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Cortical Developmental and Neuronal Migration Disorders: An Overview

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Abstract

Cortical developmental and neuronal migration disorders are a diverse group of disorders that are common causes of neurodevelopmental delay and seizures. Cortical malformations and neuronal migration abnormalities result from molecular disruption of normal cerebral cortex development. This article focusses on the pathogenesis, neuroimaging characteristics, and genetic basis of these disorders.

Normal cerebral cortical development

Cerebral cortical development is a complex dynamic embryonic process, which involves integration of multiple cellular processes like neural stem cell proliferation, migration, differentiation and organization. Abnormalities of fetal brain development including neuronal migration disorders could be due to non-genetic causes like in utero exposure to infections, maternal smoking, maternal comorbidities such as uncontrolled diabetes, untreated phenylketonuria and untreated hypothyroidism, and hypoxic-ischemic injury, or they could be due to multifactorial or genetic etiologies (Gressens, 2000; Gressens et al., 2001; Auso et al., 2004; Debillon et al., 2000).

Normal cortical development starts with formation of neuronal progenitor cells (projection neurons and interneurons) from stem cells in the pseudostratified columnar neuroepithelium of the ventricular zone (germinal zone/matrix) in the first stage. Progenitor cells in the ventricular zone give rise to progenitor cells in the subventricular zone. Subventricular zone contains two major types of progenitors: the basal progenitors and the multipotential progenitors.

In the second stage, projection neurons and interneurons migrate in a radial and tangential fashion respectively towards the pial surface and settle in an inside-out pattern within the cortical plate between the 6^{th} and 7^{th} week of gestation which peaks between the 11^{th} and 15^{th} week and is completed by around 24 weeks of gestation. Structural barriers of the pial surface and molecular signals arrest neuronal migration. Projection neuronal cells developing in the germinal zone of the lateral ventricles give rise to glutaminergic neurons of the neocortex as well as the neurons in the medial and lateral ganglionic eminence, and projection neuronal cells developing in the walls of the third ventricle give rise to neurons of the basal ganglia and GABA neurons. Interneurons developing in the rhombic lips in the roof of the fourth ventricle give rise to neurons of the cerebellar cortex.

In the third stage, final organization takes place into the typical six layers of the cortex. In this stage, the six-layered laminar structure of the cerebral cortex is formed. However, the development of the cortex and late migration from the germinal matrix into the cerebral cortex continues postnatally till the age of 5 months. Any disturbance in this process leads to cortical malformations and abnormal cerebral function in the form of cognitive and motor impairment and seizures as most frequent consequences. (Gressens, 2000; Letinic et al., 2002; Nadarajah et al., 2002).

Genetic mechanisms involved in cortical developmental disorders

Pathogenic variants in genes which affect neurogenesis cause microcephaly by altering regulation of transcription, cell cycle, mitotic

Table 1 Classification and genetic basis of microcephaly.

Microcephaly		Associated Genes and Conditions
i. Microcephaly with normal or mildly simplified gyri	Microcephaly vera	• *MCPH1, WDR62, CDK5RAP2, CASC5, ASPM, CENPJ, STIL, CEP135, CEP152, ZNF335, PHC1, CDK6, CENPE, SASS6, MFSD2A, ANKLE2, CIT, WDFY3, COPB2, KIF14, NCAPD2, NCAPD3, NCAPH, NUP37, MAP11* – Non syndromic
	Microcephaly with seizures developmental delay	• *PNKP* - Early epileptic encephalopathy 10
	Microcephaly with short stature	• *ATRX* - Seckel syndrome • *PCNT* - Microcephalic osteodysplastic primordial dwarfism type II (MOPD2)
ii. Microcephaly with simplified gyri (Microlissencephaly)		• *NDE1, TUBA1A, TUBA3E, TUBB2B, TUBB3, TUBG1* - Non syndromic • *RELN* - Norman–Roberts syndrome • *RNU4ATAC* - Microcephalic osteodysplastic primordial dwarfism type I (MOPD1)
iii. Microcephaly with other brain malformations		• *LIS1, DCX, DYNC1H1, KIF5C, TUBA1A, TUBB2B, TUBB3, TUBG1* - Non syndromic

spindle disruption, centrosome duplication and maturation, and DNA repair. Pathogenic variants in genes involved in specific pathways that control cell proliferation like the mTOR pathway are involved in the pathogenesis of megalencephaly and focal cortical dysplasias and tubers. Abnormal neuronal migration results from pathogenic variants in genes regulating the organization and stability of microtubules, cytoplasmic dynein function, conversion of nascent post-mitotic neurons to multipolar pre-migratory cells and conversion of multipolar to bipolar migratory cells that facilitate neuronal motility (Lee, 2017). Pathogenic variants in genes involved in the regional patterning of the cerebral cortex during early stages of development i.e. during the proliferation and migration phase, mainly lead to malformations of cerebral cortical development.

