A Case Report on Prenatal Diagnosis of Evolving Cortical Malformations: A Rare Ultrasound Marker

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Abstract

Malformations of cortical development are rarely diagnosed in utero. Cortical malformations are aberrations in the process of corticogenesis. We report two rare and unique cases of evolving cortical malformation with unusual ultrasonogram markers: (1) narrow cavum septum pellucidum and (2) ill-defined and irregular lateral ventricular borders on the midtrimester anomaly scan. This was further confirmed by fetal brain evaluation on magnetic resonance imaging with additional information on irregular ventricular borders, scattered hyperintensities in the cerebral parenchyma and periventricular area, loss of cerebral layering pattern at 24 weeks gestation in one case, and hemimegalencephaly in another case with a probable diagnosis of evolving cortical malformation. Literature review reveals the above as an unusual presentation on the anomaly scan.

Keywords

- malformations of cortical development
- narrow CSP
- fetal MRI
- irregular ventricular margins
- hemimegalencephaly

Introduction

Central nervous system (CNS) development is governed by three sequential, overlapping phases during the first 6 weeks of embryonic life. The three phases are (a) gastrulation (formation of the three main germ layers, ectoderm, mesoderm, and endoderm); (b) dorsal induction (creation of the neural tube with three primitive vesicles: prosencephalon, mesencephalon, and rhombencephalon); and (c) ventral induction or telencephalization (separation of two cerebral hemispheres and formation of optic vesicles, olfactory bulbs, and corresponding facial structures.[1]

The proliferation and differentiation of neurons and glial cells from multipotent neural stem (progenitor) cells are known as neurogenesis and gliogenesis, respectively, and usually begin in the brain and the spinal cord, during the late embryonic period and continues until the late second trimester. Neuronal cells are generated earlier than glial cells (oligodendrocytes and astrocytes). Normal cortical development is ensured by the migration of neurons. Neural cells from the subventricular zone that have completed their mitotic division program begin to move toward the outer zones of the developing brain. Neuronal migration occurs in waves, in radial and tangential fashions, between the 12th and 20th weeks of gestation. The six layered cortex is formed by each wave of migrating neurons traveling further past their predecessors, resulting in the later neurons being closest to the outer surface. After the completion of neuronal migration, neuronal development and cortical organization occur from approximately 22 to 24 weeks of gestation. Cortical organization is a complex process resulting in maturation of the six-layered cortex, outgrowth of axons and dendrites from cortical neurons, and development of interneuronal synapses. This continues into infancy.

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Malformations of cortical development (MCD) are a heterogeneous group of disorders, severity, and type depending on the timing of insult during the stages of corticogenesis, that is, proliferation, migration, and organization. Incidence is unknown or underestimated in the prenatal period. The difficulty in diagnosis is due to the appearance of cortical milestones beyond the time of the recommended midtrimester anomaly scan and rapid evolution of the brain throughout the gestation as described above.[2] Cortical malformations may be associated with genetic variants and have a varied spectrum of presentation including developmental delay, intellectual disability, and epilepsy.

Case Reports

Case1

A 32-year-old primigravida in a nonconsanguineous marriage conceived spontaneously and had no significant medical, surgical, or family history. She booked with us at 18 weeks of gestation. The combined first-trimester screening done elsewhere revealed a low risk for Trisomies 21, 13, and 18. The routine midtrimester anomaly scan was performed at 19 weeks 1 day on a GE Voluson s10 and E8 ultrasound equipment. A transabdominal and transvaginal ultrasound were performed with a convex 2 to 5 MHz and endocavitary 5 to 9 MHz transducer, respectively. In the standard two-dimensional grayscale imaging of the axial view of the transventricular (►**Fig. 1**) and transcerebellar plane (►**Fig. 2**), the cavum septum pellucidum (CSP) appeared unusually narrow measuring 15 mm less than −2 Standard deviation according to the nomogram published by Jou et al.[3] A multiplanar neurosonogram was performed by transvaginal approach.

In the coronal view of the transthalamic plane, the CSP appeared narrow with ill-defined margins of the frontal horn of the left lateral ventricle (►**Fig. 3**). The contralateral frontal horn appeared normal. In the midsagittal plane of the fetal brain, the corpus callosum and pericallosal artery appeared normal (►**Fig. 4**), measuring appropriate for gestational age.

Fetal biometry and the rest of the structural survey were normal. She was advised to have a repeat ultrasound examination after 4 weeks to look for evolving abnormalities. At 24 weeks in the axial view of the transventricular plane CSP continued to appear narrow with the width measuring 18 mm, less than −2 SD according to the CSP nomogram published by Jou et al[3] (►**Fig. 5**). Through transvaginal route, in the midsagittal view corpus callosum (►**Fig. 6A**) and Doppler imaging of pericallosal arteries appeared normal (►**Fig. 6B**.). Color Doppler imaging of the Circle of Willis was used as a landmark at the level of the base of the skull to visualize the optic tracts, which appeared normal (►**Fig. 6C**).

