Neurosonographic Approach to Malformations of Cortical Development

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Abstract
Malformations of cortical development (MCD) are disorders of cerebral cortex formation caused by various genetic mutations, infections, vascular abnormalities, or metabolic abnormalities. Malformations of cortical development are associated with abnormal cortical structure, ectopic gray matter, and odd brain size. It is hard to depict cortical development and its disorder by ultrasonography during the fetal period. The phenotype of cortical development does not appear until 8 months of gestation when gyrus/sulcus formation becomes apparent. Early detection of impaired cell migration and cortical maldevelopment is a challenge in the field of prenatal fetal neuroimaging. However, longitudinal neuroimaging throughout the embryological and fetal period, combined with the precise genetic investigation, fetal MCD has been diagnosed due to the development of neuroimaging and the remarkable development of the next-generation sequencing. Perhaps shortly, fetal MCD diagnosis will be possible more accurately and earlier. The combination of molecular genetics and detailed neurosonography has established “Neurosonogenetics”, a new field in multidisciplinary prenatal neurology, for prompt prenatal/postnatal management, care, prevention, and treatment in fetal and pediatric neurology.

Keywords: Fetus, Brain, Cortical development, Malformation, Proliferation, Migration, 3D ultrasound, Neurosonography, Imaging.

Introduction
During the fetal period, the embryonal premature central nervous system (CNS) structure rapidly develops into the mature structure with gyral formation. Within this rapid change of development, various developmental disorders and/or insults result in various phenotypes of fetal CNS abnormalities. For understanding fetal CNS diseases, basic knowledge of the development of the CNS is essential. The developmental stages are shown in Figure 1, and major disorders in each stage are described as shown and Table 1. The first stage is neurulation, including the primary neurulation and secondary neurulation, followed by prosencephalic development. In the neuronal proliferation stage, more than twice of surviving neurons of 100 billion neurons that exist in the adult brain were produced in the first and early second trimesters. The peak time of neuronal proliferation is 3–4 months of gestation, and the site producing neurons is mainly ventricular and subventricular zones. After that, neurons are differentiated and migrating to their final position. After neuronal migration, organization and myelination occur. Meanwhile, programmed cell death (apoptosis) arises from the middle of gestation for adjusting the number of neural cells to the target size.

During the developmental stage, the cerebral cortex is dramatically formed. The mature cerebral cortex has a layered structure consisting of six layers of nerve cells with different morphologies and functions. Still, these cells are not born in that place from the beginning. Still, the ventricular zone facing the lateral ventricle (a proliferative layer called the ventricular zone), neurons generated as a result of final division from neural progenitor cells migrate hundreds of times their cell length and reach the position of the cerebral cortex defined by a genetic program, and build a tightly controlled 6-layer structure. Neurons that have started migrating from the ventricular zone stay in the lower layer in the cortical plate for early-born cells and reach the upper layer in the cortical plate for late-born cells. This is called the inside-out principle. Excitatory neurons that make up the cerebral cortex undergo final division from neural stem cells or neural progenitor cells distributed in the ventricular zone and subventricular zone during development. They migrate radially toward the pial surface to form a cortical plate. Subplate neurons are born before these cortical plate neurons, but their types and origins are not uniform. Neurons are roughly divided into excitatory and inhibitory, and the source of excitatory neurons includes the ventricular zone and the rostral medial telencephalic wall. These excitatory neurons are born before cortical plate neurons and form preplates with Cajal–Retzius cells located in the future marginal zone. In addition to these, some GABAergic inhibitory neurons born in the basal ganglionic eminence migrated tangentially and placed on the subplate, as shown in Figure 2.

