Introduction

The cerebral cortex is a sheet of neural tissue that is outer most to the cerebrum of the mammalian brain. This is the gray area of the brain hence the name. This is caused by the nerves that lack insulation. It plays a key role in memory, attention, perceptual awareness, thoughts, language, and consciousness. It is constituted of up to six horizontal layers, each of which has a different composition in terms of neurons and connectivity. The human cerebral cortex is 2–4mm (0.08–0.16 inches) thick ***(Kandel et al., 2000)***

Stages of Development:

The development of human cerebral cortex can be divided into three overlapping stages.

The first stage:

The stem cells proliferate into neuro-blasts or glial cells deep in the forebrain, in the ventricular and subventricular zones lining the cerebral cavity ***(Rakic et al., 1988; Jansen and Andermann 2005).***

The second stage:

After their final mitotic division, cortical neurones migrate away from their place of origin in a radial or tangential fashion towards the pial surface, where each successive generation passes one another and settles in an inside-out pattern within the cortical plate ***(Dobyns et al., 1996).***

The third stage:

Represents cortical organisation within six layers associated with synaptogenesis and apoptosis. This is a dynamic process and more than one stage may occur simultaneously during several gestational weeks. In humans, the proliferation stage ranges from weeks 5–6 to weeks 16–20 of gestation, migration from weeks 6–7 to weeks 20–24 of gestation and organisation from week 16 of gestation until well into postnatal life ***(Barkovich et al., 2001).***

Classification of Developmental Brain Malformations: (Barkovich et al., 2005; 2012)

I. Malformations due to abnormal neuronal and glial proliferation or apoptosis

A. Decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis-abnormalities of brain size

1. Microcephaly with normal to thin cortex.
2. Microlissencephaly (extreme microcephaly with thick cortex).
3. Microcephaly with extensive PMG.
4. Macrocephalies

B. Abnormal proliferation (abnormal cell types)

1. Non neoplastic

    a. Cortical hamartomas of tuberous sclerosis

    b. Cortical dysplasia with balloon cells

    c. Hemimegalencephaly

2. Neoplastic (associated with disordered cortex)

    a. Dysembryoplastic neuroepithelial tumor

    b. Ganglioglioma

    c. Gangliocytoma

II. Malformations due to abnormal neuronal migration

A. Lissencephaly/subcortical band heterotopia spectrum

B. Cobblestone complex/congenital muscular dystrophy syndromes

C. Heterotopia

1. Subependymal (periventricular)
2. Subcortical (other than band heterotopia)
3. Marginal glioneuronal

III. Malformations due to abnormal cortical organization (including late neuronal migration)

A. PMG and schizencephaly

1. Bilateral PMG syndromes
2. Schizencephaly (PMG with clefts)
3. PMG or schizencephaly as part of multiple congenital anomaly/mental retardation syndromes

B. Cortical dysplasia without balloon cells

C. Microdysgenesis

IV. Malformations of cortical development, not otherwise classified

A. Malformations secondary to inborn errors of metabolism

1. Mitochondrial and pyruvate metabolic disorders

2. Peroxisomal disorders

B. Other unclassified malformations

1. Sublobar dysplasia

2. Others

Aim of the Work

Correlation of polymicrogyria with clinical, radiological and cytogenetic findings.

Provide a systematic clinical approach to the identification of the etiology of PMG and subsequently proper genetic counseling.

Delineation of new guidelines for approaching polymicrogyria patients.

Polymicrogyria (PMG)

Definition

PMG is a malformation of cortical development in which the process of normal cortical development is disturbed late in the stage of neuronal migration or early in the stage of cortical organization; thus, it is considered a disorder of neuronal organization ***(Barkovich et al., 2005).*** As a result of these disturbances to the developmental process, the deeper layers of the cerebral cortex develop abnormally and multiple small gyri form within the cortex ***(Norman et al., 1995).*** It is a relatively common malformation with a rate of at least 0.01 per 1,000 live births in a population based monitoring program (Metropolitan Atlanta Congenital Defects Program, Birth Defects and Genetic Diseases Branch, Centers for Disease Control and Prevention, Atlanta). The frequency is probably higher as affected individuals were ascertained only if the diagnosis was recorded in hospital records during the first six years of life, likely underestimating the true incidence. Further, the diagnosis of PMG was often missed because of limitations in imaging techniques and it was often confounded with pachygyria and even with schizencephalic clefts. However, the diagnosis of PMG can be made confidentialy if irregularity of the cortical–white matter junction is detected by thin section magnetic resonance imaging (MRI) ***(Raybaud et al., 1998; Jansen and Andermann, 2005).***

PMG has a wide range of histologic appearances, all having in common a derangement of the normal six-layered lamination of the cortex, an associated derangement of sulcation, and fusion of the molecular layer across sulci. In areas of PMG, no normal sulci are seen ***(Englund et al., 2005)*.**

