



Pictorial Essay *Pediatric Imaging*

## Malformations of cortical development on fetal MRI

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### ABSTRACT

Neuronal migrational anomalies, cortical dysplasias, hemimegalencephaly, and microcephalies are collectively termed malformations of cortical development (MCD). MCDs have multifactorial etiologies including genetic, environmental, vascular, and infectious insults between the late 1<sup>st</sup> trimester and late 2<sup>nd</sup> trimester. Neonatal correlates of various neuronal migration anomalies detected on fetal magnetic resonance imaging are illustrated. Physiologic immaturity of sulci and certain mimics of migration anomalies can pose a challenge, and these are also outlined.

**Keywords:** Fetal, Magnetic resonance imaging, Neuronal migrational anomalies

### INTRODUCTION

Neuronal migrational anomalies, cortical dysplasias, hemimegalencephaly (HME), and microcephalies are collectively termed malformations of cortical development (MCD). MCDs have multifactorial etiologies including genetic, environmental, vascular, and infectious insults between the late 1<sup>st</sup> trimester and late 2<sup>nd</sup> trimester. It is important to understand cerebral cortical development and normal magnetic resonance imaging (MRI) appearance of fetal cerebral cortex during various stages of gestation and utilize this knowledge to be able to recognize a variety of MCDs on fetal MRI. Neonatal correlates of various neuronal migration anomalies detected on fetal MRI are illustrated. Physiologic immaturity of sulci and certain mimics of migration anomalies can pose a challenge, and these are also outlined.

### EMBRYOLOGY OF NEURONAL MIGRATION

Neuroblast proliferation occurs during 7–16 weeks of gestation, followed by neuronal migration between 12 and 24 weeks, and cortical organization 24 weeks post-natally. Neuroglia from progenitor cells in the ventricular zone extend their processes throughout the cortex and anchor at the pia. These long fibers provide a scaffold on which neurons migrate outward to establish six layers of the cortex, originating at the subventricular ganglionic eminences.<sup>[1]</sup>

Radial migration to the cerebral hemispheres forms the primitive cerebral cortex called the pre-plate. Axonal connections with other cortical plates and subcortical neurons are established, forming a prospective zone of white matter between ventricular zone, and developing cortex called the intermediate zone. Multilaminar organization with inside-out neuronal migration takes place.<sup>[2]</sup>

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## NORMAL SULCATION

At 16–17 weeks, the interhemispheric and Sylvian fissures are formed. The cerebellar hemispheres are smooth. The cerebral parenchyma is three layered at this stage on MRI [Figure 1a].

By 20–21 weeks, Sylvian fissure deepens, prepyramidal sulcus of vermis is formed, flocculonodular lobe of the cerebellum is formed, and myelination is seen in the medulla and pons. The cerebral parenchyma is five layered,<sup>[3]</sup> with low T2 signal of ventricular and outer cortical zones, and there is a mature configuration of ventricles at this stage [Figure 1b].

Around 24–25 weeks, calcarine, cingulate, and postpyramidal vermian sulci are visible and there is early cerebellar foliation [Figure 1c]. By the late 2<sup>nd</sup> trimester, postcentral, intraparietal, frontal sulci, and all vermian fissures are apparent. There is complete cerebellar foliation and myelination is seen in the inferior and superior cerebellar peduncles. There is a blurring of the multilayer configuration with a residual five-layer appearance.

By the third trimester, inferior temporal and occipitotemporal sulci are seen. The dorsal midbrain, inferior colliculi, lateral putamina, and ventrolateral thalami are myelinated. Cerebral parenchyma is bilaminar.

Cortical malformations are divided into three categories based on embryological and genetic etiology, depending on when cortical development was disturbed [Table 1].<sup>[4]</sup>

### Severe congenital microcephalies (group 1a)

Primary microcephaly is caused by genes affecting pathways involving neurogenesis and some of the common genes

involved are ORC, MCPH, and WDR62 (also associated with polymicrogyria [PMG]).