It is hard to depict cortical development and its disorder by ultrasonography during the fetal period. The phenotype of cortical development does not appear until eight months of gestation when gyrus/sulcus formation becomes apparent. Early detection of impaired cell migration and cortical maldevelopment is a challenge in the field of prenatal fetal neuroimaging. The author believes that some sonographic features in the middle of gestation can predict future cortical maldevelopment. In this chapter, the author explains...
Malformations of Cortical Development

Malformations of cortical development (MCD) are disorders of cerebral cortex formation caused by various genetic mutations, infections, vascular abnormalities, or metabolic abnormalities. Malformations of cortical development are associated with abnormal cortical structure, ectopic gray matter, and odd brain size (microcephaly and macrocephaly). Malformations of cortical development can cause severe morbidity at any age, with symptoms such as epilepsy, developmental delay, intellectual disability, or cerebral palsy. It is estimated that about half of drug-resistant epilepsy is caused by MCD. The definitive diagnosis of MCD is usually made by advanced neuroimaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) scans.

Table 1: Developmental stages and representative disorders

| Developmental stage | Representative cerebral disorders |
|---------------------|----------------------------------|
| Neurulation (3–4 weeks’ gestation) | Cranial and spinal dysraphism (craniorachischisis totalis, anencephaly, encephalocele, myelomeningocele, myeloschisis) |
| Procencephalic development (2–3 months’ gestation) | Holoprosencephaly, agenesis of the corpus callosum, agenesis of the septum pellucidum |
| Neuronal proliferation (3–4 months’ gestation) | Micrencephaly, macrencephaly |
| Neuronal migration (3–5 months’ gestation) | Lissencephaly, pachygyria, focal cortical dysplasia, heterotopias (periventricular nodular heterotopia and band heterotopias), polymicrogyria, schizencephaly |
| Organization (5 months’ gestation–years postnatal) | Idiopathic mental retardation, learning disability, link to epilepsy and autism |
| Myelination (birth–years postnatal) | Range of disorders including adrenoleukodystrophy |

Fig. 2: Schematic illustration of neuronal cell migration. Neurons that have started migrating from the ventricular zone (VZ) stay in the lower layer in the cortical plate for early-born cells and reach the upper layer in the cortical plate (CP) for late-born cells. This is called the “inside-out” principle. Excitatory neurons that make up the cerebral cortex undergo final division from neural stem cells or neural progenitor cells distributed in the ventricular zone (VZ) and subventricular zone (SVZ) during development. They migrate radially toward the pial surface (red arrows) to form a cortical plate (CP). Subplate (SP) neurons are born before these cortical plate neurons, but their types and origins are not uniform. Neurons are roughly divided into excitatory and inhibitory, and the origin of excitatory neurons includes the ventricular zone and the rostral medial telencephalic wall. These excitatory neurons are born before cortical plate neurons and form preplates with Cajal–Retzius cells located in the future marginal zone. In addition to these, some GABAergic inhibitory neurons born in the basal ganglionic eminence (LGE, lateral ganglionic eminence, MGE, medial ganglionic eminence) migrated tangentially and placed on the subplate (blue arrows). IZ, intermediate zone between subventricular zone and subplate.
of MCD is based on neuropathological findings, but in practice, the clinical diagnosis will be based on neuroimaging. The relevant clinical phenotype and genetic results are significant. Despite the many literature reports related to MCD, the definition and classification of MCD are not clear cut, and the category of MCD can constantly be changing and becoming more difficult based on new genetic discoveries. The high pattern-specificity based on neuroimaging enables more targeted genetic testing and facilitates the discovery of new genotype–phenotype correlations, which may improve diagnostic rates. MCD results from disorders of one or more combined developmental steps. Developmental steps include neuronal proliferation, neuronal cell migration, organization, and neuronal maturation.\(^3,5,6\)

- Disorders of neuronal and glial proliferation cause focal cortical dysplasia (FCD) type II.
- Disorders of neuronal migration cause periventricular nodular heterotopia and subcortical band heterotopia.
- Disorders on post-migration cause polymicrogyria, characterized by multiple small gyri.

