

Morphological neuroimaging of malformations of cortical development

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ABSTRACT – Malformations of cortical development are classified on the basis of imaging features and stages of cortical development. They are grouped by causes of the malformation: abnormal glial and neuronal proliferation, abnormal neuronal migration and abnormal cortical organisation. Focal or multifocal and generalised forms are recognised in each of these groups. In the first group, generalised forms include microlissencephalies. Among focal-multifocal abnormalities, neoplastic forms include ganglioglioma and dysembryoplastic neuroepithelial tumours. Non-neoplastic forms include focal cortical dysplasia and tuberous sclerosis. Malformations due to abnormal migration include lissencephalies; cortical heterotopias are recognised in both focal and generalised forms. Abnormal cortical organisation includes polymicrogyria, in generalised or focal forms, and schizencephalies among the focal forms.

KEY WORDS: magnetic resonance imaging, brain development, cortex, dysplasia, migration

Malformations of cortical development (MCD) were classified by Barkovich et al. according to the appearance of their clinical and morphological features on MRI studies [1]. This proposal adopts the same classification with several modifications.

Malformations of cortical development result from abnormalities occurring in three different steps of brain development: neuronal and glial proliferation, migration and cortical organisation. Focal and multifocal forms are recognised in each group.

Focal cortical dysplasias will not be treated in this study. For a detailed discussion of the electro-clinical characteristics and available genetic data, see also the paper by Guerrini *et al.* in this issue.

Abnormal glial and neuronal proliferation

● Generalised forms:

microlissencephaly

● Focal and multifocal forms

Non-neoplastic

- Focal cortical dysplasias
- Tuberous sclerosis
- Hemimegalencephaly

Neoplastic

- Ganglioglioma
- Dysembryoplastic neuroepithelial tumor (DNT)

Generalised forms

Microlissencephaly

The main feature of microlissencephaly is severe microcephaly, which is always observed in this group. An ab-

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normal gyral pattern with few gyri and shallow sulci is also observed. Thickness of the cortex is almost always normal. Signal intensity from cerebral white matter may be normal or consistent with delayed myelination.

Barkovich *et al.* describes five different subgroups of microcephalies based on MRI features and clinical course. In these patients, microcephaly and poor brain development is supposed to be caused by reduced proliferation of neurons in the germinal zones [2].

Focal and multifocal non neoplastic forms

Tuberous sclerosis

Tuberous sclerosis (TS) is an autosomal dominant genetic disorder that involves multiple organs. Mutation of genes TSC1 and TSC2, respectively localised on chromosomes 9q34 and 16p13.3, have been identified [3, 4]. Neuro-radiological features of TS include subependymal hamartomas, cortical and subcortical hamartomas, linear white matter abnormalities and giant cell subependymal astrocytomas.

Subependymal hamartomas appear on imaging studies as nodules bulging into the lateral ventricles; they are often calcified and therefore easily recognised on CT [5]. On MRI studies of the neonatal brain, they are hyperintense on T1-w.i. and hypointense on T2-w.i. with respect to unmyelinated white matter. As the brain myelinates, subependymal hamartomas become isointense with the white matter on T1-w.i.; hypointensity on T2-w.i. is more evident in calcified nodules [6].

Cortical and subcortical hamartomas or tubers involve the cortex and subcortical white matter, often causing enlargement of the affected convolutions. Tubers are less frequently found in cerebellar hemispheres (*figure 1*). On MRI, the tubers appear as multifocal hyperintensities on T2-w.i. Signal abnormalities are mainly, though not consistently, located in the white matter and tend to spare the cortex [7].

The MRI appearance of tubers changes with age. In neonates they are hyperintense on T1- and hypointense on T2-w.i. as compared with unmyelinated white matter. As the white matter myelinates, T1-hyperintensity of the tubers decreases, and on T2-w.i, tubers become hyperintense [6]. Cortical tubers may be calcified. Calcifications tend to develop with age [5]. Linear white matter abnormalities, with signal characteristics similar to those observed in tubers, are observed almost constantly. They represent bands of unmyelinated fibers, glial cells and abnormal neurons along the pathway of the linear glial-neuronal unit [8].