Main malformations of cerebral cortical development

(Guerrini & Parrini, 2010; Barkovich et al., 2012; Najm et al., 2018; Spalice et al., 2009; Desikan et al., 2016; Kim et al., 2019; Oegema et al., 2020; Barkovich et al., 2004; Abdel Razek et al., 2009)

1. Microcephaly:

Microcephaly is defined as occipitofrontal (head) circumference (OFC) less than third centile compared to the normal standards for age, sex and ethnicity. It is caused by decreased proliferation or increased apoptosis of neuronal glial cells. See Table 1.

Clinical presentation

Microcephaly vera usually presents with mild to moderate intellectual disability, rarely seizures. and those with microlissencephaly are encephalopathic at birth and have global developmental delay (GDD) or may have normal neonatal and infantile development followed by seizures. The syndromic forms present with dysmorphic features, congenital anomalies, short stature and global developmental delay.

MRI findings

In microcephaly with simplified gyri, the cortex is of normal thickness with reduced sulcation and in microlissencephaly the cortex is abnormally thick with reduced sulcation.

2. Macrocephaly and Megalencephaly

Macrocephaly is defined as occipitofrontal (head) circumference greater than 97th centile

Table 2 Classification and genetic basis of macrocephaly and megalencephaly.

Macrocephaly/ Megalencephaly		Associated Genes and Conditions
i. Megalencephaly with or without other cerebral anomalies	With short stature	• *FGFR3* - Achondroplasia
	With gigantism	• *NSD1, NFIX, APC2* - Sotos syndrome 1,2,3 • *EZH2* - Weaver syndrome • *PTEN* - Bannayan-Riley-Ruvalcaba syndrome • *GPC3* - Simpson-Golabi-Behmel syndrome • *PIK3CA* - Congenital lipomatous overgrowth, vascular malformations, epidermal nevi and skeletal/spinal anomalies (CLOVES) syndrome
	Metabolic	**Lysosomal storage disorders** • *HEXA* - Tay-Sachs disease • *HEXB* – Sandhoff disease
		Leucoencephalopathies • *ASPA* - Canavan disease • *GFAP* - Alexander disease • *MLC1, HEPACAM* - Megalencephalic leukoencephalopathy with subcortical cysts
		Organic acidurias • *GCDH* - Glutaric aciduria type 1 • *D2HGDH* – D-2-hydroxy glutaric aciduria
ii. Megalencephaly with polymicrogyria		• *PIK3R2* - Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPH) • *PIK3CA* - Megalencephaly-capillary malformation syndrome (MCAP)
iii. Hemimegalencephaly		• *FGFR3, PIK3CA, HRAS* - somatic mutations • *AKT1*(somatic mutation)- Proteus syndrome • *PIK3CA* (somatic mutation)- Klippel-Trénaunay-Weber syndrome • Hypomelanosis of Ito

compared to age-matched and sex-matched normal standards. Megalencephaly refers to an abnormally large size of the brain and is defined as brain weight greater than average for the age and gender of the child. These are caused secondary to increased proliferation or decreased apoptosis of neuronal glial cells. See Table 2.

Clinical presentation

These cases present with features related to the specific syndrome/disorder. Hemimegalencephaly presents with contralateral hemiparesis, epilepsy, and intellectual disability.

MRI findings

The enlarged hemispheres usually show gyral abnormalities in the form of agyria/pachygyria or polymicrogyria, and the lateral ventricle is often enlarged, boundaries of gray and white matter may be blurred, and gray matter heterotopias may be found.

3. Periventricular nodular heterotopias

Periventricular nodular heterotopias are formed due to abnormal neuronal migration. See Table 3.

Clinical presentation

Around 90% of patients present with various types of seizures, mostly in adolescence. Females affected with X-linked PNH typically present with epilepsy, commonly generalized tonic-clonic or complex partial seizures and dyslexia, with usually normal intelligence.

Table 3 Classification and genetic basis of periventricular nodular heterotopias.

