Development and Dysgenesis of the Cerebral Cortex: Malformations of Cortical Development

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KEYWORDS

• Cortex, development • Focal cortical dysplasia
• Microcephaly • Macrocephaly • Lissencephaly
• Cobblestone brain • Nodular heterotopia • Schizencephaly
• Polymicrogyria

The development of the cerebral cortex results from complex and overlapping processes of cellular proliferation, differentiation, and apoptosis, of migration, and of organization (development of neuronal connections). The term malformation of cortical development (MCD) describes the structural abnormality resulting from any defect affecting any stage of this development. From a terminological point of view, it is now preferred to the name "migration defect," which is too specific (the cortex may be malformed even when the cells have migrated normally). The term cortical dysgenesis would be appropriate as well. The term "cortical dysplasia" would be acceptable, but it has been in use since as early as 1971 to describe a specific variety of cortical malformation.[1]

MCD have been known for a long time (see Refs.[2,3] for review), but it is only after the introduction of modern imaging modalities (computed tomography [CT], but above all magnetic resonance [MR] imaging) that their clinical importance has been recognized as a major cause of developmental delay, refractory epilepsy, and cerebral palsy. When the development of the brain was not yet clearly understood, they were described by pathologists according to the morphologic feature that was the most striking when looking at the brain, such as the size or the appearance of the brain surface (eg, small or big: microencephaly or megalencephaly; smooth: lissencephaly-agyria-pachygyria, cobblestone brain; too many small gyri: polymicrogyria; cavities: porencephaly-schizencephaly). This terminology has remained despite a much better understanding of the pathogenetic processes. As soon as the present model of development was established, with its phases of proliferation-apoptosis, migration, and organization,[4,5] the malformations were classified accordingly, while the names were retained[6]: microencephaly and megalencephaly as proliferation disorders; heterotopia and later lissencephaly as migration disorders; polymicrogyria and schizencephaly (which includes polymicrogyric cortex) as organization disorders. It must be mentioned that such a classification introduces a bias in the understanding of the MCD, as it suggests that the malformations would develop sequentially: proliferation disorders early, migration disorders later, and organization disorders last, which would be an oversimplification.

In the last two decades the progressive unraveling of the role of specific genetic cascades that

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control the development of the cortex, and the identification in several entities of corresponding genetic defects, have opened new avenues to understanding the MCD.[7] Putting all those facts together, Barkovich and colleagues[8] have proposed a morphologic and tentatively pathogenetic classification of MCD, which includes the developmental glioneuronal tumors in MCD (like the classification of Raymond and colleagues[9] before) and subdivides focal cortical dysplasia (FCD) into two clearly separate groups depending on whether they present with dysmorphic/balloon cells (considered as malformed cells related to an abnormal neuronal and glial genesis), or with architectural changes only (considered the result of an abnormal cortical organization). This classification, updated in 2001 and 2005, is the most widely accepted today (**Box 1**).[10,11]

Although this article fully adheres to this classification, the authors mildly diverge from it in dealing with FCD: it is described first and separately as a single group because (whatever their pathogenesis) all present in a similar and specific clinical, radiological, and surgical context. The authors then resume the classical approach and proceed with the groups of disorders of proliferation/apoptosis, of migration disorders (including the lissencephalies), and of schizencephaly and polymicrogyria. Before that, an introductory review of the imaging approach and of the development is provided.

THE IMAGING APPROACH

What to Look for

MCD are primarily disorders of the cerebral cortex, and imaging therefore should carefully investigate the cortex: sulcal/gyral pattern (all primary and secondary sulci bear names and can be identified; they are essentially symmetric) and depth (symmetric); cortical thickness (normally 1 mm in the depth of the sulcus, 2–3 mm at the crown of the gyrus) and demarcation from the white matter; T1 and T2/fluid-attenuated inversion recovery (FLAIR) signals. In addition, the white matter originates from and is functionally associated with the cortex, and it is traversed by the migration path of the cortical cells: it may have become dysplastic together with the cortex (abnormal cellularity, heterotopic neurons or monstrous cells, abnormal connectivity) as a part of the cortical malformation, or its development may have been secondarily altered by the cortical abnormality (distorted plasticity); it may also have become abnormal as a late result of the seizure activity of the overlying cortex (demyelination, gliosis). As the connectivity often is decreased, so is the volume of the white

Box 1
Malformations of cortical development

1. Malformations due to abnormal neuronal and glial proliferation or apoptosis
   a. Abnormality of brain size: decreased proliferation/increased apoptosis or increased proliferation/decreased apoptosis:
      i. Microcephaly with normal to thin cortex
      ii. Microlissencephaly (extreme microencephaly with thick cortex)
      iii. Microcephaly with extensive polymicrogyria
      iv. Macrocephalies
   b. Abnormal proliferation
      i. Nonneoplastic
         1. Cortical tubers of tuberous sclerosis
         2. Focal cortical dysplasia with balloon cells
         3. Hemimegalencephaly
      ii. Neoplastic (associated with disordered cortex)
         1. Dysembryoplastic neuroectodermal tumor (DNET)
         2. Ganglioglioma
         3. Gangliocytoma

2. Malformations due to abnormal neuronal migration
   a. Lissencephaly/band heterotopia spectrum
   b. Cobblestone cortex complex
   c. Heterotopia
      i. Periventricular nodular heterotopia
      ii. Subcortical nodular heterotopia
      iii. Marginal glioneuronal heterotopia

3. Malformation due to abnormal cortical organization/late neuronal migration
   a. Polymicrogyria and schizencephaly
      i. Bilateral polymicrogyria syndromes
      ii. Schizencephaly (polymicrogyria with clefts)
      iii. Polymicrogyria or schizencephaly as part of multiple congenital anomaly/mental retardation syndromes
   b. Focal cortical dysplasia without balloon cells
   c. Microdysgenesis

4. Malformations of cortical development not otherwise classified
   a. Malformations secondary to inborn errors of metabolism
      i. Mitochondrial and pyruvate metabolic disorders
      ii. Peroxisomal disorders
   b. Other unclassified malformations
      i. Sublobar dysplasia
      ii. Others

Data from Barkovich AJ, Kuzniecky RI, Jackson GD, et al. A developmental and genetic classification for malformations of cortical development. Neurology 2005;65:1873–87.

matter: this may be expressed by the volume of the brain, of one hemisphere or lobe, by the size and morphology of the ventricle(s), or by the asymmetry of the brainstem. Finally, many of the genes that control the cellular migration to and fate in the cerebral cortex may also control the development of the basal ganglia,[12] thalami, and brainstem nuclei, of the cerebellar cortex, and of the cord. Some even may be involved in the development of extraneural tissues (eg, cobblestone cortex and deficient white matter associated with congenital muscular dystrophy).

The Tools

Conventional imaging

The clinical importance of the MCD appeared as soon as CT became the primary diagnostic modality in Neuroradiology (mid-1970s), but in this field like elsewhere, the imaging modality of choice is MR. The "best protocols" are many, depending on the type of equipment available, on the technological advances, and on the familiarity of the neuroradiologist with the pathology.[13–19] Whatever is preferred, the study should always be multisequential and multiplanar, using high spatial definition and high contrast resolution (high signal-to-noise [S/N]). Because the abnormalities often are subtle, the most recent and most efficient machine should be used, and older cases of "non-lesional" epilepsies should be reinvestigated when the equipment is changed or updated. Obviously 3-T magnets have a better resolution power than 1.5-T magnets; multiple-phased array coils with parallel imaging are better than conventional coils, providing high S/N images while keeping the acquisition time within reasonable limits. Most modern neuroimaging centers are now equipped with PACS (picture archiving and communications system); if not, digital storage of the image is mandatory, rather than conventional films, because small, subtle lesions may escape the first review of the images and may be identified after repeated and careful review only. As much as possible, the examination should be directed by the clinical and electrographic/magnetoencephalographic (MEG) data, and if available, the results of the functional studies (single-photon emission CT [SPECT], positron emission tomography [PET]): an oriented study is more likely to be productive than a blind study.[16]

The basic conventional sequences are T1, T2, and FLAIR. T1 images ideally should be from volumic acquisition (MP-RAGE/TFE/SPGR), with 1- to 1.5-mm partitions to minimize the partial volume effects. The thickness and demarcation of the cortical ribbon are better appreciated, and focal cortical signal changes can be securely identified. The typical acquisition plane is the sagittal plane, with reformatting in whatever other plane is felt necessary, even curvilinear planes. The images provide an excellent spatial resolution and an excellent gray-white contrast, allowing for a superb anatomic study. To analyze the suprasylvian sulcal pattern, the sagittal and axial planes are the best; for the temporal structures, especially the mesial ones, coronal slices perpendicular to the long axis of the hippocampus are optimal. The cortical-subcortical definition, however, is poor in infants between the ages of a few weeks and at least 1 year.

T2 imaging is still important for anatomy, and to evaluate the microstructural changes in the parenchyma. The plane(s) should be adapted to the location of the expected abnormality; in a routine protocol, coronal and axial planes are usually chosen. Some groups prefer using true T2 spin echo (T2SE), whereas most use conventional T2 fast-spin echo (T2FSE). Some also advocate the use of 3-dimensional (3D)-FSE with 1-mm partition, and slices certainly should not be thicker than 2 to 3 mm, depending on the equipment available. In the neonatal and in the mature brain, T2-weighted imaging (T2WI) is excellent at showing the cortical involvement, the cortical thickness, and the cortical-subcortical blurring, if any.

FLAIR imaging certainly is the sequence most sensitive to structural changes, but its spatial resolution is not as good as that of T2 turbo-spin echo (T2TSE), with artifacts from flowing blood or cerebrospinal fluid (CSF) being more common. Yet it is practically the first sequence to be looked at, as it will readily demonstrate any significant abnormality of signal. Like conventional T2WI, 2- to 3-mm slices should obtained, typically axial and coronal, or even 1-mm slices using 3D FLAIR.[20] It demonstrates changes in both the cortex and the white matter, and a cortical blurring as well. It is of limited use, however, in young children. Some groups like to use proton density images instead, or in complement of FLAIR.[20]

Besides the main conventional sequences, other sequences may be useful in specific instances. Susceptibility sequences (SWI) are useful to demonstrate that an epileptogenic dysplasia is associated with vascular abnormalities such as a cavernoma or a meningoangiomatosis. Diffusion imaging (DWI/ADC) is not very contributive in the assessment of MCD: it is typically not sensitive enough to show the microstructural changes of the tissue, which will be much more confidently evaluated by quantitative diffusion tensor imaging (DTI); however, it may demonstrate restriction

due to cytotoxic edema in case of refractory seizure activity. MR venography may be used to illustrate venous abnormalities commonly associated with some MCD such as a polymicrogyria (PMG), whereas MR arteriography may show abnormal arterial patterns.

Imaging in infants

In infants and young children (as well as in developmentally delayed children) good MR imaging implies the use of sedation/general anesthesia. During the first months of life the structure of the immature brain tissue is different and the T1 relaxation time is much longer than in the mature brain, so that adapted sequences should be used. T1-weighted (T1W) sequences need a longer repetition time (TR), and T2W sequences need longer TR and echo time. Also, as mentioned earlier, if the cortex is exquisitely delineated at birth on T1 and T2, the contrast becomes lost with advancing myelination, until after 1 year on T1, and 2 years on T2. On FLAIR images the evolution is still more complex: at birth, the very high water content of the white matter is cancelled by the saturation pulse and the appearance is somewhat similar to T1; in the following weeks the myelin precursors accumulate and the signal increases to look more like a conventional T2. However, it remains fairly heterogeneous for a much longer time than on ordinary T2 sequences, as the mature pattern is not reached until about the age of 3 to 4 years. In summary, the optimal time to identify a cortical dysplasia in an infant is either early in the first weeks or much later when the mature pattern is established after 2 years, and FLAIR imaging is of limited use in young children.

Another specificity of epileptic infants is the possible occurrence of a focally accelerated myelination. Many investigators have observed that when FCD is diagnosed in the first months of life the white matter under the dysplastic cortex displays a low T2 signal,[21–25] which eventually disappears while maturation proceeds.[25] Most assumed that this appearance was a feature inherent to FCD, a reflection of an associated white matter dysplasia, and/or possibly microscopic calcification, but it was also suggested that it could result from the seizure activity itself.[26] This idea is supported by the experimental evidence that electrical activity in the axons induces the myelination, and that increasing this activity increases the myelination,[27] a process mediated by astrocytes.[28] Accelerated myelination is observed in other epileptogenic conditions such as the Stürge-Weber syndrome.[29] Finally, it explains why the change is no longer apparent when myelination is completed: this would not be expected to happen in the case of white matter dysplasia. It is important to keep in mind that as a consequence, the early myelination points to an epileptogenic focus and not necessarily to an FCD.

Special MR imaging techniques

Because of the high percentage of lesions that are not well demonstrated on MR imaging, different approaches have been proposed to increase the diagnostic yield. Various MR techniques are available to provide more insight into the structure, function, and metabolism of the epileptic brain affected with an MCD. Quantitative MR demonstrates that T2 correlates with the neuronal density in the cortex.[30] Volumetric studies suggest a relative defect of the white matter, hence of the connectivity.[31] DTI is being used extensively. Quantitative DTI is more sensitive than DWI/ADC to demonstrate a decreased diffusivity postictally, matching the epileptic focus, apparently related to a cellular swelling due to the metabolic exhaustion.[32] It also identifies an increased diffusivity interictally, which may be due to neuronal loss and gliosis in both gray and white matter,[16,33,34] as well as to a dysgenetic structural alteration.[16] DTI tractography demonstrates more extensive changes in the brain organization and connectivity beyond the cortical lesion.[35–39] Proton spectroscopy (^{1}H-MRS) is not very useful for the diagnosis of an MCD composed of normal if ill-located or ill-organized neurons and glia, but it provides insights on their metabolism. *N*-Acetylaspartic acid (NAA) appears largely unchanged or only mildly decreased in heterotopia and PMG,[40–42] choline appears either increased or normal,[41,42] and glutamate and γ-aminobutyric acid (GABA) appear increased in patients with epileptogenic heterotopias and PMG.[42] In lesions made of poorly differentiated cells such as in FCD or in the tubers of tuberous sclerosis complex (TSC), NAA appears significantly decreased[41,43] and choline increased, but less so than in cerebral tumors.[43] Perfusion also is low in cortical tubers but normal in PMG.[44] Despite it having been proved useful in the evaluation of the cortical and white matter dysplasia in tuberous sclerosis,[45–47] there is no report on the potential use of magnetization transfer imaging (MTI) in MCD in general, and in FCD in particular. One report, however, indicates that in acquired and developmental epileptogenic lesions, significantly reduced magnetization transfer ratio (MTR) was found within the MR-visible lesions (presumably gliosis with low myelin content) as well as in normal-looking white matter. These areas concurred with the

electrographic epileptic activity and the clinical seizure semiology.[48]

Cortical Function and White Matter Organization In and Around MCD: Presurgical Assessment

Imaging has become essential in preparing for epilepsy surgery, if warranted. It is expected to show the lesion, identify its nature and, as much as possible, its extent. Quantitative DTI shows microstructural changes beyond the abnormalities seen on conventional MR images, in good correlation with the MEG abnormalities.[35–39,49]

Imaging is also expected to tell whether the lesion is functional or not. MCD have an intrinsic epileptogenicity, which implies that they are interconnected with the rest of the brain; some patients with MCD present with reflex epilepsy, which means that the lesion can be activated by outside stimuli (for review see Ref.[50]). Using functional imaging (fMRI), one study demonstrated that 64% of MCD are activated by simple sensory motor or visual stimuli (71% if they are located in the corresponding eloquent areas), but only 40% become involved in complex cognitive tasks.[50] However, the response of the dysgenetic cortex depends on the severity of the malformation: all cases of organization disorders (PMG, schizencephaly, and FCD type I) become activated by simple tasks against only 47% of cases of FCD type II (Taylor) and heterotopias; this is in good agreement with the current classification of MCD (see **Box 1**).[11]

MR imaging techniques are also used to locate the main cognitive functions and white matter tracts. fMRI has, in practice, completely supplanted the sodium amobarbital Wada test.[16,51,52] It is used to locate the motor function when surgery in the sensory-motor area is considered, and to locate the language representation when the lesion to be operated on is in the so-called dominant hemisphere, as language representation is commonly atypical not only in MCD but more generally in refractory epilepsy.[37,53,54] Assessment and lateralization of memory functions can be done, but need validation and are not performed routinely as yet.[16,51,52] Finally, DTI tractography is an efficient way of locating the major axonal tracts such as the corticospinal tract[16,52,55] or the optic radiations.[16,52,56] Some groups are attempting to demonstrate the language networks[37,52] and the memory networks[16,52] as well.

As mentioned earlier, a focused MR study is more efficient than a blind one, and a multimodality approach enhances the diagnostic efficacy in demonstrating the lesional as well as the epileptogenic area: clinical semiology, scalp electroencephalography (EEG), coregistered MEG and magnetic source imaging (MSI),[57] or functional neuroimaging such as postictal/interictal SPECT[58] and PET[59] are extremely productive. A new approach using EEG-correlated fMRI is being developed and seems promising.[51,60]

DEVELOPMENT OF THE CEREBRAL CORTEX

Cortical Anatomy

The cerebral cortex comprises the trilayered olfactory paleocortex and hippocampal archicortex, and an extensive 6-layered neocortex (90% of the cortical surface in human). In advanced mammals and especially in humans, it is conspicuously folded, two-thirds of the cortical surface being located inside the sulci; cortical folding is related to the development of the connectivity. The sulci have been classified into primary sulci (pericallosal, cingulate, parieto-occipital, hippocampal sulci) and secondary sulci (such as the central, precentral and postcentral, intraparietal, frontal, temporal, calcarine and occipital sulci). The primary and secondary sulci may vary in shape slightly but are constant and symmetric in location. The sulci delineate the gyri, which more or less reflect the functional areas of Brodmann. The primary sulci become apparent shortly after mid-gestation, and the secondary sulci appear between 25 and 30 weeks. Tertiary sulci are branches of the primary and secondary sulci and appear mostly after birth; they are extremely variable.

The thickness of the neocortex varies from 1 to 3 mm, thinner in the depth of the sulci and thicker at the crown of the gyri. Pyramidal neurons (glutamatergic, excitatory) are the most numerous (80%) and establish long-range connections; interneurons (GABAergic, inhibitory) establish local, intracortical connections between the pyramidal neurons. The neurons are primarily organized in columnar units, but because of the intracortical course of the connecting fibers they become organized in layers. From the surface to the depth, the neocortical layers are as follows, albeit with some overlapping between them:

- Layer 1 or molecular layer contains mostly local connecting fibers
- Layer 2 receives corticocortical afferents (association and commissural fibers)
- Layer 3 sends corticocortical efferents (association and commissural fibers)
- Layer 4 or granular layer receives the corticothalamic afferents

- Layer 5 or pyramidal layer sends the corticosubcortical efferents (to the striatum, brainstem, and cord)
- Layer 6 or polymorphic layer sends the corticothalamic efferents.

The 6-tier layering of the cortex is due to the predominantly horizontal organization of the intracortical fiber tracts. The most prominent fiber layers are in layer 1, in layer 4 (external band of Baillarger), and between layers 5 and 6 (internal band of Baillarger). If the general cortical pattern is constant, the proportion between the layers varies according to the cortical location, resulting in the various histologic patterns that characterize the cortical functional areas of Brodmann.

Formation of the Cortex

In the last 4 decades a considerable amount of information has accumulated regarding the development of the cortex, notably in the last decade (for reviews see Refs.[4,5,61–68]) (**Fig. 1**). The early central nervous system emerges from the surface ectoderm as a band of dorsal midline neuroepithelium or neural plate during the third week (for review see Ref.[69]). This neural plate forms a groove with neural folds and closes to form the neural tube (NT) during the fourth week (neurulation); 3 cerebral vesicles (forebrain, midbrain, and hindbrain) become apparent during the fifth week, and the lateral evaginations of the cerebral hemispheres develop from the forebrain during the sixth week.[70] Under the influence of ventralization and dorsalization factors, the hemispheric vesicles become divided into a basal part or subpallium (future basal ganglia) and a dorsal part or pallium (future cortex and white matter), each with its own germinal zone, the dorsal one producing pyramidal neurons and the basal one (ganglionic eminence) producing the cortical interneurons as well as the neurons of the basal ganglia (in humans interneurons may come from the pallial germinal zone as well). The division is clearly apparent during the seventh week.[70]

Proliferation of neuroepithelial, truly neural stem cells already begins in the fourth week in the neural plate.[69] As the NT closes, its whole thickness forms a proliferating zone where the cells divide in a symmetric way (one stem cell produces two stem cells) (see **Fig. 1**A).[67] At the end of the fifth week the proliferation process switches to asymmetric divisions (one stem cell produces one stem cell and one neuron) and the differentiated neurons accumulate at the periphery: as a consequence the wall of the NT contains a deep germinative zone, which is called the ventricular zone (VZ), and a peripheral zone with the first neurons, which is called the primordial plexiform layer or preplate (PP) (see **Fig. 1**B).[62,71] The distance between the ventricular and the meningeal surfaces of the NT is short in the early stages, and the differentiated cells are able to migrate by somal translocation (nucleokinesis): from the germinal zone where they are born they extend a process toward the meningeal surface, the nucleus migrates into this process toward the surface while the ventricular process shortens and loses its ventricular contact. One of the genes that controls this nucleokinesis is the *LIS1* gene, whose defect is associated with one major form of lissencephaly.[63] The process of translocation is used by the neurons of the PP and possibly by the early neurons (future layer 6) of the cortical plate (CP).[64] The PP contains Cajal-Retzius cells and other neurons that are the first to establish extracortical connections.[68] When the cortical plate appears on about day 50 (end of week 7), it divides the PP into two layers: the superficial layer or marginal zone (MZ) contains the reelin-positive Cajal-Retzius cells (in addition to various other neurons), and the subcortical layer forms the subplate (SP) and contains reelin-negative neurons (see **Fig. 1**C).[67] Cajal-Retzius cells play a major role of controlling the migration of the neurons in the CP; the subplate is essential also, as it directs outgoing axons and maintains transient connections with the incoming axons until the cortex becomes ready.

Radial migration of glutamatergic pyramidal neuron to the CP begins at the end of week 7 in the lateral part of the telencephalon, and a week later in its posteromedial aspect; the peak migratory activity lasts until mid-gestation (weeks 20–22) and migration is essentially complete before the third trimester.[67] Radial migration uses specialized cells, the radial glia, to guide the pyramidal neuron from the germinal zone to the CP. Each radial glial cell has a process anchored on the ventricular surface, and a radial process that extends to the pial basement membrane (where it often makes contact with vessels[65]), so that the radial glia forms a scaffolding across the mantle. The newly generated neurons travel perpendicular to the surface, from the pallial VZ along the glial fibers to the CP, where they are induced to detach from the radial glia by the signal (Reelin) provided by the Cajal-Retzius cells. As a consequence early-migrating cells are in the deep cortical layers and late-arriving cells are close to the surface: this is called the inside-out pattern (see **Fig. 1**C–E). A first wave of migration toward the deep layer 6 develops at about 7 to 11 weeks; a second wave toward layer 5 occurs at about 12 to 16 weeks; a third and last wave to the more superficial layers

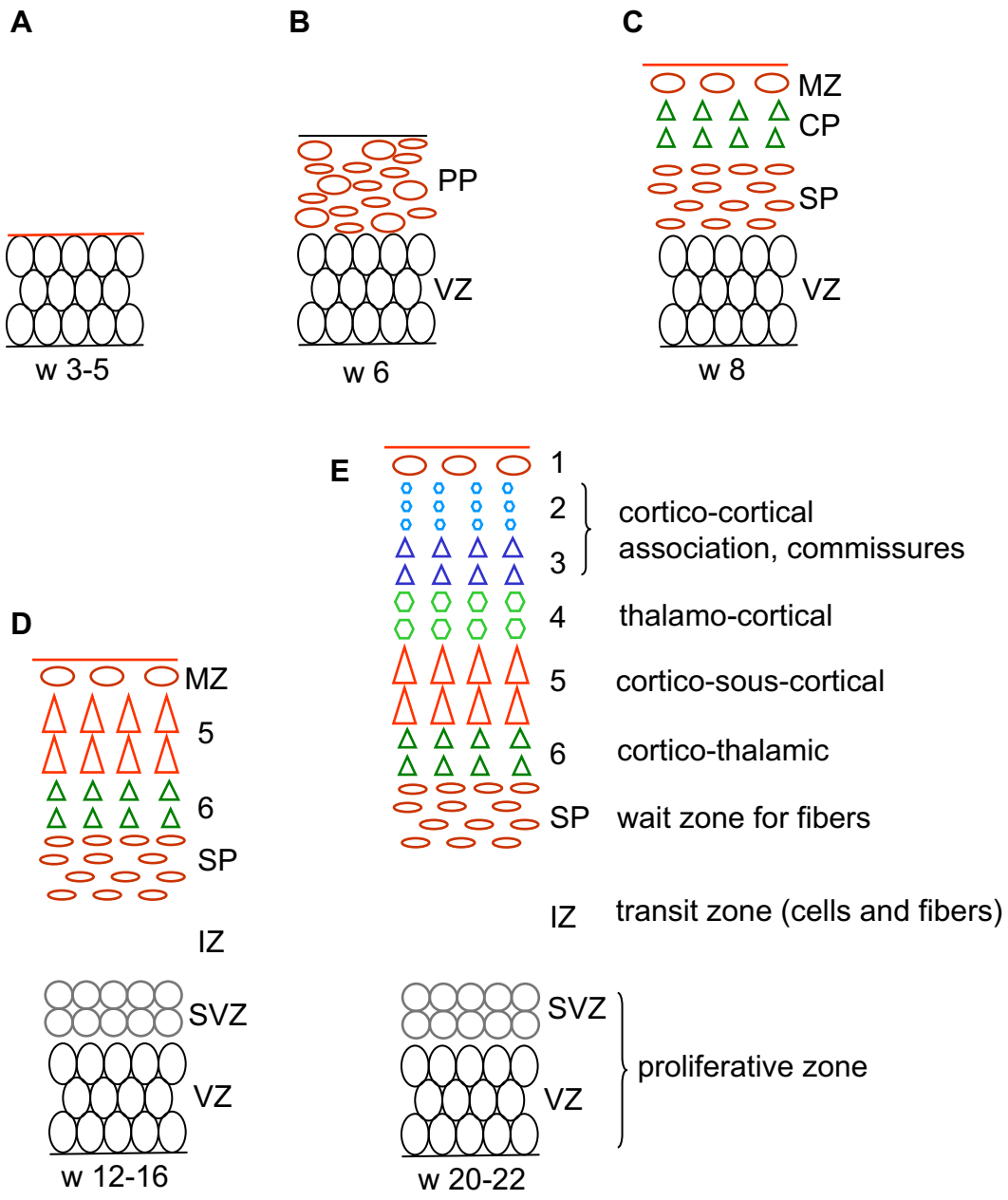

Fig. 1. Pyramidal neuronal migration to the cortex. (*A*) Weeks 3 to 5. Pseudostratified epithelium of proliferating cells. (*B*) Week 6. The pallium is subdivided into a deep proliferative layer (ventricular zone, VZ) and a superficial layer of early postmitotic neurons, the primordial plexiform layer or preplate (PP). (*C*) Week 8. Radial migration of neurons to the surface forms the cortical plate (CP), which divides the PP into a superficial marginal zone (MZ) containing the Cajal-Retzius cells (C-R) and a subcortical subplate (SP). C-R stop the migrating neurons before they reach the surface, which results in the inside-out arrangement whereby young neurons are more superficial and older ones are in the depth of the cortex. The subplate neurons guide the outgoing axons, and make transient connection with the incoming axons until their final targets are ready to become connected. (*D*) Weeks 12 to 16. More neurons migrate to the periphery after making a stop in the subventricular zone (SVZ) where they make contact with other pyramidal neurons and interneurons. An intermediate zone (IZ) develops between the SVZ and the SP: it contains radial glial fibers, migrating neurons, and early axons. (*E*). Weeks 20 to 22. Neuronal migration is essentially complete. The deep layers 5 and 6 contains neurons that project axons to the subcortical structures; layer 4 starts receiving axons from the thalamus (until then connected in the transient subplate); layers 2 and 3 later receive the long association and commissural fibers first, then around and after birth, the subcortical short association fibers.

occurs after 16 weeks.[5] This last wave is prominent in primates, including man, and corresponds to the neurons that will develop corticocortical connections.[67] Late migration of individual neurons may continue even after the end of the cellular proliferation until after birth.[5] As a consequence of the radial migration, all neurons using a single radial cell form a single column in the CP.[5] The glia-guided migration depends on the cellular microfilament network, and involves the *FLN1* gene (whose defect has been demonstrated in specific varieties of gray matter heterotopia), as well as on two proteins associated with the regulation of the actin network, Cdk5 and p35.[63] Doublecortin (DCX) also is involved with radial radiation, and defects of the *DCX* gene are associated with some human lissencephalies (for review see Ref.[63]).

Besides their role of guidance, the radial glia recently have been shown to be stem cells and to produce neuronal progenitors.[65] In a rather complex process, they divide asymmetrically in the VZ, producing another radial glial cell and a neuronal progenitor. The neuronal progenitor moves to the subventricular zone (SVZ) (phase 1) where it stays for up to 24 hours, becomes multipolar, and establishes multiple cellular contacts, moves tangentially free from radial glial attachment, and becomes dispersed within the SVZ before dividing symmetrically (phase 2). The new neurons may migrate directly to the cortex along the radial glia, but most translocate back to the VZ (phase 3), from where they make their final journey toward the CP along the radial glial fibers (phase 4).[64,65]

Tangential migration of the GABAergic inhibitory interneurons occurs in close association with the radial migration of the pyramidal neurons (the first interneurons are seen at about weeks 6–7, even before the appearance of the CP[67]). These neurons typically originate in the ventral VZ of the medial ganglionic eminence (MGE; the primordium of the globus pallidus[63]) and travel parallel to the surface of the hemisphere toward the pallium. Like the radial migration, the tangential migration is complex (for review see Ref.[64]). Studies in rodents show that there are primarily two migration streams, one along the MZ and the other along the deep IZ/SVZ (the intermediate zone [IZ] is the portion of the pallium that is located between the SP and the germinal SVZ). From their MGE origin, some interneurons disperse into the IZ/SVZ before reaching the CP either radially or obliquely; some travel along the MZ and enter the CP from above; some travel in the IZ/SVZ, then reach the MZ radially across the CP, disperse into the MZ, and enter the CP from above. However, the majority of interneurons (70%) travel through the IZ/SVZ and dive toward the ventricle to enter the VZ, where they pause before resuming their course and migrating radially to the CP.[63,65] In this process, the interneurons are likely to acquire laminar address information,[64,65] possibly mediated by GABA information.[65] The partial convergence during their migration of at least some pyramidal neurons and interneurons might allow transmission of positional information. Pyramidal neurons pause in the SVZ, become multipolar, and may contact interneurons there. The different migration speed—10 μm/h for the radial migration, 50 μm/h for the tangential ones—may favor birth-date related encounters, and cellular birth date relates to laminar position precisely. What guides the interneurons—guiding glia, axons projecting from the CP—is not clear, but the process has been shown to involve class 3 semaphorins, neuropilins, cell-adhesion molecules, neuroregulins, and the slit/robo complex.[63,64]

The organization of the pallium changes and becomes more complex as it develops (**Table 1**), and so does the terminology (see **Fig. 1**).[67] In weeks 4 to 5 the pallium is a simple homogeneous pseudostratified neuroepithelium. Between week 5 and week 7 (before the appearance of CP) it comprises a deep germinal zone VZ and a superficial postmitotic zone PP. After the CP divides the PP during week 8, the postmitotic zone is made up of 3 layers (MZ, CP, and SP), the germinal zone is made up of 2 layers (VZ and SVZ), and an IZ in between contains migrating cells, radial glia processes, and early incoming and outgoing axons. After peaking before mid-gestation, migration stops at about 25 to 27 weeks. The radial glia loses contact with the ventricle, migrates toward the cortex, and forms astrocytes (changing its nestin and PAX6 expression for glial fibrillary acidic protein). The pallial VZ disappears leaving the unicellular layer of ependyma only, but the SVZ persists and contains stem cells even in the adult brain, presumably a potential source of brain tumor cells. The germinal zone of the lateral ganglionic eminence remains prominent for some time (the so-called germinal matrix of the premature brain), before vanishing progressively during the last prenatal weeks. After a peak of complexity between 18 and 28 weeks, the cellularity of the MZ, notably the Cajal-Retzius cells, regresses and disappears before term. On the contrary, the SP expands significantly until the third trimester, being largest at week 28,[62] particularly under the frontal associative cortex, and then attenuates until about term, leaving interstitial neurons only in the white matter. As connectivity develops, white matter fibers progressively invade both the IZ and the SP area, which together form the final hemispheric white matter.

