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Lateral ventricular volume and calcarine sulcus depth: a fetal MRI analysis of mild ventriculomegaly
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Abstract

The aim of this study was to quantify changes in the lateral ventricular volume, the depth of the calcarine sulcus (CS), and apparent diffusion coefficient (ADC) values of occipital lobe in fetuses with isolated mild ventriculomegaly (IMVM) using MRI.

Seventy-one fetuses with IMVM at 25 to 38 weeks gestational age (GA) and 58 fetuses with normal lateral ventricles at 25 to 38 weeks GA were enrolled. Volumes of the lateral ventricles were measured by 3D magnetic resonance hydrography. Depths of the CS and ADC values were also evaluated. All differences were tested by t test. Bivariate correlations were performed using Pearson method.

Fetuses with IMVM had significantly larger lateral ventricular volumes and smaller CS depths than controls (volumes: 9.37 ± 2.20 mL vs 5.04 ± 1.33 mL, respectively, $P < .001$; depths: 8.27 ± 2.55 mm vs 10.30 ± 3.14 mm, respectively, $P < .001$). In IMVM cases, the CS depths were smaller on the side with the larger ventricle (8.10 ± 2.54 mm vs 9.59 ± 2.81 mm, $P < .001$). No differences were observed in occipital lobe ADC values between the 2 groups (IMVM = 1.80 ± 0.24 μm^2/ms; controls = 1.78 ± 0.28 μm^2/ms, $P > .05$).

Fetuses with IMVM had larger lateral ventricular volumes, shallower CS depths, but normal occipital lobe ADC values.

Abbreviations: ADC = apparent diffusion coefficient, CNS = central nervous system, CS = calcarine sulcus, FRFSE = fast-recovery fast-spin echo, GA = gestational age, IMVM = isolated mild ventriculomegaly, MRH = magnetic resonance hydrography, MRI = magnetic resonance imaging, SSFSE = single-shot fast-spin echo, VM = ventriculomegaly.

Keywords: calcarine sulcus, fetus, lateral ventricle, magnetic resonance imaging

1. Introduction

Fetal ventriculomegaly (VM) is the most common central nervous system (CNS) abnormality, occurring in 1% of pregnancies.[1] It is defined as a dilation of the lateral ventricular atrium to a width of 10 mm at any point during gestation.[2,3] VM severity is classified as either mild (10–15 mm) or severe (>15 mm).[4–6] At least half of VM cases have no additional CNS abnormalities, and the cause of the dilatation is usually unknown; such cases are defined as isolated VM.[7] Some studies have shown that infants with confirmed isolated mild VM (IMVM) at birth have a higher rate of neurodevelopmental delay than the general population (10%–15%[3,7–9] vs 1%–3%[10]). Additionally, an altered cerebral architecture may result in functional impairment in some cases of IMVM.[11] VM is routinely measured by magnetic resonance imaging (MRI) and ultrasonography using the ventricular atrial diameter at the level of the glomus of the choroid plexus.[12,13] VM has also been assessed by ventricular volume.[14–19] However, these methods are difficult to implement in clinical practice because they are time-consuming and technically challenging. Our previous study demonstrated that 3D MR hydrography (MRH) can be used to estimate the volume of the lateral ventricles in fetuses for the first time.[20] Meanwhile, to the best of our knowledge, further studies about measurements of ventricular volumes using 3D MRH in fetuses with IMVM have not been reported.

Also, VM may be associated with a delay in cortical folding.[21] The calcarine sulcus (CS) is located in the occipital lobe and lies adjacent to the region of common ventricular enlargement in VM. The visualization of the CS using MRI was thought to be related to the increased likelihood of normal fetal postnatal outcomes.[22] At present, although ultrasound studies have been performed to determine the depth of the CS,[11] studies of changes in CS depth in fetuses with IMVM using MRI are still lacking.

The main advantages of MRI are no shadows, good soft-tissue contrast and high resolution, particularly in the third trimester of gestation,[23] but ultrasound cannot possibly achieve the same. Additionally, the mechanism by which changes occur in the CS remains unclear. Apparent diffusion coefficient (ADC) values can be used to quantitatively measure the Brownian motion of protons, which are related to the biophysical status and microstructure of cerebral tissues.[24] The aim of this study was therefore to quantify changes in the lateral ventricular volume and the depth of the CS in fetuses with IMVM using MRI. We also evaluated the effects of IMVM on occipital lobe ADC values to explore the presence of microstructural changes due to diffusion, which may explain the mechanism by which changes occur in the CS.