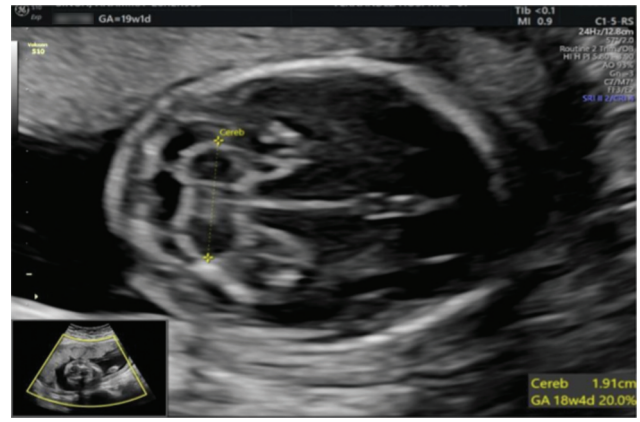

Fig. 2 Axial view of transcerebellar plane with narrow cavum septum pellucidum.

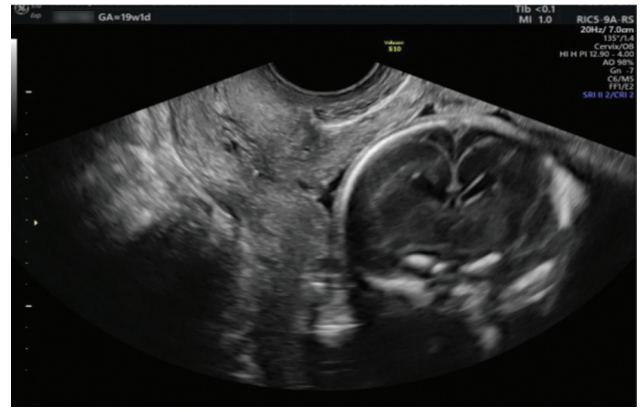

Fig. 3 Coronal view of transthalamic plane showing thin cavum septum pellucidum.

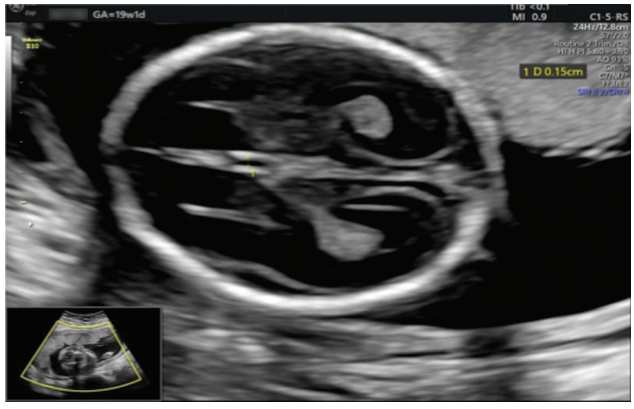

Fig. 1 Axial view of transventricular plane of head with narrow cavum septum pellucidum.

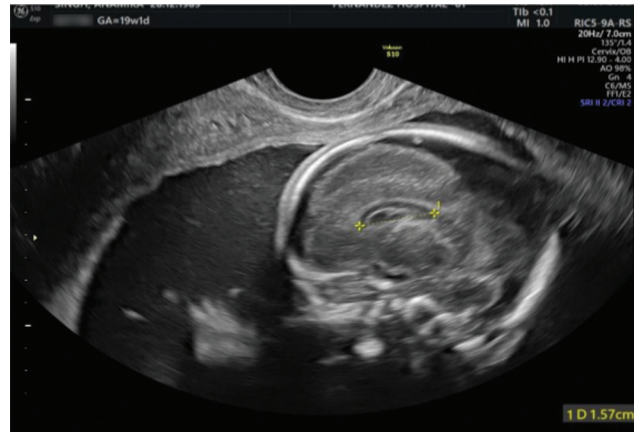

Fig. 4 Midsagittal plane of head measuring corpus callosum.

