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Ultrasound measurement of the corpus callosum and neural development of premature infants☆☆

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Research Highlights

(1) A previous study measured corpus callosum length viewed from the mid-sagittal plane in premature infants using cranial ultrasound and verified that premature infants experienced delayed motor development that was associated with a low anterior-posterior growth rate of the corpus callosum at 2–6 weeks.
(2) This study not only examined corpus callosum length in the mid-sagittal plane, but also investigated the thickness of the genu, body, and splenium, as well as the anteroposterior diameter of the genu viewed from the coronal plane, and explored the relationship between the physical development of these regions and the neurobehavioral development of premature infants. Effects of sex on corpus callosum size were also investigated.
(3) Results confirmed that corpus callosum length, and thickness of the genu and splenium can be used to evaluate corpus callosum development in premature infants. Moreover, corpus callosum development in premature infants was associated with early neurobehavioral development of newborn infants. Monitoring corpus callosum development can be used to screen premature infants, predict the likelihood of future abnormal neurobehavioral development, and provides evidence for early intervention.

Abstract

Length and thickness of 152 corpus callosa were measured in neonates within 24 hours of birth. Using ultrasonic diagnostic equipment with a neonatal brain-specific probe, corpus callosum length and thickness of the genu, body, and splenium were measured on the standard mid-sagittal plane, and the anteroposterior diameter of the genu was measured in the coronal plane. Results showed that corpus callosum length as well as thickness of the genu and splenium increased with tional age and birth weight, while other measures did not. These three factors on the standard mid-sagittal plane are therefore likely to be suitable for real-time evaluation of corpus callosum velopment in premature infants using cranial ultrasound. Further analysis revealed that thickness of the body and splenium and the anteroposterior diameter of the genu were greater in male infants than in female infants, suggesting that there are sex differences in corpus callosum size during the neonatal period. A second set of measurements were taken from 40 premature infants whose gestational age was 34 weeks or less. Corpus callosum measurements were corrected to a gestational age of 40 weeks, and infants were grouped for analysis depending on the outcome of a neonatal behavioral neurological assessment. Compared with infants with a normal neurological assessment, corpus callosum length and genu and splenium thicknesses were less in those with abnormalities, indicating that corpus callosum growth in premature infants is associated with neurobehavioral development during the early extrauterine stage.

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Key Words

neural regeneration; neurogenesis; brain injury; premature infant; cranial ultrasound; neonate; corpus callosum; neonatal neurobehavior; grants-supported paper; neuroregeneration

INTRODUCTION

The neurodevelopmental outcome of premature infants is a major concern with more than 25% of very low birth-weight infants developing serious cognitive or behavioral deficits during childhood[1]. At a gestational age of 23–33 weeks, the brain is developing rapidly. Neuronal migration is completed during this time, with cortical and subcortical connections forming, followed by myelination[2-3]. Promoters and inhibitors modify dendritic and axonal growth and movement[4]. It seems likely that the efficient organization of a limited number of structural connections within the brain permits later development of functional connectivity[5]. These varied and complex developmental changes are difficult to image directly in the premature infant[6], and some scholars have considered that corpus callosum growth might represent a synthesis of these complex structural developments[4].

The corpus callosum is the largest white matter fiber bundle in the human brain, the major interhemispheric commissure that connects the majority of the neocortical areas[7], and is important for interhemispheric communication between sensory, motor, and higher-order brain regions[8-10]. MRI studies of children spanning from young children to adolescents have indicated that functional impairments found in prematurely born individuals are associated with smaller corpus collosa. Thus, the degree of callosal abnormality in premature infants is considered an important factor that strongly affects neurodevelopmental outcome[11-13].

The basic structure of the corpus callosum is completed by gestational weeks 18–20, continues to increase in size over the third trimester[14], and grows dramatically over the first two postnatal years[15]. The corpus callosum is vulnerable to intrauterine and extra-uterine factors that can cause morphological and functional abnormality in its development[16-17]. Thus, brain development can be indirectly evaluated through serial monitoring of callosal developmental changes.

