Formation of the calcarine sulcus: a potential marker to predict the progression in utero of isolated mild fetal ventriculomegaly

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Abstract

Our previous study confirmed the negative association between the development of calcarine sulcus and the width of lateral ventricles. The purpose of current study was to evaluate the reliability of calcarine sulcus depth in the 2nd trimester to predict the prenatal enlargement of lateral ventricle in fetuses with isolated mild fetal ventriculomegaly (IMVM).

This study used a retrospective cohort study design. A total of 97 pregnant women with IMVM diagnosed between 20 and 26 weeks' gestation returned for a 2nd examination at 30 to 32 weeks. Lateral ventricular size and calcarine sulcus depth were acquired from ultrasonography and magnetic resonance imaging (MRI) scans, respectively. Progression was defined as the process of developing from a lower group toward a higher (<10 mm, 10–12 mm, 13–15 mm, and ≥16 mm).

Significant correlation was observed between calcarine sulcus depth and ventricular measurements at the 2nd scan ($r = -0.71$, $P < .0001$). Receiver-operating characteristic curves showed that calcarine sulcus depth (area under curve [AUC] = 0.83, 95% confidence interval [CI] = 0.74–0.92) had the best diagnostic performance in predicting the prenatal progression, as compared with lateral ventricle width (AUC = 0.69, 95% CI = 0.54–0.84) and gestational age (AUC = 0.70, 95% CI = 0.57–0.83) at the initial scan. The cutoff value for calcarine sulcus depth was 3.3 mm, with the corresponding sensitivity and specificity were 75.0% and 81.3%, respectively. Multivariate analyses showed that calcarine sulcus depth ≥3.3 mm (odds ratio = 0.09, 95% CI = 0.02–0.38, $P = .001$) was an independent predictor of the prenatal progression.

For IMVM, calcarine sulcus depth might be a powerful marker to identify subjects at higher risk for worse prenatal progression.

Abbreviations: CI = confidence interval, IMVM = isolated mild fetal ventriculomegaly, MRI = magnetic resonance imaging, OR = odds ratio.

Keywords: calcarine sulcus, isolated mild ventriculomegaly, magnetic resonance imaging, prenatal progression

1. Introduction

Fetal ventriculomegaly, a relatively common phenomenon during 2nd trimester obstetrical sonographic examination, occurs in approximately 1% to 2% of all pregnancies.[1] It can be caused by many different disorders and result in various impairments of neurological, motor, and/or cognitive.[2] Therefore, evaluation and research of ventriculomegaly is clinically important. Mildly enlarged ventricles in the absence of ultrasound evidence of related malformations and/or signs of aneuploidy is typically designated isolated mild fetal ventriculomegaly (IMVM), a width of the atrium of the lateral ventricle between 10 and 15 mm.[3,4] It

is the most commonly diagnosed cerebral abnormalities, about 1% of all pregnancies.[3]

Previous studies have shown that some IMVM can be a transient condition or a variant of normal structure that resolves spontaneously in later weeks of gestation.[1,5] Conversely, ventriculomegaly can also appear isolated and mild at diagnosis, but enlargement becomes evident later or even after birth.[1,6] It is, therefore, very difficult to supply adequate counseling information to pregnant women at initial diagnosis of the IMVM, particularly within the stage of 2nd trimester.[7]

Cerebral surface in humans have a convoluted characteristic trait presenting in a pattern of sulci and gyri. Previous studies have revealed that the main sulci and gyri emerge subsequently from beginning to end of the 2nd gestation in humans.[8] Therefore, the evolutionary development of sulcal extent, direction, or even pattern is considered to be able to offer the first clue to the cerebral disorders. Calcarine sulcus, 1 anatomical landmark for clinical diagnosis, surgical treatment, and functional study, is an important and consistent sulcus of the medial surface of the occipital lobe.[9] It is easy to measure the depth of the calcarine sulcus by magnetic resonance imaging (MRI) examination of live human brain tissues. Thus, it is feasible to study the development, intersubject variability, and interhemispheric asymmetry by in vivo morphometry of the human primary visual cortex. Our previous study and 1 animal-based research published recently confirmed the negative association between the development of calcarine sulcus and the width of lateral ventricles.[10,11]

However, no study has been conducted to explore whether the formation of calcarine sulcus can be used to predict the prenatal progression of IMVM. The aim of present study is therefore to evaluate the reliability of calcarine sulcus depth in the 2nd trimester to predict the prenatal enlargement of lateral ventricle in fetuses with IMVM.