Table 2 shows the details of MCD in the three developmental steps of proliferation, migration, and post-migration. More than 100 genes were clarified as being responsible for one or more types of MCD.

### Proliferation Disorders

**Microcephaly**

Microcephaly refers to the clinically small head, with frontal occipital circumference (OFC) below −2.0 standard deviations (SD).\(^7,8\) An OFC between −2.0 and −3.0 SD is considered mild microcephaly.\(^8\) While microcephaly refers to a small head circumference, micrencephaly etymologically indicates a small volume of brain tissue. The brain's growth arrest due to acquired or genetic insults results in a small head circumference.\(^1\) Therefore, microcephaly and micrencephaly are used interchangeably. The responsible gene mutations for

| Group | MCD type | Associated genes | Associated pathways and etiology | Imaging findings |
|-------|----------|------------------|----------------------------------|-----------------|
| Group I: Malformations secondary to abnormal cell proliferation or apoptosis | Microcephaly | MCPHI, CENPJ CDK5RAP2, WDR62, NDE1, NDE1, ASPM, CDK5RAP2, TUBA1A, TUBB2B, TUBB3, TUBG1, L1S1, DCX, DYNC1H, KIFSC, NDE1 | Neurogenesis and cell replication, tubulin, and microtubule-associated proteins (MAP) | Small head size, small cerebellum and pons, and lissencephaly (with tubulin and MAP-associated genes) |
| | Megalencephaly spectrum | AKT3, PIK3CA, and PIK3R2 | mTOR | Focal (localized), hemispheric or diffuse cortical enlargement, cerebellum, and deep gray nuclei also enlarged, gray/white boundary-blurring |
| | Focal cortical dysplasias (FCDs) type Ila | MTOR, DEPDC5, and PIK3CA | mTOR | Gray/white matter blurring with apparent cortical thickness |
| | Focal cortical dysplasias (FCDs) type Ilib | MTOR, DEPDC5, NPRL3 | mTOR | Cortical/sulcal T2 hyperintensity may extent to a ventricular surface (transmantic sign) |
| | Tubulinopathies | TUBA1A, TUBB2B, TUBB3, TUBG1, L1S1, DCX, DYNC1H, KIFSC, NDE1 | Microtubule structure and function | Microcephaly, lissencephaly, fused basal ganglia (BG), cortical dysgyria, callosal abnormalities, asymmetric brainstem, and small cerebellar vermis |
| Group II: Malformations secondary to abnormal cell migration | Variant lissencephalies | ARX, DCX, RELN and VLDR | Recelin | ARX-Lissencephaly, callosal abnormalities, dysmorphic BG, hydranencephaly Recelin-lissencephaly in anterior-posterior gradient, cortical thickening, small cerebellum, and vermis |
| | Gray matter heterotopia | FLNA and ARFGEF2 | Neuroependyma/neuroepithelium | Normal gray matter in abnormal locations |
| | Cobblestone malformations | GPR56, LAMB1, LAMB2, LAMC3 and SRDA3 Fukutin, POMGNT1 | Dystroglycanopathies affecting pial limiting membrane | Lissencephaly/pachygyria or polymicrogyria (PMG), possible cerebellar involvement, Fukuyama syndrome, Muscle-eye-brain disease (MEB), Walker-Warburg syndrome, also called HARD(E) syndrome |
| Group III: Malformations secondary to abnormal post-migrational development | Polymicrogyria (PMG) | 1p36.3 and 22q11.2 mutations, mTOR genes | Etiology can be from prenatal ischemic, teratogenic or infectious brain injury | Perisylvian bilateral PMG (most common), associated with schizencephaly |
microcephalies were reported, such as microcephalin (MCPH1⁹–¹²), ASPM¹³, CDK5RAP2⁶,¹⁴, CENPJ⁶,¹⁴, STIL¹⁵, WDR62⁵,⁶,¹³,¹⁶ and CEP152³,⁷ and others.