2. Materials and methods

2.1. Subjects

We enrolled and assessed fetuses referred to our hospital for fetal MRI between March 2017 and July 2018. The Research Ethics Committee of the first affiliated hospital of Chongqing Medical University approved the study, and written informed consent was obtained from all pregnant women. Fetal gestational age (GA) was estimated from an ultrasound scan during the first trimester. Normal fetal controls were from women who had a suspected placenta accreta as observed on ultrasound, a suspected fetal brain abnormality on ultrasound not present on MRI or a mild non-CNS abnormality, or a previous abnormal pregnancy. Exclusion criteria included abnormal fetal brain appearance, twin pregnancy, poor image quality, complications during delivery, chromosomal abnormality, suspicious cardiac abnormality, and an unstable clinical situation. A total of 75 fetuses had a normal brain appearance on MRI and were enrolled as the normal control cohort. Seventeen cases met the exclusion criteria: twin pregnancy (3), poor image quality (6), complications during delivery (1), suspicious cardiac abnormality (4), chromosomal abnormality (1), and unstable clinical situation (2).

Inclusion criteria for the IMVM group consisted of a singleton pregnancy and IMVM (at least 1 lateral ventricle with a width of 10–15 mm without additional CNS abnormalities). Exclusion criteria were additional brain abnormalities, twin pregnancy, inadequate image quality, chromosomal abnormality, infection, and unstable clinical situation. A total of 114 fetuses with an ultrasound diagnosis of VM were referred for MRI, with the following exclusions: additional brain abnormality (28), twin pregnancy (2), inadequate image quality (7), infection (3), chromosomal abnormality (1), and unstable clinical situation (2).

2.2. Fetal brain MRI

Fetal MRI was performed using a 1.5T scanner (GE Healthcare, Milwaukee, WI) with an 8-channel full-body coil. No sedation was used, and the scan did not exceed 45 minutes. As described in our previous study,[20] 3D fast-recovery fast-spin echo (FRFSE) was performed in the axial plane of the fetal brain using the following scanning parameters: TR = 1600 ms, TE = 500.5–508 ms, bandwidth = 62.50 Hz, slice thickness = 2 mm, matrix size = 288 × 224, field of view (FOV) = 34 × 34 cm, and fat saturation. The FOV in the direction of the slice was slightly expanded to avoid folding artifacts. All images were reformatted into standard coronal and sagittal planes with nearly 1 mm isotropic voxel dimensions. T2-weighted single-shot fast-spin echo (SSFSE) images were performed in the coronal, sagittal, and axial planes of the fetal brain. The scanning parameters were as follows: TR = 2000 ms, TE = 140 ms, slice thickness = 3–4 mm, slice overlap = 1 mm, matrix size = 256 × 192, and FOV = 38 × 38 cm. Images were acquired as overlapping slices to ensure that each part of the fetal brain was sampled. Diffusion-weighted imaging sequences were performed in the axial plane of the fetal brain with the following parameters: FOV = 38 × 38 cm, b values = 0 and 700 ms, slice thickness = 4 mm, and no gap. Second or third acquisitions were obtained if sequences were motion degraded.

2.3. Image analysis

2.3.1. Volumetric analysis. All images were transferred to an Advantage Windows Workstation (AW 4.6, GE Healthcare), and volumetric measurements were produced using Advantage Windows Volume Viewer Software (v.11.3, GE Healthcare). Postprocessing of the source images obtained from 3D FRFSE sequences was performed using volume rendering as previously described.[20] Volumes were measured automatically after semiautomatic segmentation by the software. The total ventricular volume was defined as the volume of both lateral ventricles, including the choroid plexus, but excluding the cavum septum pellucidum and the third and fourth ventricles (Fig. 1).