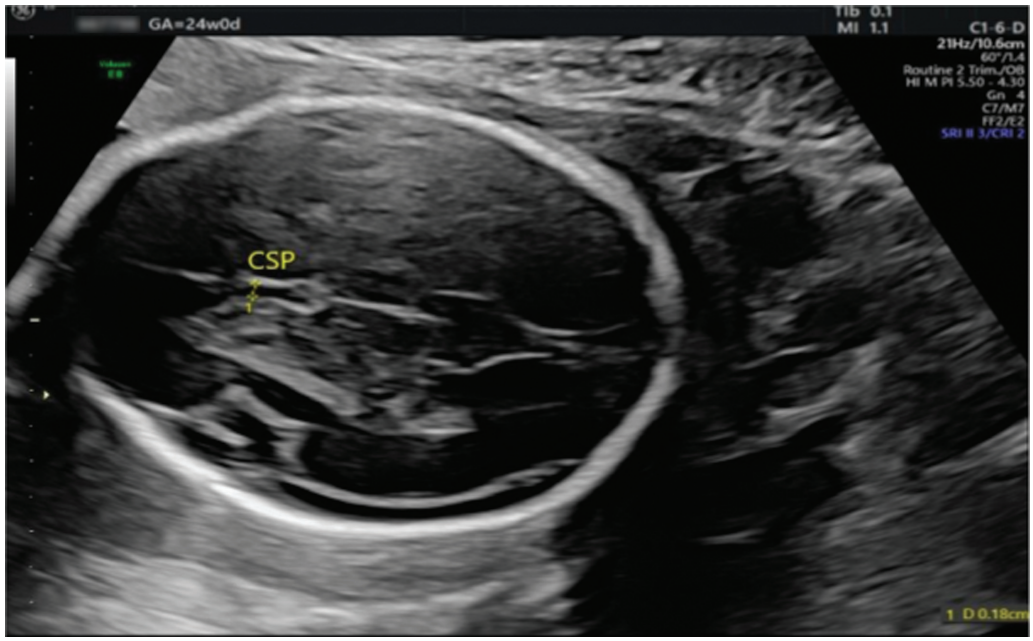

Fig. 5 Transthalamic plane at 24 weeks, narrow cavum septum pellucidum (CSP).

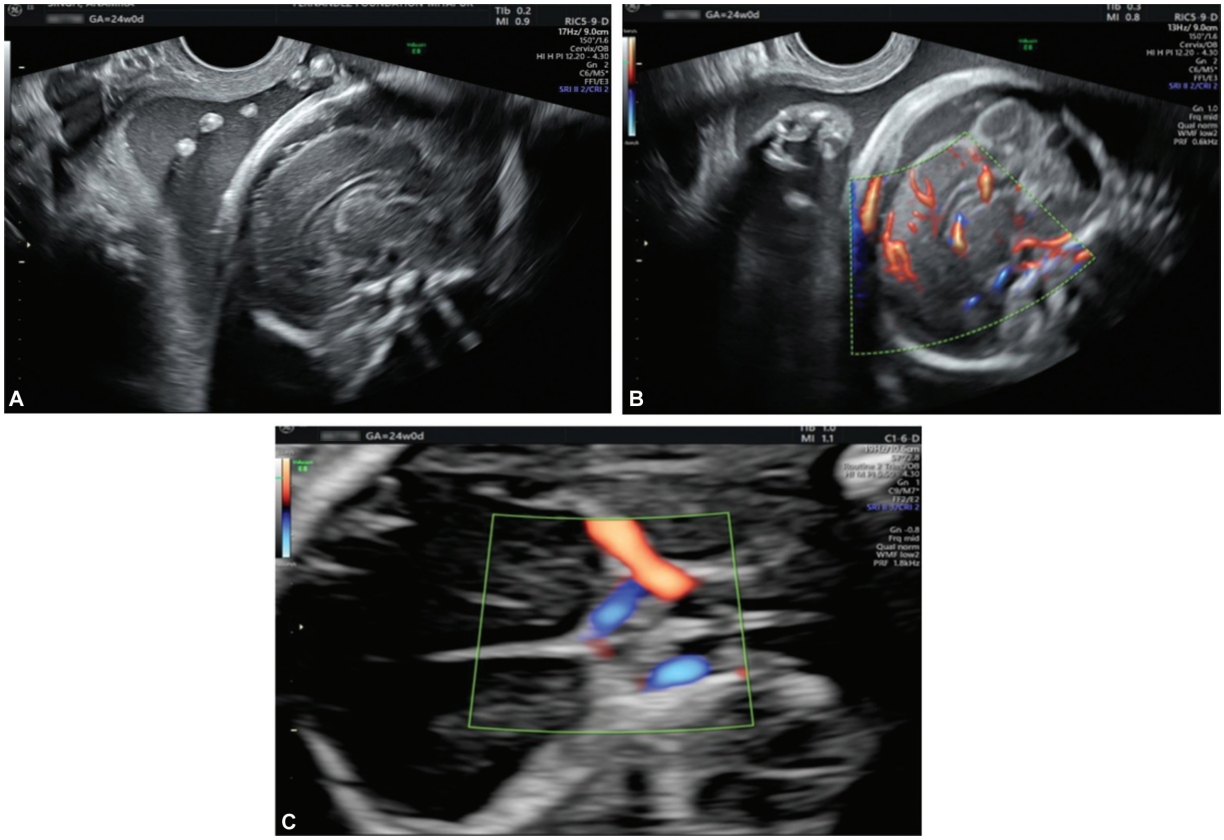

Fig. 6 (**A**) Sagittal view showing corpus callosum. (**B**) Color doppler showing corpus callosum. (**C**) This part demonstrating optic tracts.

