Published in final edited form as:

J Ultrasound Med. 2009 October ; 28(10): 1379–1384.

Prenatal Diagnostic Challenges and Pitfalls For Schizencephaly: A Case Study

Wesley Lee, M.D.^{1,2,3}, Christine H. Comstock, M.D.^{1,2}, Chris Kazmierczak, M.D.⁴, Jon Wilson, M.D.⁵, Luis F. Gonçalves, M.D.^{2,3}, Swati Mody, M.D.⁶, Lami Yeo, M.D.^{2,3}, and Roberto Romero, M.D.^{3,2,7}

¹Division of Fetal Imaging, Department of Obstetrics and Gynecology, William Beaumont Hospital, Royal Oak, MI

²Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI

³Perinatology Research Branch, NICHD/NIH/DHHS, Detroit, MI

⁴Department of Diagnostic Radiology, William Beaumont Hospital, Royal Oak, MI

⁵Department of Anatomic Pathology, William Beaumont Hospital, Royal Oak, MI

⁶Department of Pediatric Imaging, Wayne State University, Detroit, MI

⁷ Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI

Keywords

schizencephaly; prenatal diagnosis; fetus; ultrasound; 3D ultrasonography; fetal MRI

Introduction

Schizencephaly is a developmental anomaly that causes unilateral or bilateral clefts of the cerebral hemisphere as a result of disordered neuronal migration. The clefts are lined by gray matter that can extend medially from the subarachnoid cerebrospinal fluid space into the lateral ventricle as part of a disease spectrum that includes porencephaly. Closed-lip schizencephaly (Type 1) occurs when the gray-matter lined walls are in contact with each other (1). By contrast, the open lip variety (Type 2) has separated lips with a cleft of cerebrospinal fluid that extends to the ventricles (2). Barkovich and co-workers (3) have reported that the clinical manifestations of affected infants are related to the size and location of the cleft defect. Late prenatal schizencephaly has been well documented. We now report well-documented case that demonstrates diagnostic challenges and pitfalls associated with its early diagnosis by 2D/3D ultrasonography and magnetic resonance imaging (MR).

Case Report

A 19 year-old primigravida was enrolled in a research study that included serial prenatal sonographic scans beginning at 18 weeks, menstrual age (MA). She participated under informed consent that was approved by the Human Investigation Committee at William

Beaumont Hospital and the Institutional Review Board at the Eunice Kennedy Shriver National Institute of Child Health and Human Development. Past medical history was remarkable for a post-traumatic seizure disorder as a result of a motor vehicle accident eight years prior to the current pregnancy. Her MR brain study was normal. No anticonvulsants had been taken during early pregnancy although she had experienced two minor seizures during that time. The patient was employed as a house cleaner and denied any fever, substance abuse, or exposure to occupational toxins.

Serial 2D and 3D ultrasound scans were interpreted as being normal at 18.6, 19.1, and 21.3 weeks, menstrual age (Figures 1 and 2) (Voluson Expert, GE Healthcare, Milwaukee, WI). At 24.4 weeks, the anterior horns of the lateral ventricles appeared partially fused and the septum cavum pellucidum was poorly visualized. An endovaginal scan was not performed due to breech presentation. The differential diagnosis included congenital absence of the cavum septum pellucidum, septo-optic dysplasia and mild lobar holoprosencephaly. Three days later, the fetus converted to a cephalic presentation. A 1.5 Tesla MR system (Sonata, Siemens Medical Solutions, Issaquah, WA) was used to detect a large open lip cleft defect of the right frontoparietal lobe (Figure 3). The cavum septum pellucidum was confirmed to be absent. An endovaginal scan, immediately following the MR scan (6–12 MHz transducer, RIC-6-12D, GE Healthcare, Milwaukee, WI), confirmed a large open-lip cleft defect across the right cerebral hemisphere with extension into the lateral ventricle (Figures 4 and 5). A smaller closed-lip cleft defect was also suspected in the left cerebral hemisphere without involvement of the lateral ventricle. This sonographic finding, however, was not confirmed by fetal MR.

