium	0.04 ± 0.05	−0.003 ± 0.04	0.315	–
Corpus callosum area	0.03 ± 0.15	−0.12 ± 0.16	0.021	0.029
Cerebellar vermis area	1.92 ± 0.70	1.10 ± 0.44	0.006	0.020

Adjusted P value was adjusted for sex, and birth body weight.
Thickness or length was expressed in centimeter and area was expressed in square centimeters (cm^2).

with CP and 27 very premature patients as controls for final analysis (Fig. 1). In all these study patients for final analysis, the birth weight was 1005.1 ± 240.5 g and the gestational age was 27.9 ± 2.2 weeks. The birth weight and gestational age was not significantly different between study patients and the excluded population. The mean FIQ was 57.9 ± 3.5 in MR group, 75.3 ± 8.2 in CP group and 89.4 ± 12.8 in control group.

The demographic data were compared between groups (Table 1). The data showed very premature patients with CP had lower gestational age ($P = 0.043$) compared with control patients. Meanwhile, very premature patients

Table 3 Measurements in very premature with CP.

Echo parameter	Control n = 27 (mean ± SD)	CP n = 12 (mean ± SD)	P value	Adjusted P value
At 28–30wks				
Genu	0.12 ± 0.03	0.12 ± 0.02	0.686	–
Body	0.12 ± 0.03	0.13 ± 0.02	0.341	–
Splenium	0.17 ± 0.06	0.20 ± 0.04	0.088	–
Corpus callosum area	0.71 ± 0.16	0.70 ± 0.19	0.795	–
Cerebellar vermis area	2.70 ± 0.58	2.51 ± 0.30	0.479	–
At 37–40wks				
Genu	0.14 ± 0.04	0.12 ± 0.03	0.274	–
Body	0.14 ± 0.04	0.10 ± 0.02	0.005	0.015
Splenium	0.17 ± 0.06	0.15 ± 0.06	0.300	–
Corpus callosum area	0.71 ± 0.22	0.52 ± 0.18	0.010	0.055
Cerebellar vermis area	4.57 ± 0.79	4.92 ± 0.82	0.204	–
Difference				
Genu	0.02 ± 0.04	0.02 ± 0.03	0.871	–
Body	0.03 ± 0.04	−0.02 ± 0.18	0.006	0.034
Splenium	0.04 ± 0.05	−0.03 ± 0.06	0.234	–
Corpus callosum area	0.03 ± 0.15	−0.09 ± 0.10	0.036	0.080
Cerebellar vermis area	1.92 ± 0.70	2.34 ± 0.94	0.306	–

Adjusted P value was adjusted for sex and birth body weight.
Thickness or length was expressed in centimeter and area was expressed in square centimeters (cm^2).

with MR had similar demographic background as control patients. The median age of (CP was 27 ± 2.4 wks, MR was 28 ± 2.5 wks) and (normal control was 29 ± 2.7 wks). Among the prenatal factors and postnatal comorbidities, RDS was more common in very premature patients with MR than in control patients ($P = 0.037$) and cPVL was more frequent in very premature patients with CP than in control patients ($P < 0.001$). There was no significant difference in other factors between study groups.

Thickness and total area of corpus callosum as well as cerebellar length and vermis area were measured in all study patients. In very premature patients with MR, we found that all measurements at 28—30 gestational weeks were similar with control patients (Table 2). When very premature infants with MR grew up at 37—40 gestational weeks, their corpus callosum area and cerebellar vermis area were significantly smaller than in control patients ($P = 0.041$ and 0.002, respectively). From 28 to 30 to 37—40 gestational weeks, the control patients enlarged their corpus callosum area (difference = 0.03 ± 0.15) and cerebellar vermis area (difference = 1.92 ± 0.70). In contrast, the corpus callosum area in very premature patients with MR became smaller at 37—40 gestational weeks than at 28—30 gestational weeks (difference = −0.12 ± 0.16, $P = 0.021$). The difference of cerebellar vermis area between 28—30 and 37—40 gestational weeks was also smaller in very premature patients with MR than in control patients ($P = 0.006$). After adjusting for sex and birth body weight, P values were still significant in cerebellar vermis area at 37—40 weeks ($P = 0.019$) and in the difference of corpus callosum area ($P = 0.029$) and cerebellar vermis area ($P = 0.020$). This means that very premature patients with MR showed reduced growth of corpus callosum area and cerebellar vermis area from 28 to 30 to 37—40 gestational weeks and had smaller cerebellar vermis area at 37—40 gestational weeks than control patients.