The features of giant cell astrocytomas may be identical to those of subependymal hamartomas, with the difference that they typically develop close to the foramina of Monro (*figure 1*), often causing obstructive hydrocephalus. Contrast enhancement of small lesions close to the foramina of Monro is considered a marker of tendency to enlarge [8].

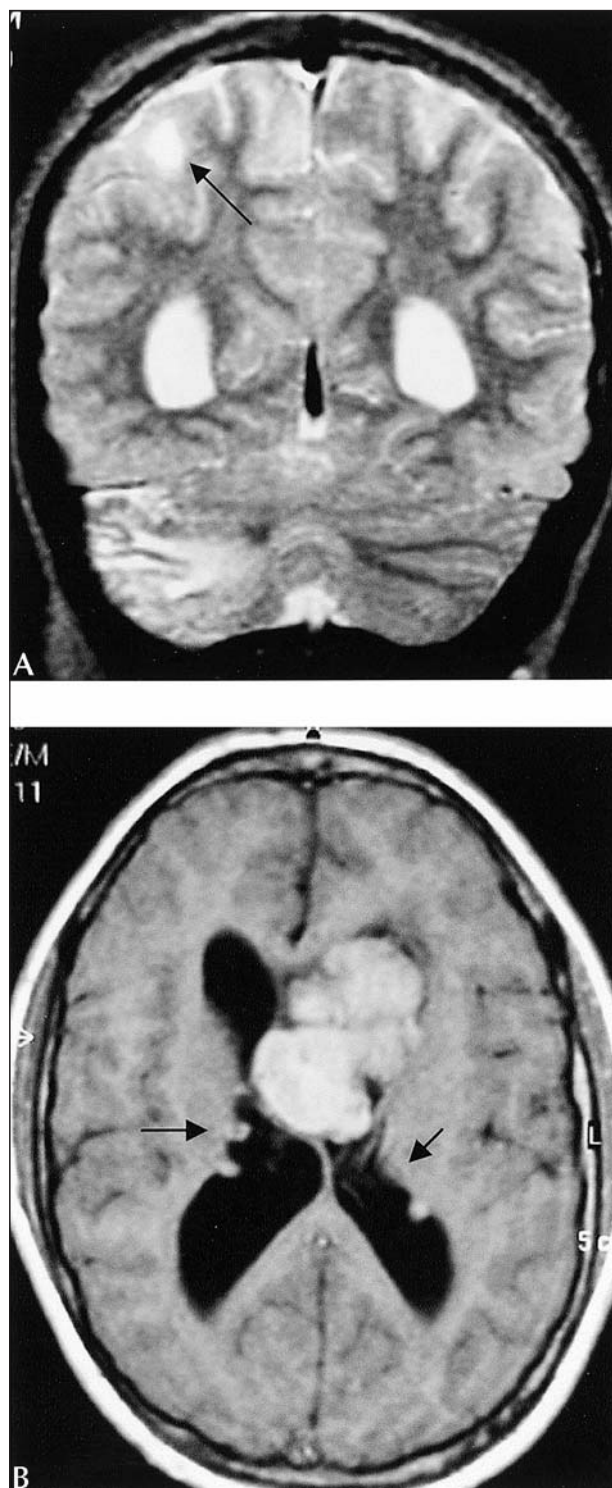


Figure 1. Tuberous sclerosis A: coronal T2-w.i. image demonstrating a cerebellar tuber in the right hemisphere. A smaller cortical tuber is also seen in the superior parietal area (arrow). B: transversal post-contrast T1-w.i. demonstrates a giant cell astrocytoma within the left lateral ventricle. Subependymal nodules bulge within the lateral ventricles (arrow).

Subependymal hamartomas, tubers and linear abnormalities derive from dysplastic stem cells in the germinal zone that give origin to dysplastic glial cells, neurons and to cells having characteristics of both. Abnormal differentiation of dysplastic cells results in accumulation of disorganised collections of dysplastic cells in the subependymal and cortical regions, as well as along the linear path between them [7, 9].