Periventricular nodular heterotopias	Associated Genes/ Chromosomal Loci and Conditions
i. X-linked periventricular heterotopia	• *FLNA* - Non syndromic
ii. Autosomal recessive periventricular heterotopia with microcephaly	• *ARFGEF2* - Non syndromic
iii. Heterotopia due to chromosomal aberration	• 1p36 deletion - 1p36 del syndrome • 4p deletion - 4p del syndrome (Wolf-Hirschhorn syndrome) • 5p deletion - Cri du chat syndrome • 7q11.2 deletion - Williams syndrome • 22q11.2 deletion - DiGeorge syndrome • Xp22.3 deletion – associated with Steroid sulfatase deficiency

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Table 4 Classification and genetic basis of lissencephaly.

Lissencephaly	Associated Genes and Conditions
i. Classic lissencephaly/ Subcortical band heterotopia	• *LIS1 –LIS1*- associated non-syndromic lissencephaly; with chromosome 17p13.3 deletion - Miller-Dieker syndrome • *ACTB, ACTG1* - Baraitser-Winter syndrome • *DCX* – Non syndromic X-linked lissencephaly 1 • *ARX* - X-linked lissencephaly 2 with abnormal genitalia • *TUB1A - TUB1A* associated lissencephaly • *TUBA1A, TUBB2B, RELN, CASK, VLDLR, WDR81, CA8, ATP8A2* - Lissencephaly with cerebellar hypoplasia
ii. Cobblestone lissencephaly	• *POMT1, POMT2, CRPPA, FKTN, FKRP, LARGE1* - Walker-Warburg syndrome • *POMGNT1* - Muscle eye brain disease • *FKTN* - Fukuyama congenital muscular dystrophy

MRI findings

The heterotopias appear as round or oval nodules in the wall of the ventricle which project into the ventricular lumen or may be in the periventricular white matter.

4. Lissencephaly spectrum

Classic lissencephaly is due to abnormal neuronal migration. Cobblestone lissencephaly is due to abnormal over-migration of neurons through breaches in the pial surface, and gliovascular proliferation. See Table 4.

Clinical presentation

Patients with classic lissencephaly tend to be neurologically abnormal from birth, with hypotonia initially followed by hypertonia and early onset of epilepsy and global developmental delay. Those who are less severely affected may achieve normal developmental milestones but develop epilepsy in late infancy or in childhood and those with cobblestone lissencephaly present with hypotonia at birth, generalized muscle weakness, and joint contractures of variable degree.

DCX mutations cause classic lissencephaly with mental retardation in hemizygous males and a milder phenotype with seizures and subcortical band heterotopia in females, sometimes in the same family. Affected females usually have normal cognitive function.

MRI findings

In classic lissencephaly (Figure 1) sulcation is completely absent (agyria) or few broad, flat gyri separated by a few shallow sulci (pachygyria)

with abnormally thick cerebral cortex may be present. The frontal and temporal opercula are not developed, leading to a characteristic 'figure of 8' appearance of the brain on axial images. In most females with *DCX* mutations and in patients with missense mutations in *LIS1*, subcortical band heterotopias are seen which is characterized by the presence of nodules or nodular curvilinear bands of gray matter that extend from the ventricular wall to the cerebral cortex as a thin layer of white matter between 2 layers of gray matter. In patients with *DCX* mutations, the band heterotopia are located in the frontal region and in *LIS1* mutations they are located in the parieto-occipital region. In *ARX*-related lissencephaly, the corpus callosum is always completely absent and the basal ganglia are either hypoplastic or dysplastic or completely absent.

Figure 1 T1-weighted MRI brain axial image of classic lissencephaly.

Cobblestone lissencephaly is seen in dystroglycanopathies. The findings in Walker-Warburg syndrome are thin cortex with few sulci, unmyelinated white matter, hydrocephalus/severe ventriculomegaly, thin/hypoplastic corpus callosum, hypoplastic cerebellum and vermis, and small and dysplastic ocular globes. Muscle-eye-brain disease has a less dysmorphic appearance of the cerebral cortex with slight irregularity of the inner and outer surfaces of the cortex, hypomyelination, hypoplastic cerebellum and vermis with abnormal folial pattern and multiple cysts in the cerebellum below the surface of the cortex, and small ocular globes with subretinal fluid collections. Fukuyama congenital muscular dystrophy has appearance of cortex which resembles that of Walker-Warburg syndrome with polymicrogyria in the frontal cortex. The myelination pattern looks similar to that seen in muscle-eye-brain disease.