PMG affects variable portions of the cerebral cortex: it may be focal, multifocal, or diffuse; it may be unilateral, bilateral, and asymmetrical; or bilateral and symmetrical ***(Barkovich, 2010).*** Several subtypes of PMG have been recognized based on differences in topography, such as frontal, perisylvian, mesial parieto-occipital, and multilobar forms ***(Kuzniecky et al., 1993; Guerrini et al., 2000; Barkovich et al., 1999).*** Several other types including posterior PMG ***(Ferrie et al., 1995),*** parasagittal PMG, and diffuse (or perisylvian) PMG with abnormal white matter, as well as frontal or posterior predominate PMG with PNH ***(Wieck et al., 2005)*.** The most common location (in 60–70% of cases ***(Leventer, 2007)*** is around the sylvian fissure, particularly the posterior aspect of the fissure; however, any part of the cerebral cortex, including the frontal, occipital, and temporal lobes, can be affected ***(Guerrini et al., 1992; Hayashi et al., 2002).***

The imaging appearance of PMG is variable. This variability is most likely a result of three factors:

1. Amount of gray matter–white matter contrast, (thickness of the slices).
2. The stage of maturity/ myelination of the brain at the time of the imaging study.
3. The type of PMG ***(Barkovich, 2010).***

Patients with PMG may have a wide variety of clinical presentations. The severity of the clinical presentation depends mostly upon the extent of cortical involvement and may also depend upon the type of PMG and the presence or absence of associated anomalies. Bilateral involvement and involvement of more than half of a single hemisphere are poor prognostic indicators, predicting moderate to severe developmental delay and epilepsy ***(Barkovich et al., 1992; Barkovich, 2010)*** that may be intractable to AEDs and significant motor dysfunction ranging from hemiparesis or quadriparesis ***(Barkovich et al., 1994; Dobyns et al., 2008).***

PMG may be an isolated brain malformation but most commonly associated with other brain malformations such as agenesis or hypogenesis of corpus callosum, cerebellar hypoplasia ***(Barkovichet al., 2007),*** periventricular nodular heterotopia ***(Wieck et al., 2005),*** and subcortical heterotopia ***(Barkovich, 2000).*** Affected patients may be microcephalic, normocephalic, or macrocephalic ***(Dobyns et al., 2008).***

Microscopically, two types of PMG are recognized: a simplified four layered form and an unlayered form. In unlayered PMG, the external molecular layer is continuous and does not follow the profile of the convolutions. The underlying neurones have radial or vertical distribution but no laminar organization. The unlayered form reflects an early disruption of normal neuronal migration with subsequent disordered cortical

organization. The four layered PMG has characteristics suggestive of a late disruption of neuronal migration or a disruption of cortical organization, as demonstrated in placental perfusion failure occurring between 20 and 24 weeks of gestation. The two types of PMG may co-occur in contiguous cortical areas, indicating that they may comprise a continuum rather than distinct malformations ***(Guerrini et al., 1996; Jansen and Andermann, 2005).***

Etiology of polymicrogyria

The etiology of PMG is unclear however, it could stem from both genetic and non-genetic (infectious, vascular and toxic) etiologies.

A) Non-genetic

The most common non genetic (environmental) causes are

1. Congenital infection (most commonly cytomegalovirus, toxoplasmosis, syphilis, and varicella-zoster)
2. Placental perfusion failure often related to twinning,
3. Maternal exposure to warfarin in the second trimester ethanol, retinoic acids, methylmercury.
4. Radiation (and point to a period of risk between 13 and 24 weeks gestation.

(Norman, 1980; Barth and van der Harten, 1985; Hayward et al., 1991; Barth, 1992; Barkovich and Lindan, 1994; Iannetti et al., 1998; Golden, 2001; Curry et al., 2005).

PMG can occur as an isolated finding with no other systemic involvement called isolated PMG syndromes (table 1, 2) or as part of a syndrome with multisystem involvement (table 3).

Table (1): Nonsyndromic Mendelian Disorders with Polymicrogyria: Clinical Findings

Syndrome	Genetic Basis	Clinical Features	Reference
Bilateral frontal polymicrogyria (BFP)	Presumed AR	Cognitive and motor delay, spastic quadriparesis and epilepsy	*(Guerrini et al., 2000)*
Bilateral frontoparietal polymicrogyria (BFPP)	AR	Severe cognitive and motor delay, seizures, dysconjugate gaze and cerebellar dysfunction	*(Piao et al., 2002, Chang et al., 2003, Piao et al., 2005)*
Bilateral perisylvian polymicrogyria (BPP)	AD, AR, X-linked	Pseudobulbar signs, cognitive impairment, epilepsy, some with arthrogryposis and/or lower motor neuron disease	*(Gropman et al., 1997, Guerreiro et al., 2000, Villard et al., 2002, Jansen et al., 2005, Clark et al., 2006)*
Bilateral parasagittal parieto-occipital polymicrogyria (BPPP)	-	Partial seizures and some with intellectual disability	*(Guerrini et al., 1997)*
Bilateral generalized polymicrogyria (BGP)	Presumed AR	Cognitive and motor delay of variable severity and seizures	*(Chang et al., 2004)*