The cellular composition of hamartomas and linear abnormalities is the same as that of focal cortical dysplasia with balloon cells [10, 11].

Cortical tubers may be solitary. Their MRI picture may be similar to that of Taylor type focal cortical dysplasia (FCD). In TS, the affected convolutions are usually more enlarged than in FCD. In FCD, the junction between the cortex and the white matter is usually blurred, while in tubers, T2 hyperintensity of the white matter is well delimited and tends to spare the cortex. Calcifications are rare in FCD, and are more frequently seen in tubers. Contrast enhancement is rare in tubers, and is usually absent in FCD.

The association of solitary tubers with linear abnormalities must also be distinguished from focal transmantle dysplasia. This form was described by Barkovich [10] as identifying a form of cortical dysplasia characterised by extension from the lateral ventricles to the surface of the brain. In the past, the same picture was referred to as '*forme fruste* of TS' [11]. In introducing the definition of focal transmantle dysplasia, Barkovich proposed to limit the term '*forme fruste*' to the cases that also have non-neurological manifestations of TS or relatives with TS [10, 12].

Solitary tubers must also be distinguished from tumours. When present, the MRI features of tubers (enlarged convolution, subcortical hyperintensity and normal signal intensity of the cortex) are considered peculiar to tubers and, together with the absence of perifocal edema, are helpful in differential diagnosis.

Hemimegalencephaly

Hemimegalencephaly, or unilateral megalencephaly, is characterised by a disproportionally enlarged hemisphere. The affected hemisphere has different malformative features involving the cortex and the white matter. Cortical abnormalities consist of abnormal lamination, cortical heterotopia and/or focal pachygyria. Intracortical calcification may also be observed.

White matter is abnormally increased, with abnormal myelination and extensive gliosis resulting in hyperintensity on T2-w.i. Cortical and white matter abnormalities may involve the ipsilateral cerebellar hemisphere [13]. Hemimegalencephaly may be associated with ipsilateral, increased somatic growth and may occur in association with neurocutaneous syndromes such as nevus linearis sebaceus, Proteus syndrome and hypomelanosis of Ito [14-16]. Reduction of hemispheric size after repeated status epilepticus has been reported [17]. Hemispherectomy

is usually indicated [18]. However, MRI studies of candidates for hemispherectomy must be very carefully examined for cortical and white matter abnormalities in the healthy hemisphere.

Focal and multifocal neoplastic forms

Ganglioglioma and dysembryoplastic neuroepithelial tumor (DNT).

The MRI features of gangliogliomas may be variable and non-specific. Hyperintensity on T2-w.i., lack or absence of perifocal edema, cysts, and contrast enhancement of the solid portion are common to low grade and pilocytic astrocytomas [19]. Superficial enhancement, sometimes extending to the leptomeninges, may also suggest the diagnosis of pleomorphic xanthoastrocytoma [20]. Calcifications are characteristic of oligodendrogliomas, but are