In view of the above findings of a narrow CSP and irregular ventricular margins, the couple were counseled about the possibility of neuronal migration disorders and offered magnetic resonance imaging (MRI) of the fetal brain to aid in the diagnosis. Multiplanar, multisequence ultrafast fetal MRI using half-Fourier acquired single-shot turbo spin-echo sequences with attention to the fetal brain was performed at 24 to 25 weeks. This was suggestive of small left lateral ventricle (►**Fig. 7A**) with irregular and ill-defined margins and nodular punctate T2 hypointensities along

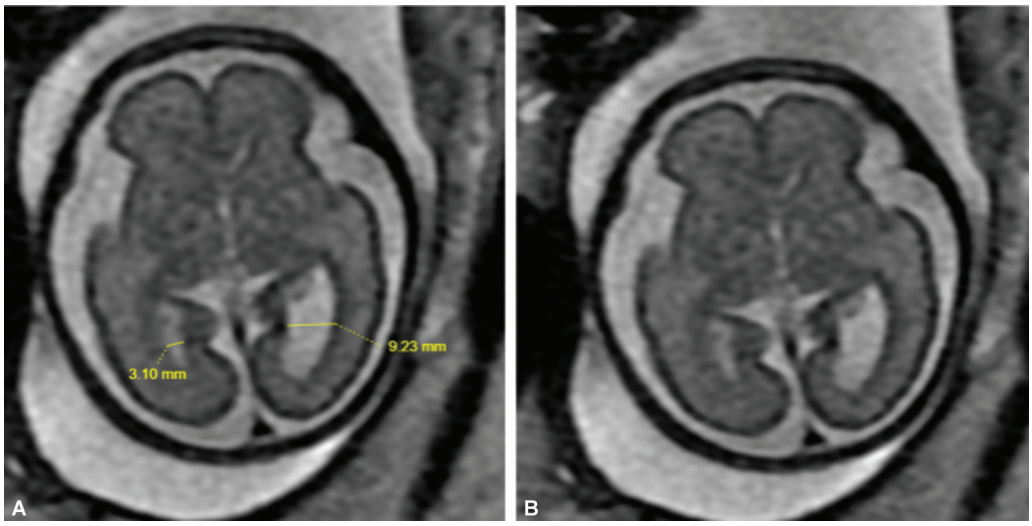

Fig. 7 (**A**, **B**) Magnetic resonance imagings showing irregular and small left lateral ventricle.

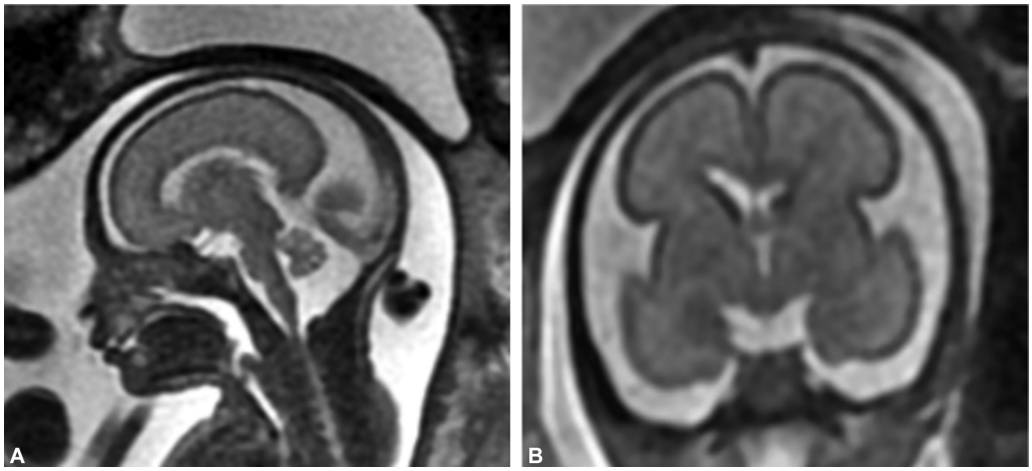

Fig. 8 (**A**) Corpus callosum margins are irregular. (**B**) Multiple punctuations in the left hemisphere.

periventricular region predominantly in frontal and perisylvian region (►**Fig. 7A, B**). The margins of the CSP and the corpus callosum appeared merged and had poor delineation (►**Fig. 8A**). There was a loss of the multilayered cerebral parenchymal pattern (layering pattern typically seen at this gestation). Multiple punctate scattered T2 hyperintensities noted in the left cerebral parenchyma (►**Fig. 8B**). The development pattern of cerebral sulcation appeared normal. The above features were suggestive of a probable diagnosis of evolving cortical malformations. The couple were counseled by their obstetrician, fetal medicine specialist, and neonatologist; the option of invasive testing (amniocentesis) was given to rule out coexisting genetic abnormalities. Serial follow-up scans were advised to monitor the growth and to perform successive assessments of the sono neuroanatomy. Detailed postnatal evaluation and follow-up were suggested as these cases may range from being completely normal to manifesting developmental delay, cognitive defects, and intractable infantile epilepsy. The couple declined any further testing and discontinued the pregnancy as they did not wish to accept any uncertainties. The drawback in this case was lack of follow-up and no further testing.