Imaging technology has progressed from two-dimensional imaging to three-dimensional imaging. Today, we can better understand corpus callosum development than was possible in the past. Using MRI, the thicknesses of corpus callosum subdivisions and even total area can be measured[18-20]. Nevertheless, ultrasonographic monitoring of corpus callosum development has some advantages over MRI. It is less expensive, can be conveniently repeated, and can be done at the bedside. The latter point is particularly important for very premature or critically ill neonates[4, 21-22].

There are few reports of callosal measurements done using ultrasonography around the time of birth for either full-term or premature infants[4, 21-22]. Studies have shown that neuromotor retardation is associated with shorter corpus collosa (anterior-posterior) in premature infants[16, 22]. However, studying corpus callosum length alone may not be enough. Corpus callosum thickness (including the genu, body, and splenium) can be measured through the anterior fontanelle on the standard mid-sagittal plane. In addition, the anteroposterior diameter of the genu can be measured on the coronal plane. Whether these ultrasound indicators can be used as estimated indicators for neurological development of premature infant needs further study.

Here, cranial ultrasound was used to measure the anteroposterior diameter of the genu on the coronal plane, and its length and thickness (genu, body, and splenium) on the standard mid-sagittal plane. We compared corpus callosum size between different gestational age groups, and different birth-weight groups. We also studied the effect of sex on corpus callosum size. Finally, we determined whether corpus callosum growth in premature infants during the early extrauterine stage was associated with their neurobehavioral development.

RESULTS

Quantitative analysis of participants

One-hundred and fifty-two neonates were included in the study, and all were included in the final analyses.

Ultrasonic measurements of the corpus callosum in neonates

Ultrasonic measurements of the corpus callosum were taken in all neonates within the first day after birth. Measurements included the anteroposterior diameter of the genu on the coronal plane (2.7 ± 0.3 mm), its length on the standard mid-sagittal plane (42.9 ± 2.7 mm), and thickness of the genu (5.0 ± 0.7 mm), body (2.7 ± 0.4 mm), and splenium (4.9 ± 0.8 mm) on the standard mid-sagittal plane (Table 1).

Table 1 Descriptive statistics for the ultrasonic measurements of the corpus callosum in 152 neonates

Corpus callosum	Mean±SD (mm)	Minimum (mm)	Maximum (mm)
On the coronal plane			
Anteroposterior diameter of the genu	2.7±0.3	2.0	4.0
On the mid-sagittal plane			
Length	42.9±2.7	36.0	49.0
Genu thickness	5.0±0.7	4.0	7.0
Body thickness	2.7±0.4	2.0	4.0
Splenium thickness	4.9±0.8	3.0	7.0

The measurements of corpus callosum size were in taken within 24 hours of birth. Each measurement was carried out three times.

Effect of gestational age on the size of corpus callosum

The 152 neonates were divided into three gestational age groups: 28–34 weeks (n = 40), 35–36 weeks (n = 46), and 37–41 weeks (n = 66). One-way analysis of variance and the Scheffé's test showed that larger gestational ages were associated with longer corpus collosa and thicker genus and spleniums on the standard mid-sagittal plane (F = 18.58–46.23, P = 0.00). However, the thickness of the body on the standard mid-sagittal plane, and the anteroposterior diameter of the genu on the coronal plane were not statistically different among the three gestational age groups (F = 1.17–2.52, P = 0.06–0.31; Figure 1).

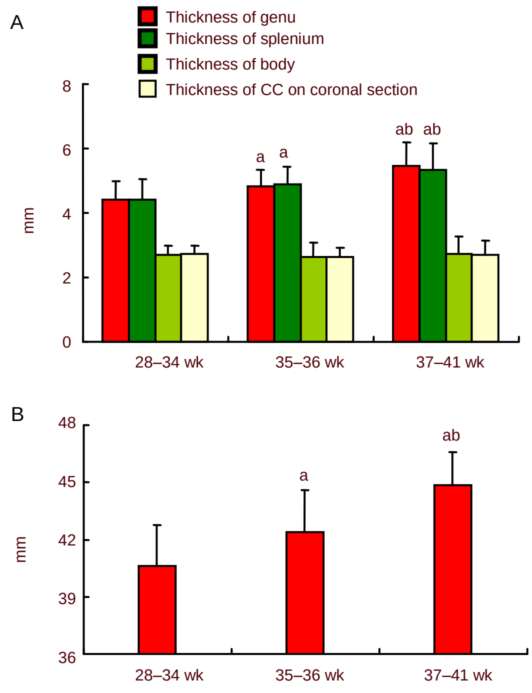

Figure 1 The effect of gestational age on the size of corpus callosum (CC) of neonates.

