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Ultrasound and MRI in fetuses with ventriculomegaly: Can cortical development be used to predict postnatal outcome?

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Abstract

OBJECTIVE—To assess conspicuity of brain cortical maturation by sonography and magnetic resonance imaging (MRI) in fetuses referred for ventriculomegaly, and to determine if sulcal visualization can be used to predict postnatal outcomes.

METHODS—374 fetuses referred for ventriculomegaly (gestational age 16 to 41 weeks, mean 26 weeks), were imaged by sonography and MRI. Four to six radiologists rated visualization of 19 fissures/sulci. Majority opinion regarding sulcal visualization was compared amongst fetuses categorized by central nervous system (CNS) abnormality: normal, isolated ventriculomegaly, and ventriculomegaly with additional CNS abnormalities. Liveborn infants were separated into normal and abnormal developmental categories. Logistic regression was used to correlate sulcal visualization and postnatal development. A sub-analysis was performed in fetuses who had prenatally been classified as either having normal brains or isolated ventriculomegaly.

RESULTS—Cortical sulci were visualized more frequently and at an earlier gestational age by MR than by ultrasound. In the entire cohort, the odds ratio of normal development ranged from 3.1–10.0 whenever the calcarine, parieto-occipital, cingulate, superior temporal, precentral or postcentral sulcus was seen on MR. In fetuses categorized as having normal brains or having isolated VM, the odds ratio of normal development ranged from 3.5–9.0 whenever the parieto-occipital, cingulate, or superior temporal sulcus was seen.

DISCUSSION—Fetal brain sulcal visualization is dependent on the imaging modality used and gestational age at time of imaging. Information regarding sulcal visualization may aid in counseling patients carrying fetuses with ventriculomegaly.

Introduction

Fetal ventriculomegaly (VM) is diagnosed when the lateral cerebral ventricles are dilated to 10 mm at the level of the atrium [1], at any gestational age. Ventriculomegaly occurs in approximately 1 out of every 1000 live births[2], and can be due to a variety of causes, including obstruction of cerebrospinal fluid flow, cerebral dysgenesis, or destruction of brain tissue after infection or infarction.

Many factors contribute to the postnatal prognosis of fetuses with VM including the degree of ventricular dilatation [3–8], gestational age at the time of diagnosis [4], in utero progression of dilatation [3, 5], and, most importantly, the presence of associated central nervous system (CNS) and non-CNS abnormalities [3, 5]. Previous studies have shown that isolated VM measuring between 10–12 mm without associated CNS abnormalities can be a transient condition that resolves later in gestation or in early postnatal life [3–6]. In some instances, this very mild degree of VM has been suggested to be a variant of normal structure [4–6].

Conversely, VM may appear to be isolated at the time of diagnosis, but associated anomalies, such as migrational abnormalities, may become evident later in gestation or after birth [9]. Because VM may be due to many etiologies, and because the condition has the potential to evolve during gestation, it is often difficult to provide adequate counseling to pregnant patients at the time of initial diagnosis, especially during the second trimester.

Previous studies have shown that MR visualization of sulci in normal fetuses follows a developmental course established by neuroanatomic studies, but lags behind gross anatomic visualization by 0–8 weeks [10, 11]. This lag is felt to be due to partial volume averaging of small structures, and motion artifacts inherent in imaging the fetus. Furthermore, compared to normal fetuses, fetuses with VM and other CNS abnormalities show a delay in sulcal visualization on US and MRI [11]. The purpose of this study is to assess US and MR visualization of cortical maturation in fetuses referred for VM, and to correlate the visualization of sulci with postnatal neurodevelopmental outcomes.

Methods

This study was part of a National Institutes of Health-funded, IRB-approved, HIPAA-compliant prospective cohort study assessing outcomes of fetuses with VM. Written informed consent was obtained from pregnant women at the time of prenatal enrollment and from parents at the time of postnatal neurodevelopmental testing.

Subjects

Between 7/1/2003 and 7/18/2008, 376 consecutive pregnant women, aged 17–44 years (mean 31 ± 5.5 years) with 384 fetuses were enrolled after a referral diagnosis of fetal VM (Fig. 1). This cohort included 6 women carrying twins, both of whom had VM, and 2 women enrolled during 2 consecutive pregnancies. Subsequently, 10 fetuses (in 9 pregnant women) were excluded. Three fetuses were excluded due to review of referral records showing that the fetus never had VM; one of these three fetuses was in a twin gestation in which the other twin had VM and remained enrolled. One subject was excluded after declining to allow collection of pregnancy and postnatal follow-up information. Three subjects were excluded for not having completed MRI studies: two pregnant women were over the MRI table weight limit and one was too claustrophobic to complete the study. One fetus was excluded for an US examination that temporally preceded the MRI by more than one week. Two fetuses were excluded secondary to lack of paperwork documenting sulcal visualization. Subsequent to these exclusions, the final prenatal study population included

367 women with 374 fetuses (369 sonograms and fetal MRIs with 2 women being enrolled in two different pregnancies).

Gestational age

Gestational age was determined by: 1) dates defined as either estimated due date (EDD) if a first trimester dating sonogram was performed and used for dating the pregnancy or gestational age determined by last menstrual period if a first trimester sonogram had not been performed or if the dates were not changed at the time of a first trimester sonogram; and 2) age by ultrasound (average of biparietal diameter, head circumference, abdominal circumference, femur length).