Case 2

A 26-year-old primigravida in a nonconsanguineous marriage conceived spontaneously and had no significant medical, surgical, or family history. She came to us for a first trimester combined screen at 12 weeks. The nasal bone was unossified (►**Fig. 9A**), and the enhanced first-trimester screening was low risk for Trisomy 21, 18, and 13. As the nasal bone remained unossified at 16 weeks, the couple were counseled and amniocentesis was performed that revealed a normal karyotype (►**Fig. 9B**). A midtrimester anomaly scan was performed at 19 weeks, in which the axial view of the transventricular plane and transcerebellar plane showed narrow CSP (►**Fig. 10A, B**),–2 SD less than normal.[3] The extended neurosonogram revealed a narrow, incomplete CSP with a discrepancy between the frontal horns and the left horn being continuous with the CSP in the coronal view of the transthalamic plane (►**Fig. 11**). In the midsagittal plane,

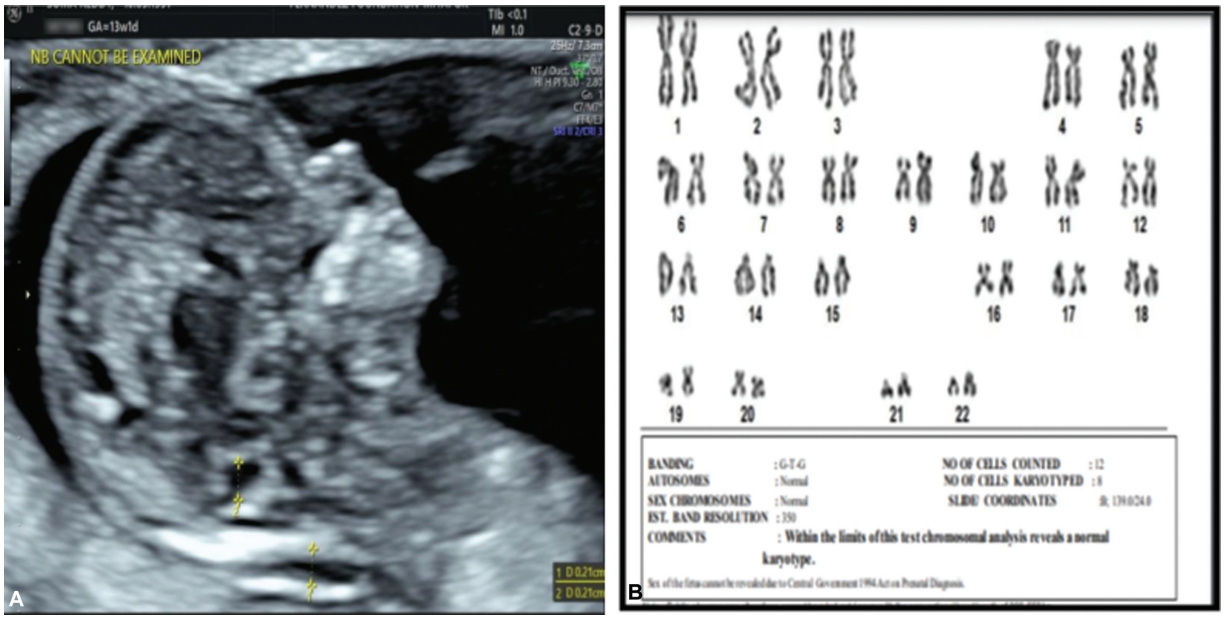

Fig. 9 (A) Unossified nasal bone. (B) Fetal karyotype.