### Dysplastic megalencephaly (Group 1b)

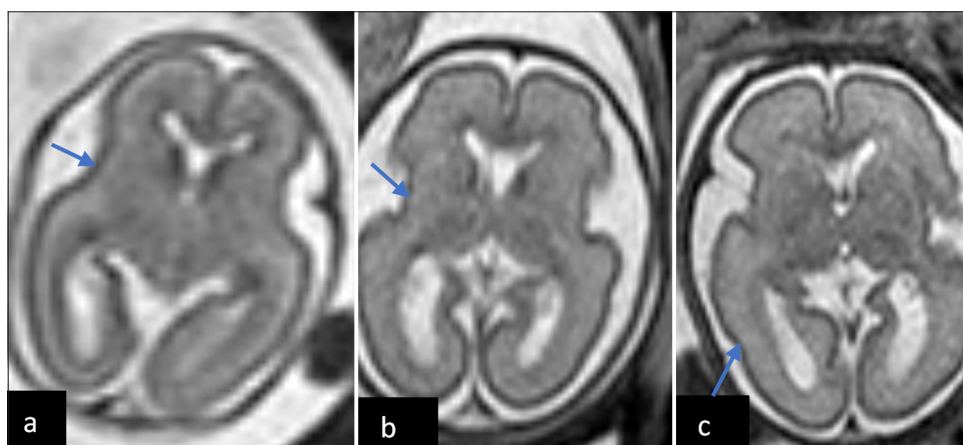
Dysplastic megalencephaly/HME occurs due to disturbances in neuronal proliferation, migration, and organization resulting in hamartomatous overgrowth of a portion or entire cerebral hemisphere with hypomyelination and nodular heterotopia [Figures 2a and 2b]. When the megalencephaly is unilateral, dysplastic changes are seen with equal frequency in the frontal and occipital lobes. With bilateral dysplastic megalencephaly, involvement is typically symmetrical. Patients with mutations involving PI3K/AKT/mTOR pathways, as seen in Proteus and Klippel-Trenaunay-Weber syndrome, and tuberous sclerosis show an increased incidence of HME.<sup>[4]</sup>

### Focal cortical dysplasias (FCDs) types IIA, IIB (Group 1c)

Type 2a FCD (transmantle dysplasias) and cortical tubers related to tuberous sclerosis, hamartomas, and type 2b FCD (mTOR pathway) fall in this category.

### Periventricular nodular heterotopia (PVNH)-Group 2a

The arrest of normal radial neuronal migration results in the rest of gray matter neurons in abnormal locations called heterotopia. Classic PVNH is associated with mutations in FLNA, and ARFGEF2, hypothesized to be associated with vesicle trafficking and neuro-ependymal repair during neuron proliferation and intracellular transport.<sup>[5]</sup> Heterotopias are characterized by location – periventricular, subcortical, and leptomeningeal. Periventricular subtype

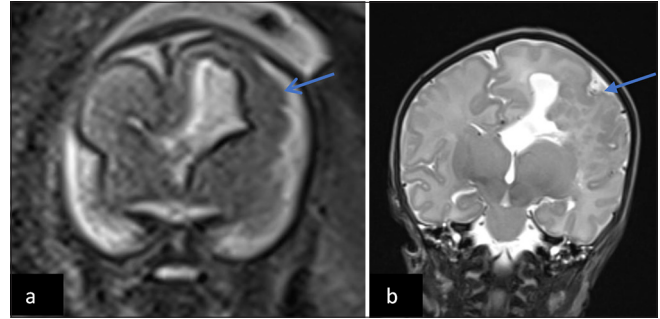


**Figure 1:** A fetal MRI on a 26 year old female. Normal sulcation on axial T2-weighted image through fetal frontal horns. (a) At 16–17 weeks, three-layer cerebral parenchyma and formation of interhemispheric fissure and beginning of sylvian fissures (blue arrows). (b) At 20–21 weeks, Sylvian fissures (blue arrows) are formed well and mature configuration of ventricles is seen. (c) At 24–25 weeks, calcarine (blue arrows) and cingulate fissures have formed.