(A) Ultrasonic measurements of genu, splenium, and body thicknesses on the standard mid-sagittal plane, and the anteroposterior diameter of the genu on the coronal plane in three different gestational age groups.

(B) Ultrasonic measurements of CC length on the standard mid-sagittal plane in three different gestational age groups.

Data are expressed as mean ± SD. Sample sizes: 28–34 weeks (wk), n = 40; 35–36 weeks, n = 52; 37–41 weeks, n = 60. $^aP < 0.05$, vs. 28–34 week group; $^bP <$ 0.05, vs. 35–36 week group using one-way analysis of variance followed by Scheffé's test.

Effect of birth weight on the size of corpus callosum

The 152 neonates were divided into three different birth-weight groups: < 1 500 g (n = 20), 1 500–2 500 g (n = 64), and > 2 500 g (n = 68). Corpus callosum length and thicknesses of the genu and splenium increased with birth weight (P < 0.05). There was no significant difference among the three different birth-weight groups in either thickness of the corpus callosum body or the anteroposterior diameter of the genu (P > 0.05; Figure 2).

Effect of gender on the size of corpus callosum

Of the 152 neonates, 80 were male and 72 were female. There was no significant difference in the mean birth weight (males: 2.7 ± 0.7 kg; females: 2.5 ± 0.8 kg; F = 1.25, P = 0.27) or mean gestational age (males: 36.7 ± 3.5 weeks; females: 36.0 ± 3.4 weeks; F = 1.35, P =

0.25) between the two groups (Table 2). However, the mean birth weight and mean gestational age of the male infants were slightly greater than those of the females. To remove the effect of birth weight, we used an analysis of covariance, with birth weight as a covariate. This analysis revealed that thickness of the corpus callosum body and splenium and the anteroposterior diameter of the genu were greater in male than in female infants (P < 0.05). There were no significant differences in corpus callosum length or thickness of the genu between male and female neonates (P > 0.05; Table 2).

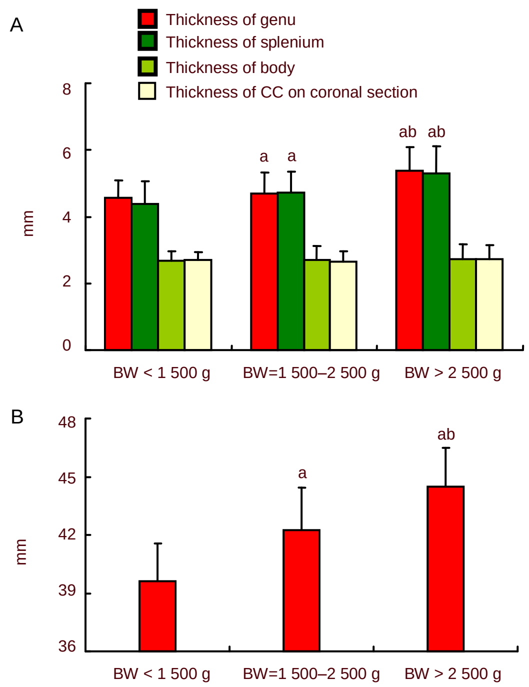

Figure 2 The effect of birth weight on the size of neonatal corpus callosum (CC).

(A) Ultrasonic measurements of genu, splenium, and body thicknesses on the standard mid-sagittal plane, and the anteroposterior diameter of the genu on the coronal plane in three different birth-weight groups.

(B) Ultrasonic measurements of CC length on the standard mid-sagittal plane in three different birth-weight groups.

Data are expressed as mean ± SD. Sample sizes: birth weight (BW) > 2 500 g, n = 68; BW between 1 500 and 2 500 g, n = 64; BW < 1 500 g, n = 20.