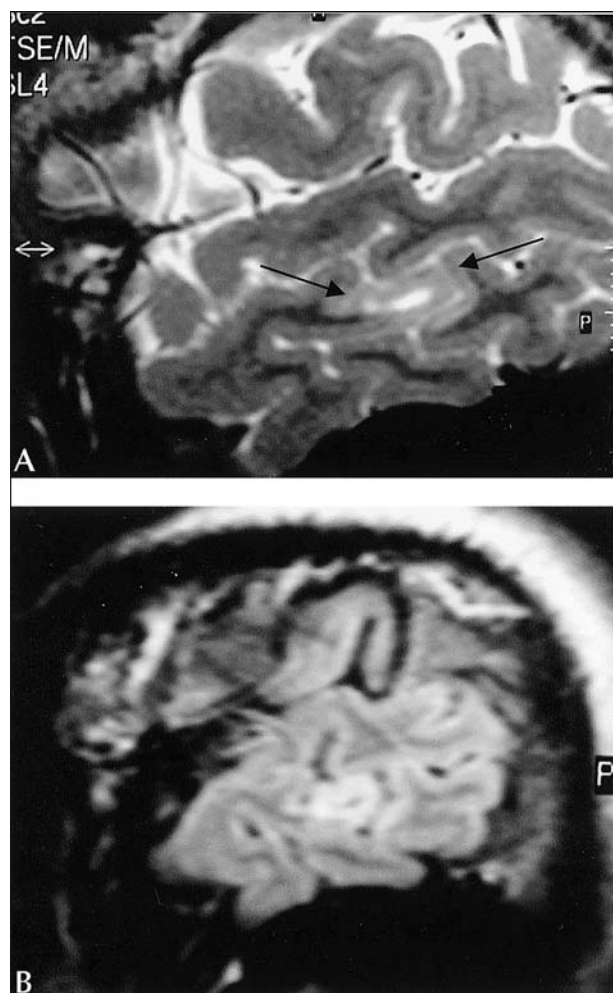


Figure 2. Ganglioglioma of the middle temporal convolution. A: sagittal T2-w.i. the lesion involves the cortex and the far peripheral white matter (arrows). B: Sagittal FLAIR section differentiates the hypointensity of the cystic components from the hyperintensity of the cortical component.

frequently observed in gangliogliomas and in DNT. Gangliogliomas may occur anywhere in the central nervous system, but more frequently develop in the temporal lobes (figure 2). Superficial locations can cause thickening of the cortex. Features of cortical dysplasia may be observed at the margins of gangliogliomas, i.e. blurring of the cortical-white matter interface and mild T2-hyperintensity of the white matter. These features suggest that gangliogliomas may arise from a disorder of stem cell development, thus justifying their classification among the developmental cortical abnormalities [11, 12].

Many of the MRI features of ganglioglioma are shared with DNT. Cortical location, particularly in the temporal lobes, is even more frequent with DNT than ganglioglioma. T2-hyperintensity is similar in DNT and in ganglioglioma, as well as the association with features of cortical dysplasia. Contrast enhancement is more rare in DNT than in ganglioglioma [21]. Association of temporal locations with ipsilateral mesial temporal sclerosis may be observed in the MRI pictures of the so-called dual pathology.

Abnormal neuronal migration

Generalised forms

- *Lissencephaly (type 1 agyria-pachygyria)*
 - Chromosome 17-linked
 - X-linked
- *Cobblestone (type 2)*
 - (Fukuyama; Walker – Warburg; MEB)
- *Heterotopia*
 - Subependymal
 - Subcortical (band heterotopia)

Focal and multifocal forms

- *Partial lissencephaly*
- *Nodular heterotopia (subependymal, subcortical)*
- *Nodular heterotopia with abnormal cortical organisation*

Lissencephaly

The smooth surface of the brain with absent or poor sulcation is the main morphological feature of this group. The term agyria or complete lissencephaly refers to the absence of sulci on the surface of the brain. Pachygyria (few and broadened gyri) is synonymous with incomplete lissencephaly [9].

Lissencephaly results from arrest of neuronal migration probably caused by disruption of radial glial fibers. This arrest causes abnormal lamination of the cortex, with characteristic disposition of the neurons in four layers. Complete lissencephaly is associated with partial deletion of chromosome 17, and is found in patients with Miller-Dicker syndrome [22].

Agyria is also observed in males whose mothers are affected by band heterotopia. These patients have a mutation of chromosome Xq 22.3 (X-linked lissencephaly) [23]. The MRI picture consists of smooth brain surface, thick cortex and reduced white matter. Interface with white matter is smooth. White matter signal intensity is always normal. Intracortical thin band which is isointense with the white matter corresponds to the 'cell-sparse zone', an area of intracortical necrosis with glial elements that seems to myelinate normally. On transverse sections, the brain has a typical figure eight appearance, resembling that of a fetal brain at about the 20th week of gestation (figure 3).

In incomplete lissencephalies, areas of pachygyria with a few shallow sulci may be present together with areas of agyria.