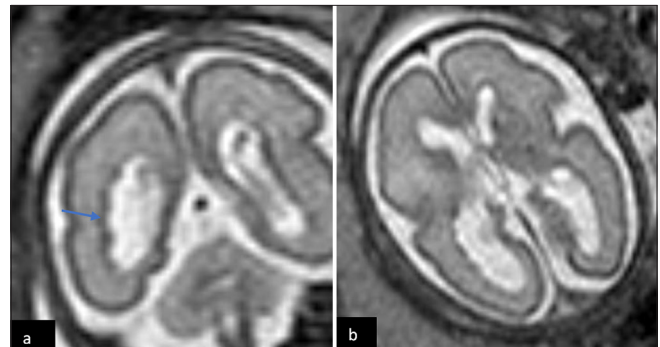
**Table 1:** Classification of malformations of cortical development.

Group 1 – Malformations secondary to abnormal stem cell proliferation or apoptosis (1 <sup>st</sup> and early 2 <sup>nd</sup> trimester)	1a. Primary microcephalies – Reduced proliferation/ accelerated apoptosis tubulin-associated proteins (TUB, DCX, MCPH1, LIS1), 1b. Megalencephaly spectrum/ Hemimegalencephaly – Increased proliferation (AKT3, PIK3 mutation pathways), cortical tubers related to tuberous sclerosis, hamartomas 1c. Cortical dysgenesis with abnormal cell proliferation focal cortical dysplasias types IIa, IIb (mTOR pathway) cortical tubers related to tuberous sclerosis, hamartomas, dysplastic megalencephaly at 23 weeks
Group 2 – Malformations secondary to abnormal neuronal migration (Early to late 2 <sup>nd</sup> Trimester)	2a. Heterotopia periventricular nodular (ARFGF2) 2b. Lissencephaly classic (TUBA1A, DCX, LIS1) variant (ARX, RELN) 2c. Subcortical heterotopia and sublobar dysplasia 2d. Cobblestone malformations (GPR56, LAMB1) – Dystroglycanopathies affecting pial limiting membrane
Group 3 – Malformations secondary to abnormal post-migrational development (mid 2 <sup>nd</sup> trimester to early 3 <sup>rd</sup> trimester)	3a and b. Polymicrogyria and schizencephaly – Etiology can be prenatal ischemia, teratogenesis, infectious brain injury, 1p22q mutations, or related to mTOR pathway 3c. Focal cortical dysplasias I and III 3d. Post-migrational microcephaly

is subdivided into anterior-predominant, posterior-predominant, and band-like. Heterotopias are clusters of smooth, round, or ovoid masses – isointense to cortex on all pulse sequences [Figures 3a and 3b]. Protrusion of these nodules into lateral ventricles must be distinguished from subependymal nodules and T2 hypointense associated with intraventricular hemorrhages [Figure 4a]. Location



**Figure 2:** A fetal MRI on a 33 year old female. (a) Coronal T2-weighted (T2W) image on fetal magnetic resonance imaging demonstrating enlarged left cerebral hemisphere and asymmetric left lateral ventriculomegaly with dysplastic frontal horn. Note the left frontotemporal shallow sulci, cortical thickening (blue arrows), and blurring of the gray-white interfaces. (b) Coronal T2W image obtained postnatally shows additional findings of polymicrogyria (blue arrows) in the left cerebral hemisphere with rests of nodular gray matter heterotopia in the left periventricular and subcortical white matter. Hyperintense left superior periventricular white matter indicates hypomyelination. The right cerebral hemisphere is unaffected.