2. Materials and methods

2.1. Participants

Present study was approved by the Institutional Review Board of the Guangzhou Women and Children's Medical Center. The obstetric MRI databases were queried for fetuses referred for MRI check due to ultrasound-diagnosed IMVM. Both original images and ultrasonographic reports were used to identify potential participants of IMVM. Entrance criteria: singleton pregnancy, diagnosed with ventriculomegaly by sonography examination (10.0–15.0 mm) at 20 to 26 weeks' gestation, with no other abnormalities on comprehensive ultrasound scans, and with at least 1 another examination (MRI or ultrasonographic) at 30 to 32 weeks' gestation. The last one was used if there is more than 1 examination at 30 to 32 weeks' gestation.

From September 2010 to January 2016, 176 consecutively eligible ultrasound-diagnosed IMVM cases referred for MRI check were founded. Seventy nine fetuses were excluded, including: 20 ultrasound performed >72 hours before MRI, 2 cases reassigned from IMVM on ultrasound to normal-sized ventricles on MRI, 1 fetuses reclassified from IMVM to moderate ventriculomegaly, 2 cases of known abnormality on karyotyping, 2 twin pregnancies, 3 cases viruses infection (toxoplasmosis, rubella, and cytomegalovirus), and 49 final scans done before 30 weeks' gestation.

2.2. Prenatal ultrasound

A Philips IU22 color Doppler ultrasound instrument (Phillips Healthcare, Andover, MA) was used for prenatal trans-abdominal ultrasound examination. During examination, a low-frequency convex array probe was used with a frequency of 2 to 5 MHz. The subjects were in a supine position. A systematic prenatal fetal ultrasound screening was performed by a sonographer with more than 5 years of experience in ultrasound examination of obstetrics and gynecology patients.

2.3. MRI image acquisition

MRI technique used in current study has been discussed in detail elsewhere[12] but is briefed here. Fetal MRI was conducted by radiologists on a Philips Acheiva 1.5-T MRI machine (Philips Medical Systems, Best, The Netherlands) using a 32 channel cardiac coil covering the abdomen of the mother in supine position. T2-weighted single-shot turbo-spin echo images were acquired according to the following parameters: time echo = 160 ms, time repetition = 15,000 ms, slice thickness of 2.5 mm, slice overlap of 1.5 mm, and flip angle = 90°. A series of fetal images were derived from 3 orthogonal planes (2 coronal, 4 transverse, and 2 sagittal acquisitions).

2.4. Image analysis

Two other ultrasound readers, not involved in the initial scanning of the fetus, independently reviewed the ultrasonographic images again. Width of the ventricular atrium was evaluated at the tail of the choroid, using the inner-to-inner wall diameter measurement. Mean of the larger ventricular measurements (including the original reports) was used for data analysis. Final prenatal sonographic diagnosis was decided by consensus.

MRI images were reviewed by 3 pediatric radiologists with at least 5 years of experience. All 3 radiologists confirmed diagnoses, measured the width of lateral ventricular, and evaluated the depth of calcarine sulcus independently without a previous knowledge of the ultrasound reports. The transverse innerdiameter of the trigones of each lateral ventricle was assessed on the axial images. We implemented Euclidean depth, the shortest distance measured from the convex hull to the vertices of the cortical surface, to evaluate the depth of calcarine sulcus.[13,14] Majority opinion on abnormality diagnosis and average values of 3 radiologists were used for statistical analysis.