Sonography

Sonography was performed with a variety of equipment during the 4 years of enrollment, including ATL 5000 (Philips Healthcare, Andover, MA), iU22 (Philips Healthcare, Andover, MA), Voluson 730 (GE, Waukesha, WI) and Siemens Sequoia 512 (Siemens Acuson Co., Mountain View, CA) with 2.5–12.0 MHz transabdominal (TA) and transvaginal (TV) transducers by one of four radiologists with 12–16 years expertise in ultrasound. The protocol stated that TV scans should be performed when the fetus was in cephalic position. Amongst sonograms performed, 147/374 (39%) included TV scans and 227/374 (61%) did not. For the 227 studies without TV scans, 113/227 (50%) were due to breech or transverse presentation of the fetus, 23/227 (10%) were due to Twin B (non-presenting fetus) with VM, 3/227 (1%) were due to patient declining TV exam, 2/227 (1%) were due to recent TV study at an outside hospital within the past 10 days, and the 86/227 (38%) were due to unknown reason/non-adherence to the protocol.

The first 190 US and MRs (performed on the first 194 fetuses, including 4 sets of twins) were independently reviewed by three radiologists who assessed CNS diagnosis, ventricular size, and visualization of the following structures (Fig. 2, 3): interhemispheric and Sylvian fissures, calcarine, parieto-occipital, cingulate, central, superior temporal, precentral, postcentral, inferior temporal, inferior frontal, insular, parietal, secondary temporal, secondary frontal, secondary parietal, superior occipital, inferior occipital, and tertiary frontal sulci. For ease of writing, fissures and sulci are considered hereafter as “sulci.” Majority opinion on sulcal visualization was used for statistical analysis. The subsequent 179 sonograms and MRs (performed on 180 fetuses, with 1 set of twins examined during the same exam) were reviewed by 2 radiologists (with a third only participating when there was a difference in opinion regarding CNS diagnosis) with only one radiologist coding for the visualization of sulci. Final prenatal sonographic diagnosis of CNS abnormalities was decided by consensus review. This consensus process for the first 199 fetuses was previously reported [12].

MR imaging

MRI examinations were performed on a 1.5-T superconducting system (Signa; GE Medical Systems, Milwaukee, WI) using an 8 or 16 element phased-array surface coil with 3–5 mm slice thickness. A scout view was obtained and used to orient the first diagnostic imaging sequence. Single-shot fast spin-echo imaging was performed in the fetal sagittal, coronal, and axial planes using parameters described previously.[13] A radiologist was present to monitor the study as it was being performed, allowing for repetition of sequences if quality was obscured by fetal motion or an oblique image plane. MR studies were performed on the same day as US imaging in 350/374 (94%) cases, 1 day later in 7/374 (2%) cases, 2 days later in 3/374 (1%) cases, 3 days later in 5/374 (1%) cases, 4 days later in 2/374 (0.5%) cases, 5 days later in 1/374 (0.2%) case, and 6 days later in 5/374 (1%) cases.

MR examinations were reviewed by one obstetric radiologist (usually the same radiologist who read the US and three pediatric neuroradiologists with 11–15 years of experience, except for the last 9 subjects in whom only two pediatric neuroradiologists participated). The pediatric neuroradiologists independently coded diagnoses, measured lateral ventricular size, and coded for visualization of the previously named sulci without knowledge of sonographic findings. Majority opinion on sulcal visualization was used for statistical analysis (2/3 neuroradiologists or majority opinion when there were only 3 readers). MR CNS diagnosis was decided by consensus, as previously described [12].

Diagnostic groups

Final overall prenatal diagnosis was obtained by combined consensus reads of the US and MR studies, as previously described [12]. The larger of the two lateral ventricles was identified, and the median of the three sonographic measurements of this ventricle was used for data analysis. The fetuses were categorized into the following prenatal diagnostic groups: 1) those felt to be normal (referred for VM, but no CNS abnormalities were found at the time of imaging); 2) isolated VM (no other CNS abnormalities); 3) VM associated with other CNS abnormalities.

Postnatal outcome

Pregnancy outcome (live birth versus pregnancy termination, stillbirth, or neonatal demise) data was obtained via hospital records and participant interviews. Parents of newborns were asked to participate in formal neurodevelopmental testing at 6 months, 1 year, 2 years, and 3 years of age. The testing consisted of a formal neurologic exam by a pediatric neurologist and psychological testing by a pediatric psychologist. At 6 months, 1 year and 2 years, the formal tests used by the psychologists were the Bayley Scale of Infant Development (2nd edition) [14], Vineland Adaptive Behavior Scale [15], and the MacArthur Communicative Development Inventory [16]. At 3 years, the outcome instruments were the Wechsler Preschool and Primary Scale of Intelligence-III [17] and the Bayley Scale of Infant Development -III Motor Scale [18]. The process of assigning infants into neurodevelopmentally normal or abnormal categories based on formal developmental testing has been previously described [19]. The same scoring system was used in the current study with the exception of head size or shape not being categorized as an abnormal finding. Patients were considered to have a normal outcome if there was an absence of abnormality on all neurologic exams between 6 months and 3 years of age, and if the results of all standardized developmental testing had scores of at least 85 (on age-referenced standard scores with 100 being normal). Patients were considered to have an abnormal outcome if there was an abnormality on any neurologic exam between 6 months and 3 years of age, or if the results of standardized developmental testing was less than 85. For all children categorized as normal based on neurodevelopmental testing, further medical record review was performed to confirm that clinical development remained normal for any child with neurologic testing up to age 5. Medical record review was similarly performed for children who did not undergo formal postnatal testing and were then assigned into normal and abnormal categories using the same criteria used for those who had formal testing.

Statistical methods

We assessed inter-rater agreement of sulcal visualization for the first 194 fetuses, each observed by 3 US readers and 4 MR readers. For each sulcus and each imaging mode, we tallied the percentage of fetuses for which all raters were in agreement as to the presence or absence of the sulcus. Kappa statistics, conventionally used to discount “chance” agreement, were not employed because a high level of agreement (seen here) makes this measure unstable [20]. We used ordinal logistic regression analysis to assess the influence of

gestational age (expressed as a continuous variable) on the distribution of prenatal diagnosis among normal, isolated VM, and VM with other CNS abnormalities.