Table 1
Development of the pallium

Age in Weeks	Forebrain	Cellular Processes	Organization of Pallium	White Matter	Metabolic Supply/ Vasculature
3	Neural plate	Stem cell proliferation	Pseudostratified	—	Amniotic fluid
4	Anterior neural plate neural tube closure	Stem cell proliferation	Pseudostratified	—	Primitive meninges
5–6	Prosencephalon then hemispheres (pallium/ subpallium)	First peripheral primordial neurons	VZ and PP	—	Choroid plexus
7–9	Pallium	Translocation First wave to layer 6	Postmitotic: MZ, CP, SP Germinal: VZ	Corticothalamic Corticospinal	Choroid plexuses First perforators to VZ/MGE
10–12	Pallium	Radial glia Progenitors Second wave to layers 5–4	Postmitotic: MZ, CP, SP Intermediate: IZ Germinal: VZ–SVZ	First thalamocortical in SP	Choroid plexuses Rich germinal plexus SVZ/VZ/MGE
16–20	Pallium	Third wave to layers 3–2	—	Thalamocortical in SP Commissural and association in SP	Rich germinal plexus SVZ/VZ/MGE
22–26	Pallium Primary and early secondary sulci	End of migration and of radial glia	Disappearance of VZ Ependyma	Thalamocortical in layer 4 Early commissural and association to layers 2–3	Rich germinal plexus SVZ/MGE Early branches in deep cortex
27–32	Pallium Secondary sulci	—	Reaches mature appearance Prominent SP	Layer 1 and Baillarger Commissural and association to layers 2–3	Germinal plexus recedes in SVZ Growing vasculature in deep cortex
33–40	Pallium Developing tertiary sulci	—	SP recedes White matter in IZ/SP	Short association to layers 2–3	Radial vasculature in superficial cortex End of germinal plexus SVZ/MGE
42–47	Pallium Developing tertiary sulci	—	End of frontal SP	Short association to layers 2–3	Steep increase of CBF

Abbreviations: CBF, cerebral blood flow; CP, cortical plate; IZ, intermediate zone; MGE, medial ganglionic eminence; MZ, marginal zone; PP, preplate; SP, subplate; SVZ, subventricular zone; VZ, ventricular zone.

Cellular apoptosis cannot be dissociated from proliferation and organization. The number of neurons in the brain peaks at week 28, but as many as 50% die through apoptosis before the end of the adolescence.[72] Two main periods of apoptosis occur prenatally. The first lasts from week 7 to week 13, and involves proliferating progenitors and young neurons in the VZ.[72] The second, regulated by synaptic activity, cellular contacts, and glial and neuronal trophic factors, eliminates

neurons within the CP itself between week 19 and week 23.[72]

Cortical Organization and Developing Connectivity

The period after 22 weeks is the period of organization and differentiation of the cortex (Fig. 2).[67] Neuronal proliferation and migration are essentially complete, while many neurons become eliminated.[69,72] Yet from 80 g at mid-gestation, the mass of the brain increases to 350 g at birth, 950 g at 1 year, and 1300 to 1400 g in adulthood. This enormous increase is related to the development of an intense synaptogenesis, which results in a mild thickening but a huge tangential growth of the hemispheric cortex, thus leading to the development of the sulcation/gyration and in a spectacular brain expansion. Each neuron develops one axon only, but axons leaving their temporary connections in the subplate elongate and develop many collateral axons to reach their cortical targets, while the dendritic tree expands dramatically as well (it is estimated that at maturity, each neuron becomes connected with approximately 10,000 neurons, which means as many axonal collaterals). In the late fetal and early postnatal months, a massive increase of the number of oligodendrocytes ("myelination gliosis") takes place, followed by an equally massive development of the myelin and of the supporting cells (astrocytes, microglia). In addition, the increasing brain diameter leads to more elongation of the axons with more myelin and more supporting tissue. The increase in volume is mostly peripheral (elongation of long-projection, commissural and association tracts; late development of the short, subcortical association tracts) while the absolute measurements of the lateral ventricular diameters remain quite stable until after birth.

Within the cortex, the developing connectivity transforms the columnar organization into a laminar pattern. In the motor cortex the cortical neurons at 5 months (22 weeks) are still organized in columns; most early synapses are within the columns and the first horizontal connections use layer 1 to travel to other columns[5,61,72]; horizontal, likely afferent fibers originating from the internal capsule and from the corpus callosum are found in the deep portion of the IZ.[61] At 7 months (about 30 weeks) the laminar pattern is better defined, especially in the deeper cortical layers, with well-defined horizontal fiber tracts in layer 1, in the developing layer 4 (future external band of Baillarger) and between layers 5 and 6 (future internal band of Baillarger).[61] Two weeks later (32 weeks, 7.5 months), the neurons have become more mature in all layers and the horizontal stratification is well apparent[61,67,72] (demonstrated by DTI at week 36[73]). At term, the cellular maturation is complete and the horizontal pattern fully established, with afferent corticocortical fibers present in layer 3. Only the complexity of the organization changes in the following months.[61] In the ferret and the cat, it has been shown that the lateral expansion of the cortex originates at the crown of the gyrus, corresponding to the late cellular maturation, organization, and connections there, while the bottom of the sulci would represent relatively fixed points, and apoptosis would be more important in the sulci than at the crown of the gyri.[74–76]

The development of the white matter is related to the development of the cortex, and accordingly connectivity proceeds from the deeper layers (corticothalamic, corticospinal, thalamocortical) to the superficial ones (long-association and commissural tracts, then short-association tracts). The single most important structure in the development of the white matter is the SP. The SP plays the essential role of a wait zone by guiding efferent axons and establishing transient connections with efferent axons until their cortical target cells are mature enough to become connected. The SP expands markedly during the gestation, assumedly both by dispersion due to accumulating incoming axons and by the addition of new cells.[67] It is most prominent about week 28, and especially so in the highly associative areas such as the anterior frontal cortex.[62,67,69,72,77] SP neurons send axons to both the cortex and the subcortical structures, which serve to guide the cortical and subcortical fibers,[77,78] and connect transiently with incoming fibers. The first efferent axons to leave the cortex are likely to be the corticothalamic axons from future layer 6 and the corticospinal (pyramidal) axons from future layer 5, although not much is found in the literature regarding their development in man. It should occur early because the corticothalamic fibers, originating from the deepest layer, are likely to be the first, while the corticospinal fibers are seen at the pyramidal decussation as early as 8 weeks[79] (before the neuronal body reaches layer 5); both are likely to be guided to the internal capsule by SP neurons (see Fig. 2A).[80] On the other hand, the first afferent axons to approach the cortex are the thalamocortical axons: pioneer fibers are seen in the SP as early as week 12,[67] more are seen accumulating in the superficial SP at week 22,[69,77,81] and cortical layer 4 becomes connected by week 26 (see Fig. 2B, C).[69] Commissural and long-association fibers reach the SP between weeks 24 and 29[77] and extend to the cortex itself about 33 to 35

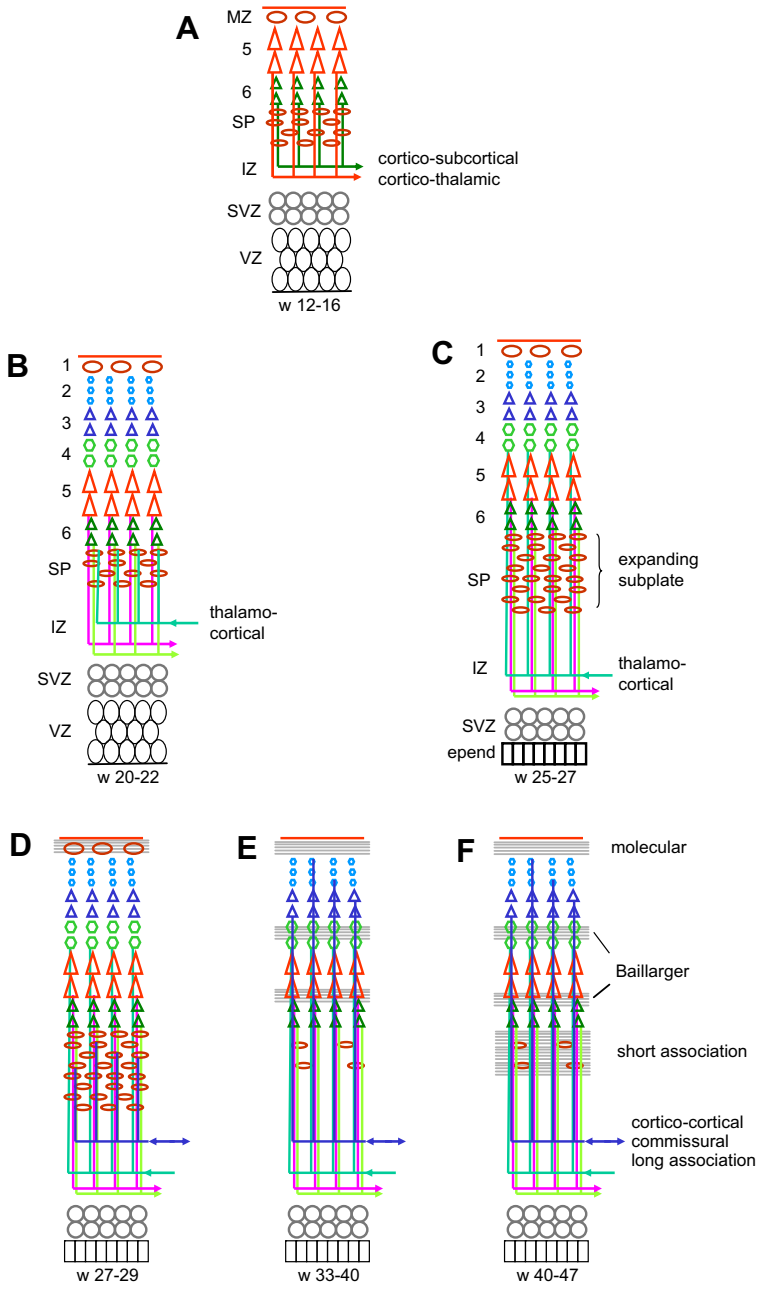

Fig. 2. Development of the connectivity. (*A*) Weeks 12 to 16. The cortico-subcortical fibers (to the thalamus, striatum, brainstem, and cord) are already present even before the neurons reach their layers 6 and 5. (*B*) Weeks 20 to 22. The neuronal migration is complete but the thalamocortical fibers are still in the SP. (*C*) Weeks 25 to 27. The thalamocortical fibers reach layer 4 from week 22 until it is complete by week 26. This is a crucial event in the maturation of the cortex, as local circuits become organized along the radial columns; the SP wait-zone reaches its maximum expansion at 28 weeks, and the thickness of the IZ increases with the number of fibers. The radial glia disappears, as well as the VZ, which leaves the ependymal lining only. (*D*, *E*) Weeks 27 to 40. The corticocortical fibers, including the interhemispheric commissural fibers, become connected to the SP first, then after 32 weeks to the superficial layers 2 to 3 while the SP attenuates. Intracortical connections develop as well, in the molecular layer and in the bands of Baillarger. (*F*) Weeks 40 to 47. Around and after term, and while the SP progressively vanishes, the short subcortical association fibers connect within layers 2 to 3.

weeks while the SP starts receding (see Fig. 2D, E). At the same time, the thalamocortical afferents are promoting local intracortical circuits, and short-association fibers start connecting with layers 2 and 3.[77] The development of these short corticocortical association fibers continues until postnatal week 7 and is related to the late persistence of the SP in the high-level associative areas (see Fig. 2F). During the first postnatal years the number of synapses increases considerably; later on, however, about age 4 to 6 years, a cortical areal specialization occurs with a corresponding pruning of the axonal branches in excess.

Development of Cortical Vascularization

During development, vascularization is continuously precisely adapted to the metabolic needs of the moment (see Ref.[82] for review) (Fig. 3). Vascularization evolves in 4 overlapping phases of amniotic, meningeal, choroidal, and intrinsic capillary supply.[83] The open neural plate in week 4 is fed by diffusion from the amniotic fluid. After its closure at the end of week 4, the NT is fed by diffusion from the surrounding primitive meningeal capillaries (see Fig. 3A, B). With the expansion of the brain vesicles and the enlargement of the ventricles, the primitive meninge invaginates into the ventricles to form the choroid plexuses: in addition to the peripheral supply from the meningeal network, oxygen, glucose, and other nutrients now diffuse from the plexus to the ventricular wall where the germinal tissue is developing; this corresponds to the preplate stage (weeks 6–7) (a major role for the choroid plexuses persists, however, as they reach their maximal size at 11 weeks[84]). After week 7, as the CP appears the NT becomes too thick to be fed by extrinsic diffusion alone, and the first intrinsic vessels, actually primitive sinusoid capillaries, enter the brain tissue from the periphery toward the deep germinal areas (VZ first and then SVZ) (see Fig. 3C). These vessels cross the CP without giving it any branch, and form arteriovenous loops in the germinal zone, which expand and develop into a rich vascular plexus by 12 to 15 weeks (see Fig. 3D). The first horizontal branches to enter the deep cortical layers appear at 20 weeks (see Fig. 3E), and progressively become more numerous until 27 weeks (see Fig. 3F). New short radial branches emerge from the superficial network during the last trimester to feed the superficial layers (see Fig. 3G).[82] The development of the cortical vascular system therefore reflects and is adapted to the progressive development of the connectivity during the second half of gestation, especially the last trimester, advancing from the deep to the superficial layers. However, this does not mean that the blood flow is significantly increased. The cerebral blood flow (CBF) measurements performed in prematures (allowing for the limitations inherent to the clinical context in such patients) seem to indicate that the CBF remains low at 10 to 20 mL/100 g/min in the last trimester until term (see Ref.[85] for review). A steep increase of the CBF values occurs after birth, peaking at 70 mL/100 g/min at 5 years before declining to adult levels of 50 mL/100 g/min at the end of the adolescence.[86,87] Surprisingly, the increase seems to occur at the same time after birth in premature and in term infants, and therefore seems to relate to the conditions of extrauterine life rather than to gestational age.[88] These figures represent an average of the blood flows of the gray and white matter: assuming that the blood flow of the white matter does not change much over time and that white matter represents 50% of the brain in volume, the perfusion values of the gray matter in young children are still more remarkable. (Quantitative blood flow data, however, are scarce in that age range and sometimes discordant, given the fragility of the patients and the use of different technical approaches.)

FOCAL CORTICAL DYSPLASIA

Definition and Classification of FCD

In 1971, Taylor and Falconer with Bruton and Corsellis published a series on 10 epileptic patients, in which the parts of the brain where the abnormal electrical activity existed were surgically removed.[1] The investigators noted histologic abnormalities, which lacked the tumor-like expansion of hamartomata and which, for that reason, they called “a particular form of localized cortical dysplasia.” The lesions were characterized histologically by “congregations of large, bizarre neurons which were littered through all but the first cortical layer” with “in most but not all cases, grotesque cells, probably of glial origin, [which] were also present in the depth of the affected cortex and in the subjacent white matter.” The study noted that in all cases the brain surface was normal with no tuber-like appearance; when cut, the cortex looked macroscopically normal in 7 of 10 cases but was wide with blurred junction with the white matter in 3 of 10 cases. Microscopically there was disorganization of the laminar architecture with large aberrant neurons scattered randomly, which stood out by their number, large size, and bizarre structure, and the common presence (7 of 10 cases) of large, multinucleated cells in the deep cortical layers and the white matter. There were reactive astrocytes but no fibrous gliosis, and sometimes a reduction of the myelinated fibers

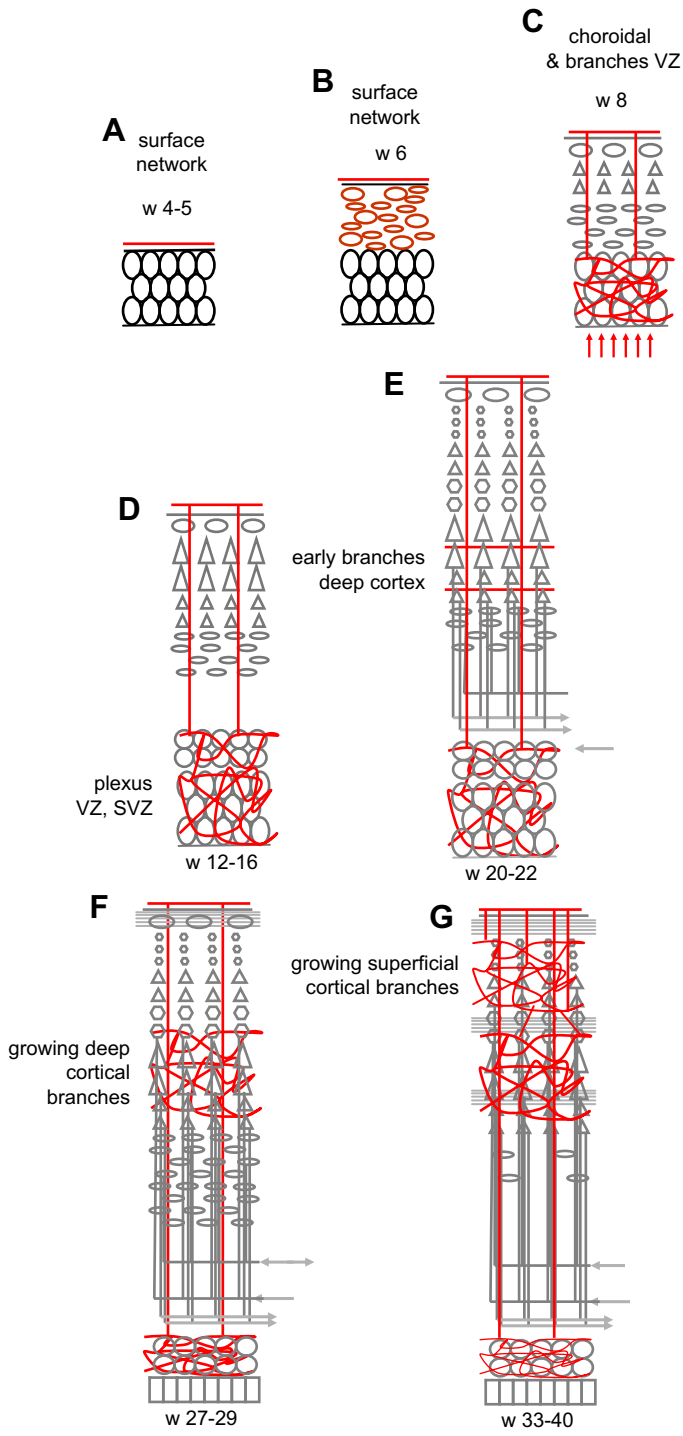

Fig. 3. Development of the vascularity. (*A*, *B*) Weeks 4 to 6. After the neural tube closes, a leptomeningeal network surrounds the brain, from which the nutrients diffuse in the neural tissue. (*C*, *D*) Weeks 8 to 16. About week 7, the choroid plexuses develop so that nutrients may diffuse from the CSF into the VZ. In addition at week 8, perforators from the surface network penetrate into the neural parenchyma toward the proliferative VZ and SVZ, and develop a rich vascular plexus there while the cortex remains essentially avascular. (*E*) Weeks 20 to 22. After midgestation a few horizontal branches develop in the deep cortical layers. (*F*) Weeks 27 to 29. Once the thalamocortical connections are established, a rich vascular network develops in the deep cortical layers. (*G*) Weeks 33 to 40. Superficial cortical vessels develop together with the corticocortical connections in the superficial layers, both from the long perforant vessels and from the pial vessels. The plexus in the proliferative zone regresses.

in the underlying white matter. The investigators mentioned previous reports of findings somewhat similar to theirs, that had been related to formes frustes of tuberous sclerosis, only to mention that their patients did not present the features, either clinical (family history, intellectual delay, other stigmata), radiologic (subependymal nodules, calcification), or histologic (tuber appearance, cellular depopulation), which characterize tuberous sclerosis.[1]

From the perspective of epilepsy surgery in children this article, which defined the entity "focal cortical dysplasia (FCD)," was probably the most seminal in the past half-century. FCD is the single most important cause of focal refractory epilepsy in children, histologically proved in almost 50% of children undergoing epilepsy surgery (20% of adults).[89] With time, it became obvious that it was a heterogeneous entity, with distinct clinical and imaging characteristics, and different surgical responses,[89–93] the surgical indications and the prognosis being closely related with the pathologic subtype, so that classifications were proposed to provide more consistency.[94–96] The classification most widely used until recently ("Cleveland" or Palmini classification[95]) was proposed in 2004 by a panel of experts. It made a clear distinction between the architectural abnormalities (dyslamination, heteropic and misoriented neurons) and the cytologic abnormalities (giant neurons, immature neurons, dysmorphic neurons, balloon cells), with the following 3-tiered classification (from the milder to the more severe histologic changes).

- *Mild malformations of cortical development (mMCD)* are characterized by ectopic neurons located in (type I) or outside (type II) layer 1 (this subgroup replaced the previous subgroup of microdysgenesis). Cases of mMCD were assumed not to be detectable by the then current MR techniques.
- *FCD type I* are characterized by architectural abnormalities (dyslamination of the cortex without or with additional features of mMCD), which may be isolated (type IA) or associated with giant or immature neurons (type IB).
- *FCD type II* are characterized by the presence of monstrous cells in addition to the architectural abnormalities, either dysmorphic neurons only (type IIA) or dysmorphic neurons and balloon cells (type IIB). FCD type II are often referred to as Taylor-type FCD.

This classification has 3 main limitations, the first being that such a grading system suggests different degrees of severity in the same disease entity. The second limitation was revealed by a blinded evaluation of interobserver and intraobserver reproducibility of histologic diagnosis in mMCD-FCD (26 specimens rotated among 8 neuropathologists), which showed that whereas the reproducibility rate was high for FCD type II (especially IIB), it was quite low for mMCD and FCD type I, meaning that except for the monstrous cells of type II, the other subgroups lack an unequivocal morphologic definition.[97] The third limitation is that the classification did not take into account the FCD associated with other disorders including obviously acquired diseases such as sequelae of perinatal hypoxic ischemic encephalopathy, trauma, infection, or strokes.[98–104] For these reasons, a more refined classification is proposed by the Diagnostic Method Commission of the International League Against Epilepsy (ILAE) (which includes the Cleveland classification experts as well).[105] Considering the FCD only (the mMCD is evaluated later), this new classification retains the group of FCD type IIA and type IIB, as it is clearly defined by the monstrous dysmorphic neurons and balloon cells. It better defines type I and introduces a new type III FCD, associated with another, principal lesion.

- FCD type I (isolated)
  - Type IA: abnormal radial cortical lamination
  - Type IB: abnormal tangential cortical lamination
  - Type IC: abnormal radial and tangential lamination
- FCD II
  - Type IIA: dysmorphic neurons
  - Type IIB: dysmorphic neurons and balloon cells
- FCD III (associated with principal lesion)
  - Type IIIA: abnormal temporal cortical lamination associated with hippocampal sclerosis (HS)
  - Type IIIB: abnormal cortical lamination adjacent to a glial or glioneuronal tumor
  - Type IIIC: abnormal cortical lamination adjacent to a vascular malformation
  - Type IIID: abnormal cortical lamination adjacent to any other lesion acquired during early life (eg, trauma, ischemia, infection).

Note that should an FCD type II be associated with another lesion, it would not be considered a subgroup of FCD III but the association of two principal lesions. Also, it is proposed that by convention the use of the term "dual pathology" be restricted to cases of HS presenting with a second principal lesion of the brain (tumor, vascular malformation, glial scar, encephalitis, MCD

including FCD type II), even outside the ipsilateral temporal lobe.

As is implicit in the classification, FCD are pathogenetically heterogeneous. FCD type II is characterized by monstrous cells and is assumed to be truly developmental (this is supported by the similarities between FCD type II and TSC brain lesions). The dysmorphic neurons may present with either a pyramidal or an interneuronal phenotype,[105] so that apparently the cellular dysplasia may affect different cellular lineages. The balloon cells are consistent with dysplastic glia,[105,106] which is the same lineage as the pyramidal dysmorphic neurons. White matter changes may be mild or severe, and have been related to a heterotopic distribution of dysplastic cells and neurons along the path of migration, a lack or loss of myelin, inflammation, oligodendrocytic satellitosis, and astrocytosis.[107] In the classification of MCD,[11] FCD type II accordingly is understood as a defect of proliferation/apoptosis. Moreover, there is some evidence that it could result from an excessive neurogenesis and retention of preplate cells in the late phases of late corticoneurogenetic (first half of second trimester).[108] FCD type I and mMCD are classified as organization disorders[11]: abnormal retention of the radial cortical pattern, lack of tangential lamination, and giant and immature neurons may relate to a true dysplasia or to a disruption of the normal cortical development occurring as late as during the neonatal period.[98–104]

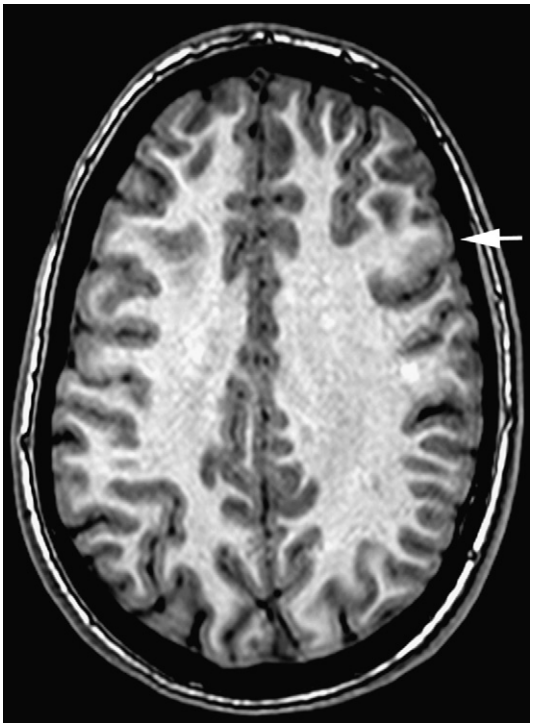

Fig. 4. Left frontal FCD II. T1 high-definition image demonstrates a cortical thickening with cortical-subcortical blurring on the sulcal side of the gyrus (*arrow*).

Imaging of FCD

In clinical situations, FCD is the most difficult MCD to diagnose with MR imaging. Various strategies have been suggested over the years to improve the detection rate of the lesion using MR, electroclinical data, and complementary functional/metabolic imaging modalities.[49,58,59,109–115] As a rule, the less severe the dysplastic changes, the more likely the MR is to appear normal.[116] The diagnostic efficacy obviously depends on better equipment (high magnetic fields, multiple phased array coils) and greater expertise of the neuroradiologist.

FCD type II presents the most characteristic appearances (**Figs. 4–8**)[22]: an increased cortical thickness with a blurring of the cortical-subcortical junction (see **Fig. 4**); a high T2/FLAIR signal of the cortex; a low T1, high T2/FLAIR signal in the subcortical white matter (see **Fig. 5**), sometimes tapering from the cortex to the ventricular wall, so reproducing the migration path (this "transmantle dysplasia" is practically pathognomonic of a FCD type IIB[117]) (see **Fig. 6**). The lesion may be small, sulcal, centered at the very bottom of a sulcus that is deeper than its contralateral counterpart[118]; there it may appear as a focal, strictly cortical clear-cut bright T1 signal (see **Fig. 7**). The lesion may extend along the walls of the sulcus, or may affect the crown of the gyrus, or the whole gyrus between 2 sulci; the gyrus then may be somewhat bulky. It may uncommonly mimic a tuber (see **Fig. 8**). Large FCD type II may also be multigyral or lobar, usually with an abnormal gyration pattern. It may rarely also be multiple, unilateral or bilateral.[119] When large FCD type II lesions are so large as to occupy a large part of the hemisphere, they are referred to as partial, or lobar, hemimegalencephalies (HME). FCD type IIB presents only rarely without any MR abnormalities (4%); this occurs more often with FCD type IIA (22%).[116] However, as mentioned earlier, a normal-appearing white matter may reflect mild pathologic changes[107] with increased diffusivity and decreased fat attenuation only.[39,112,120]

FCD type I, when typical, is different (**Figs. 9–11**). The main features are a diffusely bright T2/FLAIR signal of the white matter as compared with the other side, with a consequent loss of the gray/white contrast (often designated as a blurring of the gray-white junction, different from the progressive gradient of cellularity that is seen in

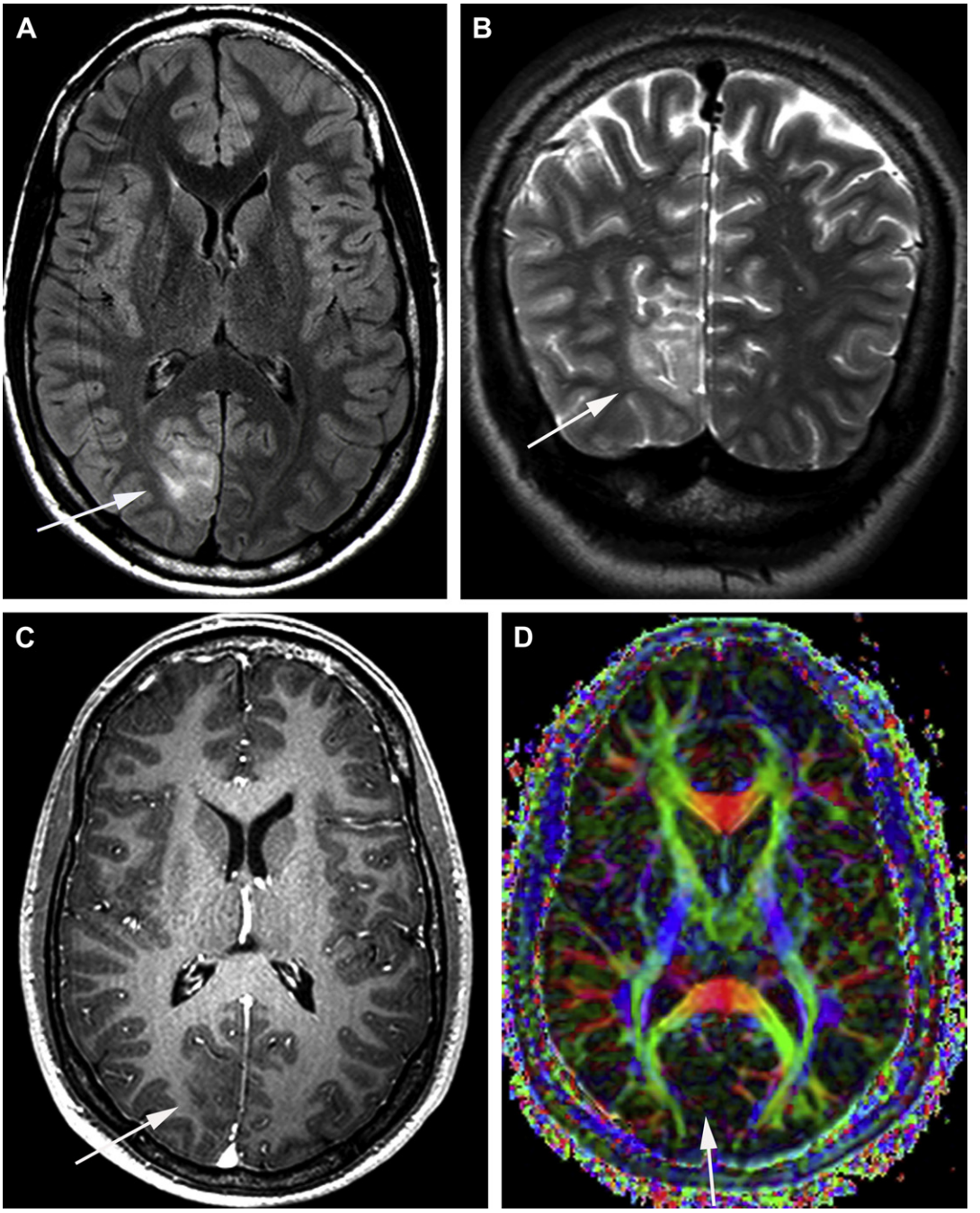

Fig. 5. Right occipital FCD II. (*A*) Bright FLAIR signal in the white matter and cortex of the cuneus (*arrow*). (*B*) Similarly bright signal on T2TSE (*arrow*). (*C*) Low T1 signal of the white matter blurring the cortico-subcortical junction (*arrow*); no contrast enhancement. (*D*) Fractional anisotropy (FA) color map demonstrates a lack of transverse fascicular organization in the white matter of the cuneus (*arrow*).