In very premature patients with CP, we found that the body thicknesses of corpus callosum and corpus callosum area were smaller than in control patients ($P = 0.005$ and 0.010, respectively) (Table 3). From 28 to 30 to 37—40 gestational weeks, the control patients enlarged the body thickness of corpus callosum and corpus callosum area but the very premature patients with CP significantly reduced both of them (difference = −0.02 ± 0.18 and −0.09 ± 0.10, respectively). After adjusting for sex and birth body weight, P values remained significant in body thickness of corpus callosum at 37—40 weeks and in the difference of body thickness between 28—30 and 37—40 gestational weeks. This indicates that very premature patients with CP showed reduced growth of corpus callosum body resulting in smaller body thickness of corpus callosum than control patients. Interestingly, we also noted that very premature patients with CP had enlarged cerebellar vermis area compared to control patients even though there was no statistical significance.

4. Discussion

In this nested case control study, we followed up 347 children born very premature until they were 5 years old. After excluding patients with congenital abnormality and no available cranial ultrasound either at 28—30 or 37—40 weeks of gestation, we found 12 patients with cognitive delay, 12 patients with cerebral palsy, and 27 control patients with normal cognitive and motor functions for analysis. We found very premature patients with MR (without CP) had reduced corpus callosum area from 28 to 30 to 37—40 gestational weeks and had smaller cerebellar vermis area than control patients. Moreover, the very premature patients with CP (without MR) had reduced growth of corpus callosum body which resulted in smaller body thickness of corpus callosum at term-equivalent age (37—40 weeks of gestation) than control patients. Thus, if one very premature patients showed reduced body thickness of corpus callosum at 37—40 gestational weeks compared to body thickness of corpus callosum at 28—30 gestational weeks, motor dysfunction might be expected in later childhood. If one very premature patient showed reduced body corpus callosum area at 37—40 gestational weeks compared to body corpus callosum area at 28—30 gestational weeks and had smaller cerebellar vermis area at 37—40 gestational weeks, this might be predictive of cognitive delay in later childhood.

The corpus callosum is the largest white matter structure in the brain. Four parts are identifiable anatomically on cranial ultrasound: the rostrum and genu anteriorly, the body centrally and the splenium posteriorly. Thickness of corpus callosum reflects the volume of the hemisphere and the number of connecting fibers.[18] The fibers of the genu curve forward as the forceps minor and connect the lateral and medial aspects of the frontal lobes.[19] The fibers of the body course laterally and interconnect with the projection fibers of the corona radiate to connect wide areas of the cerebral hemisphere. Fibers arising from the sensory-motor cortex pass through posterior body near splenium. The fibers of the splenial fibers extend along the lateral surface of the occipital and temporal horns of the lateral ventricles and the majority curve posteriorly into the occipital lobes as the forceps major.[19] From these topographies, we can presume that body thickness of corpus callosum, which was correlated with the amount of connecting fibers arising from primary motor, premotor and supplementary motor cortexes, might reflect the degree of motor cortex maturation. This could explain our finding that CP patients (without MR) who had pure motor dysfunctions had a reduction the growth of corpus callosum body which resulted in smaller thickness of corpus callosum body at term-equivalent age (37—40 weeks of gestation) than control patients. Previous studies had shown solely that corpus callosum size at 23—29 weeks of gestational age was not associated with short-term neurodevelopmental outcome, but slow growth rate of corpus callosum or small size at term-equivalent age might correlate with poor short-term neurodevelopmental outcome at 2 years old.[16,20—22] However, the Definition of short-term neurodevelopmental outcome was too heterogeneous and most outcome diagnosis could not be precise. In our study, we used long-term motor outcome at 5 years old and clearly defined the patients with CP without MR and patients with MR without CP for analysis. One recent study reported that the measurements of corpus callosum size, length, and circumference area were related to long-term neurodevelopment outcome at 5 years of age, like our study.[23]