The patient underwent multidisciplinary counseling to discuss the risk of abnormal neurodevelopment. Counseling was based on the presence of bilateral schizencephaly with a large right open-lip defect on the right side and a much smaller left-sided closed lip defect. She declined genetic testing and subsequently delivered a 2,830 gram male infant by vaginal delivery at 37.7 weeks' gestation. The Apgar scores were 9/9 at 1 and 5 minutes, respectively. Her infant was discharged in stable condition at 2 days following delivery without seizures. By the third week, he underwent an MRI scan with and without contrast using T2 and T1 weighted images. FLAIR sequences and pre- and post-contrast MP-RAGE sequences were also utilized. Postnatal MR demonstrated a closed-lip schizencephalic cleft extending from the frontal cortex to the superior right lateral ventricle (Figure 6). Cortical gray matter lined the cleft with polymicrogyria. The cavum septum pellucidum was not seen. The corpus callosum was described as hypoplastic and thin (Figure 7). Both optic nerves were present and the pituitary gland was normal. No diffusion weighted imaging abnormalities were found.

At 7 months of age, the infant returned to the Pediatrics Genetics Clinic with normal growth and development at that time. By 15 months, the infant was not walking or crawling, had developed left sided weakness, and required a brace for the left hand and foot. No seizures have been reported.

Discussion

Schizencephalic children exhibit varying degrees of developmental delay, motor impairment, and seizures (4). Barkovich, and co-workers (3) have compared clinical findings in 20 patients with schizencephaly with their magnetic resonance (MR) findings. Bilateral clefts had significantly worse intellectual and speech development than those with unilateral clefts. Patients with unilateral large or medium open lip clefts had significantly worse intellectual and speech development than those with unilateral closed lip or small open-lip defects. Liang et al. (5) have also studied children with schizencephaly with

variable neurological impairment and suggest that imaging studies can be useful for predicting the severity of neurodevelopmental outcomes. This type of clinical correlation is commonly used for guiding prenatal counseling.

Three main points are particularly relevant to this case. First, despite serial ultrasonographic scans, a large fetal brain cleft was initially unrecognized during the early second trimester. The findings are consistent with previous reports suggesting that schizencephaly is more typically identified during the third trimester (6). Denis and co-workers (7) reported two schizencephalic fetuses in which a lateral ventricle appeared enlarged at 23 weeks', although clefts were not found on abdominal sonograms. Endovaginal scans were apparently not performed. In the present case, the affected side was closest to the transducer during her early visits and may explain why the cleft was not seen on abdominal scans but could be clearly seen on the vaginal study. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) has published guidelines for sonographic screening of the fetal brain (8). The document states, "most severe cerebral lesions are bilateral or associated with a significant deviation or distortion of the midline echo, and it has been suggested that in basic examinations symmetry of the brain is assumed (9). This commonly accepted assumption was not true in this particular fetus. A large cleft was not recognized earlier because of a reverberation artifact involving the proximal cerebral hemisphere. In view of the strong association between absent cavum septum pellucidum and schizencephaly, the adjunctive use of transvaginal sonography and MRI improved our ability to characterize the anomaly. One should be aware, however, that the columns of the fornix can be mistaken for the cavum septum pellucidum (10).

Second, a thin echogenic line extended towards the left lateral ventricle and this finding was falsely suspected to represent closed-lip schizencephaly. Since this structure was not demonstrated on the neonatal MR scan, it was considered to be a normal sonographic finding of the fetal brain (Figure 8). Similar echogenic lines have been demonstrated in the white matter of other fetuses, infants, and adults. Hertzberg and co-workers (11) previously reported the sonographic appearance of similar multiple echogenic lines in five neonatal brains. Their findings were compared to postmortem specimens as evidence that these linear echoes represent small branches of major intracranial blood vessels. They also mentioned the potential pitfall of misinterpreting deep medullary veins as pathological processes such as periventricular leukomalacia. Filly and associates (12) have suggested that the sonographic appearance of echogenic lines in the fetal brain may reflect "white matter tracts" and have also proposed their relationship to pia matter. We believe that the left-sided linear structure in our patient may represent a longitudinal caudate vein as a component of the trans-cerebral venous circulation (13). The physiologic significance of the trans-cerebral venous system is poorly understood and these vessels are typically less than 20 μ m in caliber. Indeed, acoustic shadowing could easily preclude consistent demonstration of these very small venous structures (Figure 9).