FCD type II) (see **Fig. 9**) and a smaller volume of the involved portion of the brain (this is more evident when it affects the temporal lobe). The lesion is usually extensive, and its limits are not clear: multilobar or hemispheric involvement are more common in FCD type I than in FCD type II,[116] with a more common cognitive impairment. The cortex may present a high T2/FLAIR signal, though less commonly than in FCD type II,[116] and a well-defined transmantle dysplasia is never

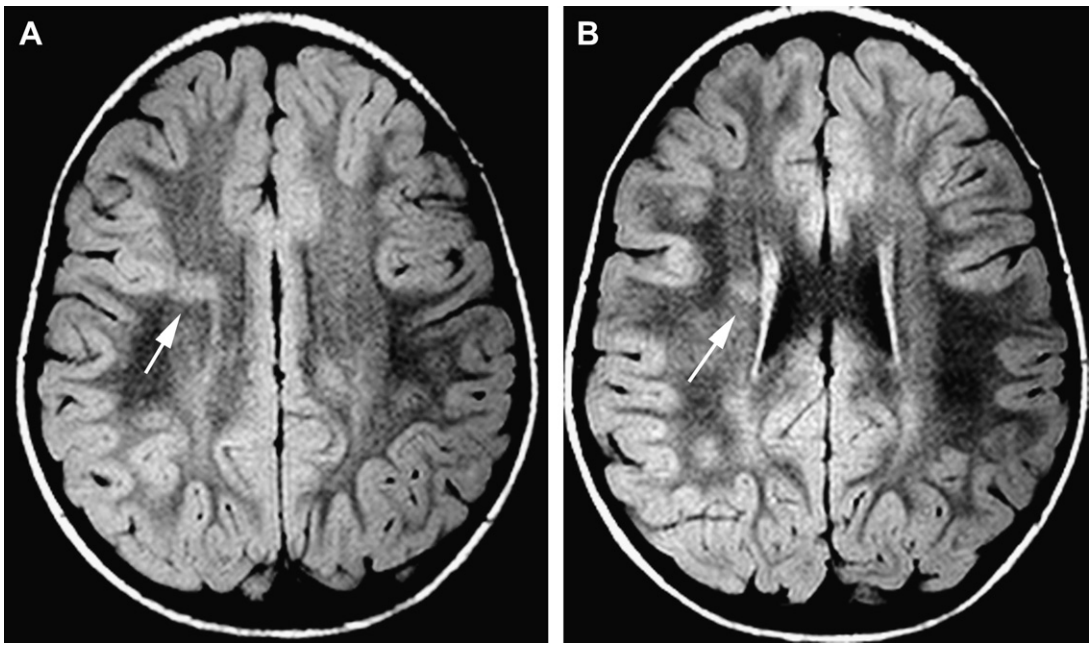

Fig. 6. Transmantle dysplasia (FCD IIB). (*A*, *B*) Axial FLAIR. There is cortico-subcortical blurring of the right precentral cortex with a streak of high FLAIR signal extending from the depth of the sulcus to the ventricular wall (*arrow*). This pattern is practically pathognomonic for FCD IIB (with balloon cells).

found in FCD type I. The brain may appear normal in 20% to 29% of the cases (see **Fig. 10**), which is not different from type IIA (22%). There is no way to differentiate the 3 subtypes of FCD type I.

FCD type III is characterized by the association of a FCD type I with a principal lesion adjacent to it[105] (**Figs. 12–16**), which may be a HS (FCD type IIIA) (see **Fig. 12**), a developmental tumor such

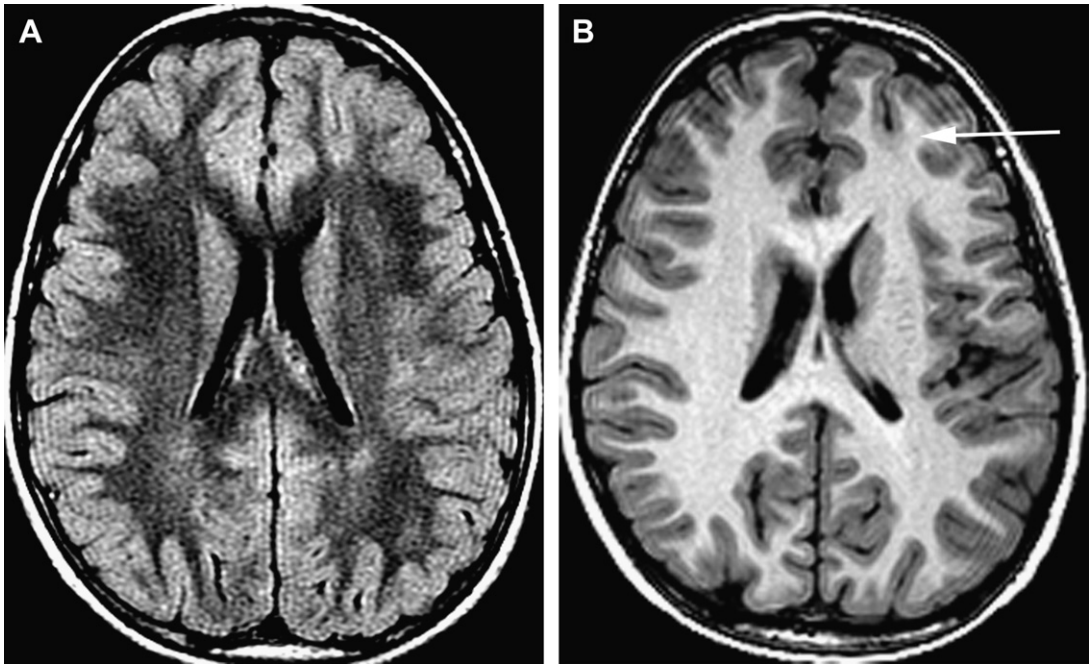

Fig. 7. Bottom-of-the-sulcus FCD II. (*A*) Axial FLAIR. The image is essentially unremarkable except that the superior frontal sulcus on the left side appears to be deeper than on the right side. (*B*) Thin T1 imaging demonstrates a bright T1 signal of the cortex in the bottom of this abnormal sulcus (*arrow*); this is highly suggestive of FCD II.

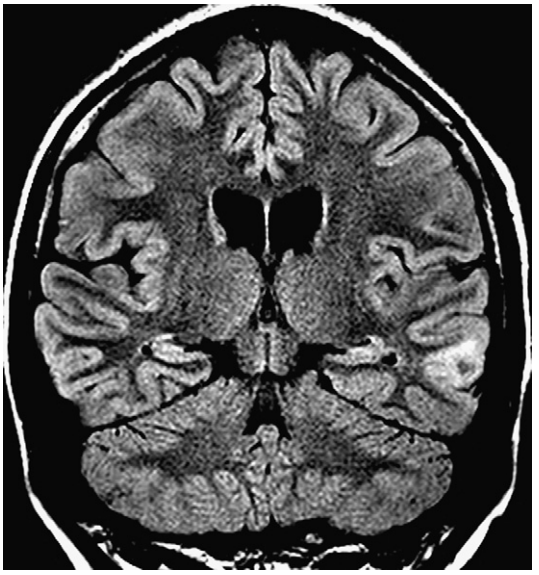

Fig. 8. Tuber-like FCD II. The appearance of the lesion would suggest a cortical tuber of TSC. The lesion, however, is isolated and no clinical or genetic evidence of TSC is found. Therefore, the name "forme fruste of TSC" is not appropriate.

as a DNET or a ganglioglioma (FCD type IIIB) (see **Fig. 13**), a vascular malformation such as a meningioangiomatosis or a cavernoma (FCD type IIIC) (see **Fig. 15**), or a destructive lesion such as an encephalomalacia or porencephaly (FCD type IIID) (see **Fig. 16**). Diffuse lesions that are not adjacent to the cortical dysplasia (periventricular leukomalacia, hydrocephalus, nonspecific atrophy, ventriculomegaly, and gliosis) are not uncommon and are associated mostly with FCD type I and mMCD.

mMCD (formerly cortical microdysgenesis) presents with normal MR more often than the other forms of cortical dysplasia (50%).[116] The most usual findings otherwise are a diffuse bright signal in the white matter effacing the contrast between gray and white, and a lobar hypoplasia (25%), which is usually not as extensive (multilobar or hemispheric) as in FCD type I[116] (**Figs. 17** and **18**). The cortex is never thick and never bright on T2/FLAIR.[116]

Other microdysgeneses

Besides the neuronal heterotopia that characterizes mMCD, other histologic abnormalities have been demonstrated in the cortex of epileptic patients, which are usually included as variants of microdysgenesis and may clinically and radiologically present like FCD. One has been described as a cortical perivascular satellitosis, or perivascular clustering, in which the cortical vessels are surrounded by rounded neural cells, presumably oligodendrocytes.[121,122] Another one is characterized by unique cortical astrocytic inclusions in young patients who presented with developmental delay and seizures in the first year of life, with intracellular accumulation of Filamin A[123] (**Fig. 19**); this has been observed in Aicardi syndrome as well.[124] A last epileptogenic disorder

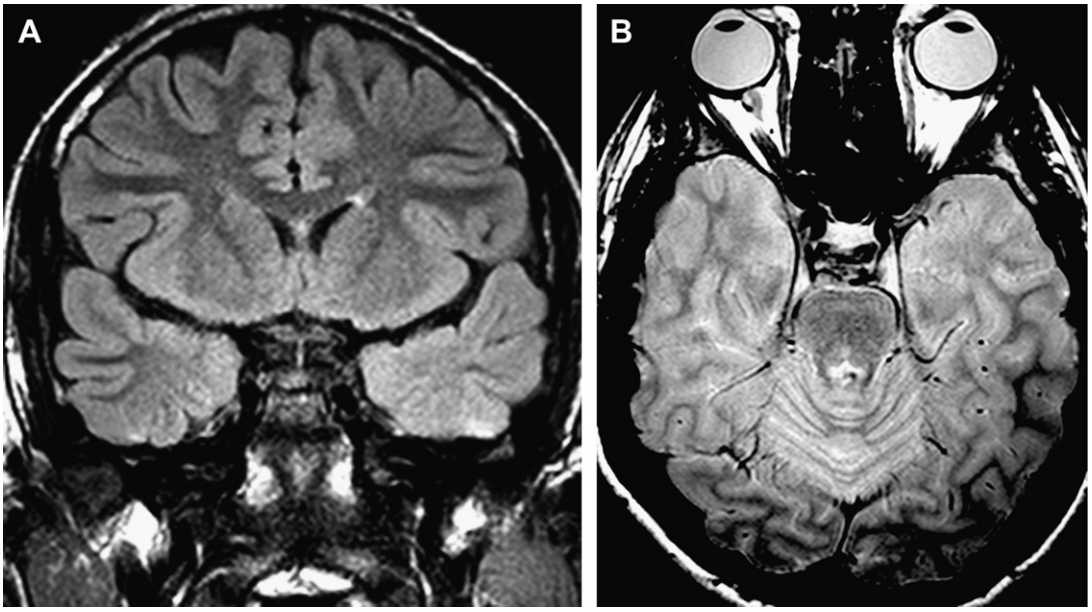

Fig. 9. Left temporal FCD I. (*A*) Coronal FLAIR. As compared with the right side, the gyral digitations of low signal appear effaced on the left. (*B*) This is also apparent on this axial PD image.

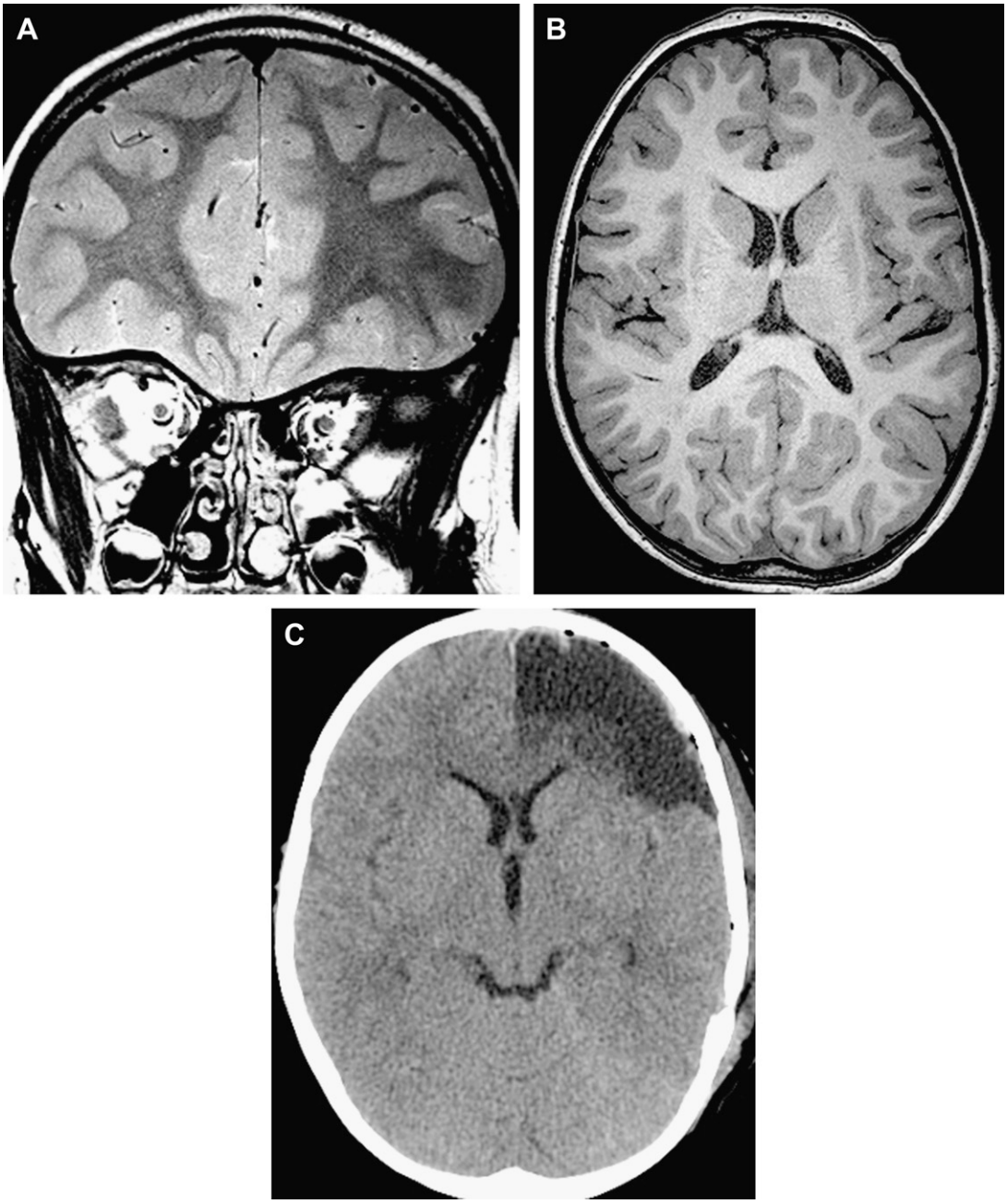

Fig. 10. FCD I, normal appearance. (*A*) Coronal PD. No abnormality was found in this patient who presents with a left frontal seizure focus. (*B*) Axial high-definition T1. No abnormality is found here either. (*C*) Postsurgical CT. The patient was operated on according to the MEG abnormalities, with large anterior frontal lobectomy. Pathology demonstrated diffuse abnormalities consistent with FCD I.

presenting like an FCD on MR imaging is oligodendroglial hyperplasia, which is an infiltration of the juxtacortical white matter by nonneoplastic oligodendrocytes (Fig. 20).[125]

The features to look for in the diagnosis of mMCD/FCD are summarized as follows:

- The cortical thickness, the gradual cortical blurring, the excessive depth of a sulcus as compared with its contralateral homolog, the bright T1, T2, and FLAIR cortical signal changes, the focal, often wedge-shaped low T1, bright T2, and FLAIR T2

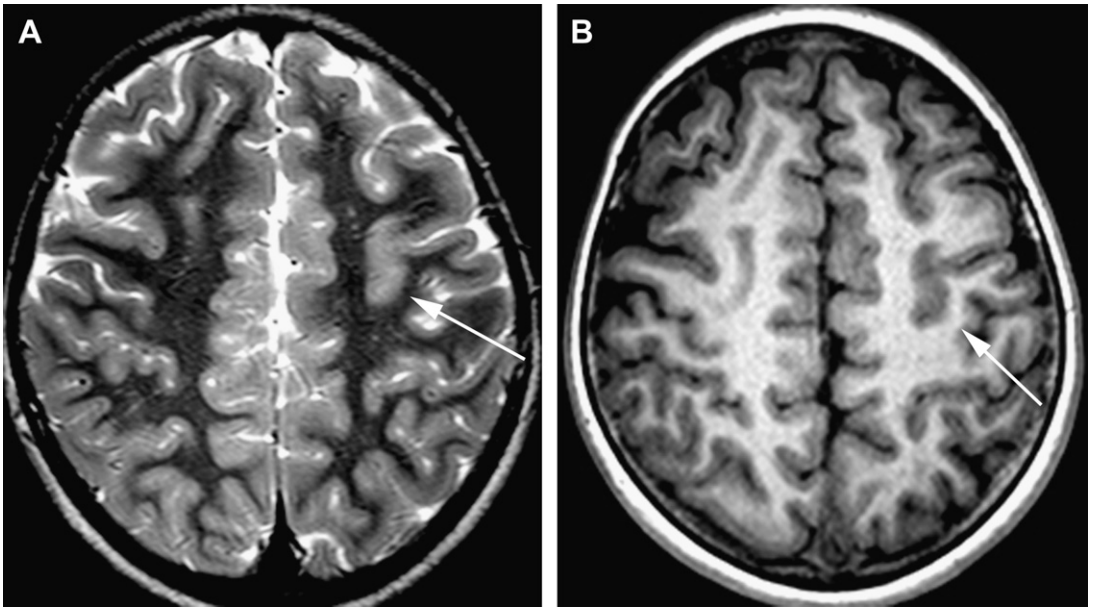

Fig. 11. FCD I. (*A, B*) Abnormal thickness and blurring of the cortex of the posterior segment of the left superior frontal sulcus on both T1 and T2 images (*arrow*), suggestive of FCD II. Pathology disclosed an FCD I, however.

signal of the white matter all suggest an FCD type II
- A normal cortical thickness, a diffusely (eg, lobar) increased signal of the white matter on T2/FLAIR, and a smaller lobe or smaller hemisphere suggest an mMCD or FCD type I
- A normal MR image does not exclude an FCD.

Hemimegalencephaly

HME is considered a hemispheric variety of FCD type II. The malformation is unilateral, characterized by the asymmetric expansion of all or most of the hemisphere (**Figs. 21–24**). Although a right predominance has been reported,[126] either hemisphere may be affected. The clinical picture associates an asymmetric macrocephaly; early onset, severe epilepsy (often Ohtahara or West syndrome); a unilateral deficit; a developmental delay; and a poor functional and vital prognosis.[126–128] The only possible treatment is an anatomic or functional hemispherectomy.[128] There are 3 groups of HME, all sporadic (except for NF1): the isolated HME (restricted to the hypertrophic/dysplastic hemisphere), the syndromic HME in which the malformation is part of a neuroectodermal syndrome (epidermal nevus/linear nevus sebaceous; hypomelanosis of Ito; Proteus; Klippel-Trénaunay; NF1; TSC) (see **Fig. 24**), and the total HME in which the ipsilateral half of the brainstem and cerebellar hemisphere are augmented as well.[126–130] The pathology, imaging, and clinical features are essentially the same in all 3 groups.

Histologically, the abnormalities are both neuronal and glial. The cortex is dislaminated with a blurring of the gray-white junction and an abnormal gyration; giant neurons are scattered in the cortex and the white matter; the glia is hypertrophic and glial balloon cells also are distributed in cortex and white matter; the hypertrophic white matter may demonstrate demyelination with association of Rosenthal fibers.[127,131] The abnormalities are so widespread that the lesion has been considered a hamartoma or a tumor.[127,131] The origin of HME is not known, and has been proposed to be an early primary disorder of neuroepithelial lineage and cellular growth with secondary migratory disturbance,[132] or on the contrary an overproliferation of progenitor cells in later cell cycles, with partial failure of postneurogenesis apoptosis in the MZ and SP.[133]

Imaging of HME rests on MR and, to a lesser extent, CT. The appearance of the brain may be very different in different patients: sometimes large but morphologically close to normal, sometimes grossly dysmorphic (see **Figs. 21–24**). The hemispheric involvement also may be only partial, either anterior or, more commonly, posterior (see **Figs. 21** and **22**).[134] The main radiological features are as follows.

- Asymmetry between the hemispheres, the large one sometimes being grossly dysmorphic. The occipital lobe may be so

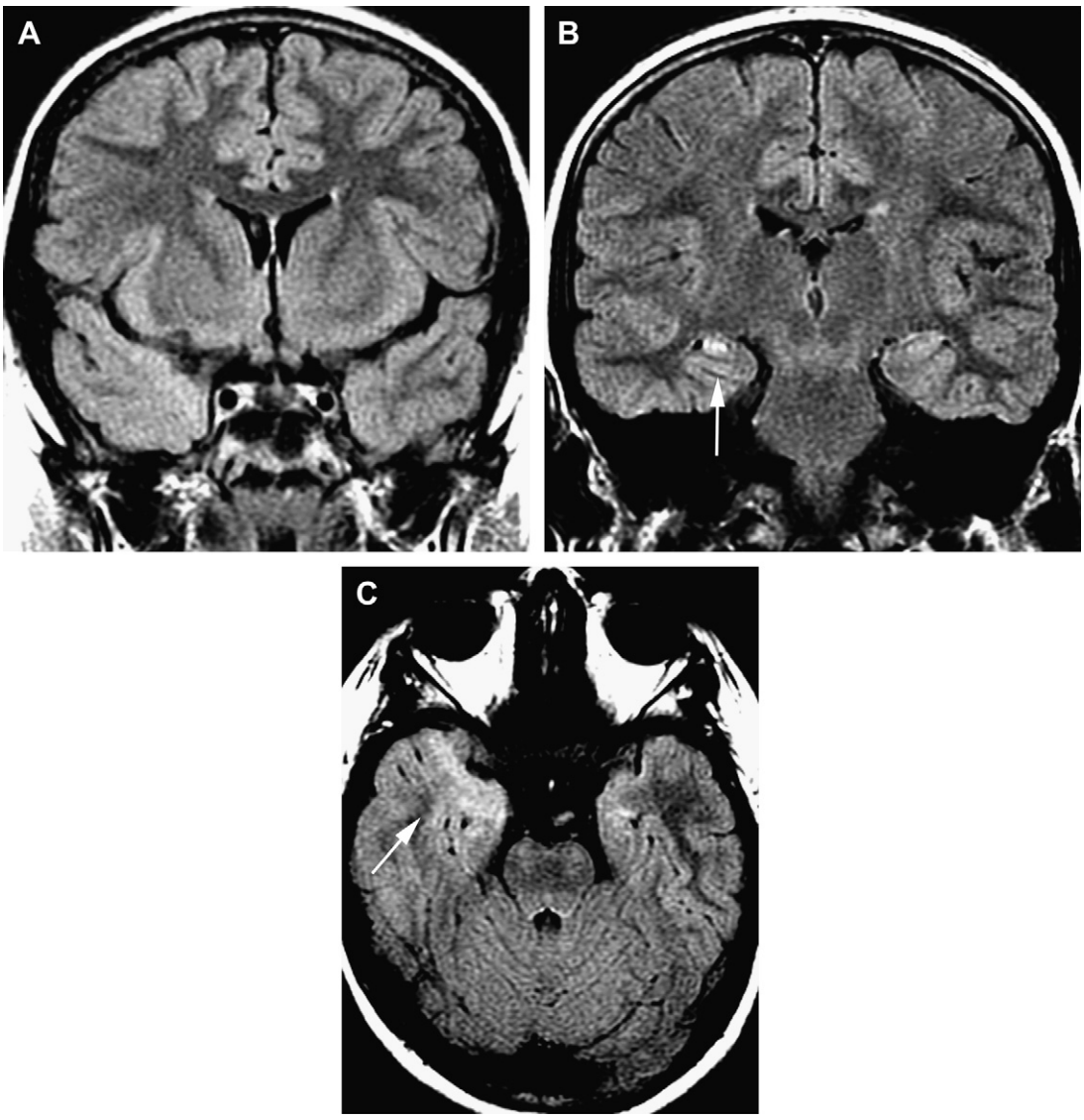

Fig. 12. FCD IIIA. (*A*) Coronal FLAIR. The normal low signal of the anterior temporal white matter is lost on the right side. (*B*) Coronal FLAIR. This posterior coronal image demonstrates a bright signal and atrophy of the right hippocampus (*arrow*). This association of hippocampal sclerosis and adjacent likely FCD of the temporal lobe characterizes FCD IIIA. (*C*) Axial FLAIR. Ill-demarcated bright signal of the anteromedial temporal pole (*arrow*).

disproportionately prominent as to be displaced with the falx across the midline toward the other side. It must be noted that in rare cases, the large hemisphere may develop atrophy, presumably because of the severe epilepsy with repeated episodes of status epilepticus.[135]

- The ipsilateral ventricle is typically enlarged (see **Figs. 21** and **23**), although it may rarely be small. It is sometimes markedly deformed, due to poor organization of the hemisphere. The frontal horn may be straightened and even effaced, presumably because of abnormal adjacent white matter tracts. The atrium may be colpocephalic.
- The gyral pattern is abnormal, often with shallow sulci, and may associate areas that resemble lissencephaly, pachygyria, and/or PMG (see **Figs. 21**, **22**, and **24**). Gray matter heterotopias also are common. The cortical ribbon usually is thick with a blurred cortico-subcortical junction (see **Fig. 23**).

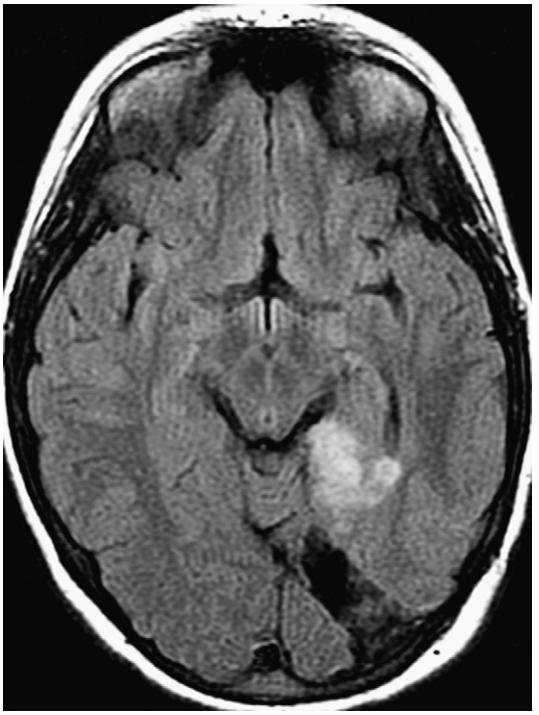

Fig. 13. FCD IIIB. Left posterior temporal DNET. Removal of the adjacent cortex disclosed an FCD. The association of a developmental tumor with adjacent FCD defines the FCD IIIB.

- The white matter is typically hypertrophied. In infants it may show early myelination,[136] presumably an effect of the seizure activity. On the contrary, in older children it may remain bright on T2/FLAIR because of absent or incomplete myelination. If looked for, calcification is not uncommon on CT, presumably dystrophic. The corpus callosum may be dysmorphic, with partial hypoplasia or, on the contrary, prominent. The septum pellucidum may be dislocated toward the abnormal frontal lobe and abnormally thick, which has been related to an abnormal fascicle of white matter (see **Fig. 22**).[137,138] The ipsilateral olfactory and optic nerves (which are truly white matter) may also be enlarged in a significant number of cases.[139]
- The contralateral hemisphere is insufficiently developed in patients with HME.[133]

DISORDERS OF PROLIFERATION/APOPTOSIS: MICROCEPHALY, MACROCEPHALY

Microcephaly

Terminology

Microcephaly describes a small head, which may be due to a destructive process (hypoxic-ischemic encephalopathy), a disruptive process (TORCH), a degenerative process, or a primary malformation. Over the last decades, the evolving terminology introduced to clarify the concept of primary malformation has resulted in some confusion. Among the attempts at finding a proper name was the early introduction of the term "microcephalia vera" (true microcephaly) to stress the developmental nature of the abnormality against any instance of prenatally or postnatally acquired microcephaly. The term "microencephaly" instead of microcephaly was meant to make it clear that it was the brain (encephalon) that was too small, not the head; it was not retained. "Radial microbrain" was proposed to express the fact that it was the radial expansion of the brain that was primarily abnormal, not so much its shape, and "microlissencephaly" to stress the importance of the simplified gyral pattern, leading, however, to some confusion with true lissencephaly. "Microcephaly with simplified gyral pattern" was then suggested, but is now replaced with "autosomal recessive primary microcephaly" (MCPH) (OMIM #251200), "autosomal dominant microcephaly" (OMIM #156580), and "X-linked microcephaly" (OMIM #309500).[140] These terms describe conditions in which the microcephaly is isolated, as opposed to the syndromic microcephalies in which the small brain is part of a constellation of features.[140,141] Finally, the use of term "primary microcephaly" should be restricted to the cases in which the small size of the brain is the principal abnormality: this restriction eliminates the instances of small brains that result from another malformation such as, for example, a lissencephaly or a holoprosencephaly.