2.3.2. CS measurements. The depth of the CS was only measured in the coronal SSFSE images with exact orthogonal orientation. After defining a baseline that conjoined the vertex of the forming cuneus and the forming lingual gyrus, the depth of the CS was measured. The depth of the CS was defined as the
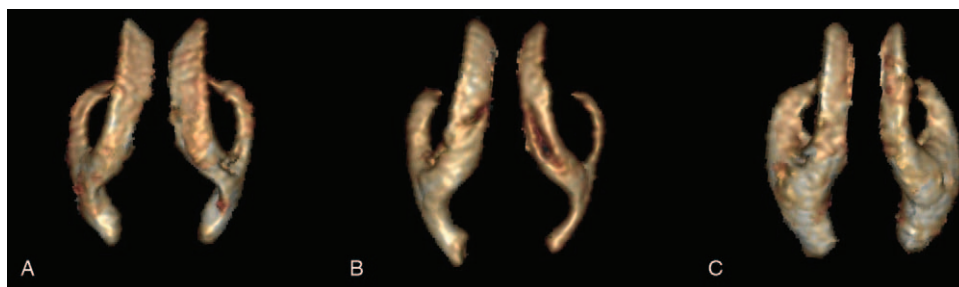
Figure 1. VR images of the lateral ventricles reconstructed by 3D magnetic resonance hydrography. (A) The 3D reconstructed lateral ventricles of a fetus with normal lateral ventricles at gestational age (GA) of 34 weeks 5 days; (B) the 3D reconstructed lateral ventricles of a fetus with unilateral ventriculomegaly (VM) at GA of 34 weeks 2 days; (c): the 3D reconstructed lateral ventricles of a fetus with bilateral VM at a GA of 30 weeks 1 day.
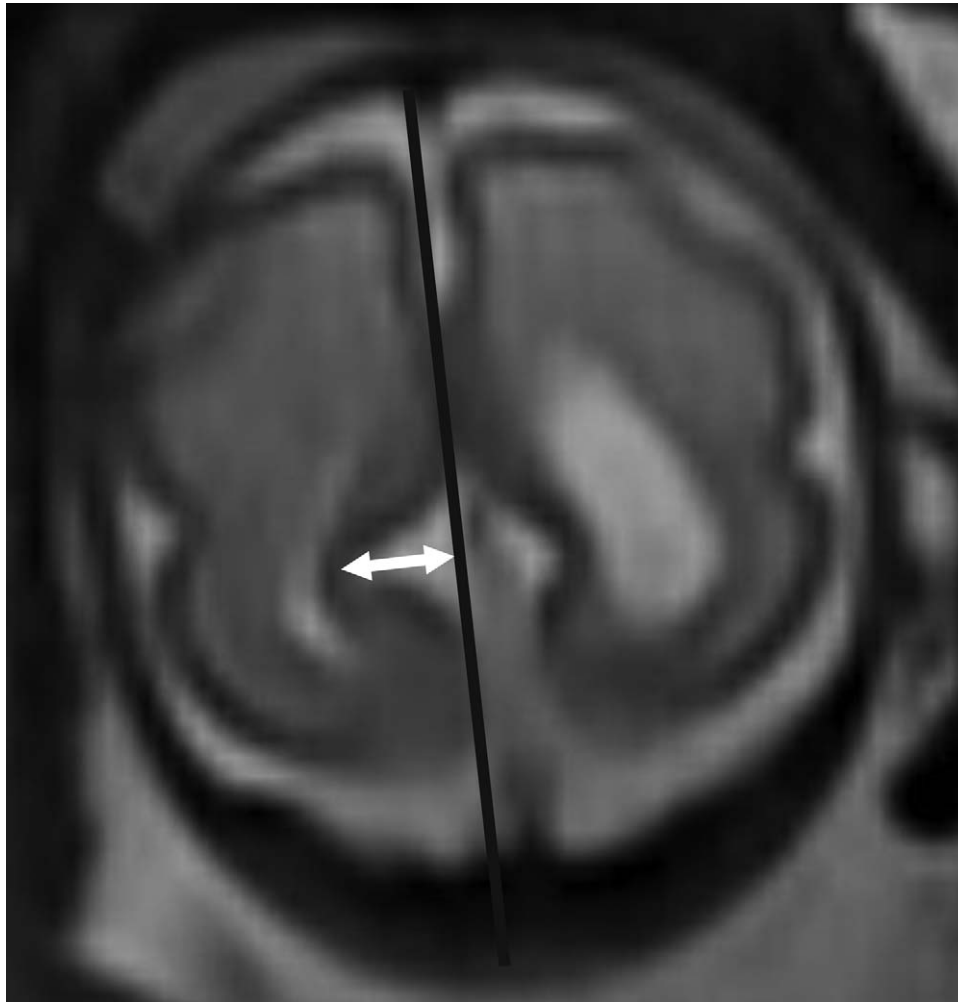
Figure 2. The depth of the calcarine sulcus (CS) was determined by the distance between the deepest point of the CS and the baseline in coronal single-shot fast-spin echo image.

distance between the deepest point of the CS and the baseline, according to the methods proposed by Gregor et al[25] regarding the measurement of the superior temporal sulcus (Fig. 2).