Third, the pediatric literature suggests that different developmental outcomes for schizencephaly depend on the nature of the cleft defect (unilateral versus bilateral, open versus closed). Hence, there is a logical tendency to base prenatal counseling on this information. In our case, a large open-lip cleft defect during mid-pregnancy was later characterized as a closed-lip defect after birth. This clinical interpretation of this information may affect prenatal counseling regarding postnatal prognosis. Health care providers should be aware of potential changes that can occur during the course of pregnancy. Serial sonographic scans and MR studies underscore some of the technical challenges and pitfalls for making an early diagnosis of schizencephaly. Developmental changes between prenatal (open-lip cleft) and postnatal (closed-lip cleft) findings described herein provide new insight into the natural history of this disorder during fetal life.

Acknowledgments

We thank the following individuals for their input regarding the potential nature of the small echogenic structure that mimicked a closed-lip schizencephalic cleft defect: Dr. James Barkovich, Dr. Catherine Garel, Dr. Jeffrey Golden, Dr. Ana Monteagudo, and Dr. Daniela Prayer. This research was supported (in part) by the Perinatology Research Branch, Division of Intramural Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH, DHHS.

References

1. Yakovlev PI, Wadsworth RC. Schizencephalies: a study of the congenital clefts in the cerebral mantle. I. Clefts with fused lips. *J Neuropathol Exp Neurol* 1946;5:116–130. [PubMed: 21026933]
2. Yakovlev PI, Wadsworth RC. Schizencephalies: a study of the congenital clefts in the cerebral mantle. II. Clefts with hydrocephalus and lips separated. *J Neuropathol Exp Neurol* 1946;5:169–206. [PubMed: 20993391]
3. Barkovich AJ, Kjos BO. Schizencephaly: correlation of clinical findings with MR characteristics. *AJNR Am J Neuroradiol* 1992;13:85–94. [PubMed: 1595498]
4. Abdel Razek AA, Kandell AY, Elsorogy LG, Elmongy A, Basett AA. Disorders of cortical formation: MR imaging features. *AJNR Am J Neuroradiol* 2009;30:4–11. [PubMed: 18687750]
5. Liang JS, Lee WT, Peng SS, Yu TW, Shen YZ. Schizencephaly: correlation between clinical and neuroimaging features. *Acta Paediatr Taiwan* 2002;43:208–213. [PubMed: 12238909]
6. Oh K, Kennedy A, Frias A, et al. Fetal schizencephaly: pre- and postnatal imaging with review of the clinical manifestations. *Radiographics* 2005;25:647–657. [PubMed: 15888615]
7. Denis D, Maugey-Laulom B, Carles D, Pedespan JM, Brun M, Chateil JF. Prenatal diagnosis of schizencephaly by fetal magnetic resonance imaging. *Fetal Diagn Ther* 2001;16:354–359. [PubMed: 11694738]
8. Pilu G, Ghi T, Carletti A, Segata M, Perolo A, Rizzo N. Three-dimensional ultrasound examination of the fetal central nervous system. *Ultrasound Obstet Gynecol* 2007;30:233–245. [PubMed: 17659665]
9. Filly RA, Cardoza JD, Goldstein RB, Barkovich AJ. Detection of fetal central nervous system anomalies: a practical level of effort for a routine sonogram. *Radiology* 1989;172:403–408. [PubMed: 2664864]
10. Callen PW, Callen AL, Glenn OA, Toi A. Columns of the fornix, not to be mistaken for the cavum septi pellucidi on prenatal sonography. *J Ultrasound Med* 2008;27:25–31. [PubMed: 18096727]
11. Hertzberg BS, Burger PC, Bowie JD, Carson SC, Feinstein KA, Boyko OB. Sonographic characteristics of small cerebral blood vessels. An *in vivo* and postmortem study. *J Ultrasound Med* 1990;9:697–703. [PubMed: 2277398]
12. Filly, RA.; Feldstein, VA. Chapter 9. Ultrasound evaluation of normal fetal anatomy in Ultrasonography in Obstetrics and Gynecology. In: Callen, PW., editor. Figures 9–104 and 9–111. 5th Edition. Philadelphia, PA: Saunders Elsevier; 2008.
13. Jimenez JL, Lasjaunias P, Terbrugge K, Flodmark O, Rodesch G. The trans-cerebral veins: normal and non-pathologic angiographic aspects. *Surg Radiol Anat* 1989;11:63–72. [PubMed: 2497536]