Adapted from ***Chang et al. (2004)***

Table (2): Non syndromic Mendelian Disorders with PMG: Radiologic Findings

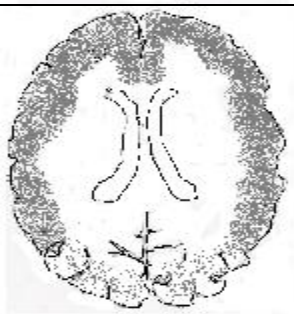
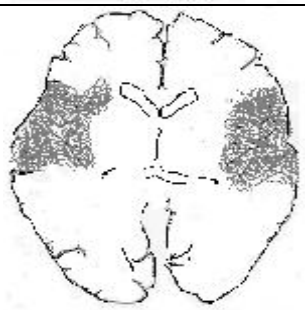
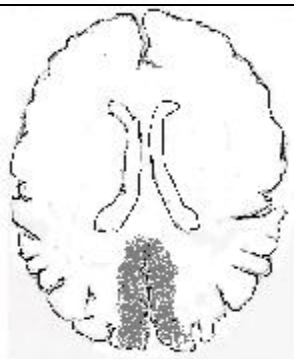
Syndrome	Affected Regions	Radiologic Findings
Bilateral frontal polymicrogyria (BFP)		Symmetric PMG extending from frontal poles posteriorly to precentral gyrus and inferiorly to frontal operculum
Bilateral frontoparietal polymicrogyria (BFPP)		Symmetric generalized PMG with decreasing anterior-posterior gradient, most prominent in frontoparietal cortex
Bilateral perisylvian polymicrogyria (BPP)		PMG in the perisylvian region, usually bilateral
Bilateral parasagittal parieto-occipital polymicrogyria (BPPP)		Bilateral PMG in parasagittal and mesial aspects of parieto-occipital cortex

Table (3): Syndromic Disorders with PMG.

Disorders	OMIM	Inheritance	Gene	Clinical features	References
Chromosomal					
22q11.2 DELETION SYNDROME DiGeorge syndrome (DGS)	**#188400**		TBX1 22q11.2	➢ Neonatal hypocalcemia and hypoplasia of the parathyroid glands ➢ Recurrent infection ➢ Cardiac malformations are seen in particular affecting the outflow tract ➢ Micrognathia, low set ears are typically. Telecanthus with short palpebral fissures, short philtrum is and the small mouth submucous or overt palatal clefting. ➢ Short stature ➢ Mild to moderate learning difficulties ➢ Renal dysplasia, hydronephrosis and unilateral renal agenesis. ➢ Anterior segment embryogenesis ➢ PMG	*Goodship et al., 1995* *Bassett et al., 2005* *Kujat et al., 2006* *Robin et al., 2006* *Binenbaum et al., 2008*
1P36 Microdeletion				➢ Distinctive facial anomalies	*Heilstedt et al.,*

Disorders	OMIM	Inheritance	Gene	Clinical features	References
syndrome				(pointed chin, flat nose and low set ears) ➢ Cardiovascular malformations (atrial septal defect, patent ductus arteriosus and tetralogy of Fallot). ➢ Central nervous system (CNS) cerebellar hypoplasia with dysplastic foliar pattern and heterotopia ➢ Autistic-like behaviors, SNHL , Blind, retinal COL, ESO, astigmatism, Nystagmus, large angle exotropia and hyperopia ➢ Horeshoe kidney ➢ Kyphosis, scoliosis, GR, Finger contractures and clinodactyly	*2003 Battaglia, 2005 Dobyns et al., 2008*
Duplication 2p16.1–p23.				➢ Normal head size and mental retardation	*Dobyns et al., 2008*

Disorders	OMIM	Inheritance	Gene	Clinical features	References
				➢ Cleft palate	
Deletion 4q21.21–q22.1.				➢ Typical features including macrocephaly, frontal bossing, small nose, flat nasalbridge, malformed ears and small jaw. ➢ Partial ACC with a short corpus callosum and small areas of PMG in the posterior perisylvian regions. ➢ Polycystic kidney disease and Infantile hepatocellular carcinoma	*Terada et al., 2001* *Velinov et al., 2005*
Deletion 6q26-qter				➢ Mental retardation and facial dysmorphism (hypertelorism, prominent nasal bridge, epicanthal, folds ear anomalies and small jaw). ➢ Seizures and short neck ➢ Retinal abnormalities ➢ Heart malformations	*Eash et al., 2005* *Bertini et al., 2006*

Disorders	OMIM	Inheritance	Gene	Clinical features	References
				➢ Genital hypoplasia including cryptorchidism ➢ The retinal changes were variously described as abnormal retinal vessels, retinal pits or macular disorders such as hypopigmentation, hypoplasia or degeneration.	
Deletion 21q22.1				➢ Mild mental retardation ➢ Holoprosencephaly ➢ Asmall telomeric deletion of 21q22.3 had normal intelligence ➢ Brain imaging in three patients was reported to show PMG, ‘‘pachygyria,’’ thin white matter, hypoplasia of the corpus callosum and variable hypoplasia of the cerebellum.	*Roland et al., 1990* *Muenke et al., 1995* *Yao et al., 2006*