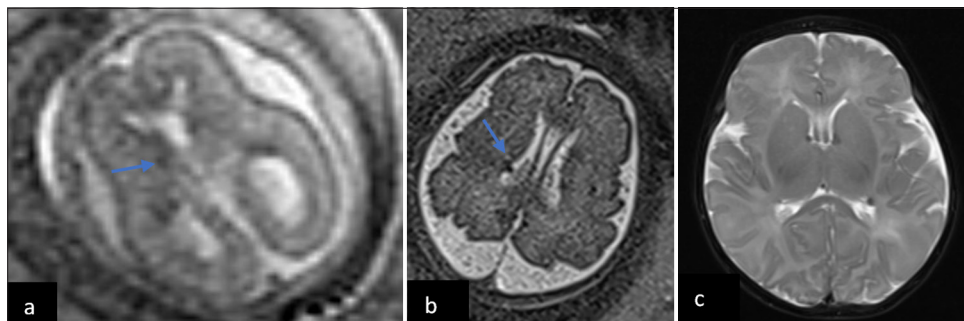


**Figure 3:** A fetal MRI on a 29 year old female. (a) Axial and (b) coronal T2-weighted (T2W) image on fetal magnetic resonance imaging show foci of nodular low signal intensity and irregular contour of the ventricles along the body and atria consistent with periventricular nodular heterotopia (PVNH) (blue arrows). Hemorrhage and subependymal nodules of tuberous sclerosis can mimic PVNH.

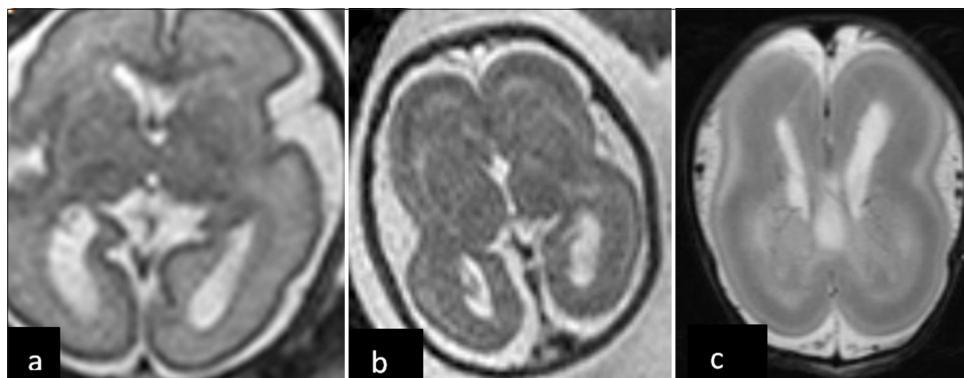
and ancillary findings such as cortical tubers are important distinguishing features [Figure 4b and c].

### Lissencephaly (Group 2b)

The lamination and smooth topography of the developing brain before 26–27 weeks should not be mistaken for lissencephaly [Figure 5a].<sup>[6]</sup> Classic lissencephaly due to incomplete neuronal migration results in a 4-tiered histologic organization. This is comprised of thin pial and outer cortical layers, a cell sparse zone, and a thick cortical layer [Figure 5b



**Figure 4:** A fetal MRI on a 21 year old female. Germinal matrix hemorrhages (blue arrows) and subependymal nodules of tuberous sclerosis at 30 weeks, mimics of periventricular nodular heterotopia. (a) Axial T2-weighted (T2W) image on fetal magnetic resonance imaging with bilateral small germinal matrix hemorrhages which are periventricular low signal intensities localized to bilateral caudothalamic grooves, without irregularity of the ventricular walls. (b) Axial T2 W image and (c) postnatal axial T2W image with subependymal nodules (blue arrows) of tuberous sclerosis.



**Figure 5:** A fetal MRI on a 33 year old female. Axial T2-weighted image (T2W) on fetal magnetic resonance imaging (MRI) at 29 weeks. (a) Normal fetal MRI at 29-week gestation shows normal primary sulcation. (b) Classic lissencephaly with primitive sulcation and diffusely thickened cortex and cell sparse zone (black arrow head in the left lower). (c) Postnatal axial T2WI of the same patient with rudimentary sulcation and smooth cerebral hemispheres, characteristic of classic lissencephaly. The hyperintense cell sparse zone is more clearly visualized.

and 5c]. Disruptions in tubulin and microtubule-associated proteins lead to agyria or pachygyria characteristic of lissencephaly. The most implicated genetic mutations are those of LIS1, DCX, and TUBA1A.