Clinically, microcephaly is defined by a head circumference at −3SD below the mean (there is some disagreement, and the mark varies from −4SD to −2SD). The body height and weight must be close to normal and if less, not in proportion to the microcephaly. Children present with a stable mental retardation, mostly affecting speech but allowing for the majority of self-care. There should be no spasticity, but seizures may occur.[142] From a neuropathological point of view, descriptions are scarce and do not help in the definition of the disease: the cerebral hemispheres are small and the convolutional pattern is simplified; this seems related to a poorly expanded cortex and white matter while the central gray matter is better preserved; the cerebellum may or may not be involved; there may be minor abnormalities of the cortical architecture, such as a retained columnar arrangement and occasional heterotopia.[2] The genetics are better known. Eight loci of MCPH have been identified.[143] Mutations in the gene *ASPM* (on MCPH5, 1q31.3) account for 50% of cases and

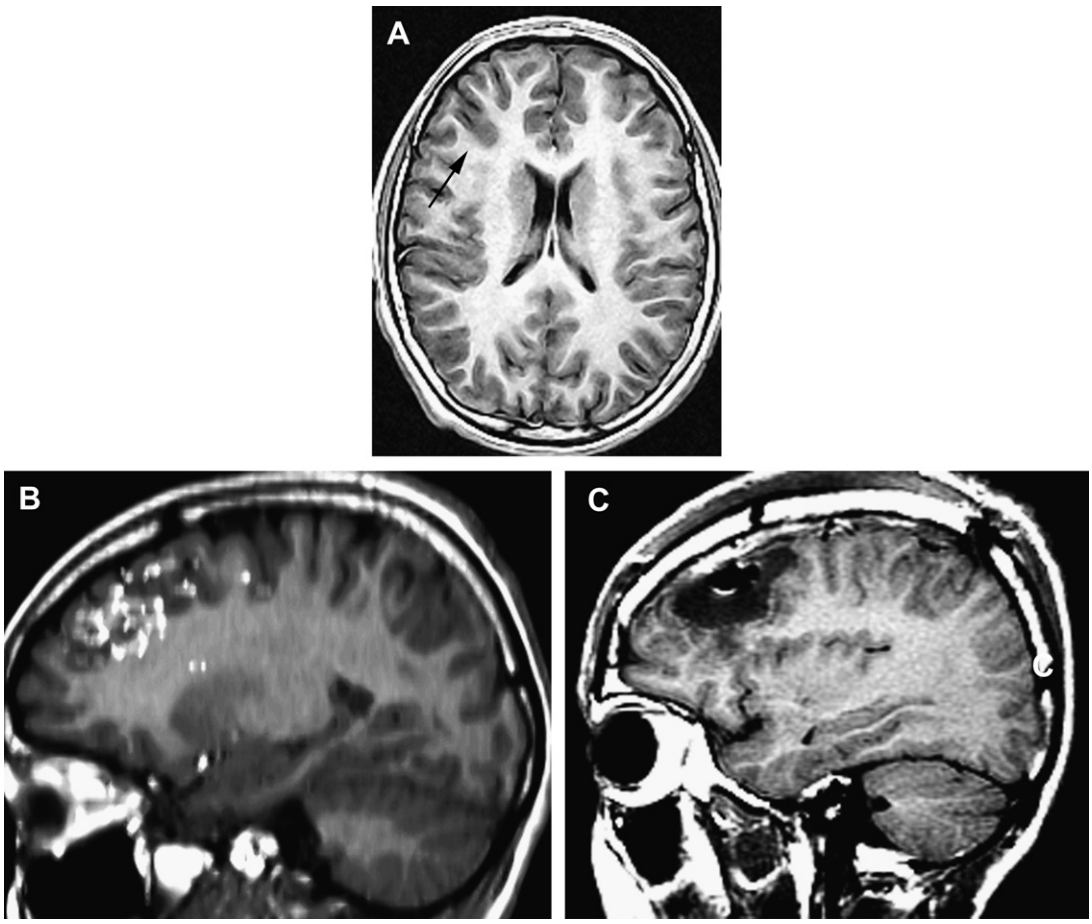

Fig. 14. FCD IIIB. (*A*) Axial high-definition T1. Thick cortex with cortico-subcortical blurring suggests FCD II (*arrow*). (*B*) MEG demonstrates an extensive epileptogenic zone. (*C*) Large frontal corticectomy. In addition to a FCD II corresponding to the abnormal cortex shown by imaging, pathology demonstrated extensive adjacent cortical changes consistent with FCD I.

mutations of MCPH2 (gene not identified) for 10%.[143] Other genes identified are *microcephalin* on MCPH1 (8p23), involved in DNA damage repair; *CDK5RAP2* on MCPH3 (9q33.2), *CENPJ/CPAP* on MCPH6 (13q12.12), and *STIL/SIL* on MCPH7 (1p33). These genes are all involved, like *ASPM* on MCPH5, in the processes of cellular mitosis.[143]

Pathogenesis

The malformation results from a disorder of brain growth. It has been observed by ultrasonography of microcephalic fetuses that the head measurements were normal until 20 weeks, while microcephaly was patent by 32 weeks and persisted afterwards.[142] Given this fact, and that the genes mutated are involved in the processes of cellular division of the radial glia and neuronal progenitors, it is assumed that the primary cause is an insufficient neurogenesis. As most of the brain growth is due to the connectivity, and therefore to the multiplication of the axonal branching within the cortex, a defective pool of neurons would result in a defective tangential growth of the cortex (less gyrus formation) and in a reduced volume of the white matter, while the cortical thickness would be grossly unchanged.

Imaging

If the child presents the features of a syndrome of which microcephaly is a defining feature, brain imaging aims to assess the brain rather than make the diagnosis.

On the contrary, the main purpose of imaging the isolated microcephaly is to rule out what is not a primary microencephaly: acquired disorders include sequelae of prenatal brain infections, perinatal injury, or a degenerative disease. Malformations in which the microcephaly is prominent without being the defining feature, such as holoprosencephaly, classical or atypical lissencephaly,

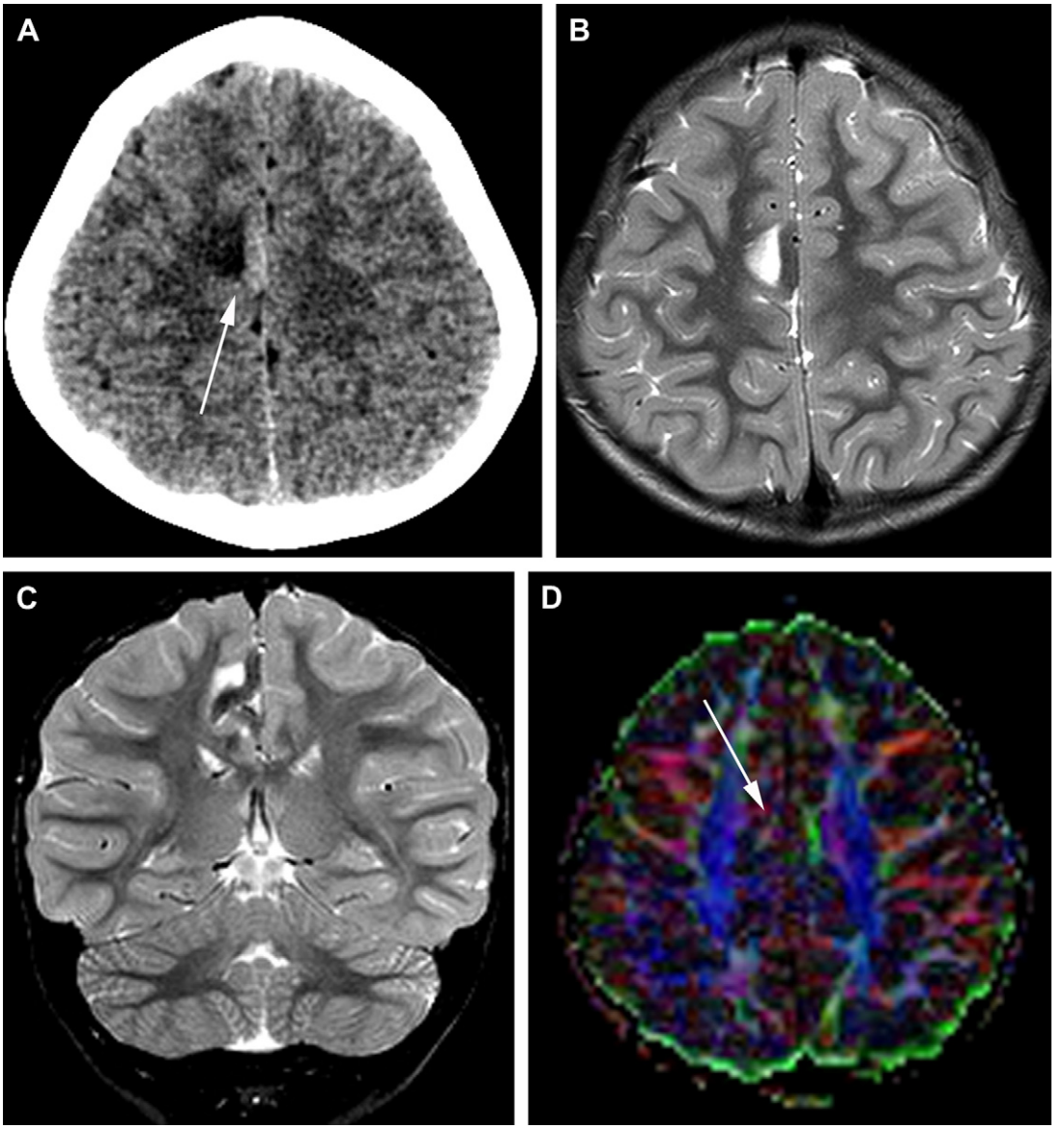

Fig. 15. FCD IIIC. Meningoangiomatosis. (*A*) Unenhanced CT. Small focal area of low attenuation with adjacent dense, likely calcified medial frontal cortex (*arrow*). (*B*) Axial T2. Demonstration of the corresponding MR image, with low signal of the calcified cortex and bright signal of the white matter. (*C*) Coronal T2. The lesion affects both the superior frontal and the cingulate gyri. (*D*) FA color mapping. The lack of parasagittal fibers of the cingulum in the lesion is demonstrated (*arrow*).

cobblestone cortex, polymicrogyria, or schizencephaly, should be excluded as well.

Once these diagnoses are ruled out the microcephaly is likely to be primary, therefore genetic. There are very few radiologic descriptions of MCPH, but in a recent study Adachi and colleagues[144] retrospectively analyzed a large series of 119 clinically diagnosed cases of presumably primary microcephaly. These investigators found that the gyral pattern could be considered as normal in 16 of 119 cases and severely abnormal in 27 of 119, and that the degree of severity globally reflected the severity of the microcephaly. The lack of volume of white matter also grossly correlated with the severity of the microcephaly. The corpus callosum was normal in 28 of 119 patients, thin in 59 of 119, and incomplete or absent in 26 of 119. These findings match the assumption that the disorder results from a deficient pool of neurons with a consequent lack of

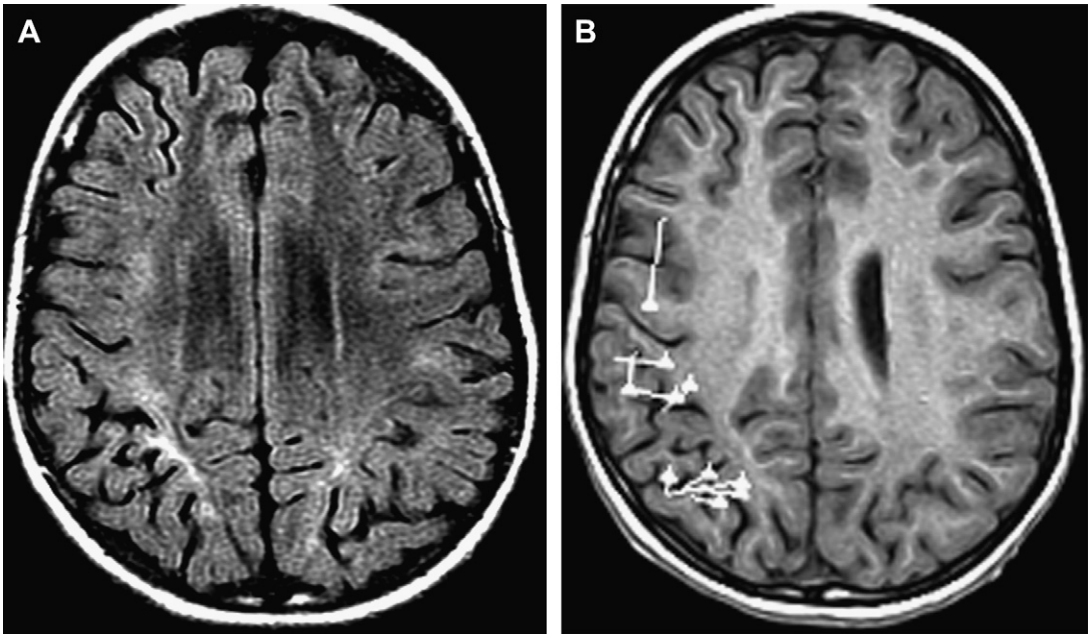

Fig. 16. FCD IIID (perinatal hypoglycemic injury). (*A*) Axial FLAIR. Bilateral parieto-occipital parasagittal bands of gliosis and ulegyria in a child who suffered from a severe hypoglycemia shortly after birth. (*B*) MEG demonstrated a unilateral, right-sided epileptogenic focus. The child was operated on and an FCD associated with the gliotic scar was demonstrated.

connectivity. Periventricular heterotopia was found in few cases (7/119); myelination was delayed in 32. The finding that the majority of patients have normal basal ganglia and thalami would suggest that in general, the pathogenesis of microcephaly relates to a disorder of the dorsal pallial germinal matrix. However, the finding that 30 of 119 patients present small basal ganglia and/or thalami may define a subgroup with a defect of the germinal matrix of the ganglionic eminence as well. Similarly, the fact that the cerebellum may be in proportion to the brain (45 cases), small relative to the brain (19 cases) or, on the contrary, large (54 cases), may also suggest different disease processes. No correlation with genetic studies could be done in this retrospective study, but the radiological phenotype of primary microcephaly appears somewhat heterogeneous (**Figs. 25** and **26**).[144]

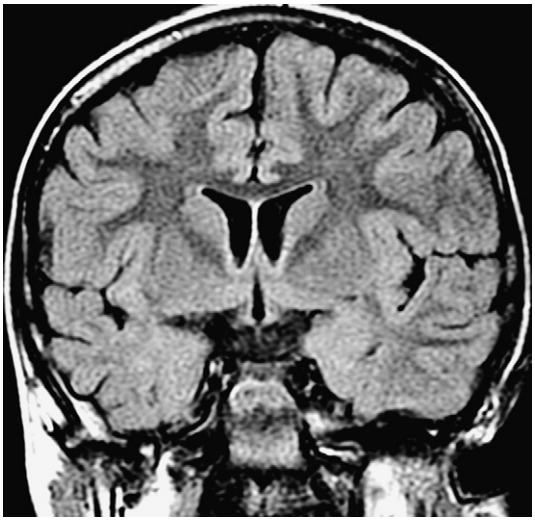

Fig. 17. mMCD (formerly microdysgenesis). This coronal FLAIR image demonstrates a loss of white matter signal in the temporal lobe and a small right hemisphere. After surgery, pathology disclosed mMCD (although the diffuse atrophy would rather suggest FCD I).

Besides the presentation of the classical "proportionate" microcephaly, a mention should be made of patients who come to MR with a diagnosis of developmental delay without a formal microcephaly, present a lack of white matter with ventriculomegaly and abnormal corpus callosum, and demonstrate a poor development of the anterior portion of the temporal lobes (this can be identified by drawing two lines along the superior and inferior borders of the temporal lobes: these line should be parallel—there is underdevelopment of the temporal lobes if they converge anteriorly).[145]

Macrocephaly/Megalencephaly Syndromes

There is no isolated primary megalencephaly, but megalencephaly may be a salient feature of many syndromes.[141,146] As a consequence, the

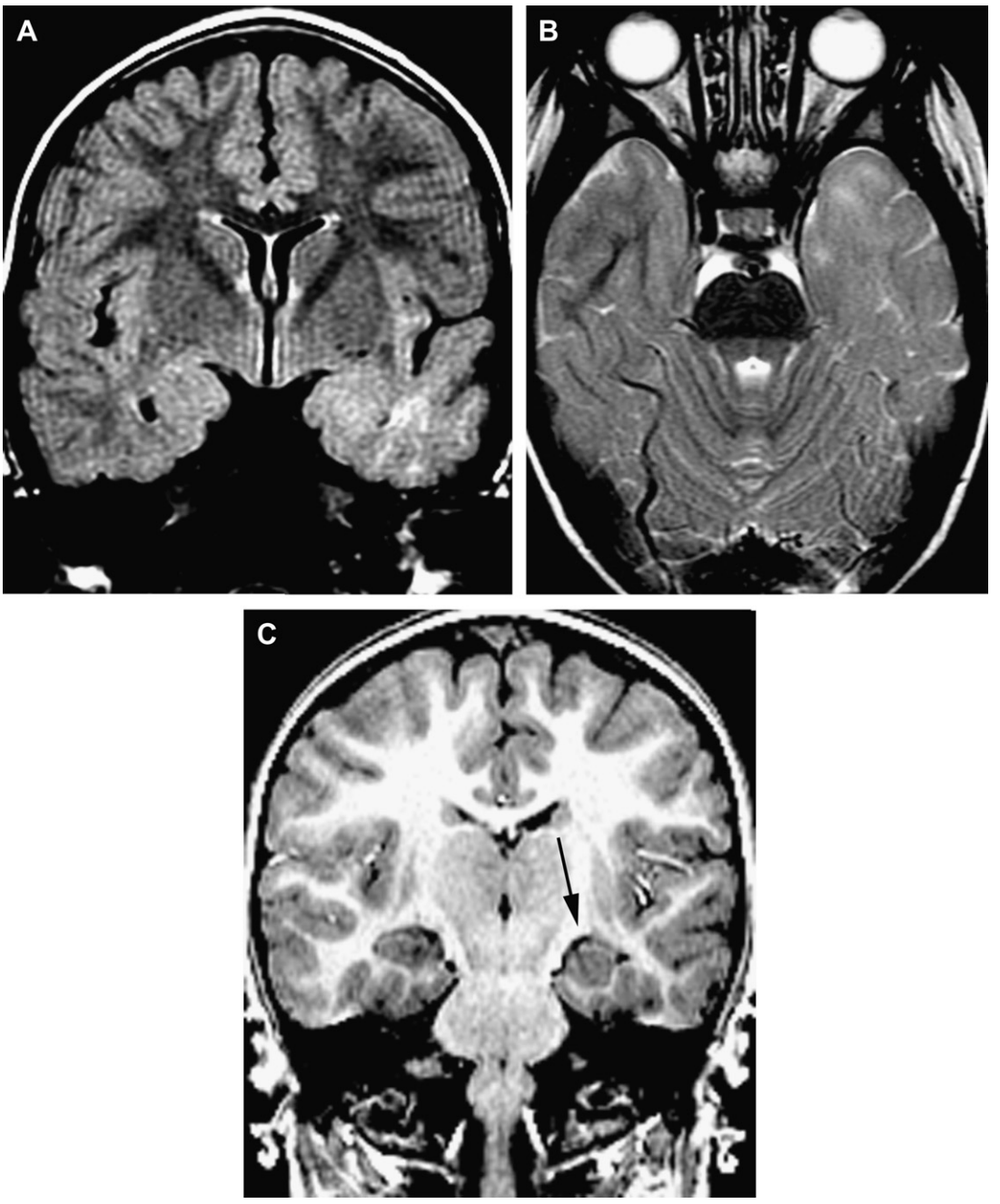

Fig. 18. mMCD (formerly microdysgenesis) associated with hippocampal dysplasia. (*A*) Coronal FLAIR demonstrates diffuse bright signal of the anterior left temporal lobe with some loss of volume. (*B*) Axial T2 demonstrates the diffuse loss of contrast between the cortex and the white matter in the left temporal lobe. (*C*) Coronal high-definition T1 demonstrates a rounded, bulky, dysplastic hippocampus (*arrow*). After surgery, pathology disclosed mMCD of the temporal lobe and dysplasia of the hippocampus.

role of imaging is either to rule out a nonmalformative cause for a macrocephaly without or with megalencephaly (thick calvarium and other skull bone dysplasia, hydrocephalus, metabolic diseases such as Alexander or Canavan, storage diseases), or to assess the brain in case of syndromic megalencephaly. The diagnosis of benign familial megalencephaly is made clinically because there is no neurologic or neurocognitive impairment. Clinically and pathologically, unilateral

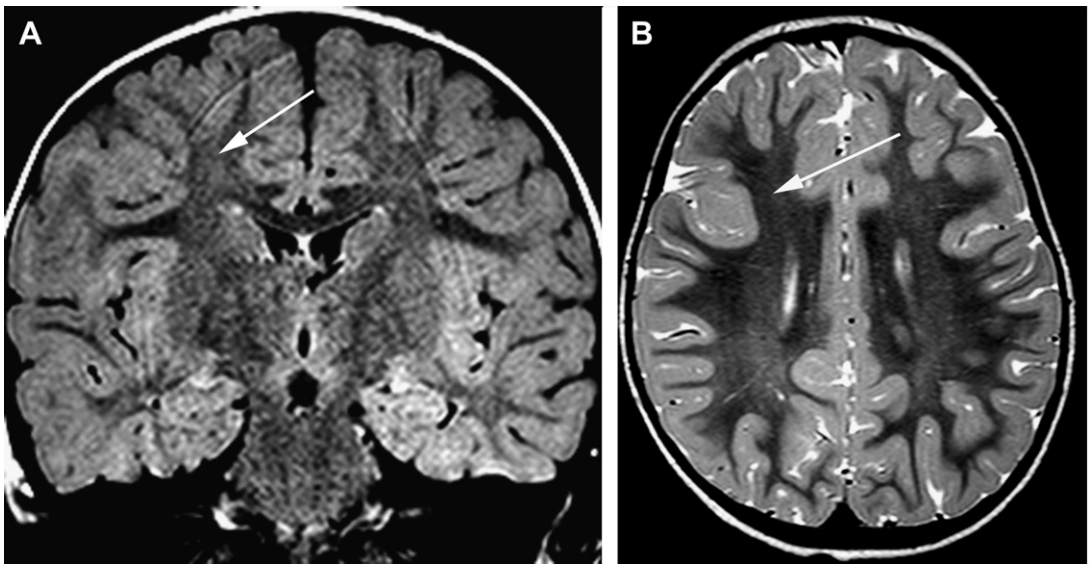

Fig. 19. Cortical dysplasia with astrocytic inclusion of filamin A. (*A, B*) Coronal FLAIR and axial T2 demonstrate an abnormal deep sulcation in the right lateral frontal lobe (*arrow*). Pathology demonstrated a dysplastic cortex and white matter, with astrocytic inclusions corresponding to intracellular accumulation of filamin A.

megalencephalies (hemimegalencephaly), either isolated or syndromic, belong to the group of the cortical dysplasia type II.

From a morphologic point of view, megalencephaly is defined by the head circumference being above 98% (+2SD), explained by the presence of a proportionately large brain parenchyma. Pathologically the volume of the brain is increased, with bulky gyri. The cerebellum typically is large (and may obliterate the foramen magnum, leading to the development of hydrosyringomyelia). The thickness of the cortex and the volume of the white matter are increased; the corpus callosum may be thick, or on the contrary thin or dysgenetic.[2] There is no clear evidence of histologic abnormality, although there has been some unconfirmed suggestion of hypercellularity.[2] It seems that the malformation would result from a true overproduction of brain cells, possibly related to a defect in the normal developmental process of apoptosis.[2]

Patients with syndromic megalencephaly present clinically with a large head already present before birth and persisting over the years. Patients may also demonstrate macrosomia, developmental delay, hypotonia, and an increased risk of developing a neoplastic disease.[146]

The radiologic abnormalities of the brain have been well described in Sotos syndrome only, the most common type of megalencephaly (**Fig. 27**). These findings associate a ventriculomegaly, a thin or defective corpus callosum, persistent midline cava (cava septi pellucidi, vergae and veli interpositi), macrocerebellum (possible cause of a Chiari I deformity), and occasional gray matter heterotopias.[147] Grossly, similar changes are mentioned in other syndromes, albeit with some specific features: a vermian hypoplasia in Simpson-Golabi-Behmel syndrome; prominent gray matter in relation to white matter (notably caudate) in the Fragile-X syndrome; hypervascularity in the Weaver syndrome; and interhemispheric and other arachnoid cysts in acrocallosal syndrome. By contrast, the brain is radiologically normal in the Bannayan-Ruvalcava-Riley syndrome.[146]

MIGRATION DISORDERS: LISSENCEPHALIES, BAND HETEROTOPIA, AND COBBLESTONE BRAIN

Although it is anything but simple, the migration process is easy to apprehend, and the concept of migration disorder is intuitively evident. The migration disorders or heterotopias are remarkable also in that many of them can be related to specific genetic defects, with a good correlation between phenotypes and genotypes. Depending on what they look like, heterotopias are described as laminar (also called band-heterotopia) or nodular; depending on where they sit, they are described as periventricular, transcerebral, subcortical, cortical, marginal (in molecular layer 1), and even extracortical meningeal (cobblestone brain). Histologically they may present a rudimentary laminar organization, with a cell-free zone

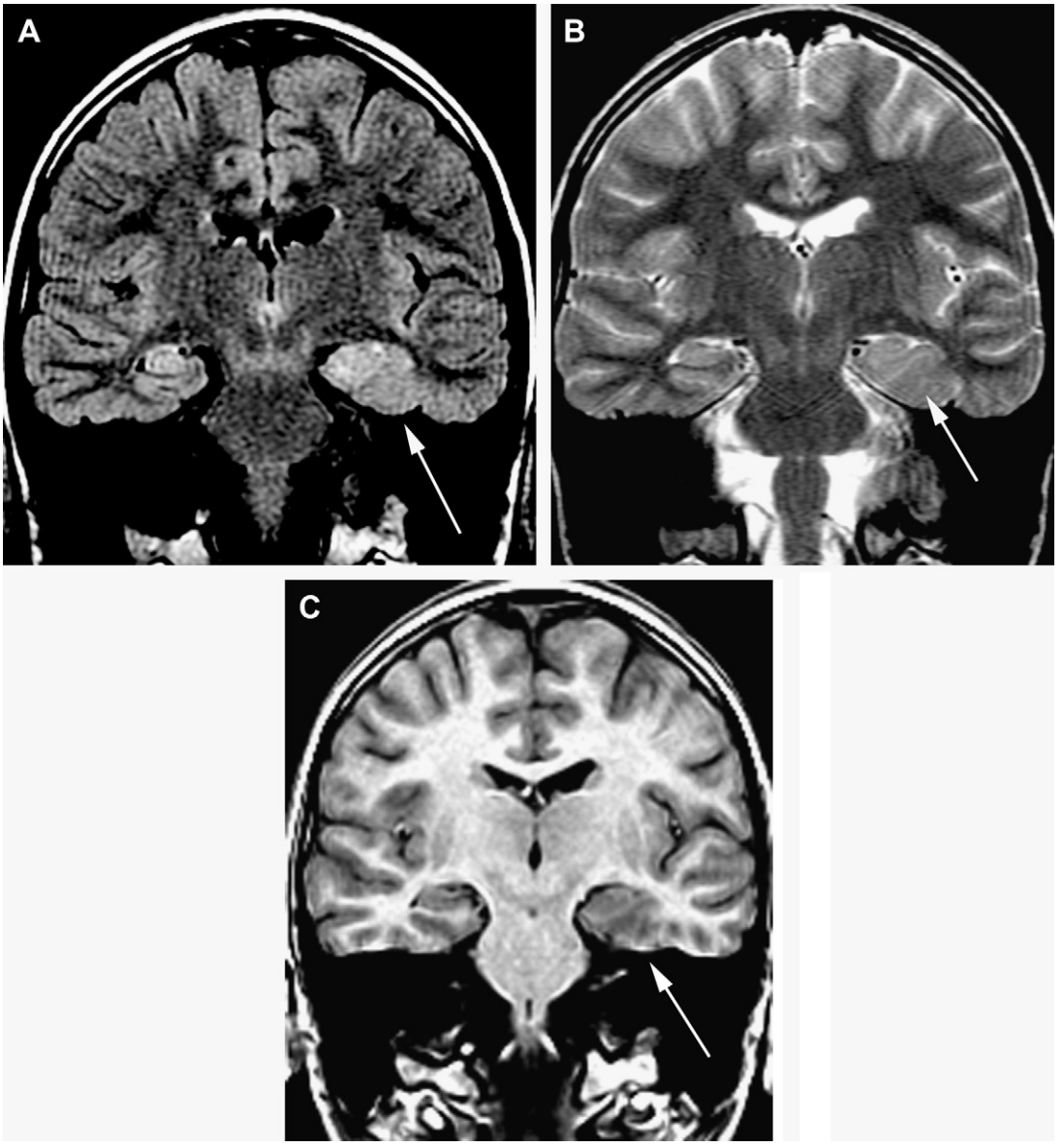

Fig. 20. Cortical dysplasia with oligodendroglial hyperplasia. (*A–C*) FLAIR, T2, and T1 coronal imaging demonstrate swelling of the left mesial temporal lobe with increased T2/FLAIR and decreased T1 signals of both cortex and white matter (*arrow*). Pathology demonstrated infiltration by nonneoplastic oligodendrocytes.

mimicking the molecular layer 1, and contain normal looking if typically disorganized pyramidal neurons and interneurons[148–150]; the architecture of the heterotopia, however, is usually different in different genetic disorders.

