

Polymicrogyria

Author: Doctor Laurent VILLARD¹

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¹Génétique médicale et développement, INSERM U491, Faculté de Médecine de la Timone, 27 Boulevard Jean Moulin, 13385 Marseille Cedex 5, France. laurent.villard@medecine.univ-mrs.fr

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Abstract

Polymicrogyria (PMG) is a cerebral cortical malformation characterized by excessive cortical folding and by shallow sulci. Microscopic examination reveals abnormal cortical layering. Topographic distribution of PMG is variable, but bilateral symmetrical perisylvian PMG (BPP) is the most frequent form. PMG is manifested by mild mental retardation, epilepsy, and pseudobulbar palsy, which causes difficulties with speech learning and feeding. The severity of PMG is highly dependent on the location and size of the affected area. Most cases are sporadic, but familial forms have been reported, and they appear to follow all the possible inheritance patterns. Two genetic forms of polymicrogyria have been identified: bilateral perisylvian on chromosome X (Xq28) and bilateral frontoparietal on chromosome 16, which is caused by mutations in the GPR56 gene. There are also non-genetic forms of PMG, which are caused by cytomegalovirus intrauterine infections and defects in placenta perfusion. The incidence of the different PMG forms is unknown, but the frequency of cortical dysplasia in general is estimated to be 1 in 2500 newborns. No treatment is available but the seizures can be treated using anti-epileptic drugs.

Keywords

Polymicrogyria, cortex, brain, neuronal migration, cortical cytoarchitecture, GPR56 gene.

Disease name and synonyms

- PMG, Polymicrogyria
- BPP, Bilateral perisylvian polymicrogyria (MIM 300388)
- BFP, Bilateral frontoparietal polymicrogyria (MIM 606854)
- PMGX, Polymicrogyria, X-linked (MIM 300388)

- CBPS, Perisylvian syndrome, congenital bilateral (MIM 300388)

Diagnosis criteria / definition

Polymicrogyria (PMG) is a cerebral cortical malformation characterized by excessive cortical folding, which results into irregular appearance of the brain surface. The cortex is thicker in appearance, due to the packing of this excessive

number of convolutions. In most PMG patients, microscopic examination reveals a simplified cortical cytoarchitecture comprised of either 4 layers or no layer (Crome 1952, Ferrer 1984). When 4 layers are present, they are numbered from I to IV, but they do not correspond to layers I-IV of a normal cortex since their cellular content is totally different. Both PMG types (layered and unlayered) are often accompanied by additional malformations: nodular heterotopias, abnormal myelination of the white matter, enlarged lateral ventricles, corpus callosum agenesis and cerebellar hypoplasia. Layered and unlayered PMG can be both found in the same individual, thus suggesting that they belong to the same malformation spectrum.

Differential diagnosis

[Zellweger syndrome](#) (MIM 214100) is often accompanied by polymicrogyria but includes additional clinical signs which are not found in isolated PMG patients. In addition, the diagnosis of Zellweger syndrome can be supported by biochemical tests, as opposed to PMG.

Patients with [Fukuyama muscular dystrophy](#) (FCMD) (MIM 253800) can also present PMG. The gene causing FCMD is known and the patients present a muscular dystrophy, which is not observed in isolated PMG patients.

Frequency

Focal cortical dysplasia and polymicrogyria are the best known of the anomalies of late cortical development. The frequency of these diseases is estimated to be 1 in 2500 newborns. This estimation is based on several studies which showed that epilepsy has a frequency of 0,5%. Among these cases, 20% are intractable and among these intractable cases, 40% of children (and 25% of adults) have cortical dysplasia (Kuzniecky and Jackson, 1995; Meencke and Veith, 1992; Vinters *et al.* 1992).

Clinical description

MRI of the brain shows evidence of an abnormal gyral pattern, an irregular brain surface, a large number of small gyri (2-5 mm) and shallow sulci. The junction between the cortex and the white matter is irregular. When the perisylvian region is affected, the sylvian fissures are abnormally oriented. The cortex appears to be abnormally large (although this is probably caused by the excess of gyri and not by an enlargement of the cortex *per se*) with a size of approximately 5-10 mm instead of the 2,5-4 mm which are usually observed.