#### Subcortical heterotopia and sublobar dysplasia (Group 2c)

Subcortical dysplasias where a large collection of neurons are found in deep cerebral white matter and sublobar dysplasia characterized by a region of dysmorphic brain fall under this category. The histology and embryogenesis of these malformations are unknown.<sup>[4]</sup>

#### Cobblestone malformations (Group 2d)

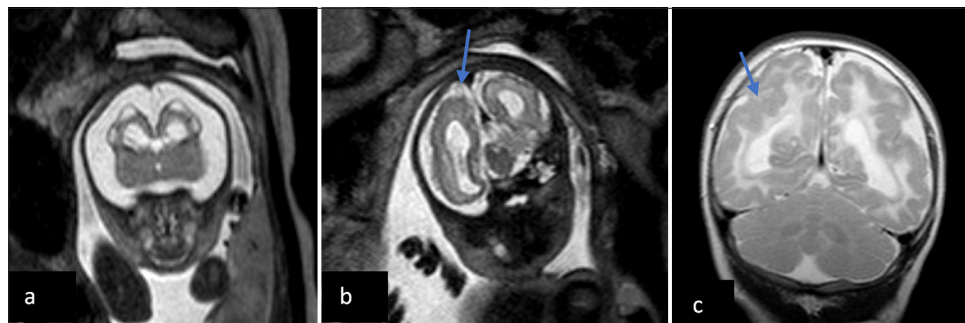
Dystroglycanopathies affecting pial limiting membrane (*GPR56*, *LAMB1* gene mutations) fall under this category.

#### PMG – group 3a and b

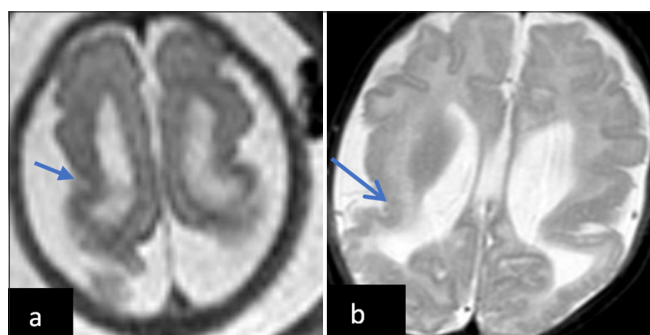
PMG results from abnormal development of the pial limiting membrane (layer 1). The primary disturbance is that of sulcation, manifesting as increased number of small gyri and relative paucity of sulci [Figures 6a-c and 7a, b]. Histologically, it is characterized by overfolding and abnormal lamination of the cortex with excessive small convolutions. While etiology is multifactorial, 22q11 and mTOR pathway mutations (*PIK3R2* and *PI4KA*) have been identified in some cases of PMG.<sup>[6]</sup>

PMG has been classified<sup>[4]</sup> as:

- A. with schizencephaly/calcifications (infective or vascular)
- B. genetic or disruptive (no cleft or calcification)
- C. as part of genetically defined congenital anomaly syndromes
- D. with inborn errors of metabolism (atypical histology).



**Figure 6:** A fetal MRI on a 29 year old female. (a) Coronal T2-weighted (T2W) image on fetal magnetic resonance imaging (MRI) at 26 weeks shows hyperintense subcortical cysts bilaterally. (b) Coronal T2W image on fetal MRI at 33 weeks shows abnormal sulcation (blue arrows) in the areas of these subcortical cysts while there is resolution of the cysts. (c) Postnatal coronal T2W image of the same patient shows cortical thickening (blue arrows) and nodularity with numerous small gyri bilaterally in the same locations, characteristic of polymicrogyria.