2.3.3. ADC measurements. The ADC values were calculated using Functool software (GE Medical Healthcare). Two circular regions of interest (ROIs) were systematically identified on the white matter of the occipital lobe (posterior to the lateral ventricles) (Fig. 3). The ADC value is expressed in $\mu m^2/ms$.

2.4. Reproducibility

Intra- and inter-rater reliability for the CS measurements were performed between 2 raters in 20 fetal datasets. A radiologist (with 6 years of MRI experience) completed the image analyses and repeated 20 measurements after 2 weeks. A second experienced radiologist (YHX, with 14 years of MRI experience) reanalyzed the same 20 data blindly.

2.5. Statistical analysis

The data were analyzed using IBM SPSS software for Windows, v.22.0 (IBM, Armonk, NY). In normal controls, data from both sides were averaged. In the IMVM cohort, data from the side of the larger ventricle of the unilateral VM cases and from both sides of the bilateral VM cases were used for analysis.[15] Q–Q plots were used to check the normality of the data. Values were expressed as the mean $\pm$ standard deviation, and categorical variables were expressed as percentages and numbers. The 2-sample t test was used to compare differences between groups. The paired t test was used to compare differences between 2 paired measurements. Bivariate correlations were performed using Pearson method. Intra- and inter-rater correlation coefficients of the CS measurements were performed between 2 raters in 20 fetal datasets. A 2-tailed P value $<.05$ was considered statistically significant in all analyses.

3. Results

3.1. Subjects

A total of 58 fetuses were selected (gestational range [GA] range 25–38 weeks; average age: 31.7 ± 3.0 weeks) as normal controls. Based on the MRI and ultrasound findings, 46 fetuses (79%, 46/58) showed no abnormalities, and 12 fetuses (21%, 15/61) showed mild non-CNS malformations (ectopic kidneys, auricle malformation, and cleft lip).
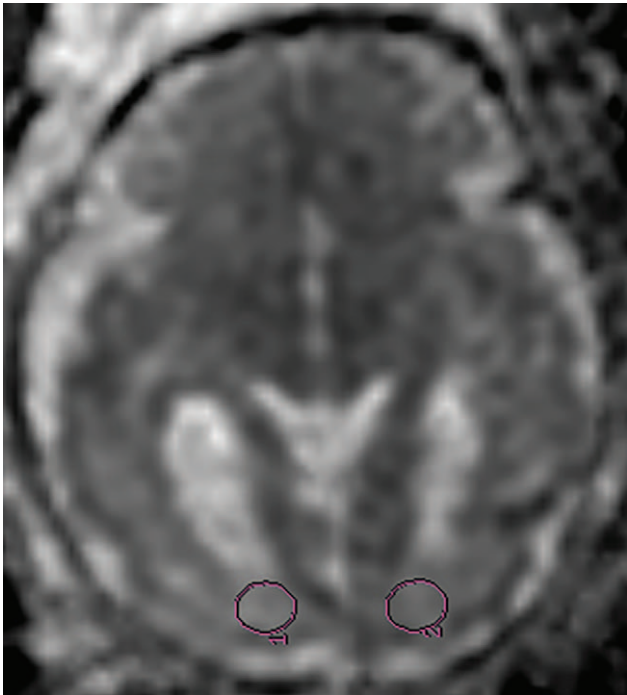
Figure 3. ADC measurement: ROIs were systematically placed on white matter of occipital lobe. ADC = apparent diffusion coefficient, ROI = regions of interest.

A total of 71 fetuses were selected (GA range 25–38 weeks; average age: 31.5±2.9 weeks) as the IMVM cohort; 47 fetuses (66.2%, 47/71) were diagnosed with unilateral VM. The distribution of the GAs of the fetuses included in this study is shown in Figure 4.