Differential diagnosis with respect to polymicrogyria is determined on the basis of the different morphology of the grey-white matter interface. In polymicrogyria, the inner margin of the cortex has microindentations due to the apposition of microgyri, whereas in pachygyria, the margin is smooth and parallel to the pial surface of the brain [9, 24].

Recently, the association of lissencephaly with cerebellar hypoplasia has been recognised as a distinct category of brain malformation, and the mutation of several genes involved in brain development has been identified in this group [25].

Cobblestone lissencephaly (Lissencephaly type 2)

Though described together with agyria-pachygyria, type 2 lissencephaly is a completely different malformation. Cobblestone lissencephaly is observed in Walker-Warburg syndrome (WWS), Fukuyama congenital muscular dystrophy (FCMD) and muscle-eye-brain disease (MEB). Walker-Warburg syndrome is the most severe of these disorders, while MEB and FCMD have a milder clinical course. The MEB is most commonly reported in the Finnish population, while FCMD is extremely rare outside of Japan [26, 27].

In contrast to agyria-pachygyria, which is caused by an arrest of neuronal migration, the pathogenesis of cobblestone lissencephaly is supposed to consist of an over migration of neurons. Disruption of pial-glial limitans results in abnormal stratification of the cortex and in migration of neurons over the pial limit, with formation of clusters of neurons within and over the leptomeninges.

The cortex consists of two disorganised layers of neurons, glial elements and collagen bundles [28]. Imaging studies of patients with WWS show thickening of the cortex with few shallow sulci. The grey matter is abnormally thick, usually less than in pachygyria, with an irregular grey-white matter interface characterised by multiple indentations of the inner margin of the cortex. Multiple smooth and nodular areas on the surface of the brain resemble a cobblestone road. The presence of neurons and glial cells