We employed a logistic regression model to assess the influence of gestational age, imaging mode, prenatal diagnosis, year of imaging, and rater variation on the likelihood of visualizing each sulcation pattern. We report the results as the odds of normal outcome when the sulcus was visualized relative to the odds when it was not visualized. We obtained a 95% confidence interval for this odds ratio (OR) and tested the null hypothesis that $OR=1$. Interhemispheric and sylvian fissures were dropped from the analysis since they were present in 100% and 80% of fetuses, respectively. An additional analysis was repeated, restricted to fetuses greater than 22 weeks gestational age.

We used SAS software version 9.2 (Cary, NC) for all computations and employed a criterion of $p<0.05$ for statistical significance for each pairing of dependent and independent variable, as recommended by Glantz and Slinker [22].

Results

For the entire cohort of 374 fetuses, the gestational age at the time of imaging was 16.3 to 41.0 weeks by dates (mean 25.9 ± 5.7 weeks). The distribution of the three fetal diagnostic groups (normal, isolate VM, and other CNS abnormalities, Table 1) did not vary with gestational age as assessed by ordinal logistic regression ($p=0.40$). Results from regression analysis were similar, when either age by dates or age by biometry was used for dating the pregnancy, therefore age by dates is used for the reporting of results in this manuscript.

Sulcal visualization

In general, more sulci were visualized at an earlier gestational age, and were visualized more frequently by MR imaging than by US imaging, either TA or TV (Fig. 4). For both US and MR, inter-rater agreement on visualization of each sulcus was highest for sulci that were visualized most frequently and least frequently (Fig. 5).

Sulci were visualized more frequently and at an earlier gestational age by TA plus TV US than by TA US alone (Table 2). Visualization by US lagged behind visualization by MR by 3.0–10.4 weeks ($p<0.001$ – 0.005). Year of imaging was not associated with sulcal visualization except for MR imaging of the inferior temporal, inferior frontal, and insular sulci, which were seen about 0.5 weeks earlier on average over the course of the study, adjusting for GA, mode of imaging, and diagnosis group ($p<0.005$). Relative to fetuses with a normal prenatal diagnosis, fetuses with a prenatal diagnosis of VM associated with other CNS anomalies showed a lag time for sulcal visualization ranging from 1.7–5.3 weeks ($p<0.001$ – 0.05). Fetuses with isolated VM did not show a statistically significant lag in sulcal visualization compared to fetuses with a normal prenatal diagnosis (Table 2).

Postnatal outcome

Of the 374 fetuses in our cohort, 37 (10%) were categorized by prenatal imaging as normal, 196 (52%) as having isolated VM, and 141 (38%) as having VM and other CNS abnormalities (Table 3). There were 63/374 (17%) terminations of pregnancy, 6/374 (2%) spontaneous abortions, 6/374 (2%) liveborns with subsequent neonatal demise, and 299/374 (80%) live borns who survived the neonatal period (Fig. 1). The six cases of neonatal demise included one case each of: holoprosencephaly, hypoxic ischemic encephalopathy, lethal cardiac defect, Chiari malformation and myelomeningocele with brainstem abnormality and central respiratory dysfunction, donor twin with twin-reversed arterial perfusion syndrome, and polymicrogyria with cerebellar hypoplasia with induced delivery at 23 weeks gestation.

Of fetuses with postnatal imaging, 16/19 (84%) of neonates prenatally diagnosed as having normal CNS development continued to be categorized as normal; 1/19 (5%) developed isolated VM; and 2/19 (10%) developed other CNS abnormalities (one with septal leaflet dysplasia and one with choroid plexus cyst). 30/119 (25%) who were prenatally diagnosed as having isolated VM continued to have isolated VM; 62/119 (52%) showed resolution of VM; and 27/119 (23%) were found to have other CNS abnormalities (the most common new diagnoses were intracranial hemorrhage N=10 and choroid plexus cysts N=8). 73/82 (89%) of those prenatally diagnosed with other CNS abnormalities continued to show other CNS abnormalities; 9/82 (11%) showed resolution of prenatal appearance of anomalies, with the most common findings that resolved being mega cisterna magna (N=4) and choroid plexus cyst (N=2, Table 3).

Postnatal follow-up was available in 209/299 (70%) children surviving the neonatal period (Fig. 1). Formal neurodevelopmental follow-up was obtained in 159 children, with assessments at 6 months (N=143), 1 year (N=127), 2 years (N=92), and 3 years (N=58). Amongst the 159 children with formal postnatal follow-up, 111/159 (69%) were considered abnormal and 48/159 (30%) were considered normal (Fig. 1). Two children considered normal by formal evaluation at 6 months had clinical neurology examinations at ages 4 and 5 that were abnormal. One child developed intractable seizures secondary to hemimegalencephaly and eventually underwent a right hemispherectomy with global developmental delays, dysarthria, mild left hemiparesis and dysconjugate gaze, last neurologic exam at age 4. One child, at 5 years of age, had bilateral hand apraxia and an inferior visual field defect.

Forty-six children were followed by clinical chart review (including the two previously mentioned with original formal testing). Amongst these, 41 were considered abnormal including one child who died at 2 years of age due to Schinzel-Gideon syndrome. Five children (age 6 months – 1 year) were considered to have normal development. Thus, there were a total of 164/215 (76%) pregnancies with abnormal outcome (111 cases of abnormal outcome by formal testing, 41 cases of abnormal outcome by clinical follow-up, 6 neonatal demises, and 6 spontaneous abortions) and 51/215 (24%) with normal outcome (Fig. 1).

In the subgroup analysis of 217 children categorized prenatally as normal or having isolated VM who survived the neonatal period, 135 (62%) had postnatal follow-up. Of these children, 44/135 (32%) were normal by neurodevelopmental testing and clinical postnatal follow-up.