Prenatal images of cases with microcephaly are shown in Figure 3. It is often quite hard to observe intracranial structure in microcephaly cases because cranial fontanels and sutures are very narrow, as shown in Figure 3B, due to microcephaly; therefore, ultrasound neuroimaging via sutures and fontanels as ultrasound windows is often tricky. Microcephaly is one of the indications for MR imaging.

Macrocephaly and Brain Overgrowth Spectrum
Macrocephaly is defined as having an OFC of at least 2.0 SD, and an OFC of 2.0–3.0 SD is considered mild macrocephaly. Macrocephaly may be associated with various causes, including hydrocephalus, dilation of the extracerebral cavity, and skeletal dysplasia.¹⁷,¹⁸

Figs 3A to F: Microcephaly at 18 weeks of gestation: (A) 3D reconstruction image of fetal craniofacial expression; (B) 3D image of craniofacial skeletal appearance. Note the narrow cranial sutures and fontanels because of microcephaly. In cases with microcephaly, transfontanel ultrasound becomes difficult because of narrow ultrasound windows; (C and D) Mid-sagittal and parasagittal sections demonstrating microbrain; (E and F) Coronal cutting sections of microbrain. Note the premature brain with prosencephalic and proliferation disorder
Of genes relating mTOR pathway. The tubers of the tuberous sclerosis complex (TSC) should be considered a subtype of type IIb FCD because the histological findings and imaging are similar, and complete hemimegalencephaly, which involves the entire hemisphere, is synonymous with classic hemimegalencephaly. On the other hand, localized megalencephaly is primarily caused by somatic mosaic mutations affecting the frontal or parietal, occipital lobes. Figure 4 shows the case of hemimegalencephaly due to somatic mutation of AKT1, with cortical maldevelopment, at 21 weeks of gestation.

**Focal Cortical Dysplasia**

The term “focal cortical dysplasia” is defined as a spectrum of localized brain malformations characterized by disturbed cortical stacking, with or without abnormal cell types. MRI more easily demonstrates type II (a and b) FCDs and the presence of morphologically abnormal cell types, especially atypical neurons characterized by irregular shapes. It is characterized by significant destruction of the cortical layer. Focal cortical dysplasia type IIa has only atypical neurons, and FCD type IIb has both atypical neurons and balloon cells. Recent studies have reported that type II FCD has germline, somatic, or germline-somatic “two-hit” mutations of genes relating mTOR pathway. The tubers of the tuberous sclerosis complex (TSC) should be considered a subtype of type IIb FCD because the histological findings and imaging are similar, and it is considered for both to share the etiology of the mTOR pathway relating genes, TSC1 and TSC2.

**Migration Disorders**

In the cerebral cortex (cerebral gray matter), neurons are arranged in order, in a part called the neocortex among them, a layered structure comprising six layers is formed. Seventy to eighty percent of neurons in the cerebral cortex are excitatory neurons, and they are produced in the ventricular zone which is the part facing the ventricle of the extravasation (pallium; broadly cerebral cortex) or in the subventricular zone, and travel toward the brain surface, to their final destination (radial migration), as shown in Figure 2. Cortical neurons are produced in very early gestation. A cortical plate is located between a marginal zone and a subplate. Cortical plate neurons subsequently move sequentially toward the brain surface. They start to migrate and overtake nerves that have already finished to progress and reach just below the marginal zone and finish their movement. In the cerebral cortex, early-bone neurons are placed closer to the brain’s inner side, and late-bone neurons are placed on the surface side (inside out mode). The cortical plate becomes gray matter after birth.