Figure 1.
Axial views of the fetal head (19.1 weeks' menstrual age, left side down). The arrow points to a structure that was originally interpreted as the cavum septum pellucidum.

Figure 2. Three-dimensional tomographic images of the fetal head (21.3 weeks' menstrual age, left side down). The cavum septum pellucidum is not clearly identified, although the bottom right image shows an anechoic area that was suggestive of this structure (arrowhead).

Figure 3. Coronal views of the fetal brain (T2-weighted MRI, 24.9 weeks' menstrual age). A large right-sided defect of the right frontoparietal lobe extends from the extra-axial space into the ventricular system. There is no evidence of a closed left-sided defect from this fetal MRI study.

Figure 4. High-frequency endovaginal sonogram of the fetal brain (24.9 weeks' menstrual age). A coronal view through the anterior fontanel shows a large open-lip cleft defect of the right frontoparietal lobe. The echogenic linear structure on the left side (arrow) was initially thought to represent a closed-lip schizencephalic cleft.

Figure 5.

Three-dimensional multiplanar image of a right brain cleft. The endovaginal scan shows a large cleft defect of the right frontoparietal area that extends into the lateral ventricle (coronal and axial planes, arrows). The cavum septum pellucidum is not shown (coronal plane). An intact corpus callosum is verified on the sagittal image (asterisk); ant indicates anterior; and post, posterior.

Figure 6.

Three week-old neonatal brain (T2-weighted images, coronal views). **A**, An anterior coronal view shows an absent cavum septum pellucidum, which is commonly associated with schizencephaly. **B**, More posteriorly, a gray matter-lined cleft traverses the right frontoparietal brain parenchyma. The lips of this defect are touching, suggesting a closed-lip type of schizencephaly (arrow). Gray matter lining the cleft is abnormally thickened as a result of a neuronal migrational disorder. Despite the fetal sonographic results, there is no MRI evidence of a closed-lip cleft defect on the left side.

Figure 7. Sagittal view of the neonatal brain (T1-weighted MRI). A thin and underdeveloped corpus callosum is commonly associated with schizencephaly.

Figure 8. Normal fetal brain (coronal view, 24.9 weeks' menstrual age). Three-dimensional tomographic images show parallel sections (top middle slice, most anterior; bottom right slice, most posterior). A midcoronal slice corresponds to a sagittal reference image (asterisk, top left). Echogenic linear structures are again visualized in unaffected second-trimester fetuses (arrow). No detectable blood flow was found within this echogenic structure on the basis of power or color Doppler sonography (not shown).

Figure 9. Normal fetal brain (25.0 weeks' menstrual age). **A**, Endovaginal sonography (10-MHz probe) shows midline structures with the use of a narrow acoustic imaging window through the anterior fontanel. **B**, By repositioning and angling the transducer laterally, one can show an echogenic linear structure (arrow) that could be misinterpreted as a closed-lip schizencephalic cleft.