Regression analyses

For the entire cohort of patients with VM, adjusting for gestational age by dates and intracranial atrial diameter at the time of imaging, when the calcarine, parieto-occipital, cingulate, central, superior temporal, precentral or postcentral sulcus was visualized on MR, the odds ratio of normal postnatal neurodevelopment ranged from 3.1–10.0 ($p < 0.001$ –0.05, Table 4, Fig. 6). US visualization of sulci had less prognostic value, with most sulci never reaching statistical significance.

In a subanalysis in which patients with a diagnosis of other CNS abnormalities were excluded, when the parieto-occipital, cingulate, or superior temporal sulcus was visualized, the odds ratio of normal postnatal development ranged from 3.5–9.0 ($p = 0.004$ –0.05, Table 4, Fig. 7). Furthermore, when terminations were excluded from the analysis, the odds ratio of normal development ranged from 3.8–9.1 when the parieto-occipital, cingulate or superior temporal sulcus were seen ($p = 0.003$ –0.04, Table 4).

In the analysis limited to fetuses greater than 22 weeks GA, whenever the calcarine, parieto-occipital, cingulate, central, superior temporal, precentral or postcentral sulcus was seen, the odds ratio of normal postnatal development ranged from 3.8–10.4 ($p<0.001$ –0.03, Table 5). After excluding fetuses with additional CNS anomalies from the analysis, the odds ratio of normal postnatal development ranged from 6.2–8.3 whenever the parieto-occipital or cingulate sulcus was seen ($p=0.006$ –0.02, Table 5). After excluding terminations, the odds ratio of normal postnatal development ranged from 5.6–7.8 whenever the parieto-occipital or cingulate sulcus was seen ($p=0.008$ –0.02, Table 5, Fig. 8).

In all subanalyses, as in the entire cohort, US visualization of sulci (either TA or combined TA/TV) was a less sensitive predictor of normal postnatal outcome than MR visualization. Although the year of imaging influenced visualization of the inferior temporal, inferior frontal, and insular sulci, it did not impact postnatal outcome, as these sulci remained nonsignificant as predictors of postnatal outcome.

Discussion

The process of cortical maturation, as represented by the development of sulci and gyri, begins around the second month of gestation and continues into the early neonatal period [23]. Since cortical maturation begins early in brain development, disturbances in sulcation may signify larger global problems with CNS development, possibly portending future functional disease [24]. In some CNS anomalies (for example agenesis of the corpus callosum with absent cingulate sulcus, or lissencephaly with multiple absent sulci), sulcal development is known to be abnormal. Fetuses with hydrocephalus may have effacement of sulci due to increased ventricular pressure; thus sulci, although present, may be difficult to visualize [25]. Certain neuropsychiatric conditions such as autism [26] and schizophrenia [27] have been associated with abnormal sulcation patterns in postnatal life.

Previous neuroanatomic [10] and imaging studies [11, 25, 28–31] have shown that sulcal development follows a predictable timetable and serves as a reliable indicator of gestational age. Sonographic studies of sulcal maturation, both in preterm neonates and in utero, have shown that sonographic visualization of sulci follows the precise sequence established by gross neuroanatomic studies, but lags behind gross anatomic visualization by 2–8 weeks [25, 29, 31]. Sonographic study of the fetal brain, however, carries several inherent limitations, including fetal position making the transfontanellar approach difficult and shadowing from the ossified fetal skull with difficulty visualizing the brain surface.

MR studies of sulcal visualization report that MR visualization lags behind anatomic visualization by roughly 2 weeks (ranging from 0–8 weeks) [11, 23]. Our study confirms the results of a prior study showing MR visualization precedes US visualization [32], as more sulci are visualized more frequently and at an earlier gestational age by MR than by US (both transabdominally and combined transabdominal and transvaginal). Other studies have shown less lag time between MR and US visualization [23, 29], with some sulci even appearing earlier on US than on MR [23]. Similar to prior reports [11], we also found that sulcal visualization was further delayed in fetuses with CNS anomalies other than VM when compared to fetuses with normal CNS development.

Discrepancies that exist amongst timelines of sulcal development in various studies using the same modality are likely due to variations in several factors: the method used to determine GA, techniques used in performance of the sonogram, and the definition of visualization (based on appearance of a particular sulcus in either 25%, 25%–50%, 50%–75%, or 100% of fetuses).

Numerous studies have correlated prenatal factors in fetuses with VM with their eventual postnatal developmental outcome [3–8, 33–37]. The association of VM with other CNS anomalies has been shown to serve as a better predictor of outcome than degree of ventricular dilation [36, 37]. In a prior report from our cohort, we showed that fetuses with additional CNS anomalies had a much higher rate of termination of pregnancy (40%, compared to 7% of fetuses with isolated VM <12mm, and 16% of fetuses with isolated VM >12mm, and 0% of fetuses categorized as normal), and that this drove the poor outcome associated with ventriculomegaly to a greater degree than did ventricular dilation [19]. Isolated mild VM, which constitutes roughly 25%–60% of patients with VM [5, 7, 36, 37], depending on the measurement cut-offs used to define mild dilatation, is of particular interest to clinicians who regularly counsel parents on postnatal outcomes because fetuses in this subgroup may have a relatively normal postnatal outcome, especially when compared to fetuses with other associated CNS anomalies [3–7, 36–39].

Our study, with an 82% abnormal outcome amongst all fetuses studied, has a much higher rate of abnormal outcome than other studies of fetuses with VM. This is likely due to our inclusion of all fetuses referred for VM, many with associated CNS abnormalities, and our strict criteria for normal postnatal outcome. Even in our subgroup of isolated VM excluding fetuses imaged at less than 22 weeks and excluding terminations, only 37% had a normal outcome. This rate is much lower than that of most other studies of isolated mild VM where a normal outcome has been reported in 93–100% of children with ventricular dilation between 10–12mm [3, 5, 6, 8] but falls within the 23–100% range reported in children with ventricular dilation between 10–15mm [3, 4, 7, 8, 33–35]. In our study, we chose to not use an arbitrary threshold for mild VM (for example up to 12 mm versus up to 15 mm) but rather to adjust our regression analysis with respect to ventricular diameter.