In addition to motor function, abnormal corpus callosum size was also been reported to be associated with learning and behavioral difficulties, speech and language delays and cognitive impairment.[24] Complex connections between functional neocortex in bilateral hemispheres passed through the corpus callosum. Reduced global or regional connectivity was reported in the fetus with intrauterine growth restriction and this correlated with poor neurodevelopmental outcome at 2 years of age.[25] Our study also found reduced growth of total corpus callosum area from 28 to 30 to 37—40 gestational weeks in very premature patients with MR. It could be presumed that MR patients had fewer connecting fibers from dysfunctional neocortex through corpus callosum, resulting in the reduction of corpus callosum size during early life. Moreover, we found that MR patients showed reduced growth of cerebellar vermis area from 28 to 30 to 37—40 gestational weeks and had smaller cerebellar vermis area at term-equivalent age than control patients. The role of the cerebellum was acknowledged to extend to short-term memory, attention and other cognitive functions in addition to motor learning and adjusting motor operations.[26,27] As shown in recent fMRI study of cerebellum, dorso-rostral dentate nucleus activation was associated with motor function, whereas cognitive tasks led to prominent activation of the caudal nucleus. The visuospatial task evoked activity bilaterally in the caudal dentate nucleus, whereas verbal working memory led to activation predominantly in the right caudal dentate.[28] Disrupted cerebellar growth caused by intraventricular hemorrhage, hydrocephalus or periventricular leukomalacia in premature children was reported to be associated with impaired neurodevelopmental outcome.[29] Thus, the reduced cerebellar volume and corpus callosum in preterm infants was likely to be associated with the impaired cognition like mental retardation in our patients.

Other possible confounding factors from the statistical point of view included RDS in the MR group and cystic PVL in the CP group. From the clinical point of view, no matter how RDS was associated with MR or cystic PVL caused CP, it did not affect our measurements on ultrasound images. Measurements of cerebral regional size or area would also reflect the brain impacts caused by RDS or the damage severity of cystic PVL. The relationship between these measurements of cerebral regional size or area and the neurological outcomes at 5 years of age could still be built up. Therefore, we did not adjust RDS or cystic PVL in our results. In addition, prenatal steroid administration was reported to be associated with a slightly improved growth rate of corpus callosum and with a slightly longer corpus callosum at term equivalency.[22] The use of prenatal steroid was similar in our three study groups (Table 1). Thus, the confounding effects of prenatal steroid might not have impacted on our results either.

The limitations of this study are the small numbers of study cases, and the possibility of selection bias because we adapted the restricted selection criteria for the normal group and left a lot of patients in the unclassified group. Our findings might be verified by a study using a larger study population. However, in our study, we clearly separated motor dysfunction without mental impairment in our CP patients and mental impairment without motor dysfunction in our MR patients guided by long-term neurodevelopmental outcome at 5 years old. We found both CP or MR patients had reduced corpus callosum, but interestingly we found that CP patients (without MR) had reduced corpus callosum body thickness but enhanced cerebellar growth in early life instead of the reduced cerebellar growth in MR patients. Even though some studies reported that the growth and development of the corpus callosum and cerebellar vermis were linked to each other in very premature infants, we believed, based on our results, that cerebellar vermis could grow independently or enlarge compensatorily while corpus callosum reduced body thickness due to decreased fibers arising from motor cortex.[16,30] Meanwhile, global reduction of cerebellar vermis and corpus callosum growth indicated mental impairment instead of motor dysfunction in long-term neurodevelopmental outcome. To our knowledge, this is the only study to use CUS for predicting the individual motor dysfunction or mental abnormality of long-term neurodevelopmental outcome in preterm babies.

In conclusion, series monitoring corpus callosum and cerebellar vermis size in early life of very preterm babies may predict the motor or mentality neurological outcome at 5 years of age.

Conflict of interest statement

All authors have no reported conflicts.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.pedneo.2018.05.012.