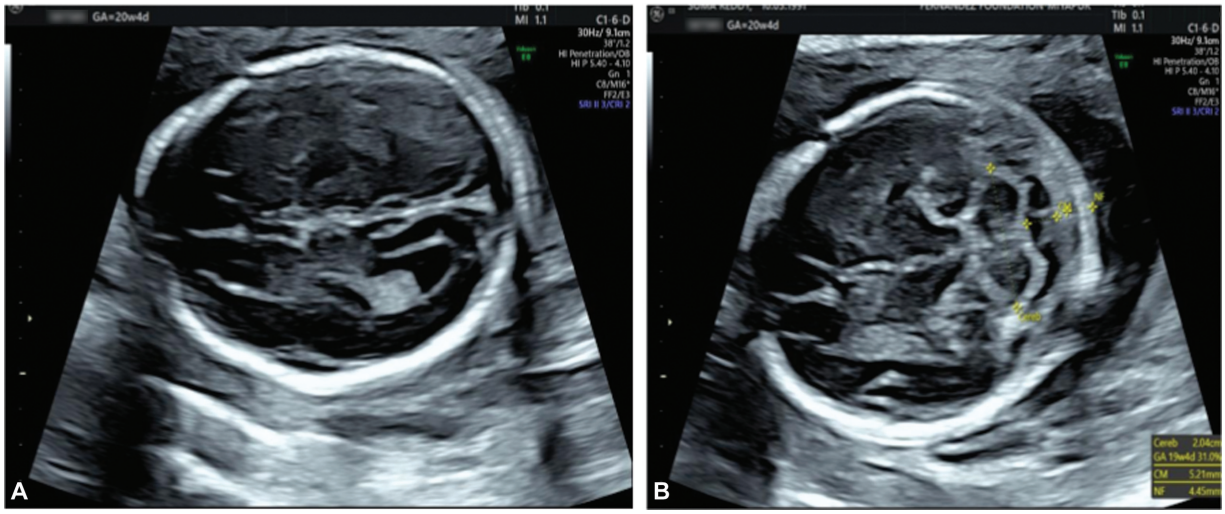

Fig. 10 (A) Transventricular plane with narrow (CSP). (B) Transcerebellar plane with narrow CSP.

corpus callosum and vermis were normal for gestational age. Fetal biometry and the rest of the structural survey were normal (►**Fig. 12**). Repeat scan after 4 weeks was recommended; however, the couple opted to do an MRI outside that reported the same findings as above in addition to the possibility of unilateral stenosis of the foramen of Munro. The couple were repeatedly counseled and motivated to do a repeat MRI at 32 weeks that was suggestive of left-sided moderate ventriculomegaly with irregular margins and punctations, asymmetric brain parenchyma with more volume on the left, and punctate nodular hypointensities along ventricular margins on the ipsilateral side (►**Fig. 13**).

The posterior fossa was normal. The above features were suggestive of hemimegalencephaly with MCD (►**Fig. 14**). The couple had multidisciplinary counseling about the prognosis and possible manifestations in neonatal period and were advised microarray on the stored DNA, detailed postnatal evaluation, and follow-up. The couple decided to go to their hometown and unfortunately had a stillbirth at 36 weeks, male baby, 2.6 kgs. They decided against any further testing.

Discussion

The cerebral cortex, the outer layer of the brain, has a six-layered cellular structure of 2 to 5 mm width. The programmed cortical expansion and folding play a key role in the development of the human brain. MCD are an important cause of epilepsy, developmental delay, and motor and sensory deficits. They can also be associated with cognitive impairment and autism. Genetic evaluation is recommended as genes are known to play an important role in etiology. MCD can also be caused by intrauterine infections, vascular

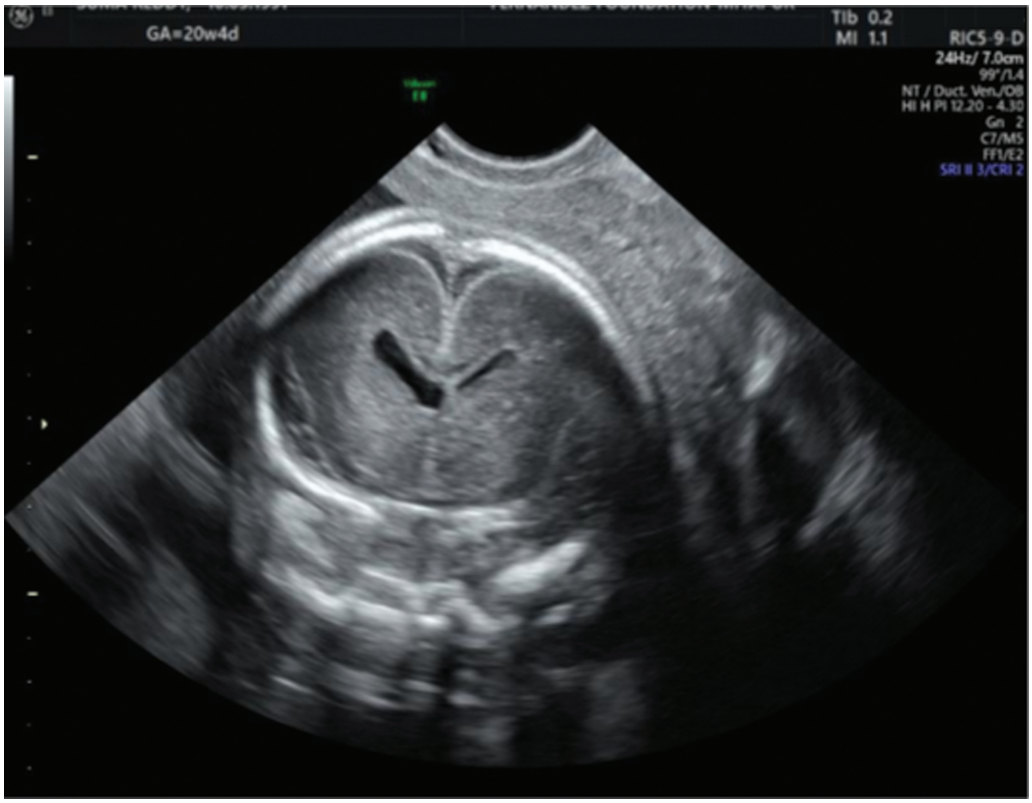

Fig. 11 Coronal plane showing lateral ventricle fused with cavum septum pellucidum.