As a consequence of migration, the brain is matured with gyration/sulcation from late 7 months’ gestation. The fastest increase in the number of significant gyri occurs between 26 weeks and 28 weeks of gestation. This further gyral elaboration continues during the third trimester and shortly after birth. Neuronal migration is controlled by a complex assortment of chemical guides and signals. When these signals are absent or incorrect, neurons cannot end up where they should belong to. This can result in structurally abnormal or missing areas in any site of intracranial structure, such as the cerebral hemispheres, cerebellum, brainstem, or hippocampus, and types of neuronal migration disorders include lissencephaly, agryria, pachygyria, microgyria, micropolygyria, neuronal heterotopias (including band heterotopia and periventricular nodular heterotopia), and schizencephaly. Neuronal migration disorders, the aberration of gyral development, usually cause seizures and neurological function disturbances from early days after birth. Migration disorder appears conspicuously on the surface of cerebral hemispheres in late pregnancy. Therefore, it does not seem to be possible to detect migration disorder before gyration. Toi et al. reported regular gyri/sulci pattern during fetal life, depicted by transabdominal ultrasound imaging. During the latter half of the second trimester, the cortical structure macroscopically develops, and the most distinct morphological difference appears to be the different structure of Sylvian fissure. Thus, the Sylvian fissure is one of the landmarks indicating cortical development by regular migration.
According to cerebral development, changing the appearance of Sylvian fissure is remarkable, and Poon et al.\textsuperscript{24} proposed the Sylvian fissure angle and described the significant decrease of the angle with advancing gestational age. Furthermore, Pooh et al.\textsuperscript{25} demonstrated 22 cases with MCDs between 18 weeks and 30 weeks of gestation and show the delayed development of Sylvian fissure angle in 22 cases with migration disorder, as shown in Figure 5.

**Lissencephaly**

The literal meaning of lissencephaly is a “smooth head” and is usually caused by neuronal migration disorders.\textsuperscript{26} The characteristic features are a thickened cortex and a gyral/sulcal abnormality ranging from absent gyration (agyria) to reduced gyration (oligogyria). Lissencephaly was conventionally divided into two types, type I with a smooth surface of the brain and type II with a cobblestone appearance. After that, many responsible genes were clarified, and classification has been changed by etiology, as shown in Table 3. However, due to recent rapid progress in molecular genetics, a conventional classification system has been insufficient to distinguish various lissencephaly patterns, and a new imaging-based classification system was proposed in 2017 for the prediction of the most likely causative gene mutation.\textsuperscript{27}

Several reports on prenatal diagnosis of lissencephaly have been published.\textsuperscript{16,40,43,44} Without a previous history of an affected child, it is pretty hard to diagnose reliably as lissencephaly until 26–28 weeks of gestation. However, Figure 6 shows microlissencephaly cases at 25 weeks and 30 weeks of gestation. In this case, migration disorder was strongly suspected from 19 weeks of gestation.

**Post-migrational Disorders**

**Polymicrogyria**

Polymicrogyria refers to an excessive number of abnormally small cerebral gyri.\textsuperscript{45} In terms of anatomical distribution, polymicrogyria may be focal, multifocal, or generalized; it may be unilateral or bilateral, and it may be bilateral symmetric or bilateral asymmetric.\textsuperscript{46} Polymicrogyria is a highly heterogeneous cortical malformation caused by both genetic and non-genetic causes. The genetic causes include chromosomal abnormalities such as 22q11 deletions and 1p36 monosomy and single gene mutations\textsuperscript{16,45,47} such as \textit{COL4A1/COL4A2, OCLN, RTTN, and GRIN1} mutations,\textsuperscript{45} while in utero infections by cytomegalovirus or Zika virus, trauma, teratogen exposure, ischemic infarction, twin-to-twin transfusion syndrome, and intrauterine co-twin death of a monochorionic twin are among the most frequent non-genetic causes of polymicrogyria.\textsuperscript{1} Although any part of the cerebral cortex including the frontal, occipital, and temporal lobes can be affected,\textsuperscript{55,47} the most common location