Heterotopias are functional and integrated in the neuronal functional loops[50,151–154]; they are typically easy to diagnose on MR imaging as nodules or band of otherwise normal-looking gray matter (identical to cortex in every sequence), located where they should not be. However, not all heterotopias can be seen radiologically: heterotopic neurons obviously, but also cortical or subpial heterotopias, and even the subcortical lentiform heterotopia found in the temporal lobes in association with FCD[105,155] cannot be identified with current clinical MR machines. Heterotopia due to undermigration (periventricular or subcortical) are caused by disorders, typically genetic, implicating genes that are involved in the homeostasis of the cellular microtubules[156] and therefore the nuclear translocation. Heterotopias due to

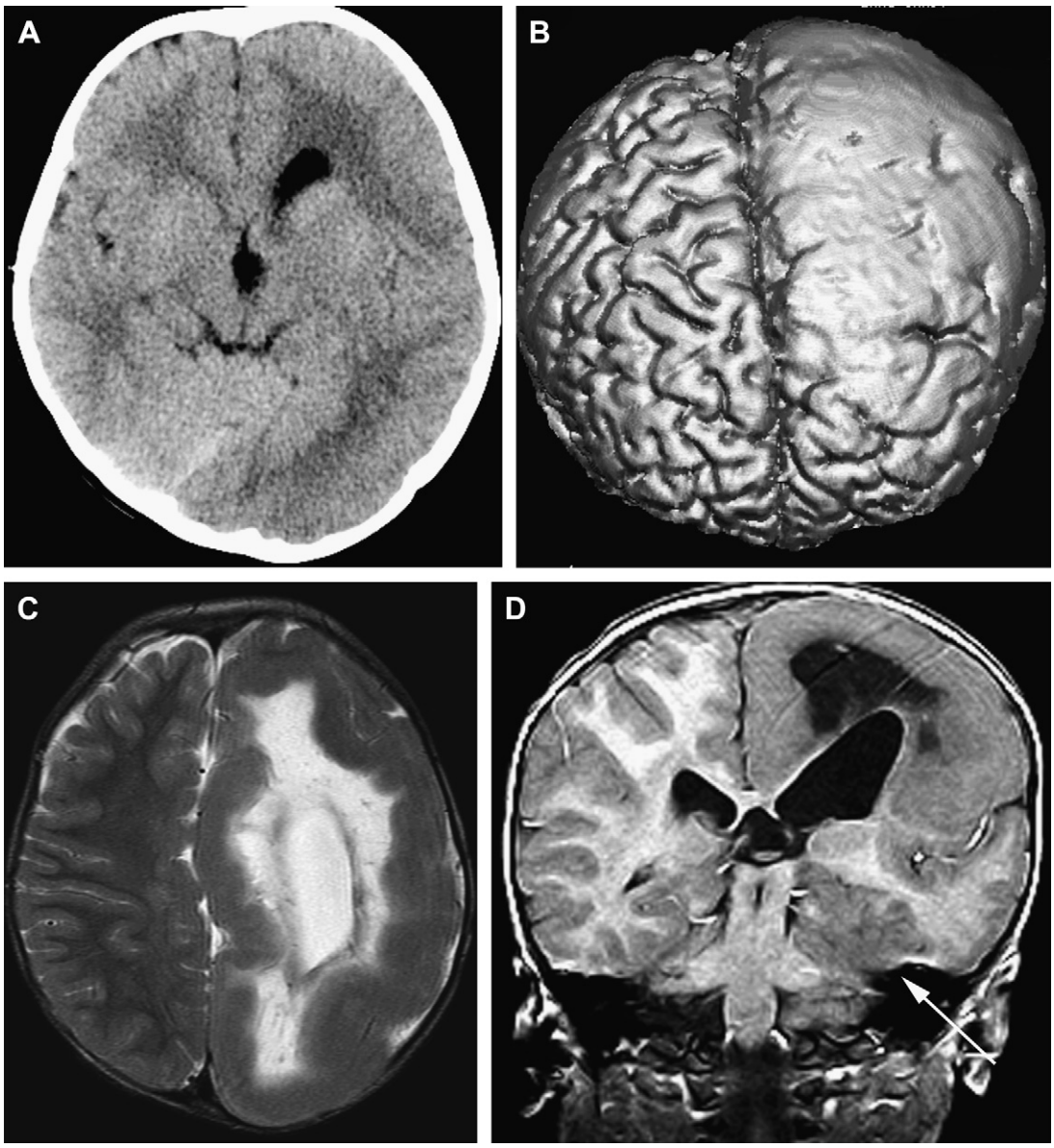

Fig. 21. Left HME. (*A*) CT image demonstrates a huge dysplastic left hemisphere with large ventricle and prominent occipital lobe. The posterior falx is dislocated to the right. (*B*) Tridimensional volume rendering shows the essentially agyric portion of the abnormal hemisphere. (*C*) Axial T2. Diffuse agyria with thick cortex and dysplastic, unmyelinated white matter; note the abnormal appearance of the right hemisphere as well, with straightening of the sulci in the rolandic area. (*D*) Coronal T1. Massive enlargement of the ventricle; the temporal lobe is relatively spared, but its medial aspect shows massive dysplasia (*arrow*).

overmigration, or an abnormal cortical layering, may be due to a defect of the reelin signaling or to defects in the pial basement membrane.

Lissencephalies

Lissencephalies have been known for a long time, and it was recognized that band heterotopia (or laminar heterotopia, or double cortex) are part of lissencephalies.[3] In the last two decades it has been demonstrated that most are related to specific gene defects,[157–159] discoveries that paved the way for further understanding of their pathogenesis.[160,161] All lissencephalies are characterized by an absence or a paucity of sulcation, and by a disorganized cortex with heterotopic gray matter that may appear as a thick cortex or as a subcortical-band heterotopia. In all, the white

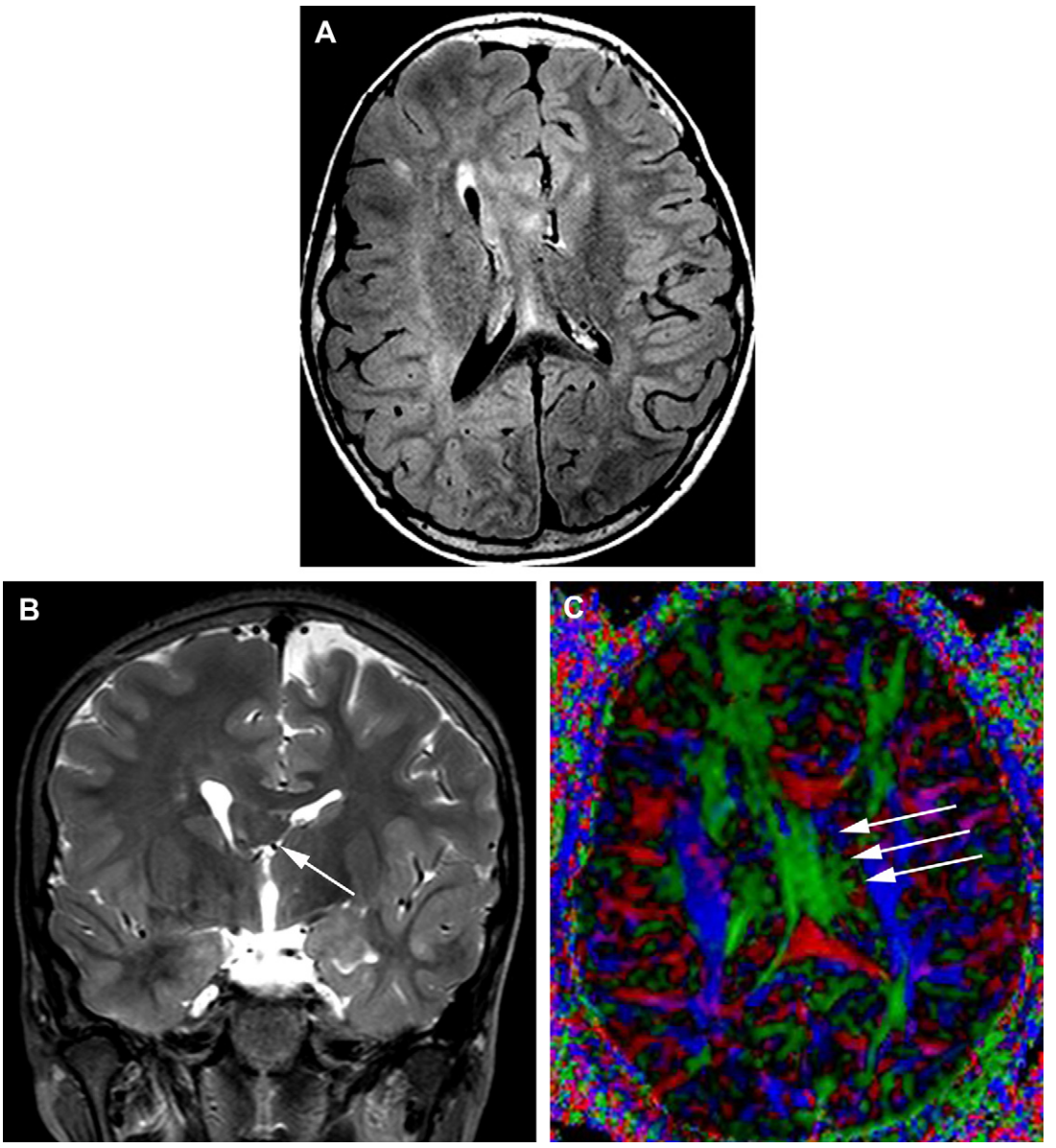

Fig. 22. Right anterior HME. (*A*) Axial FLAIR. Hypertrophy and dysplasia of the right hemisphere, predominantly its anterior portion; the signal of the white matter is heterogeneous; cortex appears thick over the whole lateral convexity, with poor gyration anteriorly; massive dysplasia of the septum pellucidum, which also appears "pulled" toward the abnormal right frontal lobe. (*B*) Coronal T2 better depicts the heterogeneous appearance of the hypertrophic septum pellucidum (*arrow*). (*C*) FA color mapping demonstrates that the septum pellucidum conveys a huge abnormal tract of white matter (*arrows*) that extends from the posterior left hemisphere to the anterior right HME.

matter is deficient as well, with a ventriculomegaly, usually a thinning of the commissures, and often a hypoplastic brainstem and cerebellum. Pathologically the cortical dysgenesis has been classified as being 4-layered (from the surface to the depth: molecular layer, cellular layer with neurons, cell-sparse layer, heterotopic layer with disorganized neurons), 3-layered (hypercellular molecular layer, no sparse cell layer), or 2-layered (molecular layer and single heterotopic layer), which correlates well with the different genetic defects identified.[162]

Classical lissencephaly (agyria, pachygyria, band heterotopia): LIS1, DCX

Clinically, patients with classical lissencephaly present during the first year of life with poor

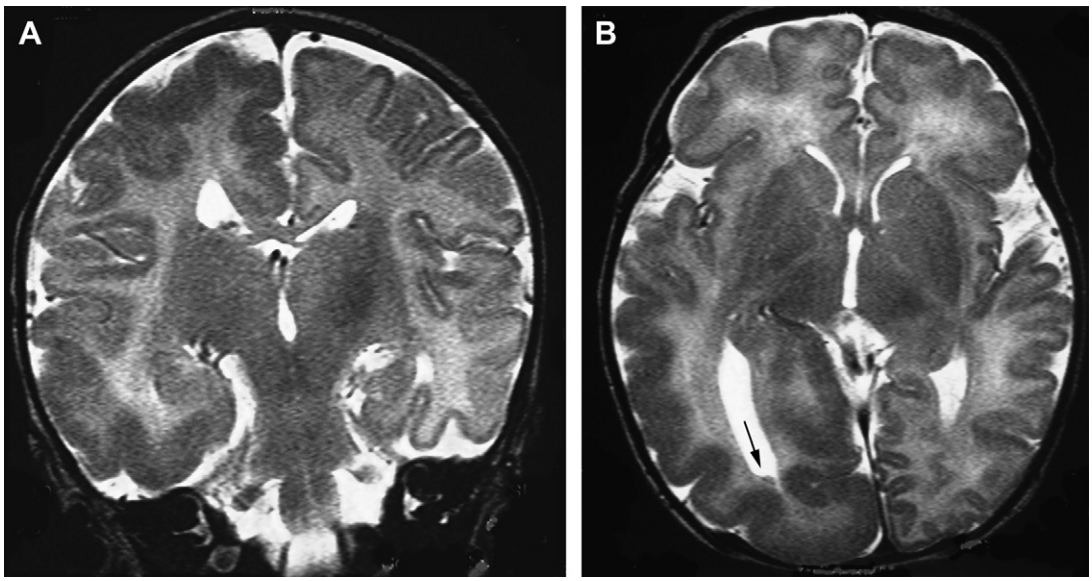

Fig. 23. Right HME in an infant. (*A*, *B*) In this 1-month-old infant, coronal and axial T2 demonstrate a large right hemisphere with large ventricle. Cortical abnormalities, predominantly posterior with dislocation of the falx, are characterized by a significant thickening of the cortical ribbon and diffuse blurring of the cortico-subcortical junction. Note the presence of a single periventricular nodular heterotopia (*arrow*).

feeding, hypotonia, opisthotonos, delayed acquisition of the developmental milestones, and epilepsy (often and characteristically infantile spasms). Depending on the severity of the malformation, however, the clinical manifestations may be milder.

Morphologically and radiologically, classical lissencephaly is characterized by the complete or partial lack or gyration, and by an excessively thick cortex (**Figs. 28–30**). The sulci are totally absent in agyria and the sylvian fissure widely open with no operculation. When present (pachygyria) the sulci are few, shallow, but are normal sulci symmetrically placed in normal locations, and can be designated by their specific names (mostly primary and main secondary sulci) (see **Fig. 29**). The cortex is very thick, up to 12 to 20 mm in complete agyria and 8 to 10 mm in pachygyria (see **Figs. 28–30**). Macroscopically the classical lissencephalic cortex presents a 4-layer organization. Its deep border is smooth and regular, well demarcated from the white matter. This cortical band does not follow the cortical pattern but rather is deeply indented by the sulci. This excessive thickness of the cortex is the cardinal feature of classical lissencephaly, which allows the MR-recognition of the disorder even in young fetuses, and makes the difference from the simplified gyral pattern of the primary microcephaly, in which the cortex is of normal or of decreased thickness. In the lesser form of classical lissencephaly, the subcortical-band heterotopia (also called laminar heterotopia, or double cortex—hence the name of doublecortin for the *DCX* gene product), the bilateral and symmetric band of heterotopic gray matter is clearly separate from an apparently normal cortical ribbon, with a more or less normal gyral pattern (**Figs. 31** and **32**).

In addition, other abnormalities are found. The white matter is not well developed and the defect correlates with the severity of the cortical malformation (ie, more severe in agyria, less severe in band heterotopia); this is apparent from the ventriculomegaly and from the appearance of the commissures, which typically are thin, although the corpus callosum may appear, paradoxically, too thick in some cases.[163–165] There is no comprehensive explanation given for this lack of white matter.[163,165] Both the molecular layer 1 and the abnormal intermediate layer 3 contain tangential fibers with presumably short-range connections. One may assume that because the neurons are dislocated and disorganized, the proper connections to and from the subpallium and with the long association and commissural fibers may fail; the location of the heterotopic layer 4 may interfere with the development, organization, and function of the subplate itself. Typically the brainstem is small also, which reflects a poor development of both the intrinsic gray matter and the long fascicles. The cerebellum may be hypoplastic, but this finding by itself is not specific or necessarily

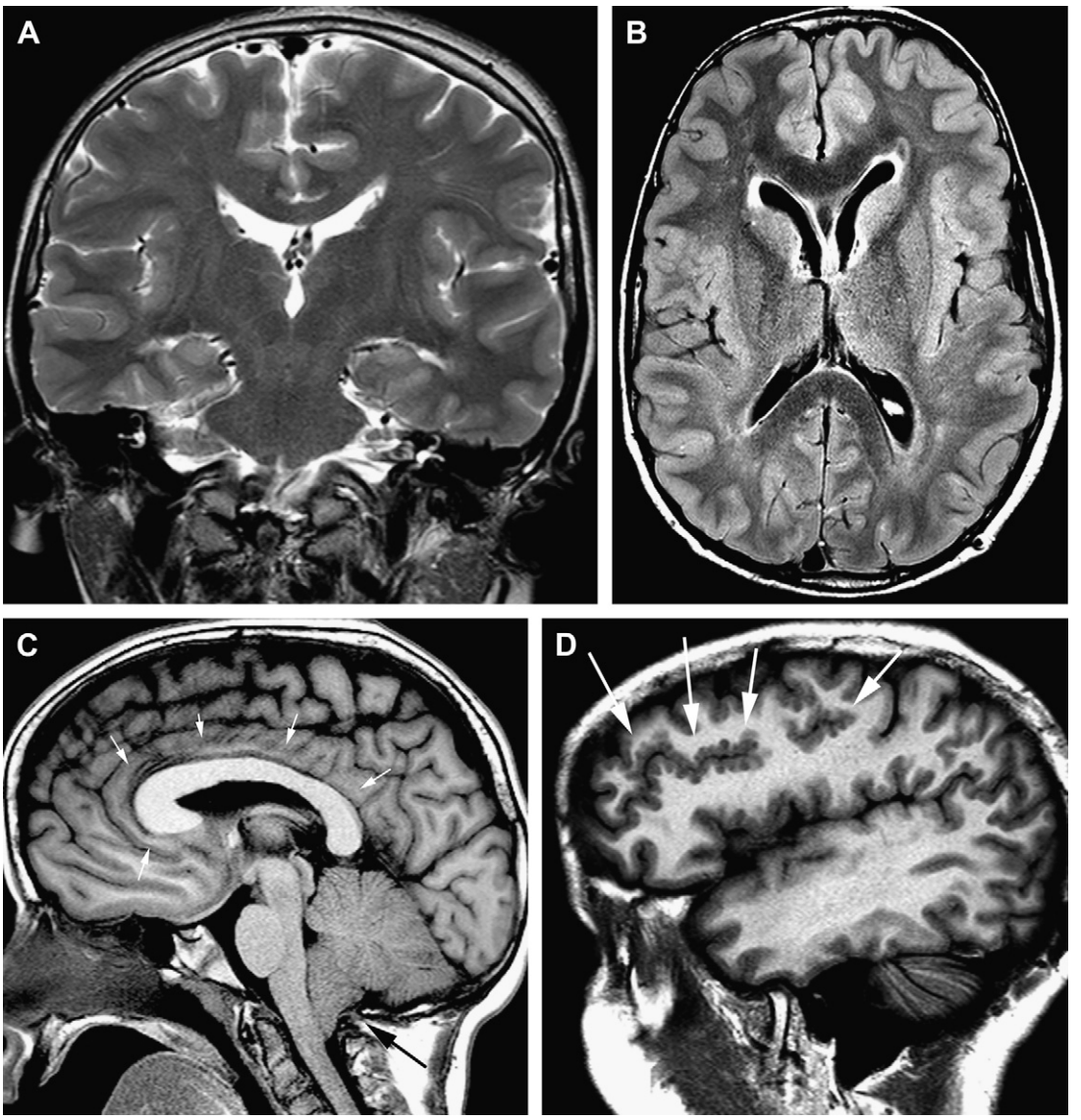

Fig. 24. Left HME, Proteus syndrome. (*A*) Coronal T2. Mild hypertrophy of left hemisphere with dysplasia of the mesial temporal lobe; prominent and ill-shaped ventricles bilaterally. (*B*) Axial FLAIR. Heterogeneous signal in the white matter and periventricular bright signals, bilaterally; note a prominent vessel in the scalp over the left parietal area. (*C*) Midline sagittal T1 demonstrates prominent corpus callosum (*white arrows*) and a Chiari I deformity (*black arrow*). (*D*) Left lateral sagittal cut demonstrates a "curly," polymicrogyric appearance of the cortex (*white arrows*) along the otherwise normally located inferior frontal gyrus.

significant in a context of lissencephaly.[166] Good correlation, however, was found between the severity of the supratentorial abnormalities and the defects of the midbrain and hindbrain, and between the callosal agenesis and the vermian hypoplasia; posterior fossa defects were more common in DCX lissencephaly (for details see Ref.[167]).

Beyond the similarities, and importantly, the appearances of the brain are different morphologically, radiologically, and neuropathologically, depending on whether the malformation results from a mutation of *LIS1* or of *DCX*.[168] In the LIS1 lissencephaly (17p13.3) and except in the rare form of complete agyria, the abnormalities are more prominent in the posterior portion of the hemisphere, more agyric posteriorly and more pachygyric anteriorly. In cases of band heterotopias the band is located posteriorly below the parieto-occipital and posterior temporal cortex; this pattern is observed mostly in males (see **Figs. 29** and **31**).[169] On the contrary, the

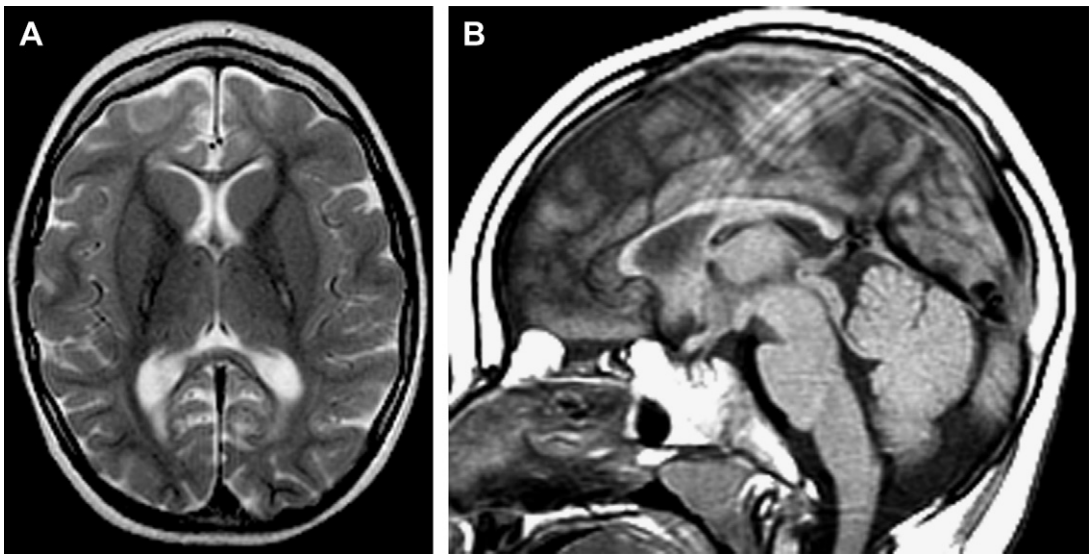

Fig. 25. Primary microcephaly. (*A*) Axial T2. Relatively normal-looking brain, apart from the size. Abnormal signal in the posterior limbs of the internal capsules. Note some excessive thickness of the anterior calvarium, pointing to a failure of cerebral growth. (*B*) Sagittal T1. The hindbrain looks normal but too large in proportion to the forebrain. The corpus callosum is thin, expressing the lack of white matter.

dysgenesis is more prominent anteriorly in the frontal lobes in cases of DCX lissencephaly (Xq22.3–q23); a complete agyria is exceptional and is seen in boys only; band heterotopia is more common and affects almost exclusively girls (with a second X chromosome) (see **Figs. 30** and **32**).[168]

Pathologically a similar 4-layer cortex was found in both genetic defects, with similar layer 1 (with Cajal-Retzius cells), and a pyramidal layer 2 grossly similar but thinner and less cellular in DCX lissencephaly, in contrast with layers 3 and 4 that contain more pyramidal cells in DCX. Below the abnormal cortex in the deep white matter, subcortical heterotopias appear more commonly and prominently in DCX, while both types share the same abnormalities in the pons (neuronal depopulation) and the medulla (simplified and heterotopic olives).[162] Grossly similar findings were reported in a second study of a DCX band heterotopia.[170] A third report found a more organized heterotopic layer in DCX.[171] At least in LIS1 lissencephaly, the severity of the malformation typically depends on the extent of the genetic defect: large deletions result in the most severe phenotypes and milder phenotypes result from intragenic mutations.[172]

Other lissencephalies

Lissencephaly associated with TUBA1A mutations (12q13.12) Patients with this variety of lissencephaly present clinically with microcephaly, severe mental delay, significant motor deficit and, commonly, epilepsy. Morphologically and radiologically, agyria, pachygyria or, less commonly, band heterotopia may be observed, more prominent in the posterior part of the hemisphere. This finding is commonly associated with white matter disorders associating ventriculomegaly and thin, dysgenetic, or agenetic corpus callosum with no or small Probst bundles, abnormal hippocampi, and significant degrees of midbrain and hindbrain hypoplasia (**Fig. 33**).[173] In a neuropathologic study of 4 fetuses, abnormal lamination with a thin, 2-layered cortex, disorganized hippocampi, abnormal white matter (including missing internal capsule and hypoplastic brainstem), immature cerebellar cortex, heterotopias in the cerebral and cerebellar white matter, fragmented dentate, and heterotopic olivary nuclei were observed.[174] As in other lissencephalies, the mutated gene *TUBA1A* (*Tubulin Alpha 1A*) is involved in the control of the cellular tubulin network.[173–175]

X-linked lissencephaly with absent corpus callosum and ambiguous genitalia Clinically, affected patients are genotypic males and present with profound mental retardation, early neonatal (prenatal, even) severe epilepsy with any type of partial or generalized seizures, temperature instability, feeding problems, epilepsy, ambiguous genitalia, and early death. On gross morphology and imaging there is microcephaly, lissencephaly more prominent posteriorly, a mildly thick cortex (5–7 mm), a defective white matter with a ventriculomegaly, a complete commissural agenesis with

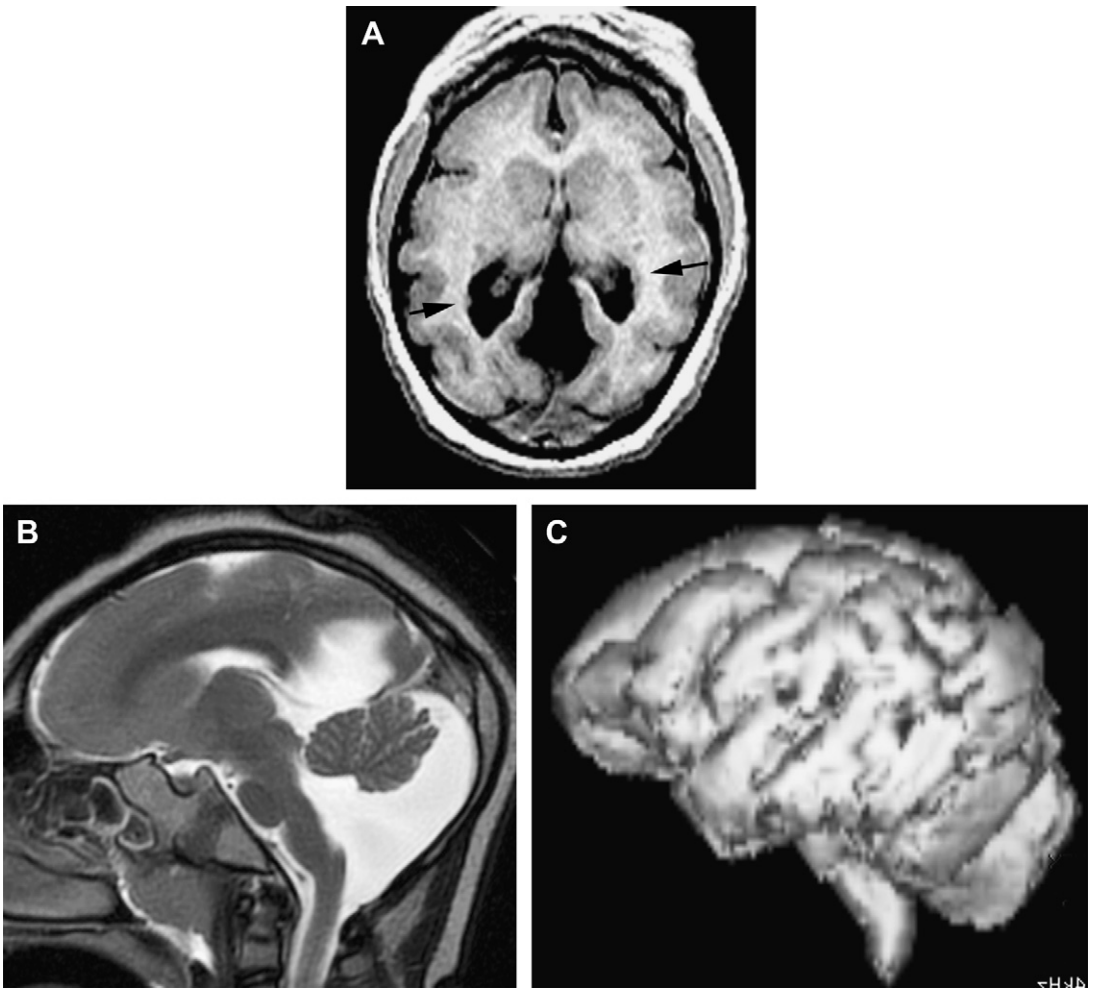

Fig. 26. Primary microcephaly. (*A*) Axial T1. Poorly developed forebrain, with markedly simplified gyral pattern. Bilateral periventricular nodular heterotopia (*black arrows*). Note the excessive thickness of the frontal calvarium, again reflecting the failure of the forebrain to grow. (*B*) Midline sagittal T2. Exceedingly small forebrain. Abnormal posterior fossa with high tentorium (due to lack of growth of the forebrain?) with rotation and inferior hypoplasia of the vermis. (*C*) Surface rendering of the brain.

no Probst bundles, no olfactory bulbs, small and disorganized basal ganglia and hypothalamus, but normal posterior fossa[176,177] (or not, see Ref.[167]). The disorder is related to a mutation of *ARX* (Xq22.13), a gene that is involved in the proliferation, differentiation, and migration of the interneurons within the germinal zone of the medial and lateral ganglionic eminence, leading to aberration in the basal ganglia, hypothalamus, and CP.[178,179] Pathologically the malformed cortex is 3-layered with a unique hypercellularity of the molecular layer and no cell-sparse layer.[162] In another study severe dysplasia of the hypothalamus, globus pallidus, putamen, thalamus, and hypothalamic nucleus was observed, with a hypoplastic pyramidal tract.[180]

The last group of lissencephalies with an identified genetic defect is the Reelin (and/or its receptors VLDLR and APOER2) lissencephaly.[181] Reelin is the substance that characterizes the Cajal-Retzius cell, and the absence of the *RELN* gene (7q22) is responsible for the neurologic disorder that characterizes the strain of Reeler mice. It controls the neuronal migration to the cortex and notably the inside-out pattern. Affected children present with microcephaly, developmental delay, and early epilepsy. On imaging the brain is small, there is a pachygyria that is more severe anteriorly than posteriorly, a moderately thick cortex of 5 to 10 mm, malformed hippocampi, mild brainstem hypoplasia with a cerebellar hypoplasia, and significant foliation defect.[166,167]

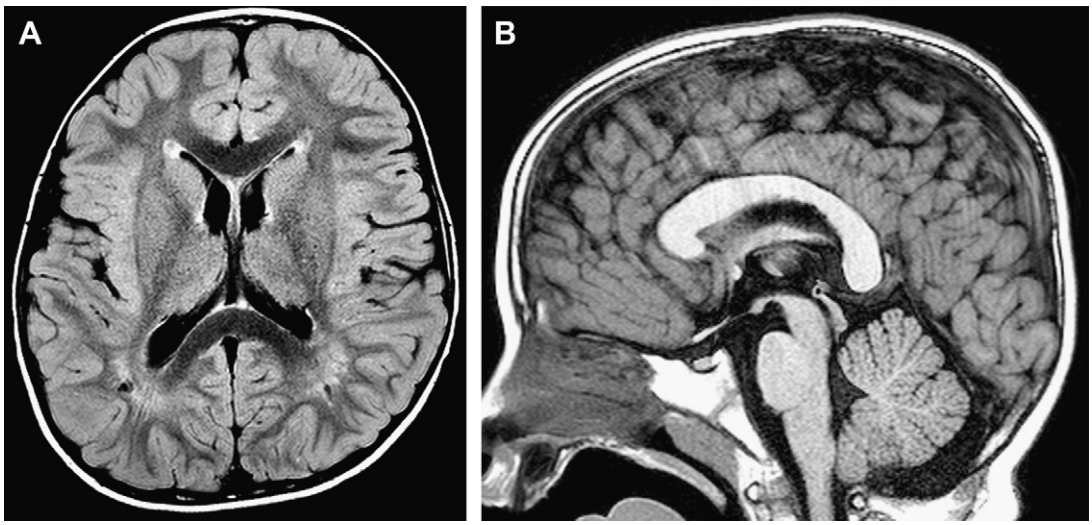

Fig. 27. Primary macrocephaly (Sotos syndrome). (*A*) Axial FLAIR. Large head, large slightly asymmetric hemispheres, prominent ventricles. Some gliotic/cystic changes in the deep posterior white matter are nonspecific. (*B*) Midline sagittal T1 demonstrates a thick corpus callosum (bulky white matter).