The lack of consensus in the literature on postnatal outcomes can be attributed to different and non-standardized methods for developmental assessment, often by generalists, evaluations at a wide range of ages and small sample sizes. Additionally, many studies were retrospective in nature, carrying the potential for selection and recall bias. In comparison, our prospective study employed a large sample size of 374 fetuses, 152 of whom had isolated VM. The importance of long-term follow-up was highlighted by Patel et al [7], where 80% of cognitive impairments eventually discovered during up to 4 years of follow-up were originally undetected at 1 year of age. Assessment of neurocognitive outcomes including language learning disabilities is particularly important, as they serve as a predictor of future cognitive development [7]. Many mild manifestations of developmental delay, such as communication disorders, learning disorders and attention deficits are not apparent until school-age.

Our study had limitations. While we had birth outcomes in 100% of our cohort, we had developmental follow-up in only 69% of non-terminated pregnancies. Consistent follow-up is difficult to obtain in large prospective cohort studies, with abnormal patients often having more incentive to follow-up than normal patients. Consequently, our follow-up is biased toward abnormal outcomes. Infants were only followed until 3 years of age, and follow-up by clinical neurology notes was biased toward abnormal outcomes, as patients with normal outcomes tended to follow-up less often. Not all patients had transvaginal sonography to assess cortical development; however, since MR visualization was better than US visualization, this was not felt to affect results. Many of our examinations were performed prior to 24 weeks GA, which is too early to visualize the majority of sulci. However, our logistic regression analysis included a correction for GA. Our findings are therefore difficult to use in the early second trimester prior to the expected time period of visualization of the sulci along the convexities, but will likely be most helpful to reassure pregnant patients when sulci are visualized.

In conclusion, in patients carrying fetuses with VM, the odds ratio of normal postnatal development ranges between 3.1–10.0 with visualization of the calcarine, parieto-occipital, cingulate, central, superior temporal, precentral or postcentral sulci. When assessing patients referred for VM without associated CNS anomalies, the odds ratio of normal postnatal development ranges from 3.9–9.0 whenever the parieto-occipital cingulate, or superior temporal sulcus is visualized. These sulci tend to be seen around by 26 weeks gestation, the time in gestation in which most fetuses in the United States will have had a structural survey and are likely to have been diagnosed with VM. Thus, we believe information on sulcal visualization in the future can aid in the prenatal counseling of pregnant women carrying fetuses with VM, particularly if a sulcus is not visualized at a gestational age when it is expected to be seen. However, future studies are needed to assess how this information can be combined with gestational age, ventricular size, and associated CNS and non-CNS abnormalities to give the best predictive information to patients. Fetal MR is helpful in assessing fetuses with VM in that it frequently depicts additional CNS abnormalities that affect prognosis. In addition, MR adds additional information about cortical maturation, beyond that available with ultrasound. In our study, we have shown that visualization of specific sulci is associated with improved outcomes. This information will potentially be helpful in counseling patients. However, the presence of other CNS and non-CNS abnormalities, associated syndromes and aneuploidy, and progression of VM in utero are of utmost importance in predicting outcome. Therefore, a careful anatomic survey by ultrasound, consideration of karyotype analysis, assessment for progression in utero, and postnatal imaging are all important in optimal care of patients carrying fetuses with VM.

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Appendix

Details of statistical model

Letting P denote the probability of visualization, the model takes the form

$$\ln(P/(1-P)) = \text{constant} + b \times \text{gestational age (wk)} + A_i + C_j + D$$

where b is the increase per week of gestational age in log odds of visualization; A_i is an increment due to imaging mode ($i=1$ for US (TA), $i=2$ for US (TA+TV), $i=3$ for MR); C_j is an increment particular to diagnostic group ($j=1$ for isolated VM, $j=2$ for VM with other CNS anomalies, $j=3$ for normal); and D is the year increment beyond 2003.

For reporting, we converted the increments in probability of visualization to equivalent horizontal lags on the gestational age scale, representing additional time required to reach a given probability of visualization:

$$\begin{aligned} A_i^* &= A_i/b - \text{Cov}(A_i, b)/b^2 + A_i V(b)/b^3 \\ C_j^* &= C_j/b - \text{Cov}(C_j, b)/b^2 + C_j V(b)/b^3, \end{aligned}$$

where $V(b)$ indicates the variance of the coefficient for gestational age and $\text{Cov}(A_i, b)$ and $\text{Cov}(C_j, b)$ denote its covariance with the respective increments for imaging mode and diagnostic group, all parameters being derived from the logistic regression analysis [21]. We also report the gestational age at which 50% of MR readers visualized each sulcus in normal fetuses, estimated by setting $P=0.5$ in the model equation above and solving for gestational age with $i=3, j=3$. A second logistic regression model was employed to determine whether each particular sulcation pattern, visualized by a particular imaging mode, was predictive of postnatal outcome among those subjects with known outcome. The prediction equation was adjusted for atrial diameter (AD) and for gestational age at the time of imaging (GA). Letting P_N denote the probability of normal outcome,

$$\ln(P_N/(1-P_N)) = \text{constant} + \beta \times S + \text{coefficient} \times \text{AD} + \text{coefficient} \times \text{GA},$$

where $S=1$ if the sulcus was detected by the appropriate majority and $S=0$ if it was not. The key hypothesis to be tested is $H_0: \beta=0$, addressing the question of whether visualization of the sulcus affected the probability of subsequent normal outcome.

Fig. 1.
Flowchart of patient enrollment, birth outcome, and postnatal outcome.

Fig. 2a

Fig. 2b

Fig. 2.