2.5. Statistical analysis

Given less than 10 of the cases went back for a 2nd MRI examination at 30 to 32 weeks' gestation during the study period. Thus, the mean of sonographic measurements on the axial ultrasonographic images of the larger side of lateral ventricle and the average depth of calcarine sulcus in the ipsilateral were used for the final analyses. The width from the 1st examination was compared with that from the 2nd examination on the basis of any change in classification described: <10 mm, 10 to 12 mm, 13 to 15 mm, and ≥16 mm. Progression was defined as the process of developing from a lower group toward a higher one or from IMVM to a ventriculomegaly with other CNS abnormalities.[15]

Categorical data were expressed as percentages and compared with Chi-square test. Quantitative traits were demonstrated as mean values and standard deviation. They were assessed for normality by the Kolmogorov–Smirnov test and compared using the Student t test. Pearson correlations were employed to ascertain the relationship between calcarine sulcus depth and lateral ventricle width. The receiver-operating characteristic curves were performed to compare the classifying performance of different predictors. The area under curve for normalized/stabilized group and progressed group were used as a parameter of performance for identifying subjects at higher risk of prenatal progression.

Unconditional logistic regressions were conducted to calculate the odds ratios (ORs) and corresponding 95% confidence intervals (CIs) for risk factors with prenatal progression. All variables that were evaluated on univariate analysis were entered into multivariable models using enter method. All tests were performed 2-tailed, and $P < .05$ were reported as significant. All statistical analyses were performed using SPSS version 19.0 (IBM, Armonk, NY).

3. Results

A total of 97 fetuses underwent at least 3 examinations (2 at 20–26 weeks' gestation: 1 ultrasonographic and 1 MRI, and 1 another ultrasonographic at 30–32 weeks' gestation). The mean age was 29.60 ± 4.68 years. The mean gestational age and ventricular measurements were 23.08 ± 2.00 weeks and 12.09 ± 1.25 mm at the initial scan, and 30.93 ± 0.79 weeks and 12.17 ± 2.54 mm at the 2nd scan, respectively. The changes in the degree of ventriculomegaly from 20–26 to 30–32 weeks' examinations, in terms of category, are shown in Fig. 1.
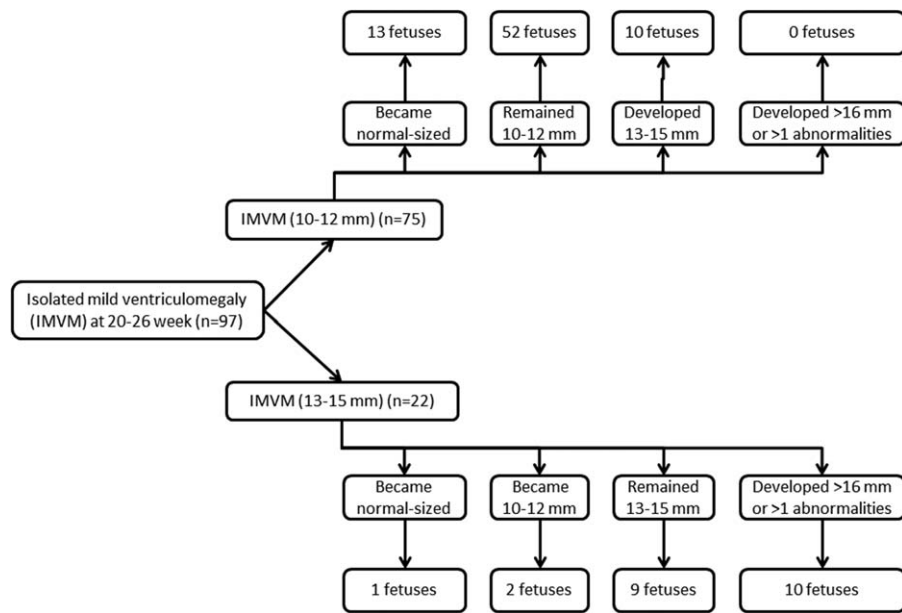
Figure 1. The change in category of isolated mild fetal ventriculomegaly between the 20–26 and the 30–32 weeks' ultrasonographic examinations.