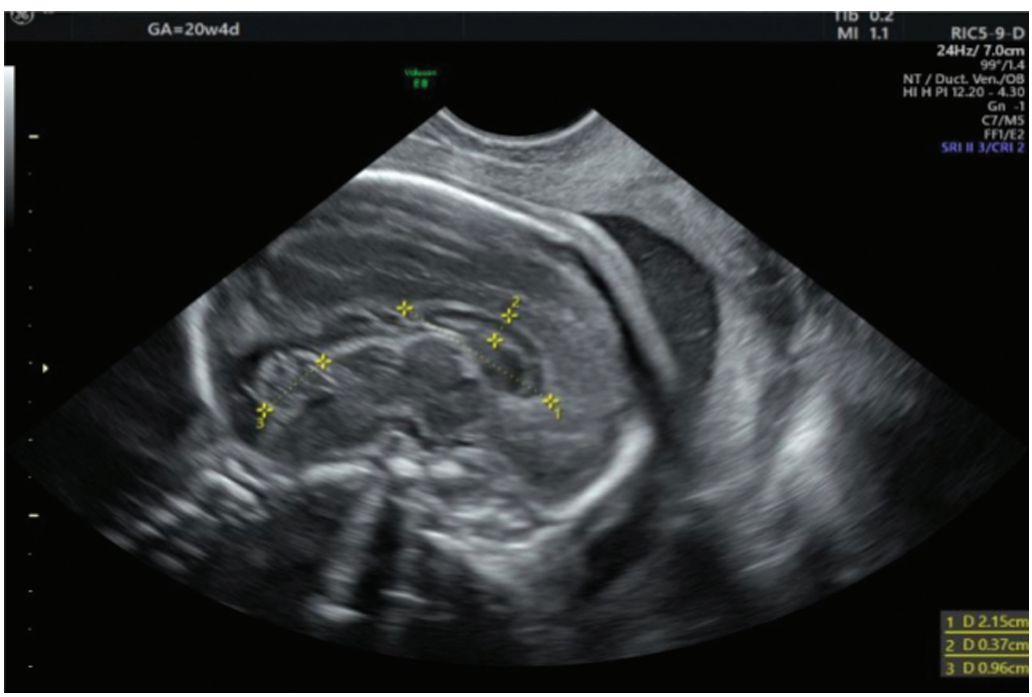

Fig. 12 Midsagittal view measuring corpus callosum and vermis.

injury, trauma, and exposure to teratogens. The earliest regulating process affecting cortical development is used to classify MCD.

Hemimegalencephaly is a rare congenital cortical malformation marked by enlargement of the unilateral cerebral hemisphere. It is an anomaly of neuronal cell migration. In utero diagnosis of hemimegalencephaly by real-time ultrasound is very rare. There are intracranial imaging markers in the ultrasound to aid in the probable diagnosis complemented by MRI evaluation of the brain to confirm the

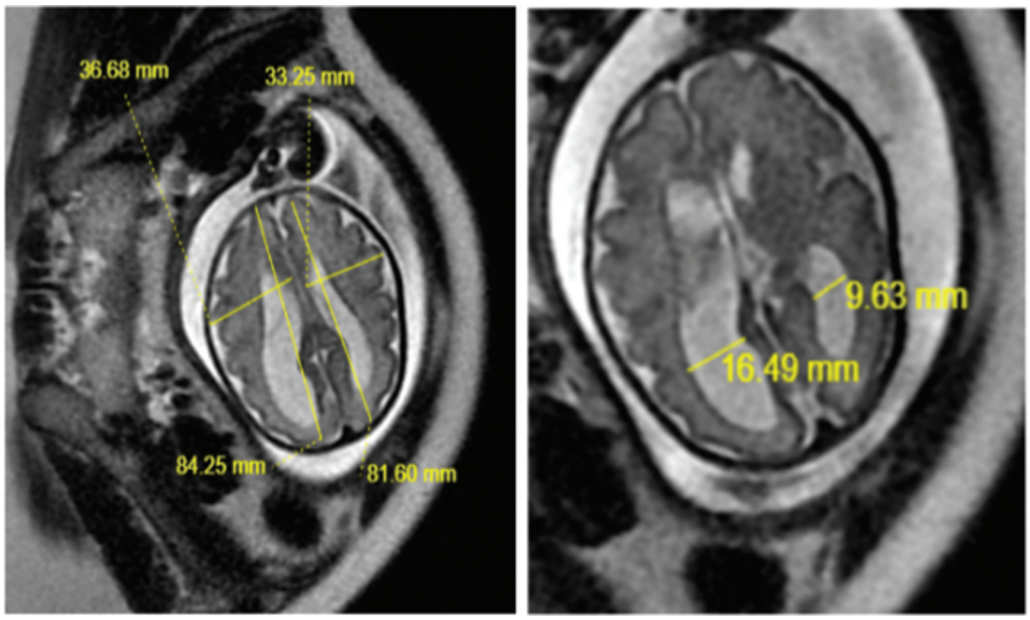

Fig. 13 Magnetic resonance imagings measuring asymmetric cerebral hemispheres.