Fig. 2a. Sagittal T2 weighted image at 28 weeks gestation showing precentral sulcus (arrowhead) and postcentral sulcus (arrow).

Fig. 2b. Sagittal T2 weighted image at 30 weeks gestation showing cingulate sulcus (arrowhead), parieto-occipital sulcus (white arrow) and calcarine sulcus (black arrow).

Fig. 3a **Fig. 3b****Fig. 3.**

Fig. 3a. Sagittal transvaginal US at 30 weeks gestation showing precentral sulcus (arrowhead) and postcentral sulcus (arrow).

Fig. 3b. Sagittal transvaginal US at 29 weeks gestation showing cingulate sulcus (arrowhead), parieto-occipital sulcus (large arrow), and calcarine sulcus (thin arrow).

Fig. 4. Percentage of readings in which each sulcus was visualized on MR and US. More sulci were visualized, and visualized more frequently, on MR than on US.

Fig. 5.
Percent agreement on visualization of each sulcus on US and MR based on first 194 fetuses. Percentage of agreement was higher for sulci that were visualized most frequently or least frequently.

Fig. 6. Percentage of subjects with a normal clinical outcome in all patients

Normal developmental outcome was more likely when sulcation patterns were visualized on prenatal MR (right) than in the sample as a whole (18%, dashed line) or when the pattern was not visualized (left). Bars indicate simple percentages with standard error, not adjusted for gestational age at time of imaging. Error bars are 1 standard error. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Fig. 7. Percentage of subjects with a normal clinical outcome in patients with a diagnosis of normal or isolated VM

Normal developmental outcome was more likely when sulcation patterns were visualized on prenatal MR (right) than in the sample as a whole (29%, dashed line) or when the pattern was not visualized (left). Bars indicate simple percentages with standard error, not adjusted for gestational age at time of imaging. Error bars are 1 standard error. * $p < 0.05$, ** $p < 0.01$

Fig. 8. Percentage of subjects with a normal clinical outcome in patients with a diagnosis of normal or isolated VM who did not undergo termination, limited to patients imaged at great than 22 weeks GA

Normal developmental outcome was more likely when sulcation patterns were visualized on prenatal MR (right) than in the sample as a whole (37%, dashed line) or when the pattern was not visualized (left). Bars indicate simple percentages with standard error, not adjusted for gestational age at time of imaging. Error bars are 1 standard error. * $p < 0.05$, ** $p < 0.01$.

Table 1

Distribution of gestational age by dates at the time of imaging amongst fetuses enrolled in the study.

	Normal	Isolated VM	Other CNS abnormalities
15–21.0 weeks	12 (32%)	52 (26%)	47 (33%)
21 wks 1day-25 wks	10 (27%)	38 (19%)	23 (16%)
25 wks 1 day – 32 wks	9 (24%)	82 (42%)	38 (27%)
32 wks 1day -term	6 (16%)	24 (12%)	33 (23%)

Table 2

Lag time for visualization of sulci, as affected by imaging mode and prenatal diagnosis, in 374 fetuses referred for confirmation of diagnosis of ventriculomegaly.

Sulcus	GA _{50%} , wk *	Lag, wk [†]			Lag, wk [‡]	
		US (TA)	US (TA+TV)	Isolated VM	Complicated VM	
Calcarine	26.3	6.9 ^a	5.5 ^a	0.3	4.1 ^a	
Parieto-occipital	25.3	7.8 ^a	5.3 ^a	0.9	4.4 ^a	
Cingulate	28.1	6.1 ^a	3.4 ^a	0.1	5.3 ^a	
Central	27.5	6.8 ^a	5.4 ^a	(0.3)	1.8 ^c	
Superior temporal	29.3	7.5 ^a	7.0 ^a	0.4	2.6 ^a	
Precentral	28.5	7.4 ^a	5.6 ^a	0.7	2.5 ^a	
Postcentral	28.8	9.8 ^a	8.2 ^a	0.5	2.2 ^a	
Inferior temporal	31.3	7.9 ^a	9.8 ^a	0.9	1.7 ^c	
Inferior frontal	31.8	8.9 ^a	10.4 ^a	0.8	2.1 ^c	
Insular	32.0	8.5 ^a	7.4 ^a	1.0	2.1 ^b	
Parietal	31.8	9.1 ^a	8.6 ^a	0.2	1.9 ^b	
Secondary frontal	35.4	0.7	(0.1)	0.9	2.8 ^b	
Secondary temporal	36.3	0.5	(0.3)	1.0	2.4 ^c	
Secondary parietal	35.8	0.4	(0.8)	1.5 ^c	3.3 ^a	
Superior occipital	36.4	5.3 ^a	3.0 ^b	0.7	2.7 ^b	

* Gestational age at which 50% of MR readers visualized the sulcus in normal fetuses.

[†] Relative to MR, all else equal. Parentheses indicate advance rather than lag (non-significant in both cases).

[‡] Relative to normal, all else equal.

^a Lag significantly different from zero, p<0.001;

^b p<0.005;

^c p<0.05.

Table 3

Distribution of postnatal diagnoses categories based on prenatal diagnoses categories for all fetuses in the study.