5. Polymicrogyria and schizencephaly

These malformations are due to abnormal post-migrational organization. See Table 5.

Clinical presentation

Clinical presentation of these patients includes global developmental delay, refractory seizures, and bilateral pyramidal and cerebellar signs, depending on the pattern of distribution of polymicrogyria. Unilateral polymicrogyria presents in infancy with congenital hemiplegia. In addition, features related to specific syndromes are noted in syndromic presentations.

Closed-lip schizencephaly often presents with hemiparesis or motor delay. Open-lip schizencephaly may present with seizures, hemiparesis or motor delay.

MRI findings

Polymicrogyria (Figure 2) involves almost any area of the cerebral cortex but those adjacent to the sylvian fissures are preferentially involved than other parts of cortex. In the neonatal period, the affected cortex appears very thin and irregularly undulating. After complete myelination, the cortex becomes thicker and smoother with irregular, bumpy inner and outer cortical surfaces, broad gyri, and shallow sulci. The MRI appearance of schizencephaly shows cerebrospinal fluid extending from the subarachnoid space into the lateral ventricle, and the walls of this cleft are lined by dysmorphic gray matter. The shape of at least a part of the lateral ventricle is seen even in large bilateral clefts which helps in differentiating this from hydranencephaly.

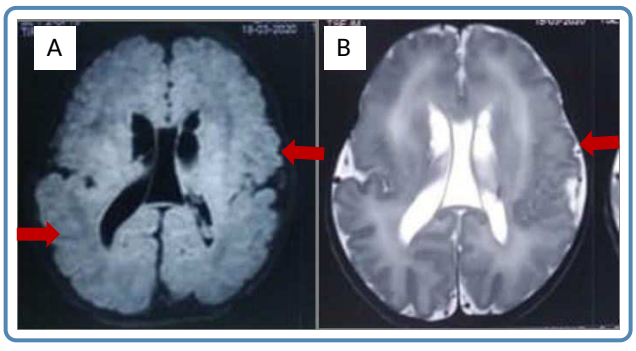

Figure 2 A. T1-weighted MRI brain axial image with extensive polymicrogyria, and B. T2-weighted axial image with shallow sulci in the frontoparietal region.

Table 5 Classification and genetic basis of polymicrogyria and schizencephaly.

Polymicrogyria/ Schizencephaly	Associated Genes and Chromosomal Loci and Conditions
i. Polymicrogyria (classic) with trans-mantle clefts (schizencephaly-closed lip/type 1 or open lip/type 2) or calcification	• *EMX2* - Non syndromic • *OCLN* – Pseudo-TORCH syndrome 1
ii. Polymicrogyria without clefts or calcifications classified by location	More than 40 genes associated with the following groups of disorders: • mTORopathies • Tubulinopathies • Alpha dystroglycanopathies • Laminopathies • Congenital disorders of glycosylation
iii. Syndromes with polymicrogyria	• *PIK3R2* - Megalencephaly-polymicrogyria-polydactyly-hydrocephalus syndrome (MPPH) • *PIK3R2* - Megalencephaly-capillary malformation syndrome (MCAP) • *KIAA1279* - Goldberg-Shprintzen megacolon syndrome • *INPP5E, TMEM216,* & more than 30 other genes - Joubert syndrome • *RAB3GAP1* – Micro syndrome • *COL3A1* - Polymicrogyria with or without vascular-type Ehlers-Danlos syndrome
iv. Polymicrogyria due to chromosomal aberration	• 22q11.2 deletion- DiGeorge syndrome • Deletion of 1p36,4q21, 6q26, 13q3, 18p11, and 21q2 • Duplication of 2p13

6. Focal cortical dysplasia (FCD)

FCD type I and Type III are due to abnormal post-migrational organization and FCD type II is due to abnormal proliferation and differentiation of neuronal glial cells. See Table 6.

Clinical presentation

Patients usually present with partial epilepsy which may generalize and typically becomes clinically apparent during the first decade of life or sometimes as early as in the early neonatal period. The epilepsy is often refractory to medication.