[a]P < 0.05, *vs*. BW < 1 500 g group; [b]P < 0.05, *vs*. 1 500–2 500 g group using one-way analysis of variance followed Scheffé's test.

Relationship between corpus callosum size and neurodevelopment in premature infants

Corpus callosum measurements were taken from premature infants who gestated 32.0 ± 1.9 weeks (n = 40; Table 3), and a neonatal behavioral neurological assessment was taken. Corpus callosum measurements were corrected to a gestational age of 40 weeks. There were 29 cases with normal neonatal behavioral neurological assessments (scores ≥ 37) and 11 cases with abnormal ones (score range: 32–35).

Table 2 Comparison of the ultrasonic corpus callosum measurements between male and female infants

Variable	Male (n = 80)	Female (n = 72)	F	P
Birth weight (kg)[a]	2.7±0.7	2.5±0.8	1.25	0.27
Gestational age (week)[a]	36.7±3.5	36.0±3.4	1.35	0.25
Coronal plane				
Anteroposterior diameter of the genu (mm)[b]	2.8±0.3	2.6±0.3	12.55	0.00
Mid-sagittal plane				
Corpus callosum length (mm)[b]	43.0±2.7	42.8±2.6	0.08	0.78
Genu thickness (mm)[b]	5.1±0.8	4.9±0.7	1.48	0.23
Body thickness (mm)[b]	2.8±0.4	2.6±0.3	9.97	0.00
Splenium thickness (mm)[b]	5.1±0.8	4.7±0.8	9.57	0.00

Data are presented as mean ± SD. [a]One-way analysis of variance; [b]one-way analysis of covariance (birth weight as a covariate). Results showed that there were significant differences in thickness of the body and splenium and anteroposterior diameter of the genu between male and female neonates.

In the normal neonatal behavioral neurological assessment group, mean birth weight was 1 783.1 ± 372.5 g, mean gestational age was 32.3 ± 1.9 weeks, four infants suffered intraventricular hemorrhage (all Grade I), seven infants received mechanical ventilation, and the mean length of hospitalization was 28.8 ± 13.2 days. In the abnormal neonatal behavioral neurological assessment group, mean birth weight was 1 881.8 ± 321.6 g, mean gestational age was 31.1 ± 2.1 weeks, two infants suffered intraventricular hemorrhage (both Grade I), three infants received mechanical ventilation, and the mean length of hospitalization was 30.3 ± 2.5 days. No significant differences in these indices were detected between the two groups (P > 0.05).

Corpus callosum length and thicknesses of the genu and splenium measured within the first day after birth were not significantly different between the two groups (P > 0.05). However, these values at 40-week corrected gestational age were smaller in the abnormal neonatal behavioral neurological assessment group than those in the normal neonatal behavioral neurological assessment group (P < 0.05; Table 3).

DISCUSSION

Partial or complete agenesis of the corpus callosum is a relatively frequent fetal brain anomaly and occurs in at least 0.1% of the general population[18].

Table 3 Comparison of corpus callosum length (mm), and thickness of the genu (mm) and splenium (mm) at different time points between normal and abnormal neonatal neurological assessment (NBNA) groups

Group	Length		Genu thickness		Splentum thickness	
	Birth	Term*	Birth	Term*	Birth	Term*
Abnormal NBNA	39.8±1.9	42.9±3.1	4.3±0.5	4.7±0.4	4.5±0.6	4.8±0.5
Normal NBNA	41.0±2.3	44.7±1.8	4.5±0.6	5.3±0.7	4.4±0.3	5.4±0.8
t	1.28	2.18	1.51	3.32	0.02	2.16
P	0.21	0.03	0.14	0.00	0.99	0.04

Data are presented as mean ± SD. Sample sizes: normal NBNA (scores ≥ 37), n = 29; abnormal NBNA (scores < 37, range: 32–35), n = 11. *T*-test showed that at a corrected gestational age of 40 weeks there were significant differences between normal and abnormal NBNA groups in corpus callosum length and thicknesses of the genu and splenium. Term*: Corrected gestational age of 40 weeks.