3.2. Volumetric analysis

The atrial diameters in the IMVM group fell between 10 and 15 mm in one or both lateral ventricles (11.33±1.04 mm), whereas the atrial diameters in the control group were <10 mm in both lateral ventricles (6.53±1.47 mm). All fetuses with IMVM had significantly larger lateral ventricular volumes than controls (9.37±2.20 mL vs 5.04±1.33 mL, respectively; $P < .001$; Table 1,
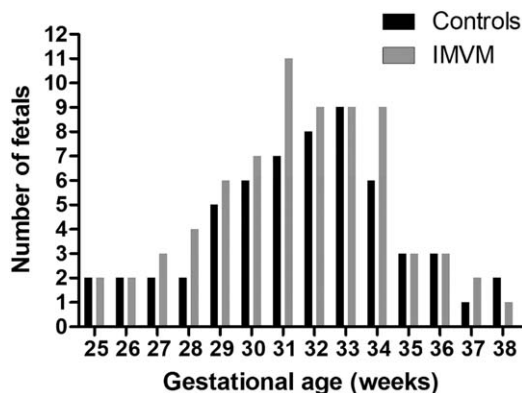

Figure 4. Histogram of the age distribution of fetal MR scans. Fetal gestational age (GA) was estimated from a first-trimester ultrasound scan.

Table 1

Measurements of atrial diameters, lateral ventricular volume, and total lateral ventricular volume in 2 groups.

	IMVM	Controls	P
No. of patients	71	58	—
GA	31.5±2.9 wk	31.7±3.0 wk	$P > .05$
Atrial diameters	11.33±1.04 mm	6.53±1.47 mm	$P < .001$
Lateral ventricular volume	9.37±2.20 mL	5.04±1.33 mL	$P < .001$
Total lateral ventricular volume	15.81±3.64 mL	10.07±2.67 mL	$P < .001$

GA = gestational weeks, IMVM = isolated mild ventriculomegaly. For atrial diameters and lateral ventricular volume comparisons, data of both sides were averaged in normal controls; data from the side with the larger ventricle in the unilateral ventriculomegaly cases and from both sides in the bilateral ventriculomegaly cases were used for analyses in IMVM cohort.

Fig. 5A). As indicated by a moderate correlation of the unilateral lateral ventricular volume ($r_N = 0.437$, $r_{IMVM} = 0.458$, all $P < .001$; N: normal controls, IMVM: IMVM cases) and total lateral ventricular volume ($r_N = 0.437$, $r_{IMVM} = 0.394$, all $P < .001$) with GA, there was an increase in both the unilateral and total lateral ventricular volumes with increasing GA (Table 2, Fig. 5A and B). There was a moderate correlation between atrial diameter and lateral ventricular volume ($r_N = 0.657$, $r_{IMVM} = 0.540$, all $P < .001$; Table 3, Fig. 5C).

3.3. CS measurements

The mean depth of the CS was significantly lower in the IMVM group than in the control group (8.27±2.55 mm vs 10.30±3.14 mm, respectively; $P < .001$; Table 4, Fig. 5D). In the IMVM cases, the CS depths were smaller on the side with the larger ventricle, and the difference was statistically significant (8.10±2.54 mm vs 9.59±2.81 mm, $P < .001$; Table 4, Fig. 6A). There was an increase in the depth of the CS with increasing GA, as indicated by a moderate correlation of the depth of the CS ($r_N = 0.842$, $r_{IMVM} = 0.800$, all $P < .001$, Table 2, Fig. 5D) with GA. There was a correlation of the depth of the CS and lateral ventricular volume in controls ($r_N = 0.333$, $P = .015$; Table 3, Fig. 5E) but not in the IMVM group ($r_{IMVM} = 0.203$, $P = .051$).

3.4. ADC measurements

The ADC values were measured in 55 controls and 63 IMVM cases. There were no significant differences in the occipital lobes between the 2 groups (controls = 1.78±0.28 μm²/ms; IMVM = 1.80±0.24 μm²/ms, $P > .05$, Fig. 6B).

Table 2

Correlation between lateral ventricular volume, total lateral ventricular volume, the depth of CS and GA.

	IMVM	Controls
	GA	
Lateral ventricular volume	0.458[*]	0.437[*]
Total lateral ventricular volume	0.458[*]	0.437[*]
Depth of the CS	0.800[*]	0.842[*]

[*] $P < .001$.