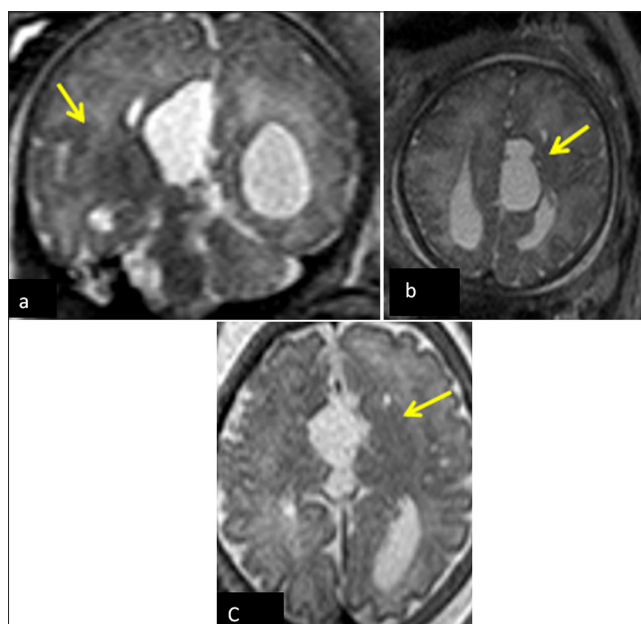


**Figure 7:** A fetal MRI on a 31 year old female. (a) Axial T2-weighted (T2W) image on fetal magnetic resonance imaging at 33 weeks (blue arrow) and (b) postnatal axial T2W image demonstrates bilaterally symmetric polymicrogyria (blue arrow) in frontoparietal and periorlandic regions with dysmorphic ventricles.

PMGs can also be seen in association with agenesis of the corpus callosum with interhemispheric cyst (IHC) [Figures 8a-c]. IHC may communicate with the ventricular system (type 1) or be non-communicating (type 2). Type 2 IHCs are often multilocular and may be associated with subcortical heterotopia or PMG.

### TIMING AND EVOLUTION OF PMG

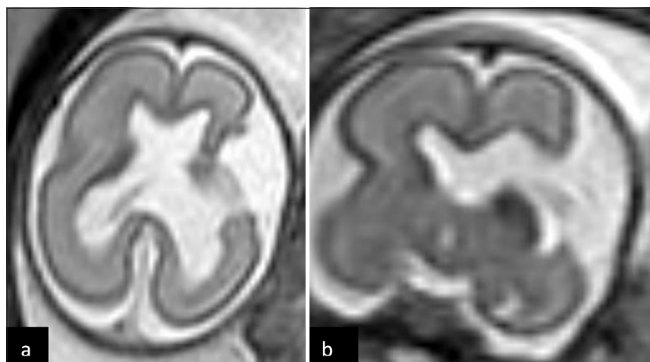
The absence of heterotopia in Figures 6a-c suggests an insult occurring in the mid to late second trimester during late migration/early organization with subcortical cysts that later resolved and manifested as PMG by third trimester. The PMG in this case is likely to be four layered, due to laminar necrosis of the outer cortical layers. In contrast, in the case of dysplastic megalencephaly illustrated in Figure 2, the insult is much earlier during the first trimester during the cell proliferation phase, well before migration had completed. The cortex is more disorganized and there is heterotopia. The PMG in this case was unlayered and more disorganized, as revealed by histopathologic specimen obtained after hemispherectomy.



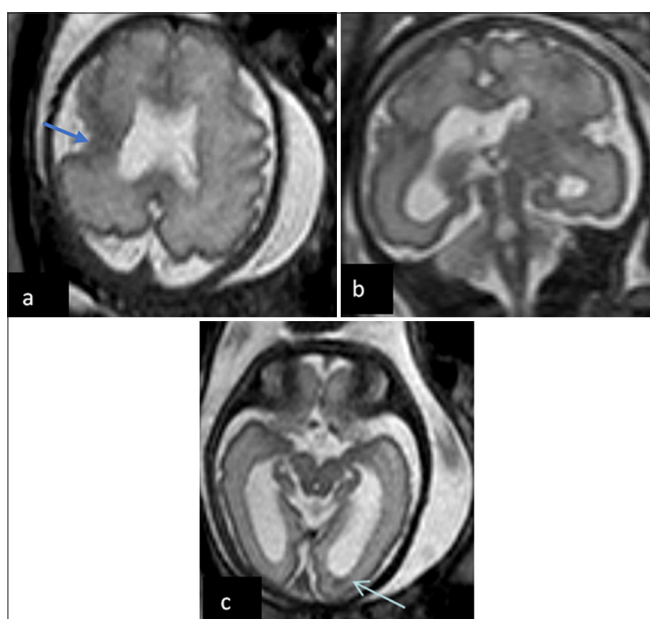
**Figure 8:** A fetal MRI on (a and b) 29 year old and (c) 35 year old females. (a) Coronal and (b) axial T2-weighted (T2W) image on fetal magnetic resonance imaging (MRI) at 37 weeks of gestation demonstrates colpocephaly with bilobed Type 2 interhemispheric cyst (IHC). Note thin intra-cystic septation and polymicrogyria in the perisylvian and interhemispheric regions (yellow arrow on a and b). (c) Axial T2W image on fetal MRI at 35 weeks of gestation with colpocephalic ventricular morphology and unilocular type 1 IHC communicating with the roof of the third ventricle. Note the polymicrogyria adjoining the IHC (yellow arrow).