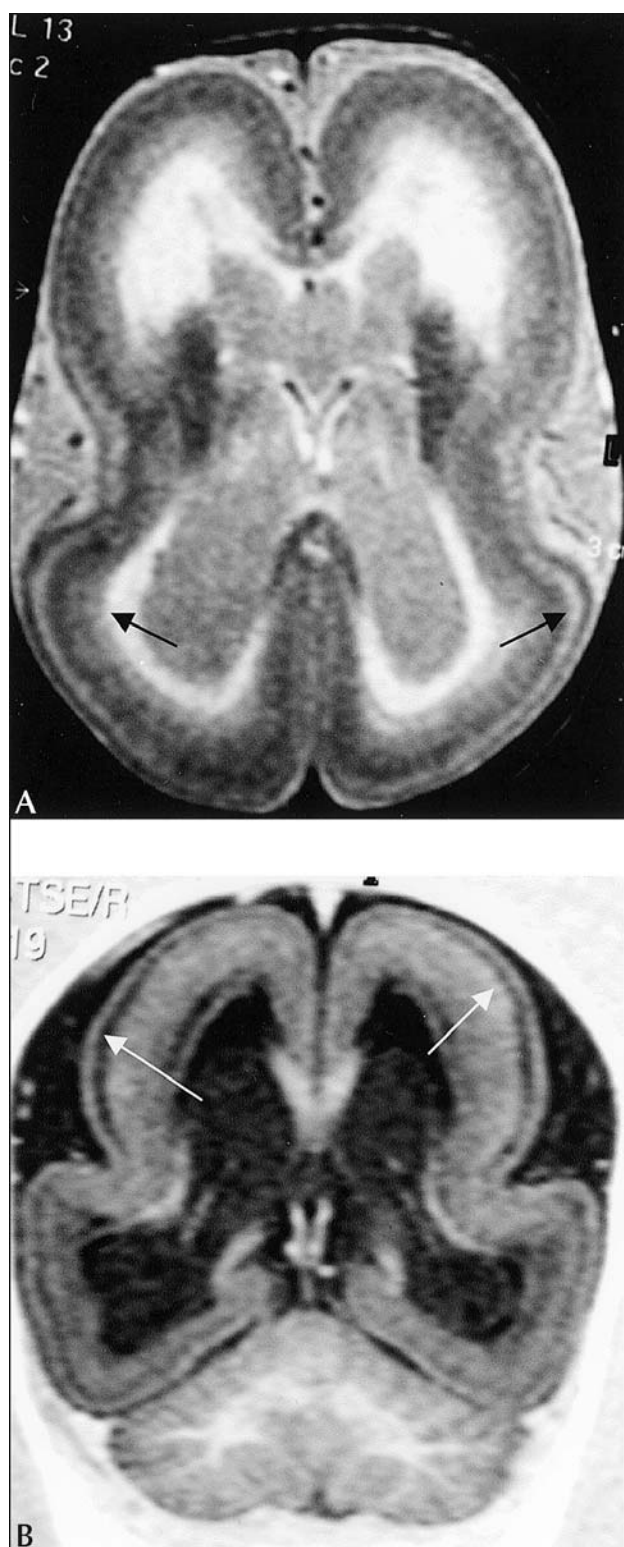


Figure 3. Agyria. Transverse T2-w.i. (A) and coronal T1-IR (B) sections. Complete absence of sulci. The sparse cells-layer is recognizable as a band hypointense to the white matter (arrows).

over the pial limit can obliterate the subarachnoid space, causing hydrocephalus [26]. In patients with hydrocephalus, the morphology of the surface of the convolutions cannot be evaluated and MRI diagnosis becomes possible only after placement of a shunt.

Brain stem hypoplasia may be observed in the most severe cases, together with cerebellar abnormalities such as vermal hypoplasia and cerebellar polymicrogyria.

Cortical abnormalities are less severe in FCMD than in WWS. Brain stem abnormalities are usually absent. Cortical dysplasia may involve the cerebellar hemispheres, and is observed together with subcortical cysts, probably due to maldevelopment of cerebellar subarachnoid spaces.

Moreover, delayed myelination with T2-hyperintensity of the cerebral white matter, is observed.

In MEB, the severity of cortical abnormalities is intermediate between WWS and FCMD. Areas of abnormal myelination in cerebral white matter, cerebellar cysts and brain stem abnormalities may also be present, although less severe than in WWS [26].

Cortical heterotopia

Cortical heterotopia are clusters of neurons in abnormal position as a result of an arrest of radial migration. They may be of variable shape and size and either unilateral or bilateral. On MRI studies, cortical heterotopia are always isointense to the normal cortex in all imaging sequences [29].

Generalised or focal and multifocal forms are recognised depending on morphology and location. Mixed focal subependymal and subcortical forms are also recognised. Both generalised and focal forms include subependymal nodular and subcortical heterotopia.

Subependymal nodular heterotopia

Subependymal nodules of cortical heterotopia may be single or few in number, unilateral or bilateral. They are more frequently observed on the walls of the trigones and of the temporal horns of the lateral ventricles. Subependymal or periventricular nodular heterotopia in its generalised form is bilateral and symmetrical. The MRI picture is characteristic, and consists of symmetrical nodules lining the lateral ventricles with slight bulging, giving a peculiarly indented profile. Signal isointensity and lack of both calcification and contrast enhancement allows differentiation from subependymal hamartomas of TS [29].

Most patients with subependymal nodular heterotopia are females with mutation of chromosome Xq 28. Sporadic cases, also affecting males, are more rarely observed. A large cisterna magna is often observed in females with X-linked subependymal heterotopia [30, 31].