CS = calcarine sulcus, GA = gestational weeks, IMVM = isolated mild ventriculomegaly. Data of both sides were averaged in normal controls; data from the side with the larger ventricle in the unilateral ventriculomegaly cases and from both sides in the bilateral ventriculomegaly cases were used for analyses in IMVM cohort.

Table 3

Correlation between lateral ventricular volume and atrial diameters, the depth of CS.

	Atrial diameters	Depth of the CS
Lateral ventricular volume in IMVM	0.540*	0.203
Lateral ventricular volume in Controls	0.657*	0.333*

* $P < .001$.

CS = calcarine sulcus, IMVM = isolated mild ventriculomegaly. Data of both sides were averaged in normal controls; data from the side with the larger ventricle in the unilateral ventriculomegaly cases and from both sides in the bilateral ventriculomegaly cases were used for analyses in IMVM cohort.

3.5. Reproducibility

The intra- and interclass correlation coefficients of the CS measurements were for both 0.99 ($P < .001$). We have demonstrated the high reproducibility of semiautomatic segmentation of lateral ventricles in our previous study.[20] ADC values have also been shown by several examiners to be highly reproducible in fetal brain.[26,27]

4. Discussion

In this study, we found differences in the lateral ventricular volumes between fetuses with normal lateral ventricles and IMVM fetuses using 3D MRH. As expected, fetuses with IMVM had significantly larger lateral ventricular volumes than controls, consistent with results from previous studies.[15,19] All of our lateral ventricular volumes were larger than those reported in

Table 4

Measurements of the depth of the CS and the ADC values in occipital lobe.

	IMVM	Controls	P
Depth of the CS	8.27 ± 2.55 mm	10.30 ± 3.14 mm	$P < .001$
	Larger side 8.10 ± 2.54 mm Smaller side 9.59 ± 2.81 mm		$P < .001$
ADC values in occipital lobe	1.80 ± 0.24 µm²/ms (63 cases)	1.78 ± 0.28 µm²/ms (55 cases)	$P > .05$

ADC = apparent diffusion coefficient, CS = calcarine sulcus, IMVM = isolated mild ventriculomegaly. For depth of the CS and ADC values comparisons, data of both sides were averaged in normal controls; data from the side with the larger ventricle in the unilateral ventriculomegaly cases and from both sides in the bilateral ventriculomegaly cases were used for analyses in IMVM cohort.

similar cohorts by Kyriakopoulou et al.[15,28] This variability may be the result of using a different volume estimation method or studying heterogeneous patients. Our results showed an increase in lateral ventricular volume with GA in both normal controls and IMVM cases. Previous studies have not reached a consensus in terms of such volume changes in lateral ventricles with GA.[15,17,18,29] We also observed a moderate positive correlation between atrial diameter and lateral ventricular volume. Although atrial diameter may be used for screening, it only provides local information about the lateral ventricles. Moreover, a previous study reported that enlarged lateral ventricles extend beyond the atrium, even in the mildest form of VM.[19] Therefore, the volume of lateral ventricles may provide more detailed and accurate information than atrial diameter.
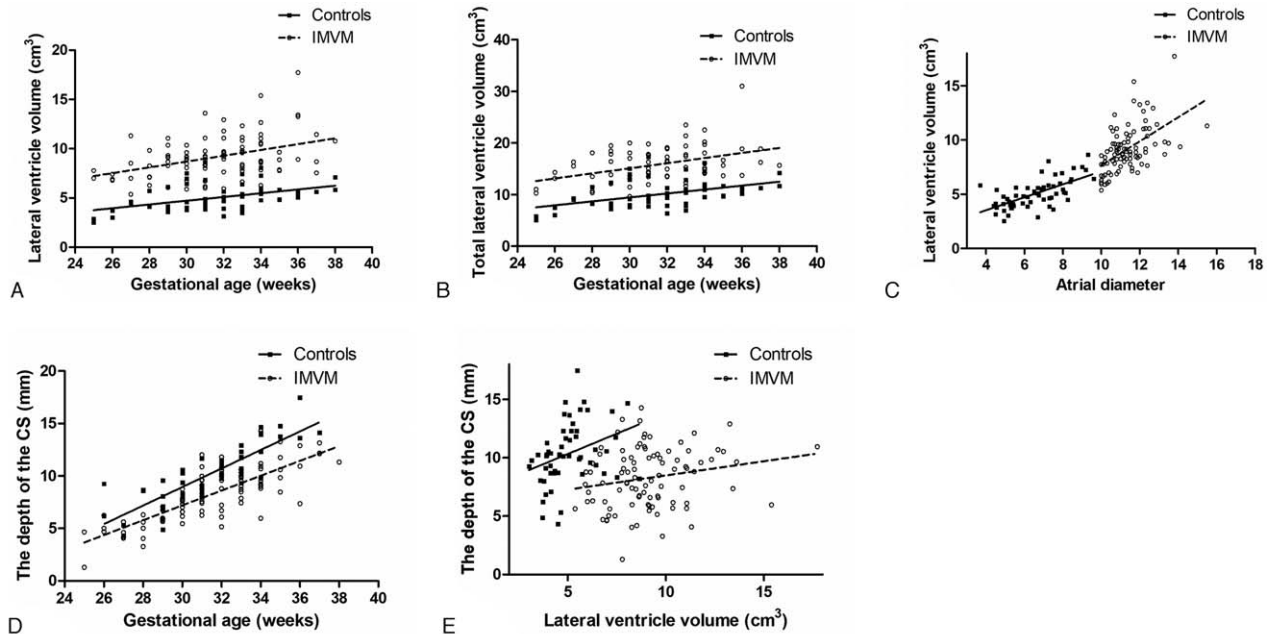