Its identification is of clinical interest because corpus callosum anomalies are frequently associated with other structural malformations and chromosomal or genetic diseases[19-20]. Moreover, even an isolated callosal anomaly can be associated with an increased risk of abnormal neurodevelopment[21]. Through transvaginal sonography, obstetricians can evaluate the development of fetal corpus collosa by measuring the length and thickness, and even the callosal area. However, this method requires time-consuming semi-manual drawings, and like MRI, it is not suitable for real-time evaluation[14, 22-24].

Although the volume and area of different parts of the corpus callosum can be calculated using MRI[25-28], it is expensive, the calculations often require time-consuming semi-manual drawings, it is not suitable for real-time evaluation, cannot be conveniently repeated, and it is not a bedside imaging technique. The latter is particularly important for very premature infants or critically ill newborns.

For newborns, corpus callosum evaluation using cranial ultrasound can overcome these disadvantages, especially in most infants whose anterior fontanelle will not be closed until they reach one and a half years of age. With this method, serial monitoring can continue for at least one and a half years. We have previously reported that with cranial ultrasound, real-time measurement of the corpus callosum length on the mid-sagittal plane is easy to repeat and relatively simple[29]. Thickness of the genu, body, and splenium are three additional indicators that can be measured in real-time on the standard mid-sagittal plane[14]. Corpus callosum length on this plane reflects the brain's overall development[4]. The anterior regions of the corpus callosum (including the genu) connect pre-frontal regions. The corpus callosum body consists of axons that connect primary motor and sensory regions. The posterior regions (including the splenium) connect posterior parietal, temporal, and occipital cortices. Examining structural features of these subdivisions can provide insight into lobular and regional patterns of long-distance connectivity[30]. The antero-posterior diameter of the genu can be measured on the coronal plane.

This paper reported corpus callosum length and thickness of the genu, body, and splenium on the standard mid-sagittal plane, and the anteroposterior diameter of the genu on the coronal plane in neonates with gestational ages ranging from 28 to 41 weeks. The corpus callosum length reported here is similar to that reported by Hai-Chun using transvaginal sonography and that by Harreld *et al* [31] using fetal MRI, measurements that were themselves in agreement[32]. Thicknesses of the genu, body, and splenium were consistent with Malinger's intrauterinely measured values[14].

Here, we also showed that corpus callosum length on the standard mid-sagittal plane was significantly associated with gestational age, a finding consistent with previously published studies[14, 33]. Width of the genu and splenium also correlated with gestational age， but neither the thickness of the body nor the anteroposterior diameter of the genu differed significantly between the three gestational age groups. This was probably because of the relatively slower growth rate, as reported in Malinger and Zakut[14], suggesting that development of the neonatal corpus callosum can be monitored using corpus callosum length and thicknesses of the genu and splenium from the standard mid-sagittal plane. However, thicknesses of the body on this plane and the antero-posterior diameter of the genu on the coronal plane are unsuitable for monitoring corpus callosum development in premature infants.

Similarly, this study showed that while corpus callosum length and thicknesses of the genu and splenium were significantly associated with birth weight, thickness of the body and the anteroposterior diameter of the genu were not. This is not surprising because birth weight always increases with gestational age in premature infants.

It is known that mean height, weight, and head circumference are larger in male neonates than female neonates[34]. We postulate that corpus callosum size in neonates also differs between male and female infants. Our data showed that thickness of the body and splenium and the anteroposterior diameter of the genu were significantly greater in male infants than in females. Although corpus callosum length and thickness of the genu in male infants were greater than in females, the difference did not reach statistical significance.

Controversy exists as to whether sex influences the size of the human corpus callosum[35]. Some studies have shown that the female splenium is more bulbous and larger than the cylindrically shaped male splenium[36-37], while other studies have reported contrary results[38]. Recently, Chura *et al* [39] investigated the effects of testosterone on corpus callosum size in a small study, and did not find a relationship between fetal testosterone exposure and mid-sagittal corpus callosum size. However, they found a significant relationship between testosterone and callosal asymmetry. Sex-related differences in the size and shape of the human corpus callosum remain controversial primarily because measurement methods differ between experiments.