Subcortical heterotopia

In subcortical heterotopia, single or multiple nodules, generally larger than the subependymal nodules, are located between the lateral ventricles and the surface of the

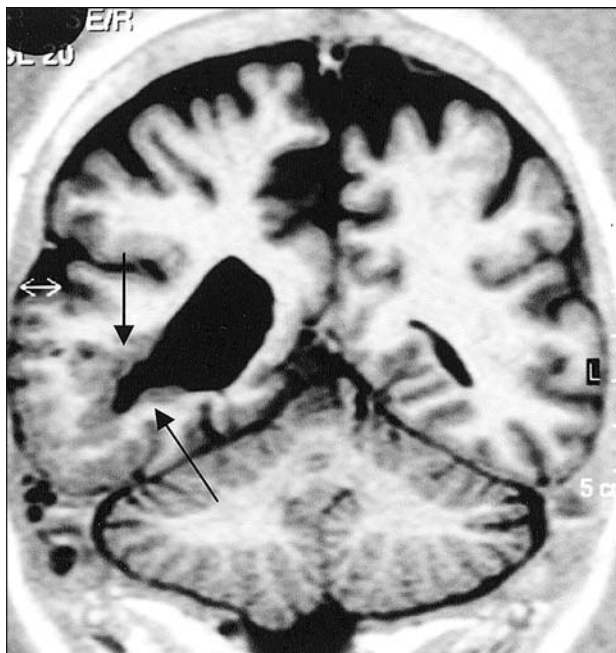


Figure 4. Coronal IR T1-w.i. Right sided subependymal nodular heterotopia (arrows) with abnormal cortical organization of the right temporoparietal region.

brain. Large nodules may be associated with focal reduction in the size of the affected hemisphere and distortion of the lateral ventricles. Cortical heterotopia must be distinguished from brain tumours. Differential diagnosis is determined on the basis of the isointensity of cortical heterotopia to the normal cortex. Large cortical heterotopia are usually associated with a small hemisphere, without swelling of convolutions. The distortion of the ventricles, frequently observed in cortical heterotopia, may be bizarre, but is not due to compression from mass effect. Furthermore, perifocal edema is always absent in cortical heterotopia. Focal subependymal and subcortical heterotopia may occur together. Large nodules of cortical heterotopia, reaching the surface of the brain, may show features similar to those of the infolding of polymicrogyria. Finally, cortical heterotopia may be associated with abnormal cortical organisation (*figure 4*) [12, 29].

Band heterotopia

Due to its characteristic appearance on imaging and pathological studies, band heterotopia is also called 'double cortex'.

On MRI studies, homogeneous bands of grey matter are interposed between the lateral ventricles and the cerebral cortex. The overlying cortex has normal thickness with shallow sulci. Band heterotopia may be complete or incomplete; in these cases, the frontal lobes seem to be preferentially involved.

The severity of cortical abnormality seems to be related to the thickness and extension of the heterotopic band [32].

Band heterotopia is preponderant in females; this is consistent with the report of a genetic locus on chromosome Xq 22.3-q23 coding for XLIS or double cortin gene [33]. Reports of males with band heterotopia are more rare [32].

Abnormal neuronal organisation

- Polymicrogyria
- Schizencephaly

Polymicrogyria

Polymicrogyria (PMG) consists of abnormal stratification of neurons in the cortex. Once migration is complete, the neurons reach the cortex, but distribute abnormally, giving rise to multiple, small gyri. The derangement of the six-layered organisation of the cortex leads to different histological appearances. On the basis of histology, two different forms are recognised: unlayered and four-layered PMG. *Unlayered PMG* is characterised by a single layer of neurons without laminar organisation; it is observed along the lips of schizencephalies and in Aicardi syndrome. In *four-layered PMG*, layers 4 and 5 are replaced by a layer with low density neurons [34].

Polymicrogyria may be unilateral or bilateral, and may involve focal areas or a whole hemisphere. In unilateral cases, PMG is more frequently observed in the perisylvian region.

Bilateral involvement of the perisylvian area is described in patients with Foix-Chavan-Marie (bilateral perisylvian syndrome) [35]. Patients with bilateral symmetrical PMG in different locations are also reported [36].

On MRI studies, the presence of packed microgyria causes thickening of the cortex, and in some cases deep infoldings that may reach the walls of the lateral ventricles. The inner margin of the cortex presents characteristic indentations that allow PMG to be distinguished from pachygyria (*figure 5*). Detection of such indentation may not be obvious, particularly in the focal forms. In these cases, thin slices and high resolution techniques are necessary for diagnosis [24].