Figure 5. Correlation between lateral ventricular volume, total lateral ventricular volume, the depth of calcarine sulcus (CS), atrial diameters, and gestational age (GA). (A) Fetuses with isolated mild ventriculomegaly (IMVM) had significantly larger lateral ventricle volumes than controls ($P < .001$). There was a moderate correlation value in the unilateral lateral ventricular volume with GA ($r_N = 0.437$, $r_{IMVM} = 0.458$, all $P < .001$; N: normal controls, IMVM: IMVM cases). (B) There was a moderate correlation value in the total lateral ventricular volume with GA ($r_N = 0.437$, $r_{IMVM} = 0.394$, all $P < .001$). (C) There was a moderate correlation value between atrial diameter and lateral ventricular volume ($r_N = 0.657$, $r_{IMVM} = 0.540$, all $P < .001$). (D) The mean depth of the CS was significantly lower in IMVM group compared with control group ($P < .001$). There was a moderate correlation value in the depth of the CS with GA ($r_N = 0.842$, $r_{IMVM} = 0.800$, $P < .001$). (E) There was a correlation between the depth of CS and lateral ventricular volume in controls ($r_N = 0.333$, $P = .015$). But this correlation was not found in IMVM group ($r_{IMVM} = 0.203$, $P = .051$). In normal controls, data from both sides were averaged. In the IMVM cohort, data from the side of the larger ventricle of the unilateral ventriculomegaly (VM) cases and from both sides of the bilateral VM cases were used for analysis. Normal control cohort: closed squares and continuous line. Ventriculomegaly cohort: open circles and stippled line.
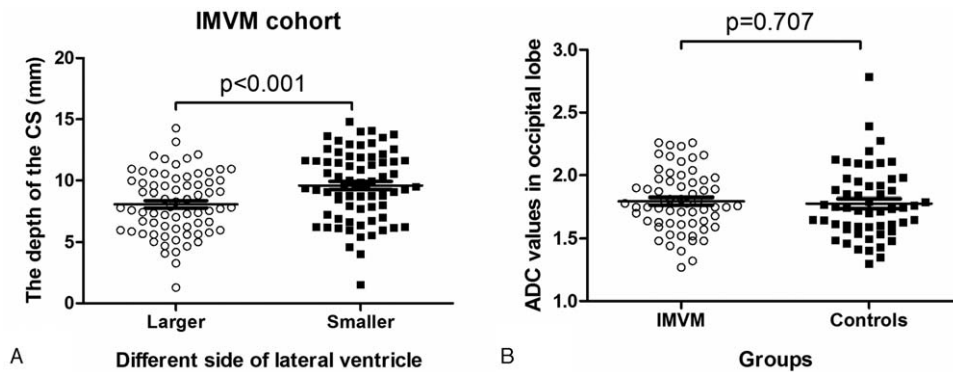
Figure 6. Difference of the calcarine sulcus (CS) depths (between the different side of lateral ventricle in isolated mild ventriculomegaly [IMVM] cohort) and ADC values (between 55 controls and 63 IMVM cases). (A) The CS depths were smaller on the larger side in IMVM cohort ($P < .001$). (B) There was no significant difference of ADC values in occipital lobe between the 2 groups ($P > .05$). Data of both sides was averaged in normal controls; data from the side with the larger ventricle in the unilateral ventriculomegaly (VM) cases and from both sides in the bilateral VM cases were used for analyses in IMVM cohort.