3.1. Correlation between calcarine sulcus depth and lateral ventricle width

As shown in Fig. 2, the Pearson correlation coefficient was 0.70 between the lateral ventricle width at the initial scan and ventricular measurements at the 2nd scan ($P < .0001$), whereas the correlation coefficient was -0.71 between the calcarine sulcus depth and ventricular measurements at the 2nd scan ($P < .0001$).

3.2. Value of calcarine sulcus depth in predicting the prenatal ventricle enlargement

Calcarine sulcus depth had the best performance in predicting the prenatal progression, as compared with lateral ventricle width and gestational age (Fig. 3). The area under curve increased from 0.69 for lateral ventricle width, 0.70 for gestational age, to 0.83 for calcarine sulcus depth. However, no significant differences in discrimination between any 2 indices were found (calcarine sulcus depth vs lateral ventricle width: $z = 1.94$, $P = .05$; calcarine sulcus depth vs gestational age: $z = 1.74$, $P = .08$; and lateral ventricle width vs gestational age: $z = 0.06$, $P = .95$). The optimal

cut points to detect the prenatal progression were 13.6 mm for lateral ventricle width, 24.5 weeks for gestational age, 3.3 mm for calcarine sulcus depth, and the corresponding sensitivity and specificity were 50.0% and 91.3%, 55.0% and 76.3%, 75.0% and 81.3%, respectively.

3.3. Characteristics of normalized/stabilized and progressed fetuses

As shown in Table 1, the gestational age, lateral ventricle width, and calcarine sulcus depth at the 1st scan and the lateral ventricle width at the 2nd scan were all significantly different between 2 groups (all $P < .05$).

3.4. Determinants of prenatal progression of IMVM

As shown in Table 2, with the exception of age, all other variables including gestational age, lateral ventricle width, and calcarine sulcus depth at the 1st scan and period between 2 examinations were significantly correlated with the prenatal progression. The adjusted estimates, however, were not in complete agreement
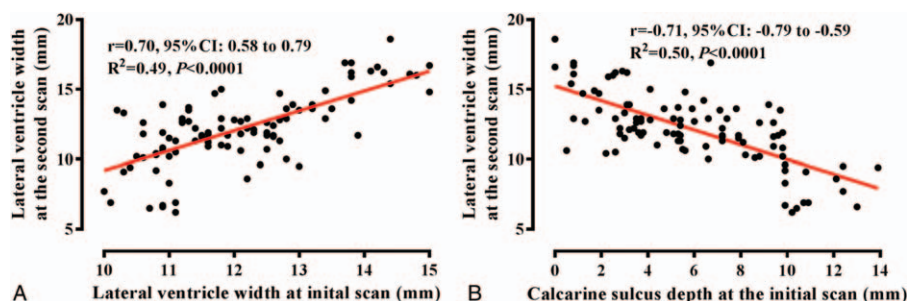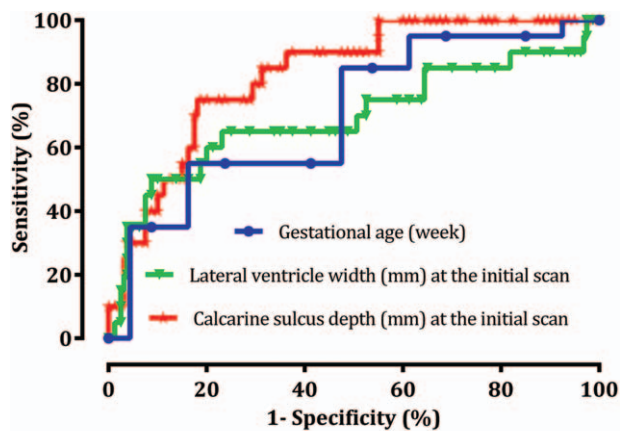

Figure 2. Correlation between the prenatal lateral ventricle width on ultrasound and calcarine sulcus depth on magnetic resonance imaging (MRI). (A) Lateral ventricle widths at initial and the 2nd scans; (B) calcarine sulcus depth at initial scan and lateral ventricle widths at the 2nd scan.