Several types of PMG are described depending on their topography. The most common forms are frontal bilateral, bilateral perisylvian and

bilateral meso-occipital (Barkovich *et al.* 1999; Guerrini *et al.* 1997, 1998, 2000; Kuzniecky *et al.* 1993).

Affected individuals present a variable phenotype which is largely dependent on the location and size of the affected area. The clinical spectrum thus ranges from individuals with severe neonatal encephalopathies to normal adults with very specific cognitive defects caused by a limited PMG focus, which is only detected on pathological brain studies (Galaburda *et al.* 1985). In the case of BPP, the patients have speech and articulation problems. Mental retardation is usually present together with epilepsy (Barkovich *et al.* 1999). The seizures begin at about 4-12 years of age and they are not controlled in approximately 65% of the patients. A small number of patients have partial seizures. The most frequent seizure types are atypical absences, tonic or atonic drop attacks and tonic-clonic seizures (Guerrini and Carrozzo 2001).

Management including treatment

No treatment is available but the seizures can be treated using anti-epileptic drugs.

Etiology

The pathogenesis of PMG is still mysterious. It was initially considered to be a neuronal migration disorder because the cortex of the patients was thick and the cortical lamination was disturbed. However, further studies concluded that PMG was caused by an injury or an abnormal process, which takes place after the migration of neurons, when the last wave (layer II) of cortical neurons reaches its destination.

Extrinsic causes to PMG comprise cytomegalovirus intrauterine infections (Barkovich and Lindan, 1994; Ianetti *et al.* 1998) and defects in placenta perfusion. A number of observations led to the conclusion that PMG was caused by events occurring between the 12th and the 24th week of gestation.

Several papers have reported familial recurrences for PMG (Hilburger *et al.* 1993; Ferrie *et al.* 1995; Bartolomei *et al.* 1999; Borgatti *et al.* 1999) and, in one case, 12 families with multiple cases of BPP have been described (Guerreiro *et al.* 2000).

Following these descriptions, two PMG loci have been localized in the human genome. The locus for bilateral perisylvian PMG has been localized to chromosome Xq28 (Villard *et al.* 2002), and the locus for bilateral frontoparietal PMG to chromosome 16 (Piao *et al.* 2002). It thus appears that a number of PMG cases have a genetic basis, but that PMG is genetically

heterogeneous. In addition, a number of patients with deletion syndromes (del22q11 for instance) are sometimes affected by PMG (Ghariani *et al.* 2002). The chromosome 16 gene was recently identified (Piao *et al.* 2004). It encodes an orphan G protein-coupled receptor called GPR56. Mutations were found in 22 radiographically and clinically confirmed bilateral frontoparietal polymicrogyria patients from 12 pedigrees (Piao *et al.* 2004). How GPR56 dysfunction leads to the presence of polymicrogyria is currently not known.

Studies using freeze lesions in rats to induce microgyria (the closest animal model to human polymicrogyria) show that the abnormal cortical areas are characterized by a decreased sensitivity of gamma-aminobutyric acid A (GABA-A) receptors (Hablitz and DeFazio, 2000). In this model, hyperexcitability is present in the cortical areas adjacent to microgyri and several observations suggest that cellular differentiation could be delayed in these microgyric brains (Jacobs *et al.* 1999). Other studies show an increased number of postsynaptic glutamate receptors.

Diagnostic methods

PMG can be evidenced using tomodensitometry but MRI is much more powerful to reveal its morphology, topography and associated malformations. It is recommended to perform acquisition of thin-section (3 or 4-mm) sagittal images through the entire brain (Barkovich *et al.* 1999), since different angulations of the axial images can lead to misinterpretation of the actual site of the lesion.

Genetic counseling

Given the possible inheritance modes of PMG, a minimum recurrence risk of 25% should be given to parents. If X-linked inheritance is assumed, a recurrence risk up to 50% can even be reached in the case of a male offspring. Screening for a GPR56 mutation can be proposed in the cases of bilateral frontoparietal polymicrogyria.

Antenatal diagnosis

In the presence of a documented GPR56 mutation in a first child, prenatal diagnosis can be proposed for future pregnancies. No gene responsible for the other types of PMG has been identified.

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