The demonstration of microgyria, in association with signal isointensity to the normal cortex, also distinguishes PMG from brain tumours involving the cortex.

Since PMG is usually caused by injury occurring in the late phase of cortical organisation, gliosis of the subjacent grey matter, corresponding to hyperintensity on T2-w.i., may occur.

Polymicrogyria must also be distinguished from ulegyria, caused by a mild anoxic ischemic lesion in full-term newborns. In ulegyria, the affected gyri are atrophic and hyperintense on T2-w.i. in the sulcal portion of the cortex; cortical thickness and signal intensity are normal in the crown of the convolutions (so-called mushroom gyri) [12].

Schizencephaly

Schizencephaly is characterised by the presence of clefts extending from the lateral ventricles to the pial surface of

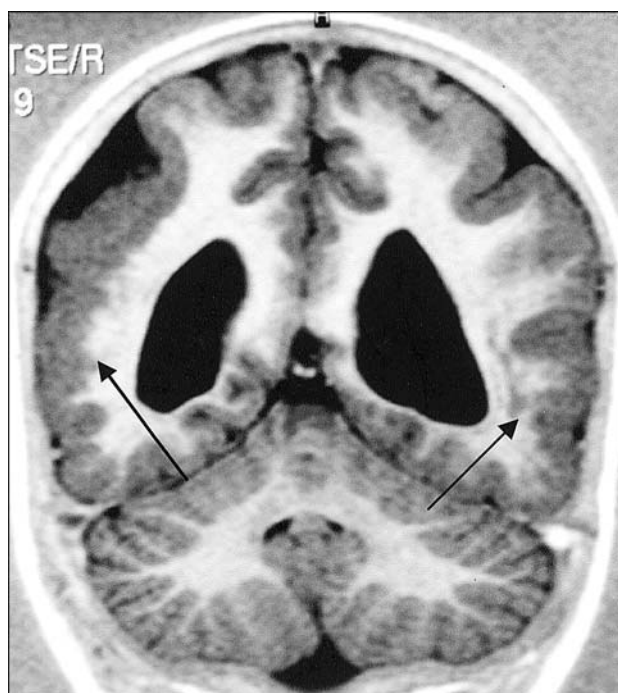


Figure 5. Bilateral parietal polymicrogyria. Coronal IR-T1-w.i.. Thickening of the cortex of both parietal regions. Microindentations along the lower margin of the cortex are consistent with multiple small gyri (arrows).

the brain. Two different forms of schizencephaly are recognised: closed lip schizencephaly, in which the margins of the clefts are opposed to one another, and open lip schizencephaly, in which the lips are separated, the CSF filling the space between the walls of the cleft [37, 38]. The clefts may be unilateral or bilateral.

In closed lip schizencephaly, a dimple is always present on the wall of the lateral ventricle where it communicates with the cleft. The dimple is often the diagnostic clue, suggesting diagnosis even in cases of small schizencephalies. What differentiates closed lip schizencephalies from infolding of polymicrogyria and from nodules of heterotopic grey matter reaching the surface of the brain, is the recognition of a band of normal white matter that separates the abnormal cortex from the wall of the ventricle. [39].

The grey matter lining the walls of the cleft is dysplastic, with features of polymicrogyria.

The septum pellucidum is almost always absent in bilateral schizencephaly and in unilateral open lip schizencephaly.

Open lip schizencephaly may be isolated or part of a complex malformative picture.

Partial or complete agenesis of the corpus callosum is frequently observed. In 30% of cases, open lip schizencephaly is associated with septo-optic dysplasia, consisting of optic nerve hypoplasia and the absence of septum

pellucidum [40]. Therefore, chiasma and optic nerves should always be scrutinised in patients affected by open lip schizencephaly.

Extended cortical abnormalities may be associated with more severe open lip schizencephaly.

Familial cases of schizencephaly are described, and are associated with mutation of EMX 2 homeobox gene, a gene expressed in the germinal matrix of the developing cerebral neocortex [41, 42]. □

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