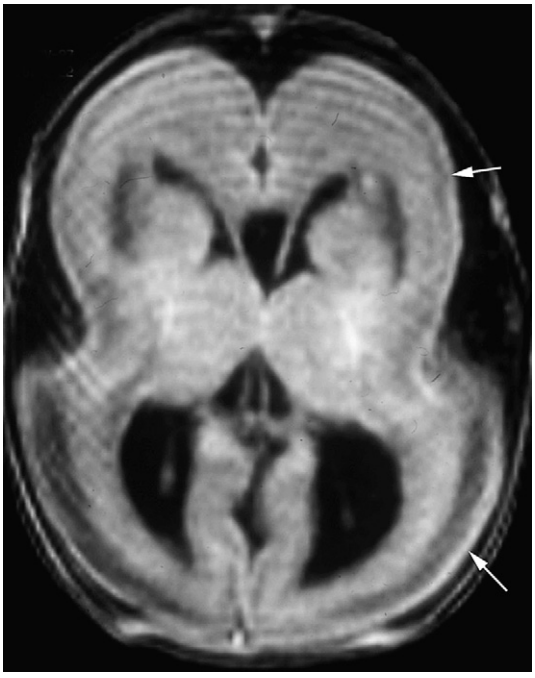

Fig. 28. Complete agyria (Miller-Dieker syndrome, *LIS1*). Axial T1. Four-layered cortex: the molecular layer cannot be seen but the thin cortex, the cell-sparse layer, and the thick heterotopic layer are well apparent (*arrows*). Note the colpocephaly (lack of white matter).

Many other isolated cases of lissencephaly with or without cerebellar hypoplasia and with or without commissural agenesis have been reported in the literature, as well as cases apparently related to fetal cytomegalovirus (CMV) infections.

Abnormalities of the Pial Basement Membrane: Cobblestone Brain and Related Disorders

Dystroglycanopathies with cerebral involvement

Dystroglycanopathies are, above all, a group of severe muscular diseases, the congenital muscular dystrophies (CMD). Considerable advances in the understanding of the pathogenesis of these diseases have occurred in the last two decades (see Refs.[182,183] for review). The defects result from mutations of the genes that encode for glycosyltransferase enzymes with a reduction of the glycosylated α-dystroglycan. Involvement of the brain and eyes results from the defective glycosylation preventing the linking of the α-dystroglycan with laminin $\alpha 2$, a major constituent of the glial basement membrane (also known as glial limiting membrane). In the developing brain α-dystroglycan is expressed in the VZ and in the pial basement membrane, and seems to participate in the neuronal proliferation, in the constitution of the meningeal layers, and in the migration and lamination processes as the radial glia is attached to the pial limiting membrane. In mouse models of dystroglycan defects, the disease leads to the rupture of this membrane and results in a cobblestone appearance.[183] Six genes have been identified

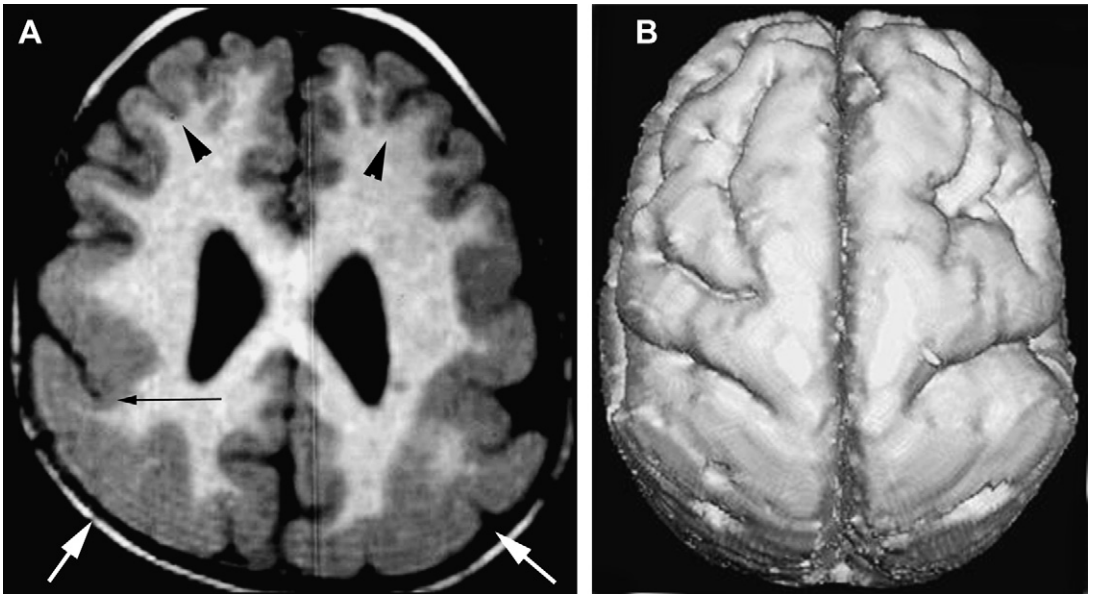

Fig. 29. Posterior pachygyria (presumably *LIS1*). (*A*) Axial T1. Very thick cortex (*white arrows*) contrasting with the more normal anterior cortex (*black arrowheads*). Note that the sulci indent the thick heterotopic cortical layer deeply (*thin black arrow*). (*B*) Surface rendering. The sulci are few but normally located and symmetric (can be named).

whose mutation may result in cerebral involvement: *Fukutin* (*FKTN*, 9q31), *Fukutin*-related protein (*FKRP*, 19q13.3), Protein-*o*-mannosyl transferase 1 (*POMT1*, 9q34.1), Protein-*o*-mannosyl transferase 2 (*POMT2*, 14q24), Protein-*o*-mannose 1,2-*N*-acetylglucosaminyltransferase (*POMGnT1*, 1p33–34), and *LARGE* (22q12.3–q13.1).[183,184] Although it was initially assumed that there was a correlation between the genotype and the phenotype (eg, *Fukutin* with Fukuyama; *POMT1* with muscle-eye-brain [MEB] disease; *POMT1* or *POMT2* with Walker-Warburg syndrome) it appears today that there is a wide range of variation of severity whatever the genotype, the most severe phenotype being the Walker-Warburg syndrome,[182–184] so that the clinical features may vary from a complete clinical and radiological normality, a clinical normality with minimal MR changes, to various combinations of supratentorial and infratentorial malformations and possibly to major syndromes.[182–184]

Clinically the range of variations is broad: all patients present with variable muscular weakness.

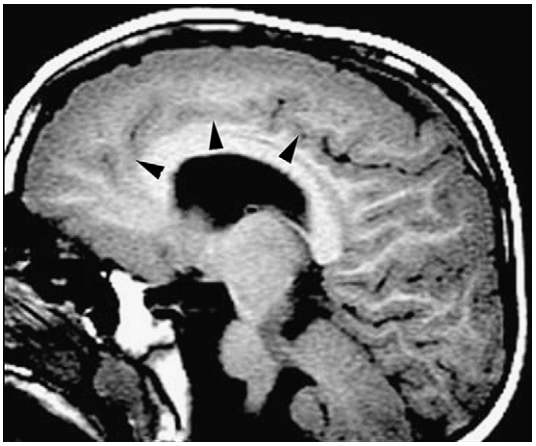

Fig. 30. Anterior pachygyria (*DCX*). Parasagittal T1. Note the paucity of sulcation in the superior frontal gyrus (*arrowheads*) contrasting with the normal parieto-occipital cortex.

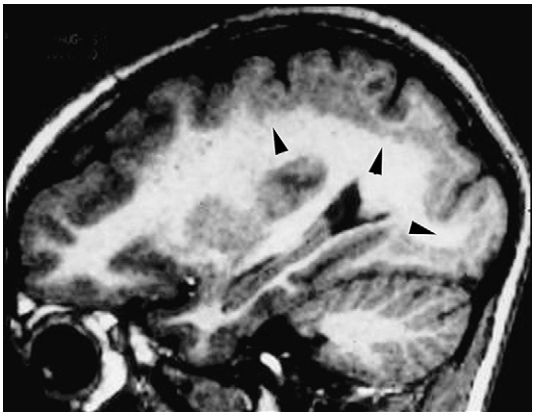

Fig. 31. Posterior band heterotopia (double-cortex) in a boy (*LIS1*). Sagittal T1. Parieto-occipital band heterotopia under an almost normal-looking cortex (*black arrowheads*).

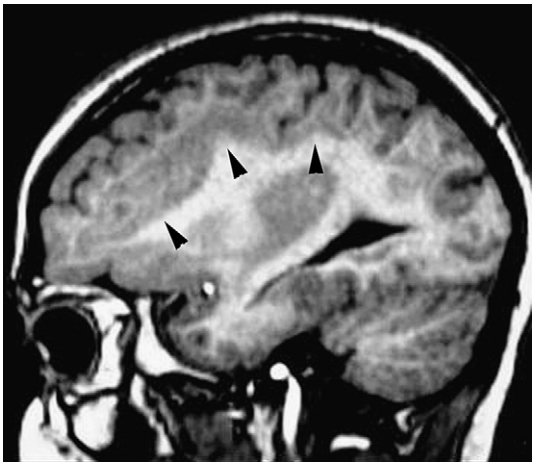

Fig. 32. Anterior band heterotopia (double cortex) in a girl (*DCX*). A thick band of subcortical heterotopic gray matter underlines the frontal and the perirolandic cortices (*arrowheads*).

Neurologically they may be normal, or present variable degrees of cognitive delay, more or less severe seizures, feeding difficulties, and premature death.

Morphologically the spectrum of abnormality was well described by Clement and colleagues.[184] The brain may be normal, or show mild deep white matter changes and/or ventriculomegaly. There may be isolated cerebellar hypoplasia, or cerebellar cysts or hypoplasia with pontine hypoplasia, There may be bilateral frontoparietotemporal polymicrogyria without any posterior fossa abnormality. There may be cortical dysgenesis with cerebellar dysplasia and posteriorly concave brainstem, with normal pons. The classic phenotypes are not the most frequent[184] but they are the most severe expressions of the genetic disorders.[182]

The classical Fukuyama phenotype corresponds to the gene mutation as it is found in Japan (where it is the most complete) (**Fig. 34**). It seems to correlate well with the *Fukutin FKTN* mutation. It includes cerebral and cerebellar PMG, fibroglial proliferation of the leptomeninges and interhemispheric fusion, and hypoplasia of the corticospinal tracts, but hydrocephalus is rare. The white matter abnormalities are present but may be transient, and the posterior part of the hemisphere may appear as a cobblestone cortex. Hypoplasia of the pons and vermis, and cerebellar cysts may be present.

In the classical MEB disease the cortex may variably appear agyric, pachygyric, or polymicrogyric with white matter changes, in association with cerebellar hypoplasia and flat brainstem (**Fig. 35**). The MEB phenotype does not correlate well with any gene mutation: besides *POMGnT1*, it can be observed in association with a mutation of *FKRP*, *Fukutin FKTN*, *POMT1*, and *POMT2.*

Finally, the classical Walker-Warburg syndrome is the most severe, clinically (no survival beyond 3 years) and morphologically (**Fig. 36**). It can be observed with the mutation of any of the dystroglycanopathy genes: *FKTN*, *FKRP*, *POMT1*, *POMT2*, *POMGnT1*, and *LARGE*. The neuronal overmigration results in a diffuse cobblestone brain appearance with heterotopic neurons, leptomeningeal

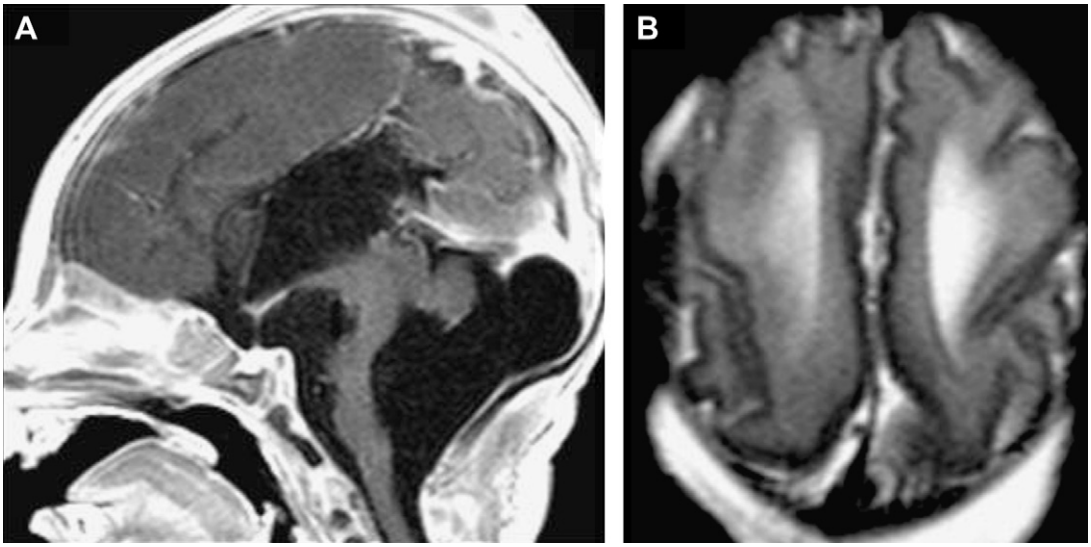

Fig. 33. Lissencephaly with microcephaly, absent commissures, and hindbrain hypoplasia (presumably *TUBA1A*). (*A*) Sagittal T1 demonstrates the lack of any commissure (anterior, hippocampal, callosal), the gross pachygyria, and the posteriorly concave brainstem with pontocerebellar hypoplasia. The tentorium is deficient posteriorly. (*B*) Axial T2. Pachygyria with thin cortex and ventriculomegaly.

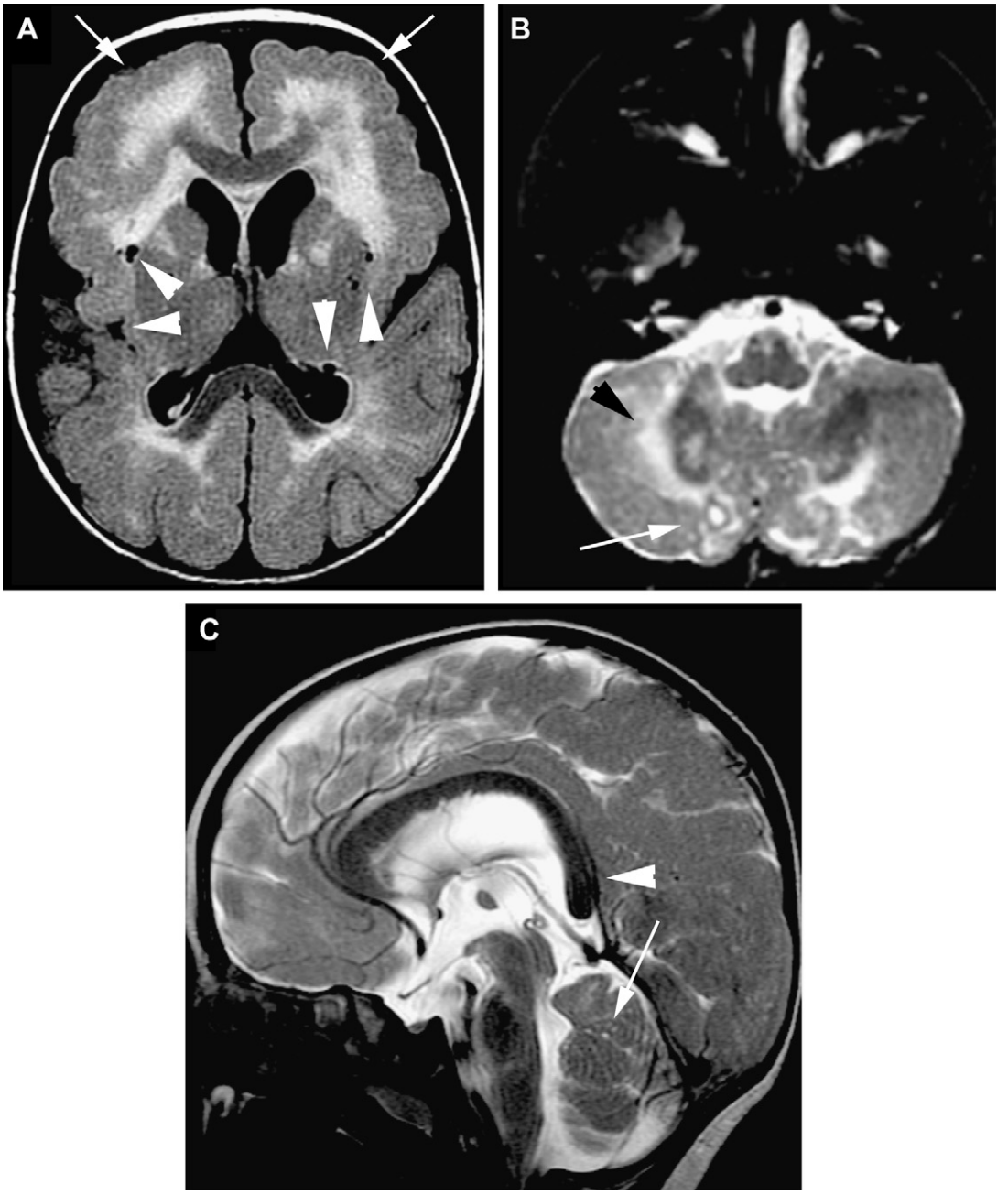

Fig. 34. Fukuyama congenital muscular dystrophy. (*A*) Axial FLAIR. Polymicrogyria-like appearance of the frontal cortex bilaterally (*arrows*), with abnormal myelination that predominates anteriorly but also affects the posterior part of the hemisphere. Microcysts are seen in the external capsules (*arrowheads*). (*B*) Axial T2, cerebellum. Abnormal myelination (*black arrowhead*) and cystic changes (*white arrow*). (*C*) Midline sagittal T2. Extended, verticalized splenium (*arrowhead*); microcysts in vermis (*arrow*).

gliomesodermal proliferation, a fusion of the hemispheres along the midline and a huge ventriculomegaly with or without hydrocephalus, a commissural agenesis, a pontocerebellar hypoplasia with a hypoplastic concave brainstem (Z appearance), and midline clefting of the pons. The fourth ventricle may be enlarged and even cystic, and classically a cephalocele may be found.

Bilateral frontoparietal polymicrogyria

Bilateral frontoparietal polymicrogyria (BFPP) is not a real polymicrogyria, nor a dystroglycanopathy,

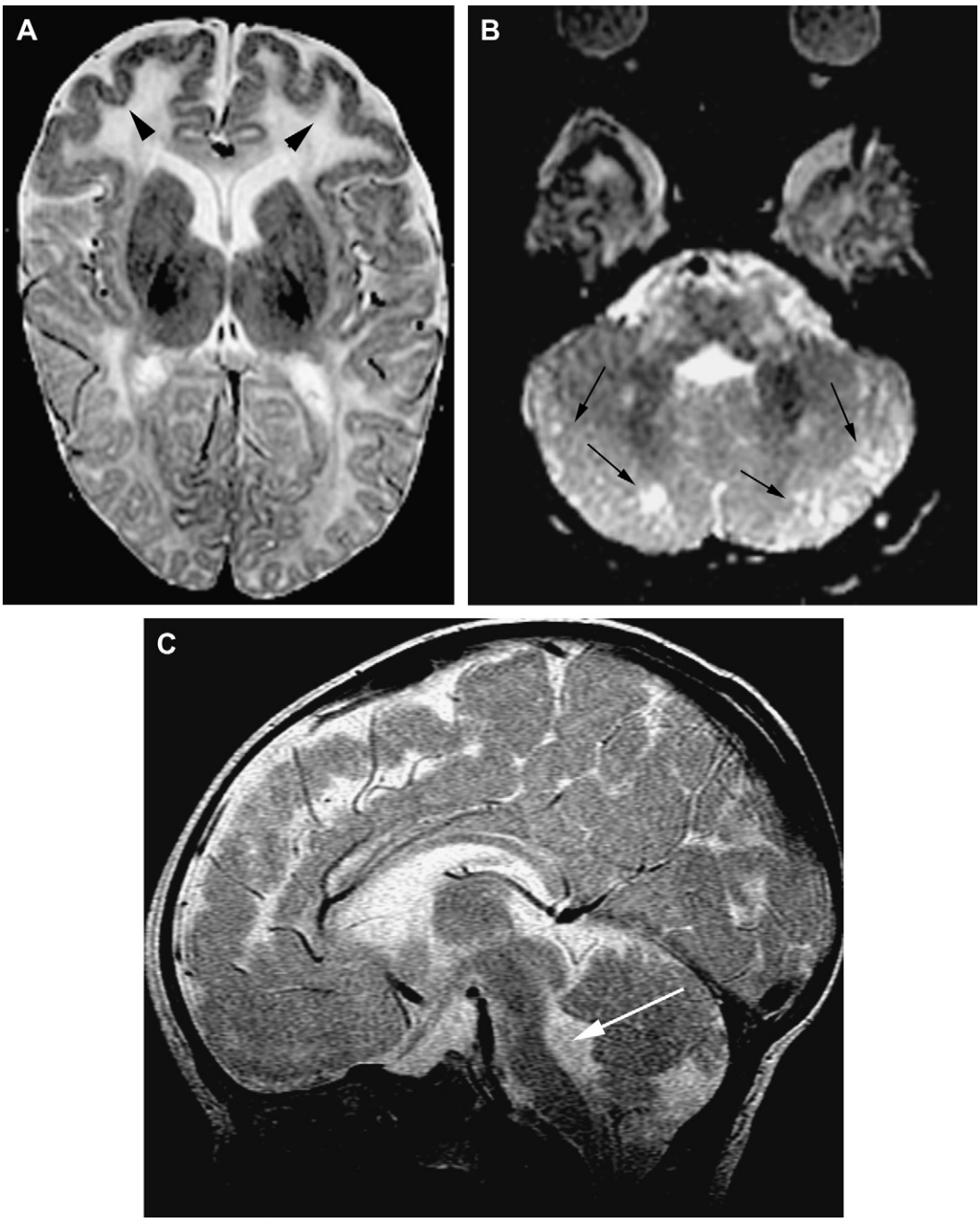

Fig. 35. MEB syndrome. (*A*) Axial T2, forebrain. Polymicrogyria-like changes of the frontal cortex bilaterally (*arrowheads*). Abnormal appearance of the frontal white matter in this 5-month-old infant (compare with the posterior part of the hemispheres). (*B*) Axial T2, cerebellum. Diffuse microcystic changes (*arrows*). (*C*) Midline sagittal T2. Thin corpus callosum, posterior concavity of the brainstem (*arrow*).

but it does result from gaps in the pial basement membrane and has close similarities with cobblestone brain pathogenetically, morphologically, and clinically.[185]

Pathogenetically, BFPP is related to a mutation of the *GPR56* gene (16q13), which encodes a G-protein–coupled receptor that is expressed in radial glial endfeet and presumably participates

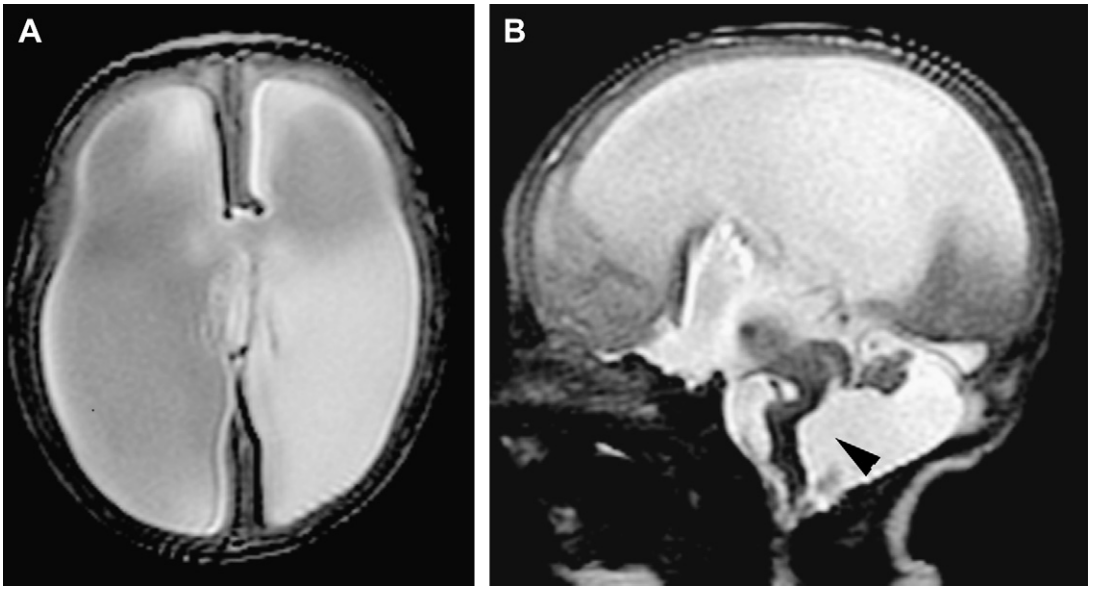

Fig. 36. Walker-Warburg syndrome. (*A*) Axial T2, forebrain. Extremely thin cortex and white matter. Huge ventriculomegaly, due to both a lack of white matter and hydrocephalus. Corpus callosum and septum pellucidum are absent. (*B*) Midline sagittal T2. Huge ventriculomegaly with markedly dilated third ventricle. Very abnormal hypoplastic brainstem with posterior concavity (Z-shaped) (*arrowhead*) and hypoplastic, rotated vermis (pseudo Dandy-Walker).

in the maintenance of the pial basement membrane. In a knocked-out mouse model, there is a major regional lamination defect in the frontoparietal areas with leptomeningeal cortical ectopia containing neurons from both the deep and the superficial layers; this overmigration can be explained by the breaches in the pial basement membrane, by the disorganization of the radial glia with abnormal anchorage of the glial endfeet into the ectopia, and by the fact that the Cajal-Retzius cells are dislocalized into the ectopia as well.[186]

Clinically the patients present with an early hypotonia with pseudo-myopathic features, then a severe motor and mental retardation, and later pyramidal and cerebellar symptoms with abnormal eye movements and severe generalized epilepsy.[185]

Radiologically the hemispheres are severely abnormal with a bilateral symmetric polymicrogyria-like cortical malformation; it may be typically frontoparietal but more often extends to most of the hemisphere, with an anterior to posterior gradient (A>P). There is a lack of white matter with ventriculomegaly and thin, dysgenetic corpus callosum; in addition the myelination is abnormal, with marked hypomyelination in infants evolving toward a pattern of patchy areas of bright T2/FLAIR signal; these abnormalities are prominent in the parieto-occipital subcortical white matter.[185] In the posterior fossa there is disorganization of the superior vermian foliation, subpial and cortical vermian and hemispheric cysts, and poor demarcation and flattening of the ventral pons with in some cases a posterior concavity of the brainstem.[185]

MIGRATION DISORDERS: NODULAR HETEROTOPIA

Nodular heterotopia are different from band heterotopias in that they form gray matter nodules that may be unilateral or bilateral but never perfectly symmetric; they are often consistent with a normal intelligence, and epilepsy typically develops late (second decade). Depending on their location, they are classified as periventricular nodular heterotopia (PVNH) and subcortical nodular heterotopia (SCNH), which are usually transcerebral.

Periventricular Nodular Heterotopia

Periventricular nodular heterotopia typically encroach on the ventricular lumen, and for this reason the authors believe that the term subependymal heterotopia that is sometimes used is not appropriate (however, this term may apply to the extremely uncommon occurrence of a deep laminar heterotopia that lines the ventricular wall).

Morphologically, PVNH are aggregates of neurons organized in nodules of gray matter: on CT, but now preferably on MR, their appearance is similar to that of the cortex, whatever the

modality or the sequences used. They are never calcified, and they never enhance (different from the subependymal nodules of the TSC, which typically have signals always different from those of the gray matter on MR imaging, are calcified, and enhance). There is no mass effect and no surrounding edema. Their location is important: they develop from the germinal zone of the pallium, and therefore are never found on the ventricular surface of the basal ganglia, but always on the ventricular surface of the white matter except, importantly, on the septum pellucidum and the callosal roof of the lateral ventricles. The fact that they protrude into the ventricles suggests that they developed within the VZ and were left there after the ventricular zone disappeared at week 26.

PVNH may be single, multiple, or diffuse; they may be uni- or bilateral but, as mentioned earlier, they are asymmetrical even when distributed along symmetric portions of the ventricles (**Figs. 37–41**). When unilateral they seem to be preferentially located on the right side.[187] PVNH affect the posterior part of the ventricles (atrium/occipital horns, temporal horns) more commonly than the body, and especially than the frontal horns[187,188] (where they appear squeezed between the head of the caudate and the corpus callosum). Often they are sporadic, but they also occur in families (then typically affecting girls[187,188]), or in syndromes. PVNH may be associated also with a remarkably high frequency in some brain malformations: Chiari II, cephaloceles, commissural agenesis, and septo-optic dysplasia (de Morsier type). When familial, they are often associated

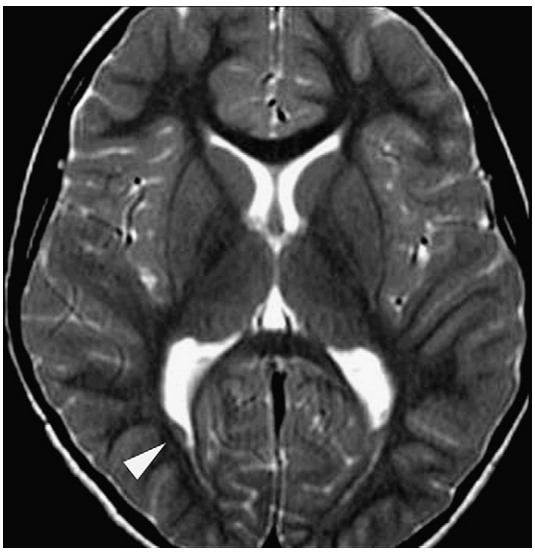

Fig. 37. Isolated small periventricular nodular heterotopia (*arrowhead*). Associated mild ventriculomegaly (T2 axial).

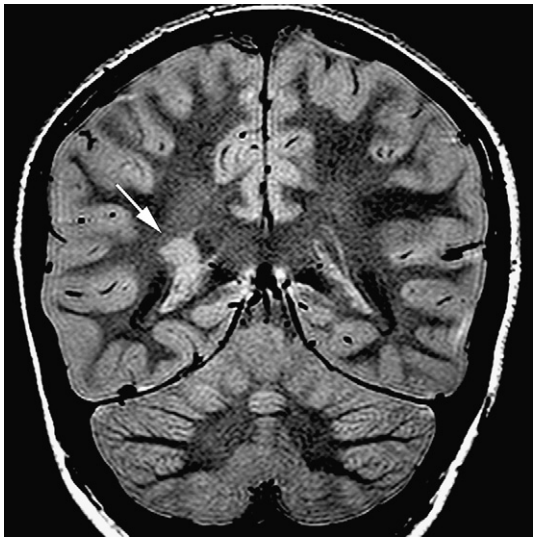

Fig. 38. Isolated large periventricular nodular heterotopia (*arrow*) (proton density).

with a mega cisterna magna.[189] Among the MCD they are more commonly associated with microcephaly, subcortical nodular heterotopia, schizencephaly, and polymicrogyria.[188] FCD type I in the overlying cortex has been identified on specimens of surgical cases of PVNH with refractory epilepsy.[155] Volumetric studies have shown a negative correlation between the volume of the PVNH and that of the gray matter, suggesting that the arrested neurons should have belonged to the overlying cortex.[190]

Pathogenesis

For years it has been considered that PVNH would result from an insult to the VZ and occur late in the

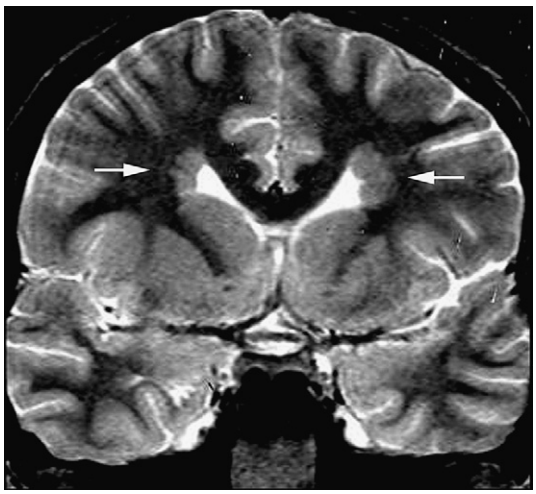

Fig. 39. Bilateral frontal periventricular nodular heterotopia between the corpus callosum and the caudate nuclei (*arrows*) (T2 coronal).