	Prenatal imaging diagnoses			
	Normal	Isolated VM	Other CNS Abnormalities	Total
Postnatal imaging diagnoses				
Normal	16	62	6 ***	84
Isolated VM	1	30	3 ****	33
Other CNS Abnormalities	2 *	27 **	73	103
Other follow-up				
Spontaneous Abortion/Neonatal Demise	0	3	9	12
Terminated	0	16	47	63
Lost to follow-up	18	58	3	79
Total	37	196	141	374

* Postnatal new diagnosis of choroid plexus cyst (N=1) and septal leaflet abnormality (N=1)

** Postnatal new diagnosis of intracranial hemorrhage (N=5), choroid plexus cyst (N=4), dysgenesis of the corpus callosum (N=3), septal leaflet abnormalities (N=2), and one case each of Chiari I; abnormal myelination and mega cisterna magna; choroid plexus cyst and heterotopias; dysgenesis of the corpus callosum and inferior vermis defect; cerebral calcifications; porencephaly; cerebral calcifications with intracranial hemorrhage; intracranial hemorrhage and porencephaly; CNS tumor and intracranial hemorrhage; scalp mass and intracranial hemorrhage; choroid plexus cyst and intracranial hemorrhage; dysgenesis of the corpus callosum with small brainstem, polymicrogyria and choroid plexus cyst; ectopic pituitary gland and abnormal white matter signal on MRI.

*** Prenatal megacistna magna in fetuses with VM diagnosed as VM only postnatal (N=3)

**** Postnatal diagnosis of normal in neonates with fetal diagnosis of choroid plexus cyst (N=2), and one case each of intracranial hemorrhage, mega cisterna magna, defect of septum pellucidum, and inferior vermian hypoplasia.

Table 4

Prenatal visualization of sulci as a predictor of normal clinical outcome, in fetuses referred for suspected ventriculomegaly.

Imaging mode	Sulcus	All with known outcome (278)		Excluding complicated VM (152)		Also excluding terminations (138)	
		Visualized (%) [*]	OR (p) [†]	Visualized (%)	OR (p)	Visualized (%)	OR (p)
MR	Interhemispheric	276 (99)	— [‡]	152 (100)	—	138 (100)	—
	Calcarine	122 (44)	5.46 (0.002)	72 (47)	2.80 (0.09)	71 (51)	2.97 (0.07)
	Parieto-occipital	124 (45)	10.0 (<.001)	74 (49)	4.86 (0.01)	74 (54)	4.30 (0.02)
	Cingulate	96 (35)	6.74 (<.001)	65 (43)	8.97 (0.004)	65 (47)	9.05 (0.003)
	Central	120 (43)	5.13 (0.010)	69 (45)	3.24 (0.10)	68 (49)	3.64 (0.07)
	Superior temporal	97 (35)	5.27 (0.006)	54 (36)	3.54 (0.05)	54 (39)	3.76 (0.04)
	Precentral	90 (32)	3.08 (0.05)	49 (32)	3.21 (0.08)	49 (36)	3.69 (0.06)
	Postcentral	88 (32)	3.48 (0.03)	49 (32)	3.21 (0.08)	49 (36)	3.69 (0.06)
	Inferior temporal	64 (23)	0.68 (0.44)	32 (21)	0.71 (0.56)	32 (23)	0.82 (0.75)
	Inferior frontal	54 (19)	0.88 (0.78)	30 (20)	0.67 (0.50)	30 (22)	0.76 (0.64)
	Insular	55 (20)	0.69 (0.44)	30 (20)	0.65 (0.47)	30 (22)	0.73 (0.61)
	Parietal	57 (21)	0.79 (0.63)	30 (20)	0.65 (0.47)	30 (22)	0.74 (0.61)
	Secondary frontal	16 (6)	0.98 (0.97)	10 (7)	1.26 (0.75)	10 (7)	1.38 (0.66)
	Secondary temporal	9 (3)	0.85 (0.84)	5 (3)	1.75 (0.57)	5 (4)	1.97 (0.49)
	Secondary parietal	8 (3)	0.84 (0.83)	5 (3)	1.75 (0.57)	5 (4)	2.05 (0.47)
	Superior occipital	6 (2)	0.74 (0.75)	4 (3)	1.08 (0.95)	4 (3)	1.23 (0.84)
	Tertiary frontal	0 (0)	—	0 (0)	—	0 (0)	—
	Inferior occipital	5 (2)	0.77 (0.79)	4 (3)	1.08 (0.95)	4 (3)	1.23 (0.84)
US	Interhemispheric	171 (62)	0.44 (0.01)	90 (59)	0.36 (0.007)	78 (57)	0.39 (0.02)
	Calcarine	19 (7)	0.96 (0.95)	15 (10)	0.79 (0.69)	15 (11)	0.80 (0.70)
	Parieto-occipital	30 (11)	1.45 (0.39)	24 (16)	0.63 (0.37)	24 (17)	0.62 (0.36)
	Cingulate	23 (8)	1.04 (0.94)	17 (11)	0.56 (0.34)	17 (12)	0.58 (0.36)
	Central	18 (6)	1.56 (0.43)	9 (6)	1.98 (0.35)	9 (7)	2.12 (0.30)
	Superior temporal	0 (0)	—	0 (0)	—	0 (0)	—
	Precentral	4 (1)	1.86 (0.53)	3 (2)	3.16 (0.36)	3 (2)	3.41 (0.33)
	Postcentral	0 (0)	—	0 (0)	—	0 (0)	—

All with known outcome (278)		Excluding complicated VM (152)		Also excluding terminations (138)	
Imaging mode	Sulcus	Visualized (%) [*]	OR (p) [†]	Visualized (%)	OR (p)
	Inferior temporal	0 (0)	—	0 (0)	—
	Inferior frontal	0 (0)	—	0 (0)	—
	Insular	0 (0)	—	0 (0)	—
	Parietal	0 (0)	—	0 (0)	—
	Secondary frontal	3 (1)	1.96 (0.61)	1 (1)	—
	Secondary temporal	3 (1)	1.96 (0.61)	1 (1)	—
	Secondary parietal	2 (1)	—	1 (1)	—
	Superior occipital	0 (0)	—	0 (0)	—
	Tertiary frontal	0 (0)	—	0 (0)	—
	Inferior occipital	0 (0)	—	0 (0)	—

^{*} By majority of readers (1/1, 2/2, or 2/3).