Figure 3. The receiver-operating characteristic (ROC) curves for gestational age, lateral ventricle width, and calcarine sulcus depth to predict the progression in utero of isolated mild fetal ventriculomegaly.

with univariate analyses. In multivariable logistic regression analysis, lateral ventricle width >13.6 mm (OR=6.36; 95%CI: 1.28–31.68; P=.02), and calcarine sulcus depth ≥3.3 mm (OR=0.09; 95%CI: 0.02–0.38; P=.001) at the 1st scan were 2 independent predictors of the prenatal progression.

4. Discussion

Current study is the first to explore the predictive value of calcarine sulcus formation in the 2nd trimester on the occurrence of the prenatal lateral ventricle enlargement. We found that more than 21% fetuses diagnosed with IMVM at the 2nd trimester faced a continuous challenge of prenatal enlargement of lateral ventricle. Lateral ventricle width and calcarine sulcus depth at diagnosis are 2 independent predictors for the prenatal progression. Taken together, these results reveal that calcarine sulcus formation may be a potential auxiliary marker of subsequent progression of IMVM.

Recent studies have questioned whether IMVM is a truly abnormal at all. For example, Gaglioti et al[5] demonstrated that fetuses diagnosed with IMVM had a 98% probability of being alive at equal to or more than 2 years old, and 93% of those who were alive had a normal evaluation of 2-year neurodevelopmental. This opinion has also been sustained by another recent study by Falip et al,[16] who demonstrated that the prognosis of IMVM was excellent in 94% and 85% of fetuses with 10 to 11.9 mm and 12 to 15 mm trigones width, respectively. Conversely, however, ventriculomegaly can also appear IMVM at diagnosis, but have continuous challenge of enlargement of the size of lateral ventricles across and even after the intrauterine life.[1,3] According to current study, more than 14% of the fetuses of sonographically diagnosed IMVM resolved prenatally. Particularly, of 75 cases measuring 12 mm or less, 13 normalized later (17.3%). Clinically, lateral ventricle width is typically used as the single indicator of IMVM. Obviously, measuring this single parameter cannot evaluate the IMVM comprehensively. Thus, identification of markers that could predict the pre- and postnatal progression is particularly important to provide adequate counseling to pregnant patients.

Table 1

Demographic characteristics of normalized/stablized and progressed fetuses with mild isolated fetal ventriculomegaly.

Variables	Prenatal outcome		t	P
	Unprogressed (n=77)	Progressed (n=20)		
Age, y	30.06±4.92	27.80±3.05	1.96	.05
Gestational age, wk, at the 1st scan	22.79±1.96	24.20±1.80	2.92	.004
Gestational age, wk, at the 2nd scan	30.96±0.77	30.80±0.89	0.42	.16
Lateral ventricle width, mm, at the 1st scan	11.87±1.06	12.94±1.57	3.60	.001
Lateral ventricle width, mm, at the 2nd scan	11.36±2.08	14.98±1.36	7.38	<.001
Calcarine sulcus depth, mm, at the 1st scan	6.63±3.26	2.79±2.02	5.03	<.001

Table 2

Factors influencing the progression in utero of mild isolated fetal ventriculomegaly.