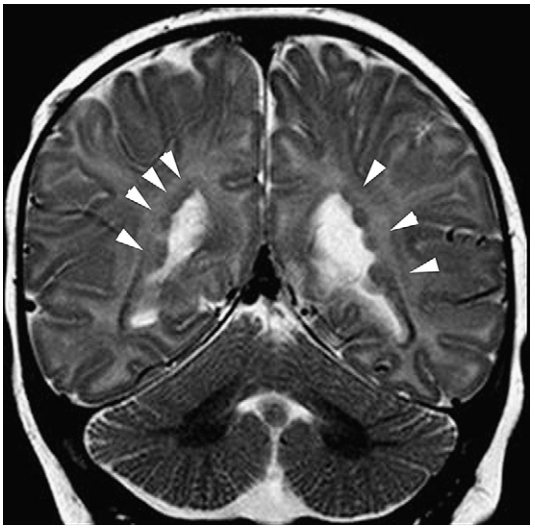

Fig. 40. Multiple bilateral periventricular nodular heterotopia in an infant girl (*arrowheads*), possibly due to *FLNA* mutation (T2 coronal).

process of migration. However, the occurrence of the malformations in families and the preponderance of affected females in most of the series made a genetic defect likely. A locus on Xq28 was identified in 1996,[191] and the responsible gene *filamin 1* (*FLN1*), now *filamin A (FLNA*), in 1998.[192] *FLNA* encodes for a protein that is essential in the cross-binding of intracellular actin. It plays a crucial role in angiogenesis, coagulation, cellular migration (notably melanocytes), and neuronal migration.[192] Boys affected with the mutation tend to die in utero from hemorrhages, whereas girls survive but present with PVNH: among the patients with the mutation, 93% are female and only 7% male.[193] The mutation is found in 49% of patients with bilateral PVNH as a group (see **Fig. 40**), but in 100% of the familial cases against only 26% of the sporadic cases. The mutation is found also in patients in whom PVNH is part of an Ehlers-Danlos syndrome. It is extremely uncommon (4%) in the other phenotypes, including those in which the PVNH are isolated, unilateral, or associated with other MCD.[193] The mutation has never been reported in cases where the PVNH are associated with commissural agenesis, septo-optic dysplasia, cephaloceles, or Chiari II malformation.

Subcortical Nodular Heterotopia

Subcortical nodular heterotopia (SCNH) may appear as small nodules of gray matter distributed between the ventricular wall and the cortex (typically multiple, rarely single) or, more commonly, as transcerebral aggregates of gray matter extending from the ventricle to, and continuous with the cortex, which typically is dysgenetic over the malformation (**Figs. 42–47**). Such transcerebral SCNH may be bulky, or may form relatively thin streaks of gray matter crossing the white matter, often bilateral and symmetric. SCNH may be found isolated, or in association with other MCD, notably schizencephaly and polymicrogyria (which confirms that these two entities involve migration disorders in addition to the poor organization of the cortex[11]), but also PVNH (see **Fig. 45**). Together with a polymicrogyria-like cortical dysgenesis, SCNH are a prominent feature

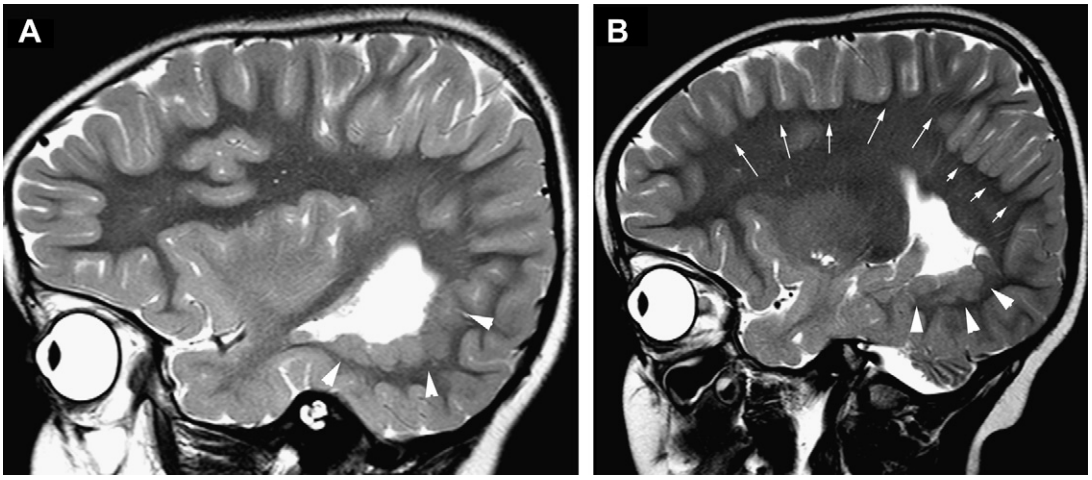

Fig. 41. Diffuse bilateral periventricular nodular heterotopias. (*A, B*) T2 sagittal through the temporal horns demonstrates the continuous coating of the ventricular wall (*arrowheads*). Note the dislocated hippocampus and associated cortical polygyria (*arrows*).

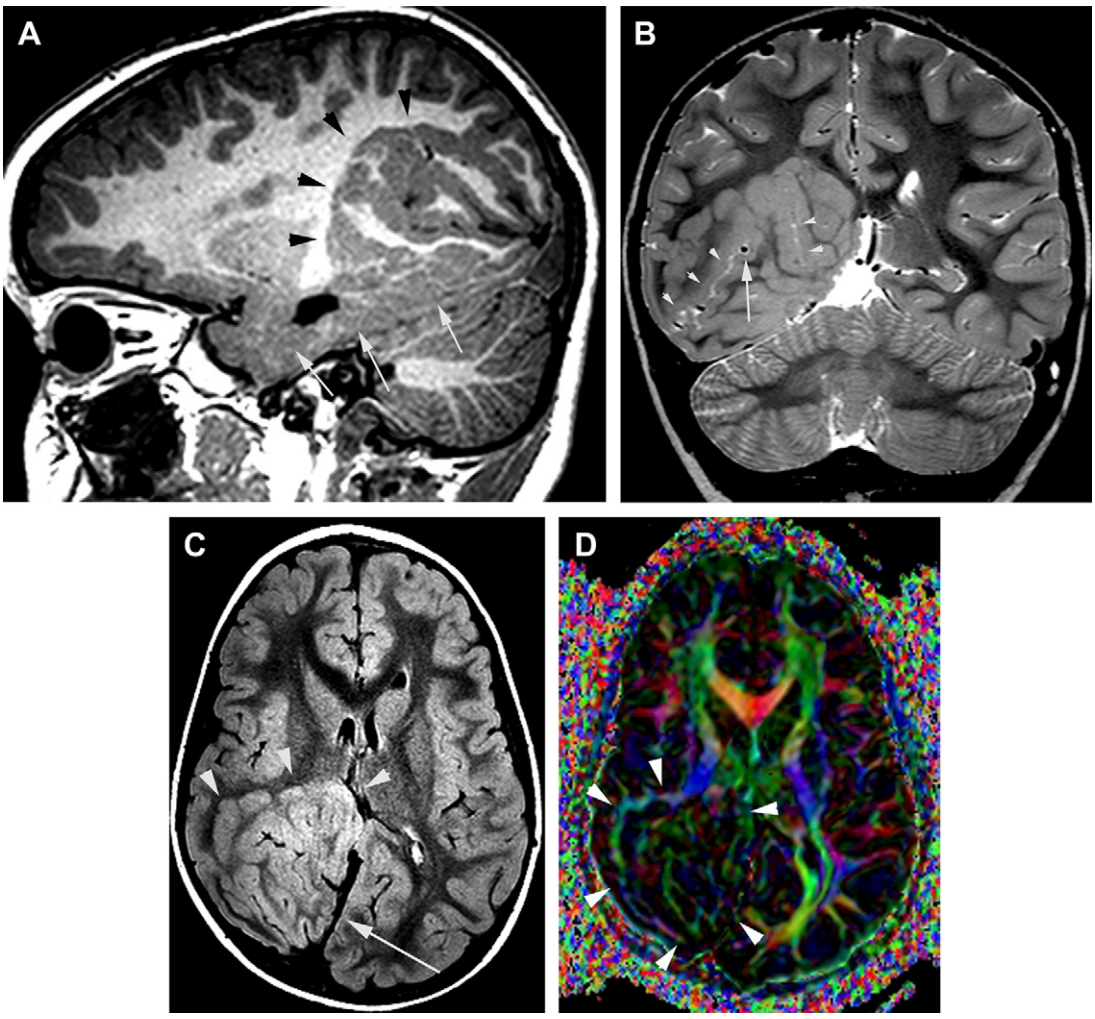

Fig. 42. Subcortical nodular heterotopia. (*A*) Lateral sagittal T1. Large nodular conglomerate of intermingled gray and white matter (*black arrowheads*); the malformation extends along the inferior aspect of the temporal lobe (*arrows*). (*B*) Coronal T2. Besides cortical-like gray matter and the associated white matter, the malformation presents with a deep CSF-containing and vessel-containing fissure (*arrowheads*). (*C*) Axial FLAIR. Despite its volume, the SCNH (*arrowheads*) is associated with focal hypoplasia of the hemisphere with dislocated falx (*arrow*). (*D*) FA color mapping. The hemispheric white matter fascicles are disorganized at the level of the SCNH (*arrowheads*), but within the heterotopia, the white matter appears organized in a coherent fashion (appearing mostly *green*—dorsoventral, or *blue*—craniocaudal, in this image).

of the commissural agenesis with interhemispheric dysplastic cysts (including the Aicardi syndrome).

Small SCNH, except for location, are no different from PVNH: well-circumscribed nodules of gray matter, without any mass effect or edema, never calcified, never enhancing with contrast media. Small SCNH may be bilateral but not symmetric. Typically the hemisphere, including the cortex and the ventricle, looks otherwise normal.

Large SCNH look different (see **Fig. 42**),[194] and are almost always unilateral. Large SCNH always extend from the ventricular wall to the cortex and have no anatomically consistent topography: they may be sublobar, lobar or interlobar, or multilobar. When they sit on the medial aspect of the frontoparietal lobes they are typically associated with a partial or complete commissural agenesis (see **Fig. 43**).[195] Their appearance is unusual, as they are made of intermingled gray and white matter, may contain signal void indicating the presence of prominent vessels (larger than the usual transcerebral perforators), and even bright CSF-like signals, which is assumed to be from perivascular spaces accompanying the vessel

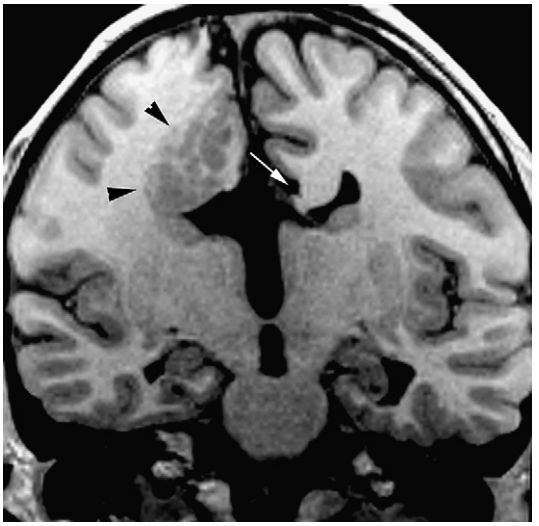

Fig. 43. Subcortical nodular heterotopia with callosal dysgenesis. Coronal T1. The SCNH lies at the level of the cingulate gyrus and ventricular roof (*arrowheads*). Assumedly it prevented the development of the corpus callosum as well as of the septum pellucidum (septocingulate fibers), as well as of a bundle of Probst (compare with left side, *white arrow*). Hippocampi appear dysplastic.

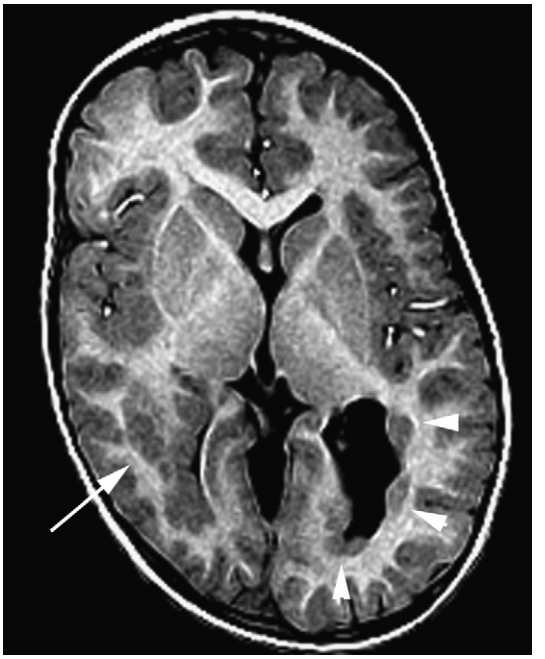

Fig. 45. Associated subcortical and periventricular nodular heterotopia. Axial T1. The SCNH extends medially to coat the ventricular wall (*arrow*), and is associated with contralateral PVNH (*arrowheads*).

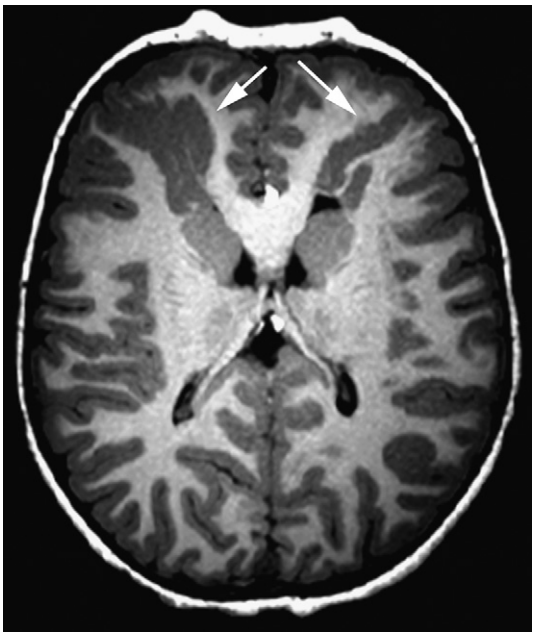

Fig. 44. Bilateral streak-like subcortical nodular heterotopia. Axial T1. Patient with frontonasal dysplasia, interhemispheric lipoma, and callosal dysgenesis. Bilateral streaks of gray matter extending from the frontal horns to the frontal cortex (*arrows*).

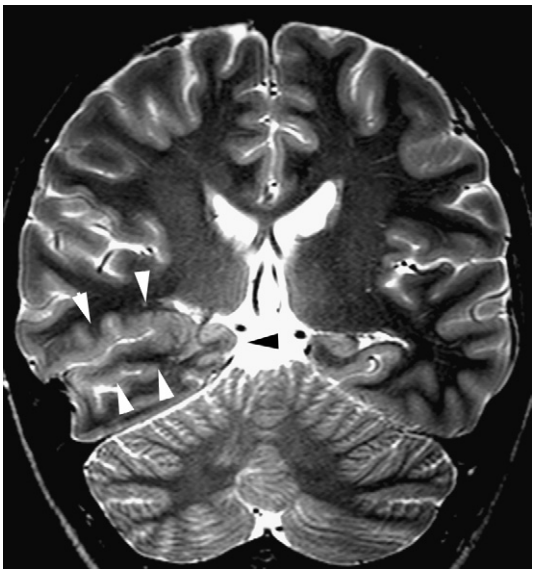

Fig. 46. Subcortical nodular heterotopia. Coronal T2. The SCNH extends to the ventricle (*arrowheads*) and is centered by a deep sulcus which, however, does not open in the ventricle; therefore it is not a true schizencephaly (although the pathogenesis may be similar). Note the right hippocampal dysplasia.

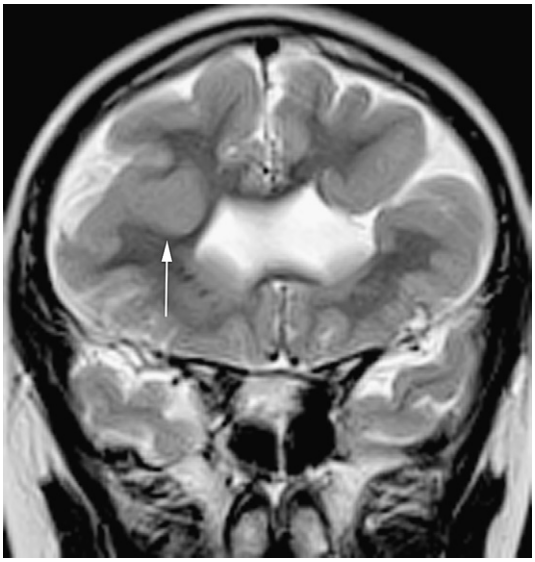

Fig. 47. Subcortical nodular heterotopia and schizencephaly. Coronal T2. This pattern of left frontal schizencephaly with contralateral SCNH (*arrow*) suggests a common pathogenesis.

within the heterotopia[194] (different, however, from the usual Virchow-Robin spaces as are ordinarily seen in the normal white matter) (see **Fig. 42**). Large SCNH often encroach on the ventricle, and the ventricle is deformed accordingly, sometimes narrowed but most often enlarged, likely because of lack of white matter. The cortex continuous with and overlying the SCNH is dysgenetic with abnormal sulcation, sometimes described as "polymicrogyria." The basal ganglia often are dysplastic as well. Independent small SCNH and/or PVNH may be seen in the white matter adjacent to the main SCNH or along the ventricle, and even contralaterally.[196] The hemisphere is typically smaller on the affected side: this is likely due to a lack of volume of the white matter, which cannot connect properly in such a dysmorphic hemisphere[194] (whether there is a specific abnormality of the subplate is not known, but it would seem likely). Sometimes, however, the SCNH may be giant, resulting in an enlargement of a portion the affected hemisphere.[197] The gray-white matter mixture of the heterotopia sometimes has the pseudo-brain appearance of a glioneuronal heterotopia.

Whereas PVNH are common in patients with the classical form of commissural agenesis, SCNH are more common in patients with commissural agenesis with multiple dysplastic interhemispheric cysts.[195] In a subgroup of such patients the heterotopia and the associated cortical dysgenesis are on the medial aspect of the hemisphere, adjacent to the interhemispheric cysts. Besides callosal agenesis, the white matter abnormalities include unilateral absence of the septum pellucidum and of the Probst bundle: it seems logical to assume that the dysplastic gray matter in that location may prevent the axonal pathfinding. In fact a similar SCNH and callosal agenesis may be seen uncommonly without interhemispheric cysts (see **Fig. 43**).[195] In other cases the SCNH may be small and dispersed, apparently unilaterally.

Uncommonly a streak-like SCNH can be seen, which appears as a relatively thin streak of gray matter that crosses the hemisphere from the ventricular wall to the surface; it may be bilateral and quite symmetric (see **Fig. 44**). Like every heterotopia, it presents with the same signals as the cortex on all sequences, which differentiates it from the "transmantle dysplasia" of some FCD type IIB; also it has parallel borders rather than being wedge shaped. It may be confused with a closed-lip schizencephaly, but there is no dimple on the ventricular end and no converging sulci around the pial end (see **Fig. 46**). Yet there are rare instances in which such a streak-like SCNH can be seen contralateral to a true schizencephaly, so that both types of lesions may actually overlap pathogenetically (see **Fig. 47**).

SCHIZENCEPHALY AND POLYMICROGYRIAS

Schizencephaly and classical PMG share many features, and one may wonder whether they are different degrees of the same pathology. Above all, the cortex lining a schizencephalic cleft, and extending more or less over the hemispheric surface, is typically polymicrogyric. Both types of lesion are usually located in the perisylvian regions. Both may be unilateral or bilateral, but when bilateral are usually not perfectly symmetric. Their clinical manifestations are similar: epilepsy, neurologic deficits, spasticity and, when extensive, developmental delay. In most instances, both schizencephaly and PMG are idiopathic, but both may develop in similar contexts such as a fetal CMV infections, or (in relatively frequent if anecdotal gestational records) following second-trimester incidents such as maternal trauma, bleeding, anoxia, or other potential causes of fetal injury. There are significant differences, however. Specific phenotypes of familial/genetic PMG have been identified, while it is still uncertain whether specific genes or loci are involved in schizencephaly. Another difference is that while the definition of schizencephaly is clear (a transcerebral cleft lined with cortex with a pial-ependymal seam), the definition of PMG is much less specific ("too many small gyri") and used to describe very different disorders.

Schizencephaly

Porencephaly (transcerebral cavities from the ventricle to the surface) was initially described by Heschl (quoted in Ref.[198]). In the following decades it became evident that some of the porencephalies were lined with gliotic white matter and therefore occurred late, whereas others were lined with microgyric cortex, therefore occurring relatively early before the end of the fourth month or earlier (for review see Ref.[198]). To make a clear distinction between destructive and what they considered to be agenetic porencephalies, Yakovlev and Wadsworth, in two articles published in 1946, promoted the use of the term schizencephaly for the latter, and described two subtypes, one with closed lips (no real porus)[199] and one with open lips (CSF-containing cavity),[200] and they maintained that both variants were agenetic in origin, for identical reasons: mostly because they share the "same embryonic relationship between the cortical gray matter and the ventricular ependyma," the same "pial-ependymal seam," the same identity of location, and the same associated heterotopia (they also describe a same early myelination that the authors now assume to be secondary to the seizure activity).[200]

In opposition to these arguments, and reflecting the "adult" cerebrovascular diseases, the proponents of the encephaloclastic pathogenesis argued for the location of the clefts in the territories of the main cerebral arteries.[198,201] A proximal occlusion of one of the main cortical arteries however is unlikely, as on angiography of patients with schizencephaly the arterial branches can be seen coursing over the roof of an open schizencephalic cleft to supply the cortex beyond it.[202] As a CP lines the whole cleft, it may be assumed that the defect developed before the end of the neuronal migration, which is a time when the SVZ-VZ only is vascularized. As an initial lesion, a portion of the proliferative zone must have been absent or destroyed: obviously, a vascular lesion is a possibility (arterial or venous) but so also is a focal hemorrhage or an infection (eg, CMV). Such a lesion has been experimentally induced in hamsters by injection of mumps virus.[203] In humans, it may occur in the period between 10 weeks (when vessels proliferate in the germinal tissue) and 16 weeks (before the start of the third wave of migration). The cleft would be due to the agenetic/destructive event and the PMG to an incomplete migration/distorted connection. In the distinction between malformative disorder (inborn), disruptive disorder (distorted anatomy due to injury during development), and acquired disorder (scarring process), classical schizencephaly may be considered an early disruptive lesion, although it is generally idiopathic. In addition, familial cases have been reported.[204,205] From a genetic point of view a role for a germline mutation in the *EMX2* gene was considered,[206] but is not supported by later reports.

Clinically, patients with schizencephaly present mostly with motor defects, either unilateral or bilateral. A second common feature is epilepsy, which may develop late during the second decade, and may become refractory in a significant number of cases. Developmental delays vary depending on the extent of the lesions (not only the cleft but also the commonly associated surrounding PMG), and their unilaterality or bilaterality. Speech may be significantly altered both in the motor and the comprehension aspects.

Morphologically the diagnosis is relatively simple.[207] Schizencephaly is characterized by the presence of a transcerebral cleft extending from the ventricle to the surface and completely lined with cortex, so that the cortical pial surface is continuous with the ventricular ependymal lining: the pial-ependymal seam of Yakovlev and Wadsworth (see **Fig. 47**; **Figs. 48–52**).[199,200] The cleft may be closed (fused lips), with no visible CSF in it (see **Figs. 48**, **50**, and **52**); or it may be open (see **Figs. 47**, **49**, and **51**). Even when it is closed, a dimple on the ventricular surface and often an umbilication with converging sulci on the hemispheric surface may be seen. The cortex lining

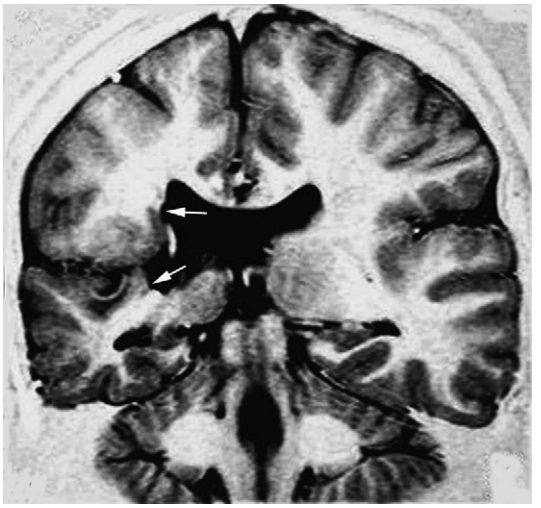

Fig. 48. Unilateral closed-lips schizencephaly. Coronal T1. Deep transcerebral cleft on the right side, lined with cortex so that the cortical ribbon joins the ependyma (*arrows*). Right hemispheric hypoplasia and absent pellucidum.

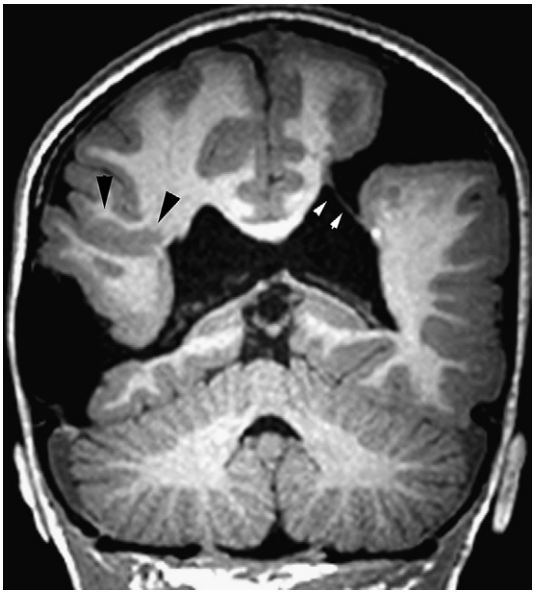

Fig. 49. Multiple bilateral schizencephaly. Coronal T1. Left parietal and right temporal open clefts, the latter with a thin closing membrane (*white arrowheads*), right parietal closed cleft (*black arrowheads*).

the cyst is polymicrogyric, as well as, often, the cortex surrounding the cleft on the hemispheric surface. The most common location of the clefts is suprasylvian, but they can be found anywhere on the lateral, medial, or inferior surface of the hemispheres. The clefts may be unilateral or bilateral, and sometimes more than 2 clefts may be seen when the images are carefully analyzed (eg, anterior temporal lobes, inferior occipital lobes). When bilateral, the clefts are usually not strictly symmetric, and may present as a closed cleft on one side and an open cleft on the other. Strictly symmetric schizencephalies may be seen, however (see **Figs. 50** and **52**) and may well be genetic (not all familial schizencephalies, however, are symmetric or even bilateral). Also, unilateral schizencephaly may present with a contralateral PMG, or even with a contralateral transmantle streak-like SCNH (see **Fig. 47**).

As in most MCD, the white matter is affected and its volume is reduced so that the brainstem may be hypoplastic. More specifically, the pellucidum is characteristically absent when the clefts are suprasylvian, either unilaterally or bilaterally.[208] There is no ready explanation for this, as the fibers that constitute the septum pellucidum are limbic, not neocortical.[195] Together with the pellucidum, the anterior optic pathway may be hypoplastic, suggesting that at least some variants of schizencephaly could be complex forms of septo-optic dysplasia[209]; it may also be that optic and pituitary hypoplasia may be nonspecifically associated with diverse disorders. More consistently with what is known of brain development, the corpus callosum may be at least partially defective when the schizencephalic clefts involve the medial aspect of the hemisphere (see **Fig. 50**). Of interest, PVNH may be observed lining the ventricle around the ventricular opening of the cleft as well as at some distance from it.

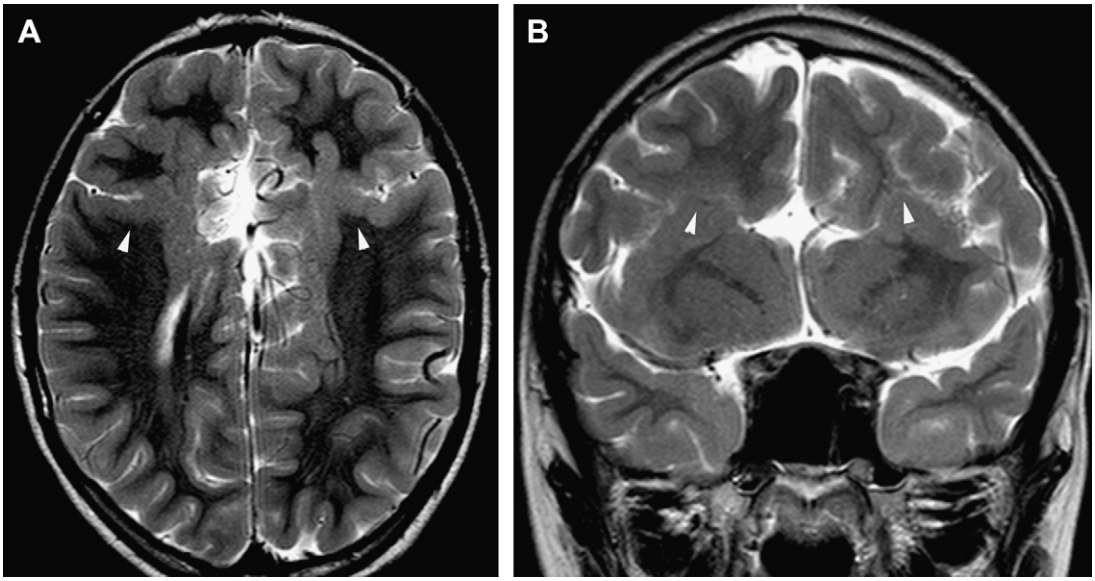

Fig. 50. Schizencephaly with commissural agenesis. (*A*, axial and *B*, coronal T2). The bilateral clefts extend to the medial cortex and cingulate gyrus (*arrowheads*), thereby preventing the development of the commissural plate.