[†] Odds ratio for normal outcome when sulcus was seen, relative to odds when sulcus was not seen. OR estimated by logistic regression analysis with normal outcome as dependent variable, visualization of individual sulcus as predictor, adjusted for prenatal measurement of atrial diameter and gestational age by last menstrual period. *p* tests OR=1. Boldface indicates statistically significant prediction *p*≤0.05 or smaller. Normal outcome defined as live birth without complications, followed by at least one postnatal examination at 6 mo, 1 yr, 2 yr, or 3 yr, with no abnormal findings at any postnatal exam.

[‡] Null or sparse data, regression parameters not estimable.

Table 5

Prenatal visualization of sulci as a predictor of normal clinical outcome in fetuses referred for suspected ventriculomegaly who were greater than 22 weeks gestational age at time of imaging.

Imaging mode	Sulcus	All with known outcome (166)		Excluding complicated VM(98)		Also excluding terminations (96)	
		Visualized (%) [*]	OR (p) [†]	Visualized (%)	OR (p)	Visualized (%)	OR (p)
MR	Interhemispheric	166 (100)	— [‡]	98 (100)	—	96 (100)	—
	Calcarine	121 (73)	4.74 (0.009)	71 (72)	2.94 (0.11)	70 (73)	3.06 (0.10)
	Parieto-occipital	123 (74)	10.4 (<.001)	73 (74)	6.18 (0.02)	73 (76)	5.65 (0.02)
	Cingulate	96 (58)	5.70 (0.002)	65 (66)	8.33 (0.006)	65 (68)	7.79 (0.008)
	Central	120 (72)	3.94 (0.03)	69 (70)	2.87 (0.15)	68 (71)	3.08 (0.12)
	Superior temporal	97 (58)	5.56 (0.006)	54 (55)	3.64 (0.06)	54 (56)	3.52 (0.06)
	Precentral	90 (54)	3.84 (0.02)	49 (50)	3.95 (0.06)	49 (51)	3.90 (0.07)
	Postcentral	88 (53)	4.51 (0.01)	49 (50)	3.95 (0.06)	49 (51)	3.90 (0.07)
	Inferior temporal	64 (39)	0.83 (0.74)	32 (33)	0.65 (0.53)	32 (33)	0.67 (0.55)
	Inferior frontal	54 (33)	1.11 (0.85)	30 (31)	0.63 (0.48)	30 (31)	0.64 (0.50)
	Insular	55 (33)	0.85 (0.76)	30 (31)	0.60 (0.45)	30 (31)	0.61 (0.48)
	Parietal	57 (34)	1.00 (0.99)	30 (31)	0.60 (0.45)	30 (31)	0.61 (0.47)
	Secondary frontal	16 (10)	1.19 (0.78)	10 (10)	1.31 (0.72)	10 (10)	1.33 (0.70)
	Secondary temporal	9 (5)	1.10 (0.91)	5 (5)	1.86 (0.54)	5 (5)	1.92 (0.52)
	Secondary parietal	8 (5)	1.06 (0.94)	5 (5)	1.83 (0.55)	5 (5)	1.89 (0.53)
	Superior occipital	6 (4)	0.95 (0.95)	4 (4)	1.11 (0.93)	4 (4)	1.14 (0.91)
	Tertiary frontal	0 (0)	—	0 (0)	—	0 (0)	—
	Inferior occipital	5 (3)	0.99 (0.99)	4 (4)	1.11 (0.93)	4 (4)	1.14 (0.91)
US	Interhemispheric	102 (61)	0.44 (0.02)	55 (56)	0.35 (0.02)	53 (55)	0.36 (0.02)
	Calcarine	19 (11)	0.94 (0.90)	15 (15)	0.76 (0.65)	15 (16)	0.74 (0.63)
	Parieto-occipital	29 (17)	1.37 (0.47)	23 (23)	0.63 (0.38)	23 (24)	0.62 (0.36)
	Cingulate	23 (14)	0.99 (0.99)	17 (17)	0.54 (0.31)	17 (18)	0.54 (0.31)
	Central	18 (11)	1.64 (0.38)	9 (9)	1.94 (0.37)	9 (9)	1.94 (0.37)
	Superior temporal	0 (0)	—	0 (0)	—	0 (0)	—
	Precentral	4 (2)	1.88 (0.53)	3 (3)	3.05 (0.38)	3 (3)	3.03 (0.38)

All with known outcome (166)		Excluding complicated VM(98)		Also excluding terminations (96)	
Imaging mode	Sulcus	Visualized (%) [*]	OR (p) [†]	Visualized (%)	OR (p)
	Postcentral	0 (0)	—	0 (0)	—
	Inferior temporal	0 (0)	—	0 (0)	—
	Inferior frontal	0 (0)	—	0 (0)	—
	Insular	0 (0)	—	0 (0)	—
	Parietal	0 (0)	—	0 (0)	—
	Secondary frontal	3 (2)	2.09 (0.57)	1 (1)	—
	Secondary temporal	3 (2)	2.09 (0.57)	1 (1)	—
	Secondary parietal	2 (1)	—	1 (1)	—
	Superior occipital	0 (0)	—	0 (0)	—
	Tertiary frontal	0 (0)	—	0 (0)	—
	Inferior occipital	0 (0)	—	0 (0)	—

^{*}By majority of readers (1/1, 2/2, or 2/3).

[†]Odds ratio for normal outcome when sulcus was seen, relative to odds when sulcus was not seen. OR estimated by logistic regression analysis with normal outcome as dependent variable, visualization of individual sulcus as predictor, adjusted for prenatal measurement of arial diameter and gestational age by last menstrual period. *p* tests OR=1. Boldface indicates statistically significant prediction *p*=0.05 or smaller. Normal outcome defined as live birth without complications, followed by at least one postnatal examination at 6 mo, 1 yr, 2 yr, or 3 yr, with no abnormal findings at any postnatal exam.

[‡]Null or sparse data, regression parameters not estimable.