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**Table 3:** Classification of lissencephaly

| Category                        | Types                        |
|---------------------------------|------------------------------|
| Classic lissencephaly           | \textit{LIS1}\textsuperscript{28–30} (17p13.3): lissencephaly due to \textit{PAFAH1B1}\textsuperscript{31} gene mutation, which subdivides into: Miller–Dieker syndrome \textit{DCX}\textsuperscript{5,6,10–12} lissencephaly due to doublecortin mutation Isolated lissencephaly, without other known genetic defects |
| Cobblestone lissencephaly       | \textit{POMGNT1}\textsuperscript{33–38} Muscle-eye-brain disease (MEB), Walker–Warburg syndrome Fukutin\textsuperscript{36,38–40} Fukuyama syndrome |
| X-linked lissencephaly          | \textit{ARX}\textsuperscript{6,37} gene (Xq22.13) mutation |
| Lissencephaly with cerebellar hypoplasia | \textit{Reelin}\textsuperscript{1,41,42} (7q22.1): Norman–Roberts syndrome |
| Microlissencephaly              | Lissencephaly + microcephaly |
for polymicrogyria is in the area containing the Sylvian fissures in approximately 60–70% of cases.

**Schizencephaly**

Schizencephaly classically refers to a cleft lined by polymicrogyria gray matter and heterotopia extending across the cerebral hemispheres' entire thickness from the ventricular surface (ependyma) to the periphery (pial surface) of the brain as a "pial ependymal seam". This malformation is probably the consequence of an early prenatal focal injury of the germinal matrix or might result from insults in the immature cerebrum with the liquefaction of insulted tissue. It is subdivided into open and closed lip types depending on whether the cleft is fully open and filled with CSF or, instead, sealed by the cortical marginal layer. In neuroimaging, differentiation of schizencephaly from porencephaly is based on the fact that the schizencephalic cleft is lined by gray matter instead of white matter with variable grades of gliosis.

Schizencephaly is a disorder characterized by congenital clefts in the cerebral mantle, which is lined by pial-ependymal sea, with communication between the subarachnoid space laterally and the ventricular system medially. Unilateral schizencephaly occurs in 63% and bilateral in 37%. A possible cause is a disruption of vascular development during cerebral development, genetic origins including **WDR62** gene mutation, which causes microcephaly as well as schizencephaly in some cases, indicating relations between processes underlying proliferation and the genesis of schizencephaly, and **COL4A1** gene mutation associated with schizencephaly as well as other CNS abnormalities. Figure 7 shows prenatal neuroimaging in a case of schizencephaly at 25 weeks and 27 weeks of gestation.

**Future Perspective**

Malformations of cortical development are a significant cause of childhood epilepsy and frequently associate with cognitive deficits and behavioral alterations. Epileptogenicity of MCD determines the behavior and function of the brain and is characterized by many molecular, cellular, and structural changes that affect epileptic processes and epilepsy expression during early brain development. That is, it occurs during the fetal period. Fetal neuroimaging diagnosis of MCDs has not been established. However, as described and shown in this chapter, longitudinal neuroimaging throughout the embryological and fetal period, combined with the precise genetic investigation, fetal MCD has been diagnosed due to the development of neuroimaging and the remarkable development of the next-generation sequencing. Perhaps shortly, fetal MCD diagnosis will be possible more accurately and earlier. The combination of molecular genetics and detailed neurosonography has established "Neurosonogenetics", a new field in multidisciplinary prenatal neurology, for prompt prenatal/postnatal management, care, prevention, and treatment in the fetal and pediatric neurology.

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Figs 7A to D: Schizencephaly at 25 and 27 weeks of gestation: (A) Coronal section of the fetal brain at 25 weeks. Arrowheads indicate congenital lined by pia-ependyma, with communication between the subarachnoid space laterally and the lateral ventricle. The choroid plexus (hyperechoic part) exists from intraventricular space to subarachnoid space; (B) Coronal section image at 27 weeks; (C) Illustration of Figure A; (D) Illustration of Figure B

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