Two biological factors are important for understanding the sex differences: sex hormones and sex chromosomes. Early exposure to sex steroids plays a major organizing influence on expression of later sexual dimorphism, including parts of the human brain[40]. There are not many reports of sexual differences in neonatal corpus collosa. The current study suggests that sexual dimorphism in corpus callosum size may exist in newborns, similar to birth weight and head circumference, which are slightly larger in male neonates compared with female neonates. Answering this question definitively will require a study with a large sample size.

The increasing number of children who survive preterm births continue to have a high prevalence of neurodevelopmental impairment, including cognitive deficits, developmental coordination disorder, behavioral problems such as attention deficit hyperactivity disorder, and lower academic performance[41-42]. The role of the corpus callosum is thought to relate to interhemispheric function and coordination, allowing the two cerebral hemispheres to share learning and memory. The posterior corpus callosum has a role in visual discrimination. Its fibers comprise 11% of the supratentorial brain tissue. Damage to the structure may result in minor motor dysfunction, attention deficits, or learning disability[43].

Studies have shown that motor dysfunction in infancy and childhood is associated with corpus callosum abnormalities in prematurely born infants[4, 21-22]. Another study has shown that specific neurodevelopmental impairments in infants born preterm are precisely associated with microstructural abnormalities in particular regions of cerebral white matter including some parts of the corpus callosum[44]. Furthermore, there is a strong association between corpus callosum size and motor function in children who were born prematurely[45]. When examined after reaching school age, these children displayed poorer scores on the Movement Assessment Battery for Children and had smaller corpus collosa. Larger corpus collosa were strongly associated with better standard Visual Motor Integration scores. These data indicate larger corpus collosa are associated with better motor performance in children who were born prematurely.

Our previous study showed that a neuromotor delay in premature infants at 3 months corrected gestational age is associated with decreased anteroposterior growth of the corpus callosum from between 2 and 6 weeks of after birth[29].

Here, we prospectively investigated the relationship between corpus callosum growth in premature infants and their early neurobehavioral development. Results showed that anterior-posterior growth, as well as growth of the genu and splenium during early extrauterine stages, was significantly associated with premature neurobehavioral development. Compared with infants with normal neurobehavioral assessments, corpus callosum length, and thicknesses of the genu and splenium were smaller in those whose assessments were abnormal. This suggests that monitoring corpus callosum growth preterm can sort out infants who might have a high-risk of abnormal neurobehavioral development in the future, and it may provide a basis for early intervention and treatment.

In conclusion, using cranial ultrasound, corpus callosum length, and thickness of the genu and splenium on the standard mid-sagittal plane are suitable for real-time evaluation of corpus callosum development. Gender differences in the size of corpus callosum during the neonatal period may be similar to gender differences in height, weight, and head circumference.

During the early extrauterine stage, corpus callosum growth in premature infants was associated with their neurobehavioral development.

SUBJECTS AND METHODS

Design

A prospective observational clinical study.

Time and setting

We conducted a study in newborns admitted to the Newborn Service of Bethune International Peace Hospital in Shijiazhuang, Hebei Province, China from May 2011 to May 2012.

Subjects

Infants satisfying the following criteria were included: (1) appropriate for gestational age; (2) postnatal age ≤ 24 hours; (3) no intrauterine hypoxia and/or birth asphyxia; (4) no infection; (5) all mothers were free of chronic hepatitis, diabetes, heart disease, malnutrition, and severe anemia, and their liver and kidney functions during pregnancy were normal. Infants were excluded if they had congenital malformations, chromosomal abnormalities, or a suspected inborn error in metabolism.

One hundred and fifty-two neonates satisfied the criteria, with 78 delivered vaginally and 74 by cesarean section. Eighty-six were premature and 66 were full-term. Mean gestational age was 36.4 ± 3.4 weeks (range: 28–41 weeks), mean birth weight was 2 620 ± 760 g (range: 1 100–4 400 g).

An informed verbal consent was obtained from the parents before newborn enrollment. The ethics of this study were approved by the Ethical Committee of Bethune International Peace Hospital and in accordance with the *Declaration of Helsinki*.