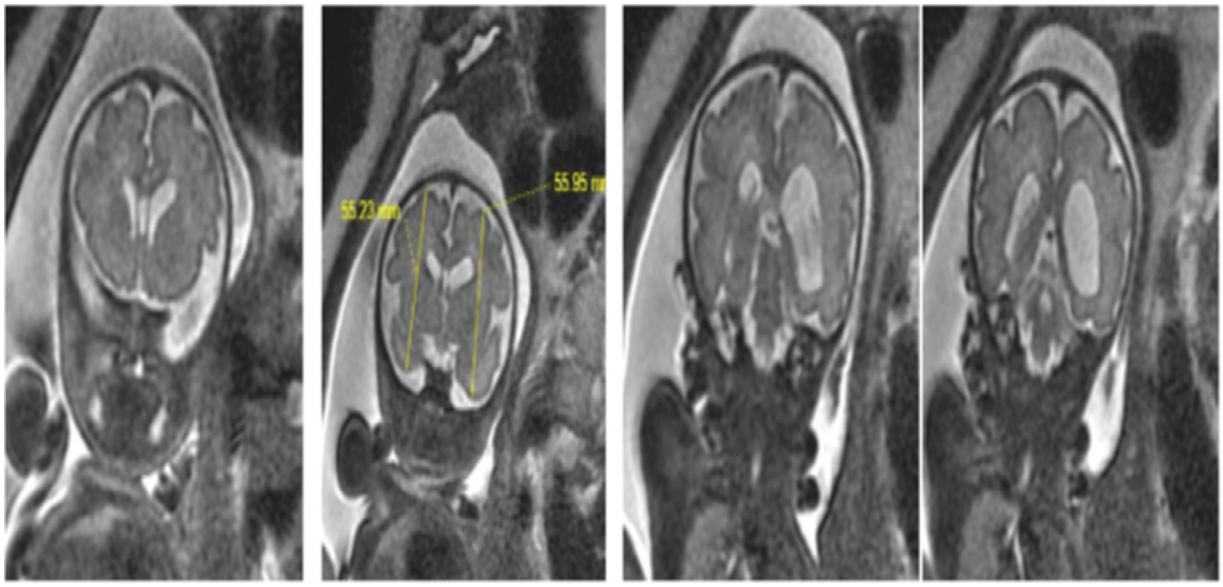

Fig. 14 Magnetic resonance imagings of hemimegalencephaly.

diagnosis.[4] As reported by Malinger et al, an MCD should be suspected in utero when the following intracranial imaging signs are present: abnormal development of the sylvian[5] fissure; delayed achievement of cortical milestones, premature appearance of sulcation; irregular ventricular borders, abnormal cortical thickness (thick, thin); abnormal shape and orientation of the sulci and gyri; irregular, abnormal, asymmetric, and enlarged hemisphere; simplified cortex; noncontinuous cortex or cleft; and intraparenchymal echogenic nodules.[1] There are other indirect imaging signs in midtrimester scan like ventriculomegaly, asymmetric ventricles, hemispheric or cerebellar anomalies, abnormal or absent CSP, abnormal head circumference(microcephaly, macrocephaly), and multiple CNS malformations. The challenge in diagnosis is due to the appearance of cortical milestones beyond the recommended time for midtrimester anomaly scan, unsatisfactory knowledge on rapidly developing brain and its gyration/sulcation pattern. MRI aids in the diagnosis, particularly when performed at the right time —on or after 26 weeks and by personnel who are trained in the accurate interpretation of images. The lack of genetic testing and noncompliance with detailed postnatal examination is a major limitation in the above cases.

Conclusion

With the advent of ultrasound equipment, adequate training in performing the neurosonogram, and the knowledge of

gyration and sulcation of the brain, there is a rise in the prenatal diagnosis or suspicion of MCD. The timing and the expertise of persons reporting the fetal MRI are crucial in the diagnosis. A thorough knowledge on the normal ultrasonography landmarks and its deviations in the basic axial screening planes is required for the suspicion and to refer for further investigations. Option of chromosomal microarray by invasive testing and clinical correlation with the fetal autopsy will guide in the accurate diagnosis of the type and improve the knowledge on MCD and help in establishing the risk of recurrence.

A complete dedicated multiplanar neurosonogram even with minimal suspicion of mild ventriculomegaly by three routine basic axial planes complemented by coronal and sagittal views aids in the diagnosis of MCD. In the above two reported cases, the only indirect signs are narrow CSP and asymmetric ventricles; with the aid of MRI we could diagnose the evolving cortical malformations.

Conflict of Interest

None declared.

Acknowledgments

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