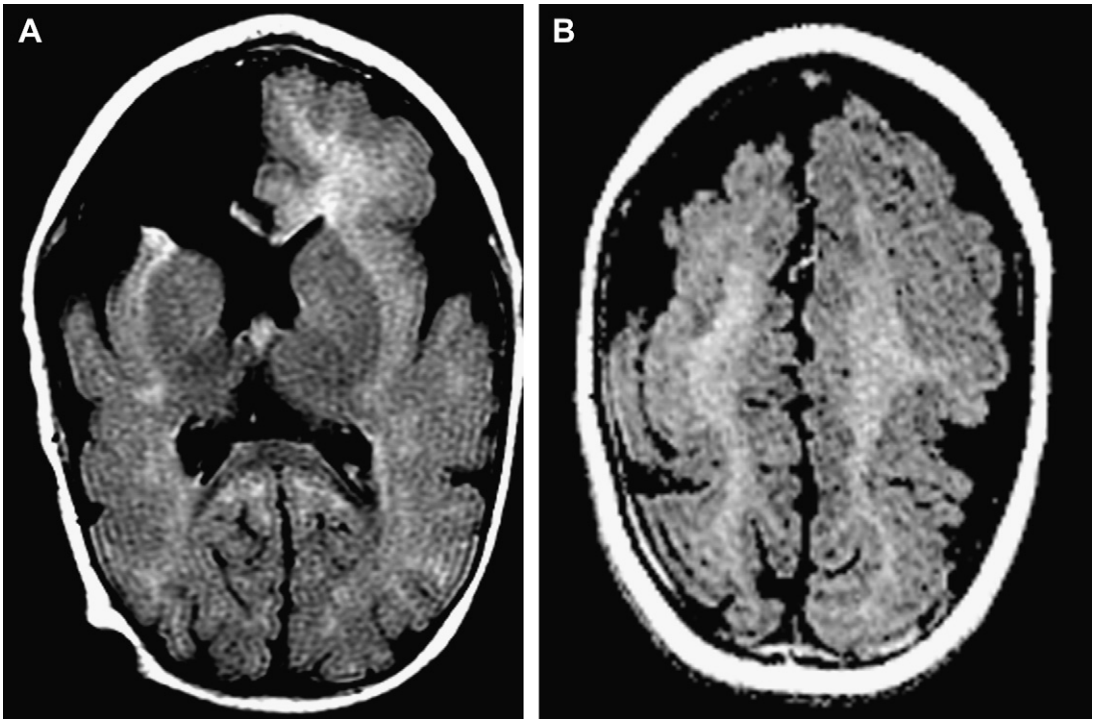

Fig. 51. Fetal brain infection with cytomegalovirus. (*A*, *B*) Axial T1. Right frontal open cleft with diffuse polymicrogyria.

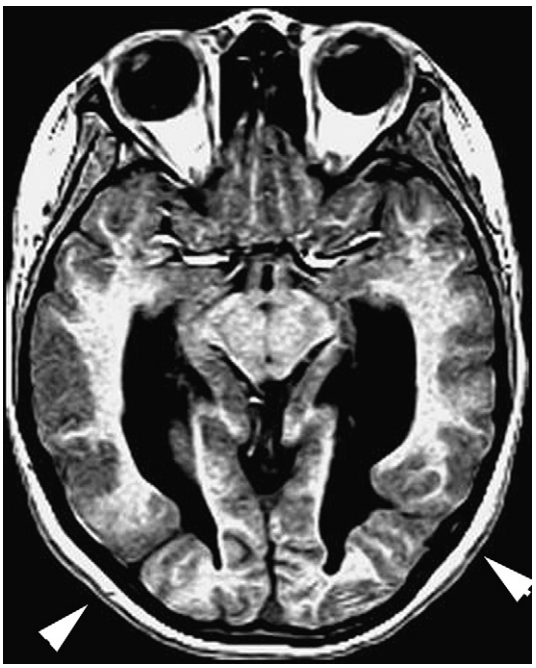

Fig. 52. Bilateral symmetric schizencephaly. Axial T1. Such a pattern of symmetric clefts (*arrowheads*) and the temporo-occipital location are unusual, and may suggest a genetic origin.

The differential diagnosis of schizencephaly is both easy—the anatomic definition of the lesion is clear—and difficult, as the pathogenesis is uncertain. Obviously it can be differentiated from congenital encephaloclastic porencephalies by the fact that the walls of the cavity of the latter are made of white matter, not cortex. In the case of fetal infection with CMV, the importance of the brain alteration (especially the microcephaly) sometimes makes it difficult to tell whether the cleft is lined with cortex or not: the diffuse PMG and the common white matter abnormality suggest that it is a real, if acquired, schizencephaly (see **Fig. 51**). As mentioned before, streak-like SCNH can be differentiated by the absence of a ventricular dimple, but the 2 entities may be somewhat related. A common source of uncertainty is when a sulcus lined with PMG extends deep into the hemisphere, being separated from the ventricle by a thin layer of subcortical white matter only: this is technically not a schizencephaly (no pial-ependymal seam), but a complete or incomplete layer of white matter has been described partially forming the floor of the cleft in true schizencephaly (compare **Figs. 46** and **49**),[207] so that it is uncertain whether such abnormalities might be intermediate degrees of severity in a wide spectrum of schizencephaly-PMG.

The Polymicrogyrias

Histopathologically, polymicrogyria is a specific disorder: under a smooth (but irregular, compared with a cauliflower or with morocco leather) and pachygyric-like surface, PMG is made of a piling upon each other of numerous small, somewhat irregular folds under a fused surface.[3] The development of these irregular undulations does not correspond to the normal mechanism of gyration-sulcation, as the abnormality may be observed as early as 18 gestational weeks,[210] well before the first normal primary sulci form after mid-gestation: it is rather an early primary dysplastic development of the CP, resulting in an undulated, serrated appearance under the preexisting MZ/molecular layer. Because it is a primary cortical disorder that antecedes their development, the connectivity and the related gyration/sulcation become severely abnormal in classical PMG. In addition, the meninges overlying the PMG are commonly

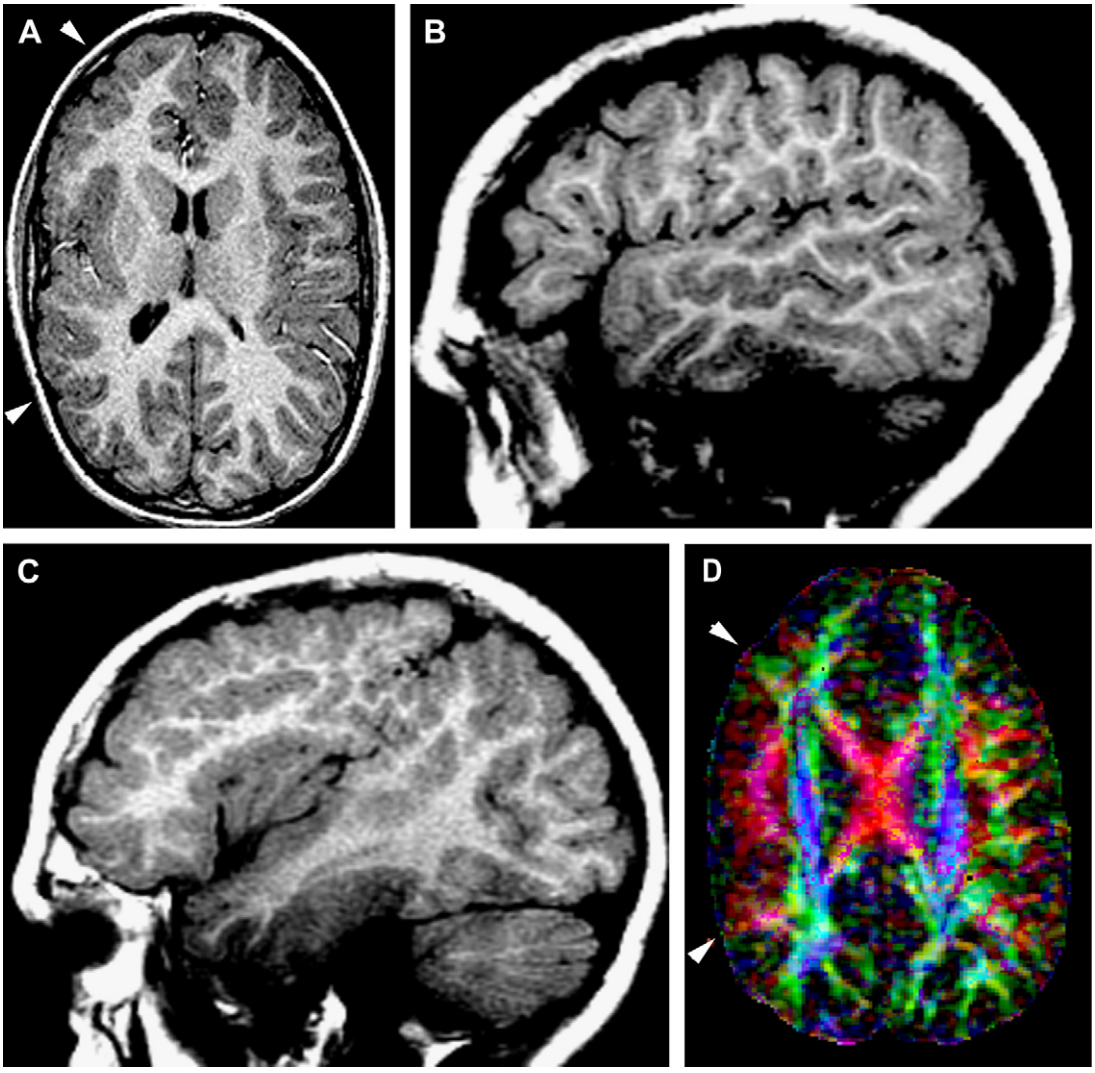

Fig. 53. Unilateral classical polymicrogyria. (*A*) Axial T1. The right perisylvian cortex (*between arrowheads*) demonstrates flattening and loss of the normal opercular anatomy. (*B*) Lateral sagittal T1, left side. Normal sulcal anatomy of the right hemisphere. (*C*) Lateral sagittal T1, right side. The sulcal anatomy is distorted: the sylvian fissure extends into the rolandic-parietal region; the sulci present are aberrant. (*D*) FA color mapping. Disorganization of the fascicular pattern; possibly because of the flattening of the lateral hemispheric cortex, the subcortical fibers all appear transverse (*between arrowheads*).

abnormal and thickened, with (unexplained) vascular proliferation[3,210] and leptomeningeal heterotopia.[210] The PMG cortex is described as either 4-layered or unlayered. It is characterized by an abnormal arrangement of the cell layers and intracortical fiber plexus, and by an excessive folding of the upper or all cellular layers under the continuous smooth molecular layer. The 4-layered cortex is made of the molecular layer, an upper dense cell layer, a layer of low cellular density with horizontal myelinated fibers, and a deep cell layer.[3] The neurons may be small, even immature. The molecular layer may contain too many fibers. The CP is thinner than normal, but does appear thick because of the excessive folding[3] (something like the Spanish collar worn in the sixteenth century). The gray-white junction may be either sharp or histologically blurred by heterotopic neurons or nodules.[210]

More severe (unlayered) patterns associate a molecular layer with a single cellular layer.[3] Abnormal persistence of Cajal-Retzius cells has been described in the molecular layer and in the leptomeningeal heterotopia, as well as in the apparently normal adjacent surrounding cortex[211]; to the best of the authors' knowledge, there is nothing in the literature regarding the subplate in PMG. The undulation involves the CP but not the smooth molecular layer (normal gyration involves the cortical plate and the molecular layer together)[3,210]; this may be due to different rates of expansion of the cellular layers[3] but cannot be due to an abnormal connectivity, as the afferent connectivity does not reach the cortex until after week 22. On the other hand, PMG results in an abnormal connectivity that is demonstrated by a poor, aberrant sulcation (the sulci cannot be named) and by a decreased volume of white matter in the corresponding portion of the

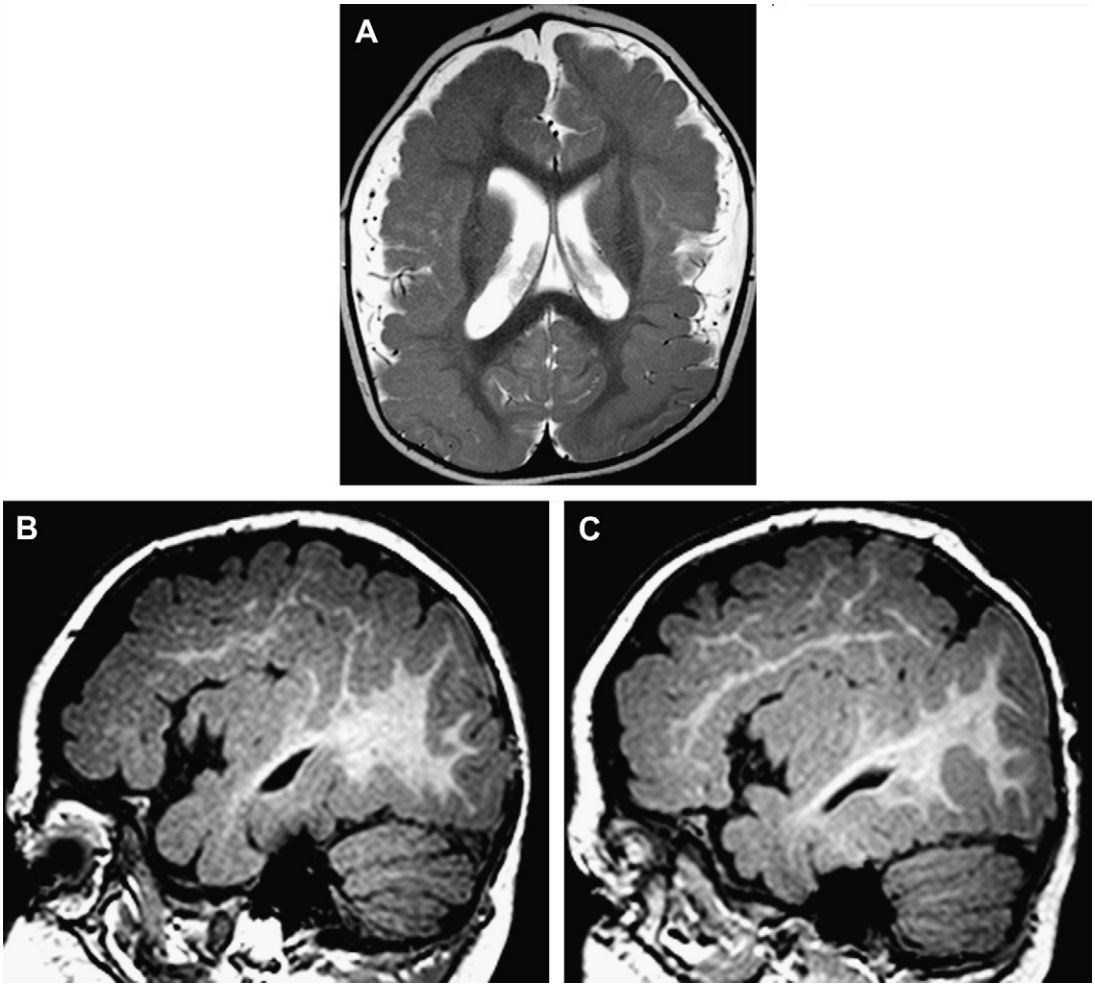

Fig. 54. Bilateral classical polymicrogyria. (*A*) Axial T2. The perisylvian cortex on both sides is abnormal. (*B*, *C*) Lateral sagittal T1. Major distortion of the perisylvian cortical pattern bilaterally.

hemisphere and the brainstem. This pattern corresponds to that of classical PMG, which assumedly is a specific malformation. However, the diagnosis of PMG is not made by pathology but mostly by MR imaging, and the name PMG (many small gyri) is commonly used as a descriptive term to designate a multiplicity of likely different entities, such as the cortical abnormalities seen in Zellweger syndrome, hemimegalencephaly, the cortex overlying a giant SCNH, the cobblestone cortex resulting from pial basement membrane defects (eg, Fukuyama, MEB, "bilateral frontal polymicrogyria" due to *GPR56* mutation), and even in Chiari II malformation (for which a special name, stenogyria, has been coined to describe a specific cortical pattern): all are different diseases from, and not variants of, PMG.

What causes a PMG? There are many well-defined genetic PMG syndromes,[212,213] but the vast majority of PMG cases observed in clinical practice are idiopathic. Because of the common location of the abnormalities in the perisylvian regions, and because of anecdotal reports of possible anoxic-ischemic injury in the second trimester, a hemodynamic mechanism is commonly proposed, as for schizencephaly. Yet it should be remembered that there is no cortical vascularization before week 22, so that any vascular event before that time would affect the germinal zone, not the cortex, and would be consistent with PMG being considered a milder form of a group of injuries of which schizencephaly could be the most severe form. An event occurring during the third wave of neuronal migration (after week 16) and before 18 weeks would sound logical, as definite PMG can be seen at this gestational age: yet it seems odd that the most common cortical malformation would result from an event occurring within such a very limited period of 2 weeks in the early third trimester. Therefore, PMG may be the end result of many events occurring at any time during the neuronal migration before 18 weeks (or less).

Beyond the "many small gyri," Barkovich proposed a distinction between "coarse" PMG (which corresponds to the classical appearance) and a "delicate" type (which the authors call a "curly" cortical ribbon).[214] It seems logical that these two different appearances would reflect different pathologies, especially as the curly (or "delicate") PMG seems not to be necessarily associated with aberrant sulcation (see **Fig. 24**D). As a consequence, the authors classify PMG as:

- Classical, idiopathic PMG
- PMG syndromes
- PMG-like malformations.

Classical (idiopathic) PMG

Classical idiopathic PMG is typically found in the perisylvian regions (**Figs. 53** and **54**). The sylvian fissure itself often is exceedingly oblique and extends posterosuperiorly into what apparently is the parietal lobe (given the abnormal sulcation, a precise lobar identification is uncertain). In roughly half the cases PMG is unilateral (see **Fig. 53**) and in half it is bilateral; when it is bilateral, it is not strictly symmetric (see **Fig. 54**). It may be restricted to the opercular region or may extend further, even over the vertex toward the medial wall of the hemisphere; however, it seems never to affect the limbic structures.

The cortex appears irregular. Although it may appear thick on 4- to 5-mm cuts, use of thin 3D-T1 acquisition has shown that the cortical ribbon itself is thin, and the apparent thickening results from juxtaposition of the folds.[215] The molecular layer is difficult to identify on MR images. The cortical-subcortical junction appears well demarcated, if irregular. The sulcation is aberrant, without any recognizable pattern; this may extend even beyond the recognizable area of PMG, presumably because of a distorted connectivity (see **Figs. 53** and **54**).[215] The sulci may be shallow or, on the contrary, indent deeply in the parenchyma. The white matter is decreased in volume, with a corresponding ventriculomegaly and thin interhemispheric commissures. This hypoplasia extends to the cerebral peduncles, pons, and medullary pyramids, resulting in a striking asymmetry when the malformation is unilateral. There may be some delay in myelination; however,

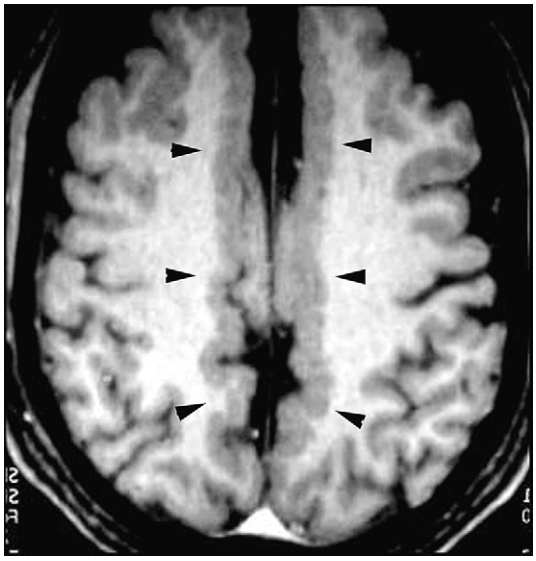

Fig. 55. Bilateral medial frontal polymicrogyria (*arrowheads*).

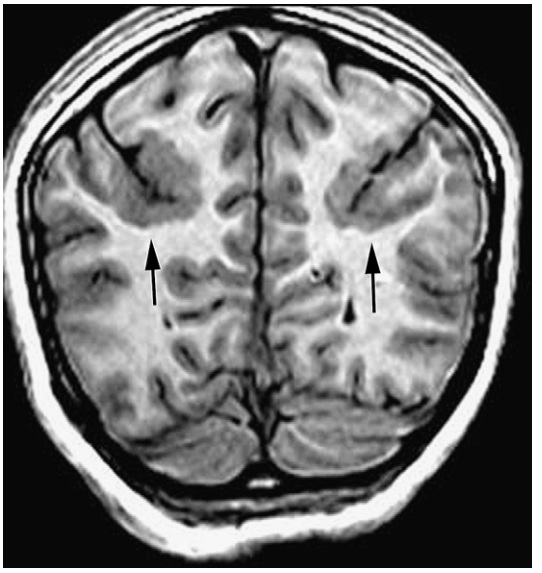

Fig. 56. Bilateral parietal polymicrogyria (*arrows*).

significant bright T2/FLAIR changes in the white matter, especially when organized in subcortical and periventricular layers,[215] are highly suggestive of PMG secondary to cytomegalovirus infection (see **Fig. 51**).[216] Over the brain surface dysplastic vessels, mostly veins, are common and correlate well with the pathologic finding of leptomeningeal vascular dysplasia.

Secondary and possibly secondary PMG

CMV has for a long time been shown to be associated with PMG.[217,218] The PMG features may be

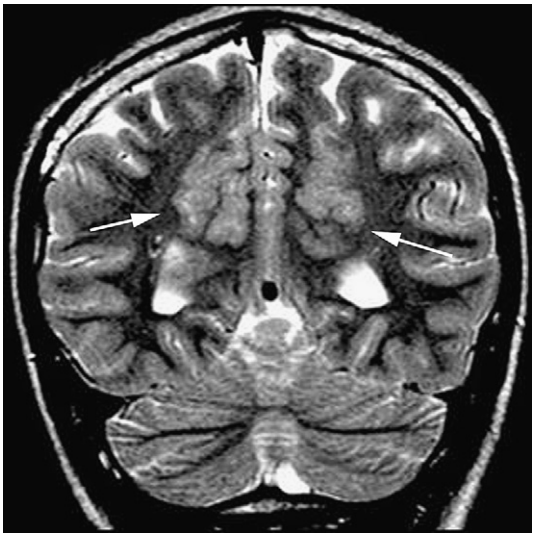

Fig. 57. Bilateral parieto-occipital polymicrogyria (*arrows*).

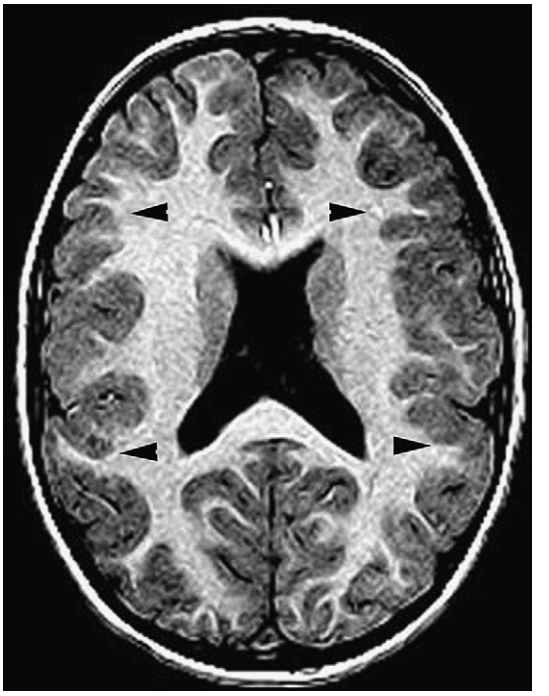

Fig. 58. Bilateral perisylvian polymicrogyria with septal agenesis (*arrowheads*).

severe, associating PMG and schizencephalic clefts supratentorially as well as infratentorially, and with microcephaly (see **Fig. 51**). In other instances the lesions may be milder. As mentioned

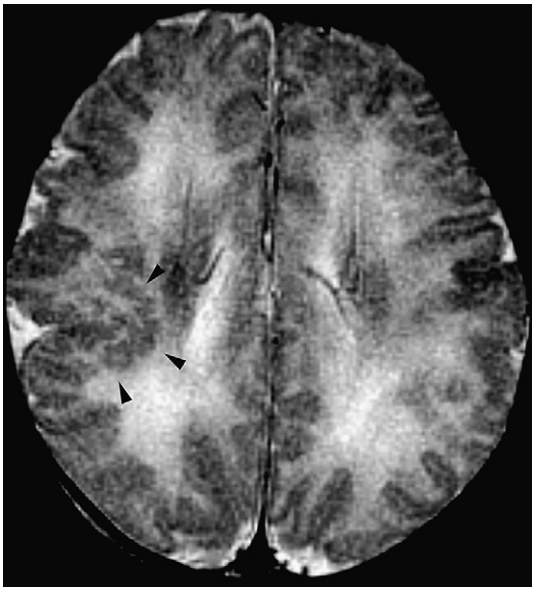

Fig. 59. Zellweger disease. The PMG-like cortical abnormality is typically located in the posterior insular/opercular area (*arrowheads*).

earlier, the presence of large areas of unmyelinated white matter often organized in two separate layers is very suggestive of the etiology.

PMG may be associated with meningeal dysplasia. The association is common in commissural agenesis with dysplastic interhemispheric meningeal cysts, often in association with SCNHs (see earlier discussion). It may be observed in cases of meningeal angiomatosis[219] or meningeal lipoma.[3,220]

Bilateral symmetric PMG

Not all presumably genetic PMG are bilateral, and there are familial instances of unilateral PMG,[221,222] not necessarily on the same side, in different family members (Charles Raybaud,

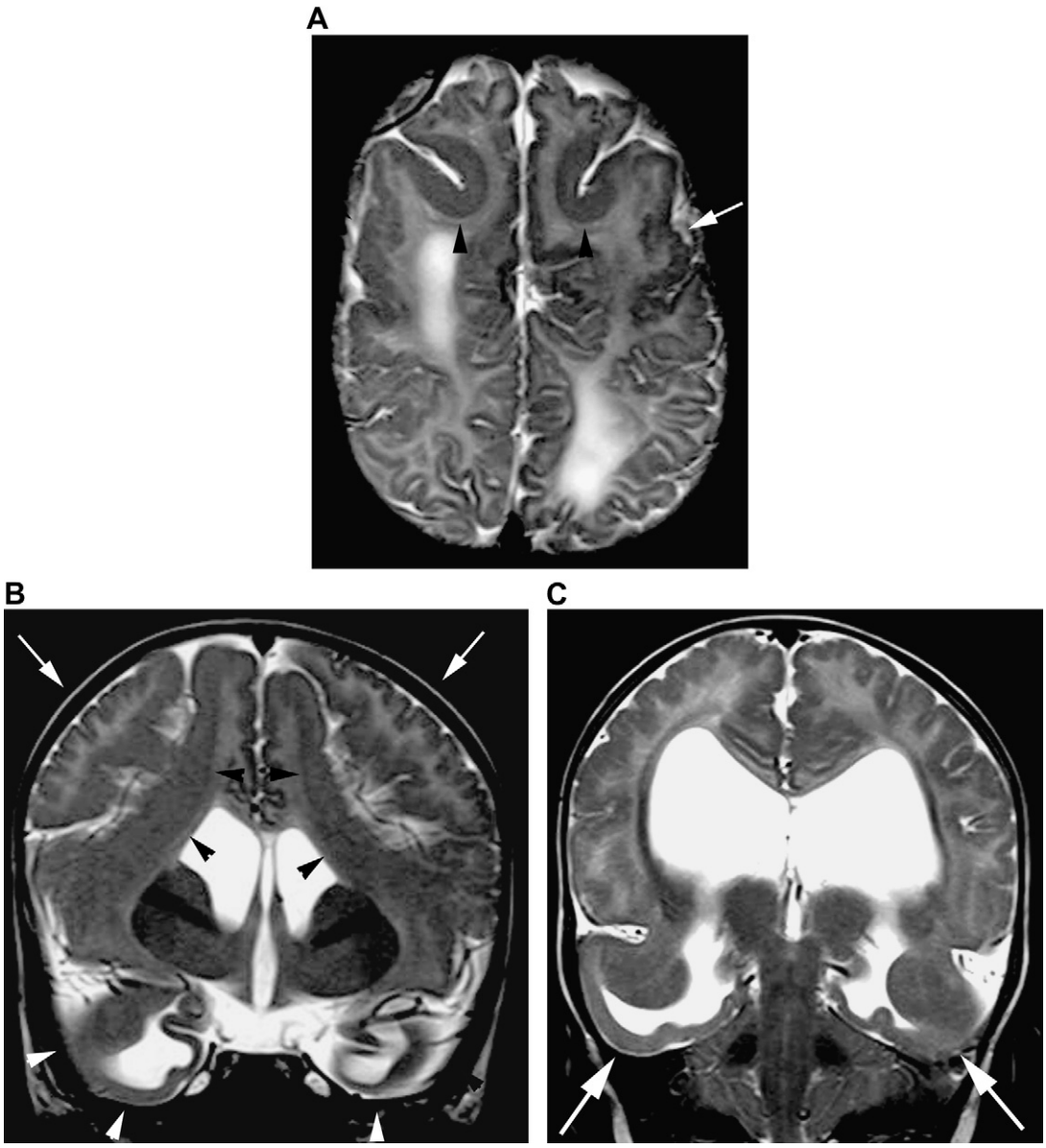

Fig. 60. Undetermined complex cortical malformative syndrome. (*A*) Axial T2. Bilateral symmetric deep frontal clefts (*arrow*) lined with thick dysgenetic cortex (*arrowheads*) associated with diffuse medial and lateral frontal polymicrogyria; the posterior parts of the hemispheres appear normal. (*B*) Coronal T2. The deep bilateral frontal clefts are associated with thick cortex (*black arrowheads*) and polymicrogyria (*white arrows*); anterior temporal agyria (*white arrowheads*). (*C*) Coronal T2. Marked ventriculomegaly. The anterior temporal cortex is smooth (agyric) with dysplastic hippocampi. (*Courtesy of* Dr Xin-Chang Wei, Calgary, AB.)

personal data). Yet most cases of genetic PMG are bilateral and symmetric (**Figs. 55–58**). In contrast to the idiopathic form of PMG, bilateral symmetric PMG may also involve the cortex that lines abnormally deep but normally located sulci. Such PMG syndromes are: the bilateral perisylvian polymicrogyria syndromes (Xq21.33–q23/SRPX2; 22q11.2; Xq28)[223]; the BFPP, better identified now as a pial basement membrane disease (GPR56) (see earlier); the bilateral symmetric frontal polymicrogyria[224]; the bilateral medial parietal-occipital polymicrogyria[225]; a megalencephaly with polymicrogyria and hydrocephalus, or with polymicrogyria, polydactyly, and hydrocephalus[226]; and a syndrome of mega-corpus callosum, polymicrogyria, and psychomotor retardation.[227] It is likely that more will be recognized over the years. Finally, the rare occurrence of a bilateral, symmetric polymicrogyria with absent septum pellucidum is more likely related to an inborn defect than to a forme fruste of porencephaly (see **Fig. 58**).[228]

PMG-like cortical malformations are common and have been described in different contexts of MCD: microcephaly, hemimegalencephaly, bilateral frontoparietal PMG, Fukuyama syndrome (see earlier), and massive subcortical nodular heterotopia,[229] but also in metabolic diseases such as the peroxisomal disorders (**Fig. 59**), mitochondrial disorders, and glycogenosis type III.[230] It is felt that when the PMG is found in a context other than pure PMG with or without schizencephaly, the descriptive term "PMG-like" should be used to differentiate it from the true PMG, either idiopathic, disruptive, or inborn.

SUMMARY

Malformations of cortical development are a confusing group of disorders, with similar phenotypes resulting from acquired or metabolic disorders or genetic mutation. Although the main morphologic subtypes (microcephaly, heterotopia, lissencephaly, polymicrogyria, and so forth) have been related to different mechanisms, the findings of different types of malformations associated in the same brain (eg, cortical dysplasia, agyria, heterotopia, polymicrogyria, schizencephaly) (see **Figs. 24**, **26**, and **47**; **Fig. 60**) suggest that several processes of corticogenesis are commonly compromised together in the same patient. Each pattern is a malformative feature only, and together these features may form various combinations, which depend on the etiopathogenetic process involved (genetic mutation, metabolic disease, infection, syndromic association and so forth).

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