Variables	Prenatal outcome		OR (95%CI)	P	OR (95%CI)*	P
	Unprogressed (n=77)	Progressed (n=20)				
Age, y	30.06±4.92	27.80±3.05	0.88 (0.78–1.00)	.05	0.90 (0.75–1.08)	.24
Gestational age at the 1st scan						
<=24.5 wk	58 (86.6%)	9 (13.4%)	Reference		Reference	
>24.5 wk	19 (63.3%)	11 (36.7%)	3.73 (1.34–10.37)	.01	1.16 (0.14–9.83)	.90
Period between the 2 examinations, wk	8.17±2.01	6.60±2.37	0.69 (0.54–0.90)	.006	0.67 (0.40–1.13)	.13
Lateral ventricle width at the 1st scan						
<=13.6 mm	72 (87.8%)	10 (12.2%)	Reference		Reference	
>13.6 mm	5 (33.3%)	10 (66.7%)	14.40 (4.08–50.81)	<.001	6.36 (1.28–31.68)	.02
Calcarine sulcus depth at the 1st scan						
<3.3 mm	13 (46.4%)	15 (53.6%)	Reference		Reference	
>=3.3 mm	64 (92.8%)	5 (7.2%)	0.07 (0.02–0.22)	<.001	0.09 (0.02–0.38)	.001

CI=confidence interval, OR=odds ratio.
* All variables that were evaluated on univariate analysis were adjusted.

Morphological development of insular sulci and gyri can be seen from the 2nd month to the end of intrauterine life or even later after delivery. Calcarine sulcus, one of the primary macroscopical structures on the surface of the fetal cerebral hemisphere, appears as shallow grooves at the earlier stage and become increasingly deeper in-folds during the process of gyration.[17] Under normal circumstances, the calcarine sulcus is fully developed at 16 to 22 weeks' gestation, indicating the formation and maturity of each functional area of the occipital lobe.[18] Thus, the calcarine sulcus may be a potential marker to predict the structural maturity levels of the fetal brain. Present study demonstrated that isolated fetal ventriculomegaly was significantly related to the underdevelopment of the calcarine sulcus. These results suggested the possibility that, in the absence of other anomalies, the depth of calcarine sulcus may be another sign of developmental anomalies of patients with IMVM. For example, in a recent study of Macaca fascicularis fetuses, researchers tried to explore the relationship between calcarine sulcus formation and the extension of the abnormal lateral ventricle morphology, and to propose biomarkers for the comprehensive assessment of the IMVM.[11] Results concluded that the calcarine sulcus infolding degree can be used as a gross anatomic landmark to evaluate the morphological maturation of the cerebral in Macaca fascicularis fetuses. Our later study confirmed this finding among human.[10]

According to our findings, 21% of the fetuses progressed prenatally. However, of the 28 cases measuring <3.3 mm of the calcarine sulcus depth, none normalized, while 15 cases progressed. Furthermore, both univariate (OR = 0.07, 95% CI = 0.02–0.22) and multivariate (OR = 0.09, 95% CI = 0.02–0.38) analyses showed that ≥3.3 mm is an independent protective factor against prenatal progression. Therefore, if fetal ultrasound reveals an abnormal size of the ventricles, sonographers should pay attention to the development of the calcarine sulcus, and MRI scans should be performed if necessary to observe the maturity of the calcarine sulcus. After birth, the child should be followed up to monitor any occipital lobe dysfunction (such as amblyopia) and receive timely surgical intervention.

Obviously, our findings are useful for the obstetricians and pediatric radiologists when counseled by the pregnant patients about the prenatal course of IMVM. However, the outcome of most concern is that how is the predictive value of the calcarine sulcus depth on the postnatal developmental delays. In current study, the study period was short. Therefore, it is not known whether the prenatal depth of calcarine sulcus is also a predictive marker for developmental problems after delivery. In addition, the small number size of present study does not allow to extrapolate our findings to other population. Finally, because of financial and clinical reasons, the formation of calcarine sulcus and the diameters of lateral ventricles were obtained from MRI and ultrasonographic images, respectively. Although inconsistency between 2 different measurements may raise potential conflicting classifications, previous study indicated excellent consistency between fetal brain sonographic examination and MRI scans when performed for the diagnosis of fetal IMVM.[19] Further studies, including postnatal follow-up, will provide new insights into the prediction value of the depth of calcarine sulcus for the nervous system development.

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