### Schizencephaly – Group 3a and b

Schizencephalies [Figures 9a, b and 10a-c] are malformations of abnormal cortical organization characterized by dysplastic gray matter-lined clefts extending from the ependymal surface of the lateral ventricles through the cerebral mantle to the pial surface.<sup>[7]</sup> Schizencephaly is a disorder with heterogeneous causes, many of which are vascular in



**Figure 9:** (a) Axial and (b) coronal T2-weighted image on fetal magnetic resonance imaging at 23 weeks of gestation with left open lip schizencephaly. A wide transmantle perisylvian cerebrospinal fluid cleft is lined with T2 hypointense dysplastic gray matter. The septum pellucidum is absent.



**Figure 10:** (a) Axial and (b) coronal T2-weighted (T2W) image on fetal magnetic resonance imaging (MRI) at 31 weeks demonstrates right perirolandic closed-lip schizencephaly. Note right frontoparietal polymicrogyria (blue arrows) with dysplastic gray matter extending to the ependymal surface of right lateral ventricle and absent septum pellucidum. (c) Axial T2W image on fetal MRI at the level of occipital horn demonstrates concurrent subcortical gray matter heterotopia along the left lateral ventricle (light blue arrow).

etiology. Common associations include young maternal age, maternal alcohol use, lack of prenatal care, and non-central nervous system abnormalities, many of which could be classified as secondary to vascular disruption (including gastroschisis, bowel atresias, and amniotic band syndrome). Schizencephaly may be unilateral (approximately 60%) or bilateral (approximately 40%), with an increased frequency of epilepsy among those with unilateral malformations.

Closed lip schizencephaly implies apposed/fused cleft without visible interposed cerebrospinal fluid (CSF) and may mimic transmantle heterotopia. In open lip schizencephaly, CSF cleft divides dysplastic gray matter and may be narrow or wide. Schizencephaly is frequently seen in the setting of septo-optic dysplasia and PMG, although optic nerve hypoplasia may be difficult to appreciate by fetal MRI.<sup>[8]</sup> Although schizencephaly is grouped as a malformation secondary to abnormal post-migrational development, the case in Figure 9 illustrates that the insult can occur before migration is completed.

### FCDs types 1 and 3 – group 3c

FCD type 1 is a heterogeneous entity that occurs from injury/insult to cortex during later stages of cortical development.

### Post migrational microcephaly – group 3D

Those born with small heads but develop severe microcephaly in the first 1–2 years after birth are designated postmigrational microcephaly because brain growth seems to slow during late gestation or the early postnatal period after normal early development.<sup>[4]</sup>

## CONCLUSION

Familiarity with embryology of neuronal migration and pattern of sulcation is essential for early diagnosis of cortical malformations and migrational anomalies by fetal MRI. Prenatal diagnosis of cortical malformations and migrational anomalies renders a host of advantages to treating providers, providing insight into the expected outcomes.

MCD pathogenesis stems from molecular disruption due to insults that can occur at various stages of gestation. The type and the severity of malformation depend on the timing and nature of the insult. An understanding of the embryology is helpful to precisely characterize these abnormalities on a fetal MRI during various stages of gestation and for recommending appropriate post-natal genetic testing.

**Ethical approval:** The research/study was approved by the Institutional Review Board at Akron Children's Hospital, number 1408174, dated March 27, 2019.

**Declaration of patient consent:** Patient consent was waived by IRB 1408174, at Akron Children's Hospital for the study. This was because the study is retrospective and a patient consent was not feasible considering the number of cases studied.

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