Methods

Corpus callosum measurements

The ultrasonographic measurements were taken with a Philips M2540A ultrasound system (Amsterdam, The Netherlands), employing a C8-5 neonatal craniocerebral probe with a frequency of 5–8 MHz. All measurements were taken at the bedside by the same ultrasound practitioner, with infants in a supine position, either resting or sleeping. The anteroposterior diameter of the genu was measured on the coronal plane (Figure 3A). On the standard mid-sagittal plane (which simultaneously shows the third and fourth ventricles, and the cerebellum), the corpus callosum measurements were done through the anterior fontanelle and included the anterior-posterior length, and the thickness of the genu, body, and splenium (Figure 3B). Corpus callosum length on the standard mid-sagittal plane refers to the distance between the genu and the splenium (Figure 3B, C). Each measurement was carried out three times, and values were averaged. The first measurements were completed within 24 hours of birth for all infants. A second set of measurements was taken at a corrected gestational age of 40 weeks from infants who gestated 34 weeks or less.

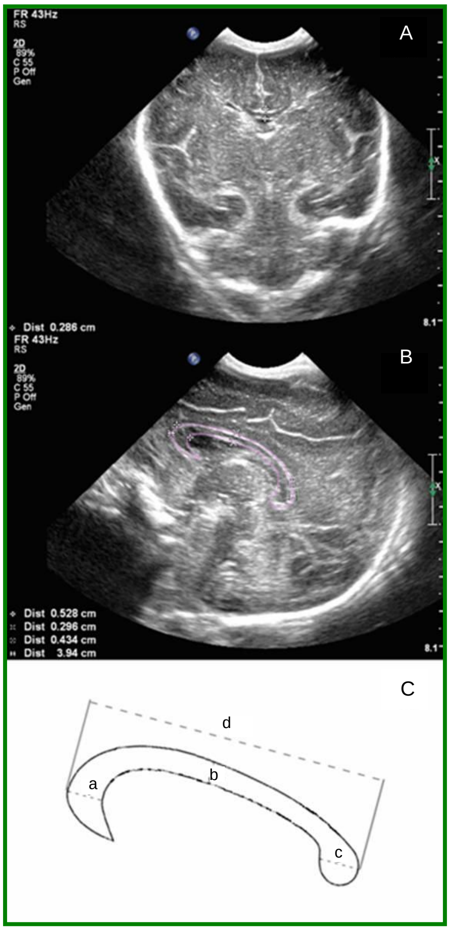

Figure 3 Ultrasonic image of the corpus callosum (CC) in a neonate within 24 hours of birth.

(A) Coronal section: anteroposterior diameter of the genu was the distance between two points (++).

(B) The CC in the standard mid-sagittal plane.

(C) Schematic of the CC on the standard mid-sagittal plane. Thicknesses of the genu, body, and splenium were measured as delineated by the dashed lines (a, b, and c, respectively). The CC length was measured from the anterior tip of the genu to the posterior tip of the splenium as delineated by the dashed line (d).

Intraventricular hemorrhage detected by ultrasound

Intraventricular hemorrhage is the most common intracranial hemorrhage. Ultrasound, a noninvasive imaging test, is used to look at the brain for signs of hemorrhage. In this study, babies born at a gestational age of less than 34 weeks had three routine ultrasound screenings for intraventricular hemorrhage, one in the first week of life, one at 2 weeks, and one at a corrected gestational age of 40 weeks. Detected hemorrhages were graded in severity from I to IV[46].

Neonatal behavioral neurological assessment

Infants who gestated 34 weeks or less were given neonatal behavioral neurological assessments at a corrected gestational age of 40 weeks. Twenty items were used and divided into five parts: behavioral ability (six items), passive muscular tension (four items), active muscular tension (four items), initial reflection (three items), and general evaluation (three items). A perfect assessment score was 40, and scores 37 or greater were considered normal. Scores less than 37 were considered abnormal[47].

Statistical analysis

SPSS 15.0 software for Windows (SPSS, Chicago, IL, USA) was used for statistical analysis, and quantitative variables are described as mean ± SD. Categorical variables are expressed as numbers and percentages. One-way analyses of variance/covariance and *t*-tests were used to compare quantitative data. Scheffé's test was used for all pairwise comparisons of means. A chi-square test was used to compare categorical variables. A value of $P < 0.05$ was considered statistically significant.

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