MRI findings

Focal cortical thickening and blurring of the cortical-white matter junction with abnormal signal intensity can be identified extending from the cortical-white matter junction to the superolateral margin of the lateral ventricular surface (Figure 3). The signal intensity of this abnormality varies with the age of the patient. In neonates and infants, it is bright on T1-weighted images and dark on T2-weighted images. In late childhood and adults, it is seen as T2 hyperintensity. Single photon emission computed tomography (SPECT) or positron emission tomography (PET) are sometimes needed for identifying the anomaly as the dysplasia may not be identified in standard MRI images.

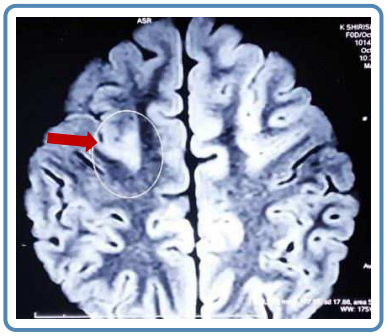

Figure 3 MRI brain showing focal cortical dysplasia type 1b in the frontoparietal region.

Table 6 Classification and genetic basis of focal cortical dysplasia.

Focal cortical dysplasia (FCD)		Associated Genes and Conditions
i. Focal cortical dysplasia type I	FCD Ia - Focal cortical dysplasia with abnormal radial cortical lamination	-
	FCD Ib - Focal cortical dysplasia with abnormal tangential cortical lamination	-
	FCD Ic - Focal cortical dysplasia with abnormal radial and tangential cortical lamination	-
ii. Focal cortical dysplasia type II	FCD IIA - Focal cortical dysplasia with dysmorphic neurons	*MTOR, DEPDC5, PIK3CA*
	FCD IIB -Taylor type- Focal cortical dysplasia with dysmorphic neurons and balloon cells	*MTOR*, *DEPDC5*, *NPRL3*
iii. Focal cortical dysplasia type III	FCD IIIa - Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis	-
	FCD IIIb - Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor	-
	FCD IIIc - Cortical lamination abnormalities adjacent to vascular malformation	-
	FCD IIId - Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis	-

7. Dysgyria

Dysgyria is described as variable cortical thickness with an abnormal gyral pattern characterized by abnormalities in depth or orientation of sulci and does not meet the classic features of any of the above mentioned main cortical malformations.

Approach to cerebral cortical malformations (Oegema et al., 2020)

The following clinical and investigative approach is recommended for evaluation of patients with cerebral cortical malformations and neuronal migration disorders.

i. History (including family history):

- Prenatal history of maternal fever or rash to rule out infectious etiology; maternal comorbidities like uncontrolled hypothyroid and diabetes; ultrasound abnormalities; reduced fetal movements to rule out dystroglycanopathies.
- Detailed three-generation family pedigree, history of consanguinity and family history of congenital anomalies, global developmental delay and seizures.

ii. Clinical assessment; common clinical findings include:

- **Symptoms -** Seizures/epilepsy; feeding difficulties; breathing difficulties; global developmental delay; visual defects
- **Signs -** Microcephaly or macrocephaly; dysmorphic features; congenital malformations; hypotonia or hypertonia

iii. Genetic evaluation:

The genetic test to be done would depend on the clinical diagnosis. Whole exome sequencing (preferably patient-parents trio) would be preferred for evaluation of monogenic conditions, while chromosomal microarray would help detect chromosomal copy number variations. For clinically suspected specific microdeletion syndromes such as Miller-Dieker syndrome, targeted testing through fluorescence in situ hybridization (FISH) or multiplex

ligation-dependent probe amplification (MLPA) may be done.

iv. Additional tests (as applicable): Ophthalmological evaluation; hearing evaluation; serum creatine phosphokinase and electromyography; metabolic testing

v. Management: There is no disease-specific treatment available at present for the cortical malformations and neuronal migration disorders. Management includes symptomatic and supportive care including physiotherapy, occupational therapy, and antiseizures medication. Surgical intervention is often considered for patients with refractory epilepsy as in cases with focal cortical dysplasia.

Conclusion

Malformations of cortical development have been increasingly recognized by MRI Brain. With the availability of next-generation sequencing based molecular genetic testing over the last few years, the exact etiological diagnosis of cortical malformations is being made in more and more cases, and novel associated genes are being identified. Identification of the exact disease-causing mutation in the index child helps in appropriate counseling of the family, ascertaining the pattern of inheritance, the recurrence risk in future offspring and in definitive prenatal testing of their subsequent conceptions. The exact understanding of molecular pathways and causative genes of normal cerebral cortical development may facilitate early therapeutic options/interventions in the near future.

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