Our study showed an increase in the depth of the CS with GA in both normal controls and IMVM cases. At the same time, we found that lateral ventricular volume was correlated with the depth of the CS in the control cohort. However, there was no similar correlation observed in the IMVM cohort, which may suggest there are multiple different types of etiologies in cases of IMVM.

In the present study, we showed that the CS is shallower in fetuses with IMVM than in controls, consistent with results from previous studies.[11] In IMVM cases, the CS depths were also smaller on the side with the larger ventricle. A 2-week mean lag in the time of appearance of the sulci in IMVM cases compared with normal fetuses has been reported,[30] although it is unknown whether this lag is a true delay or caused by sulcus deformation. Some studies have speculated that such delays may simply be related to mechanical interference caused by the dilated ventricles rather than by abnormal corticogenesis.[19,31] In our study, however, a shallow CS was not found in all IMVM cases. Additionally, several studies have indicated that after 25 weeks, there is a decrease in both inner subventricular and ventricular zone proliferation, as neurons in these areas migrate to the subplate and cortical plate. After such migration, immature sulci and gyri deepen and fold.[32–34] Therefore, in some IMVM fetuses, a delay in the migration of neurons may cause a delay in sulcus maturation. We, therefore, believe that a smaller CS depth may not be exclusively explained by sulcus deformation affected by ventricular dilation.

ADC values can be quantitatively used to assess the Brownian motion of water molecules in a specific area. These values have also been used to assess brain maturation during fetal development.[26,27,35,36] Several studies have shown that ADC values are altered as a result of neurological pathology,[24,37,38] including increased cellular density.[39] We, therefore, used the ADC values to speculate the mechanism of shallower CS. In our study, we did not find any significant difference in the occipital lobe ADC values in IMVM cases and controls, similar to findings by Yaniv et al.[37] We hypothesized that if the shallower CS observed in IMVM cases is merely caused by the mechanical interference of enlarged ventricles, a higher cellular density and a decreased interstitial volume would likely result, restricting proton motion. Furthermore, the ADC values of the occipital lobe should be reduced as reported in the temporal and frontal lobes by Yaniv et al.[37] This hypothesis is inconsistent with our

findings and suggests that additional mechanisms of cortical folding may occur in some fetuses with IMVM. As we know, transependymal flow of cerebrospinal fluid, decreased size of the extracellular space, impaired migration, impaired axonal growth could all theoretically affect ADC values in different directions. In other words, although 2 brain regions have the same ADC values, that does not mean they have the same microstructure. Further studies, including follow-up fetal and postnatal imaging, should be undertaken to clarify the mechanism. Moreover, the view that a shallower sulcus in fetuses with IMVM is only related to sulcus deformation should be carefully reexamined.[19,31] A postnatal follow-up study could also be used to examine occipital lobe dysfunction (such as amblyopia).

Although we only found subtle alterations of the CS in our IMVM cases, other sulci may also potentially be associated with ventricular enlargement. Most fetuses with IMVM undergo normal neurodevelopment, but a fraction will have a neurodevelopmental delay.[3,40] The mechanisms behind the disturbances in cortical folding may be associated with poorer neurodevelopmental outcomes in some IMVM cases and in some severe forms of VM in which cortical malformations have been observed.[12,41]

Our study had several limitations. First, we did not correlate our results with any clinical findings. Such correlations will be discussed in a future study. Second, we had limited ability to control for an absolutely consistent coronal imaging plane. Finally, some fetuses with extra-CNS abnormalities were included to improve the sample size of the normal controls. However, the influence of certain pathologies (ectopic kidneys, auricle malformation, and cleft lip) on fetal brain development cannot be fully excluded.

In conclusion, our study demonstrated that fetuses with IMVM have larger lateral ventricular volumes, shallower CS depths, but normal occipital lobe ADC values. Further studies are required to explore cortical folding in fetuses with IMVM. Occipital lobe dysfunction could also be monitored during postnatal follow-up examinations.

Acknowledgments

Author contributions

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Writing – review & editing: Fu rong Lv.

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