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Imaging surgical epilepsy in children

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Abstract
Introduction Epilepsy surgery rests heavily upon magnetic resonance imaging (MRI). Technical developments have brought significantly improved efficacy of MR imaging in detecting and assessing surgical epileptogenic lesions, while more clinical experience has brought better definition of the pathological groups.
Discussion MRI is fairly efficient in identifying developmental, epilepsy-associated tumors such as ganglioglioma (with its variants gangliocytoma and desmoplastic infantile ganglioglioma), the complex, simple and nonspecific forms of dysembryoplastic neuroepithelial tumor, and the rare pleomorphic xanthoastrocytoma. The efficacy of MR imaging is not as good for the diagnosis of focal cortical dysplasia (FCD), as it does not necessarily correlate with histopathological FCD subtypes and does not show the real extent of the dysplasia which may even be missed in a high percentage of cases. Further developments with better, multichannel coils, higher magnetic fields, specific sequences, and different approaches (such as diffusion tensor imaging) for depicting the structural abnormalities may hopefully improve this efficacy. A general review of the MR features of the diverse pathologies concerned with epilepsy surgery in the pediatric context is provided with illustrative images.

Keywords MR imaging · Epilepsy · Ganglioglioma · DNT · PXA · FCD · Hypothalamic hamartoma · Meningioangiomatosis

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Introduction

Epilepsy surgery in children addresses severe refractory epilepsy mainly, which threatens the child's development, when a constant epileptogenic focus can be identified from the clinical and the electroencephalogram (EEG) data and be removed. Imaging must demonstrate a corresponding focal epileptogenic lesion, locate it precisely in relation to the brain eloquent areas, and provide anatomic support for complementary functional studies [magnetoencephalography (MEG) where available, functional magnetic resonance imaging (fMRI) for functional cortex, positron emission tomography (PET) or ictal/interictal single-photon emission computed tomography (SPECT) for the epileptogenic cortex] and for neuronavigational systems.

With the successive advances in medical imaging, the identification of the cortical lesion responsible for the disease tends to become the rule. But the structural changes may be subtle. To demonstrate them, the best available technique (sequences, parameters, coils, etc.) should be used. The study should be oriented: the neuroradiologist should know what to look for (what types of pathology and where); good communication with the clinical team is essential. Relevant details of the patient's epilepsy must be

shared. On the other hand, the fact that epilepsy is a functional disease should not be overlooked: the epileptogenic cortex may be somewhat different from the structural abnormalities demonstrated by imaging.

Imaging tools and strategies

Structural imaging

Various protocols have been provided in the past decades [1–4]. The imaging technique must be the best available at the moment. Today, it is obviously magnetic resonance imaging (MRI), with its latest developments, and computed tomography (CT) comes as a complementary tool only. Besides the conventional sequences, advanced structural studies such as diffusion tensor imaging (DTI), high fields, high-definition imaging matrix, built-in motion correction and whatever enhances the sensitivity and the definition of the method are likely to improve the yield of imaging.

Axial, coronal, and sagittal planes must be used. For a good anatomical assessment, the reference *axial examination plane* should be chosen according to the expected location of the pathology: the bi-hippocampal plane (parallel to the hippocampi) for the temporo-occipital cortex; the classical universal bi-commissural plane (Talairach's plane, parallel to the anterior commissure–posterior commissure plane) is better for the fronto-parietal structures. The head should be stable, precisely positioned, and perfectly symmetrical so that one side can be compared to the other one. A perfect immobility is required, meaning sedation in young children and in those who are unable to cooperate because of an associated mental delay. An efficient sedation is often difficult to reach in patients who have taken anti-epileptic medications for years, and a general anesthesia provided by an anesthesiologist allows for optimal results.

Routine sequences include at least T2 FSE, T1 IR (inversion recovery), flow attenuation inversion recovery (FLAIR, T2 imaging with cancellation of water), and 3D-FT millimetric T1W GE depicting the brain in the three planes, the most useful being usually the coronal and the axial planes. Other sequences – T2 GE (so-called T2*), magnetization transfer (MT), and diffusion weighted imaging – are to be used according to the needs. Contrast agent should always be used in recent-onset epilepsy (initial assessment) and obviously whenever a lesion needs to be characterized as a tumor vs dysplasia. In infants, sequences should be adapted to the longer T1 of the immature brain by using longer repetition times and longer echo times.

Magnetic resonance spectroscopy (MRS) shows the relative concentration of three main metabolites: *N*-acetyl aspartate (NAA), a marker of the neuronal activity; Choline (Cho), a marker of the membrane turn-over; and Creatine (Cr), a marker of energy metabolism, which is assumed to remain constant and is used to semi-quantitatively evaluate the other components through the ratios NAA/Cr or Cho/Cr; *myo*-Inositol expresses astrocytic proliferation. As opposed to the single-voxel MRS that provides the metabolic spectrum of a selected volume of the brain only, MRSI nowadays displays the spectra over a whole slice or even volume of the brain. Spectroscopy is used to try to better characterize a lesion (mostly between tumors or tumor vs dysplasia according to the spectral profile) or, by showing a decreased NAA, to locate the epileptogenic area. However, the changes may reflect both the structural abnormalities and the metabolic alterations related to the seizures, making the interpretation of the results difficult [5–7]. Normal metabolic heterogeneity intrinsic to the brain should also be accounted for [8].

Diffusion imaging has shown striking abnormalities during status epilepticus, reflecting cytotoxic edema both locally and remotely in the ipsilateral pulvinar [9, 10], the ipsilateral hippocampus [10], the contralateral cerebellum (diaschizis-like response) [9] as well as in the corpus callosum [9]. This brain response to repeated/prolonged seizures may be useful to locate a focus. These changes are typically regressive [9, 10] but, in rare cases, the (ill-understood) underlying mechanisms may lead to irreversible lesions of the involved hemisphere and produce the classical features of the hemiconvulsion–hemiplegia syndrome (HH syndrome) or of the hemiconvulsion–hemiplegia–epilepsy syndrome (HHE) [11]. In an animal model of status epilepticus, restricted diffusion was also demonstrated in the limbic structures and correlated the neuronal loss [12].

Perfusion imaging may be performed in two ways [13]. A bolus of gadolinium contrast agent is injected; the transit through the brain of this paramagnetic agent causes changes in the T2*, and a quantified transit curve of the bolus can be traced; this is called the dynamic susceptibility contrast method. Instead of infusing paramagnetic contrast, the other method uses the radiofrequency and gradient pulses to selectively label the water nuclei in the in-flowing arterial blood; this is called the arterial spin labeling method. Calculated from the transit curves, the bolus/peak ratio reflects the perfusion of the tissue. Preliminary studies have shown focal changes during seizure activity [13]. Although still in the experimental stage, this method has the potential of replacing nuclear medicine studies to help in locating an epileptic focus.

Structural image analysis describes the various computer-assisted methods devised to improve the rate of detection of subtle brain abnormalities in epilepsy [14]. Most use segmentation methods and post-processing algorithms aimed at quantifying the volume of various compartments of the brain such as gray and white matter or specific lobes or structures such as the hippocampus or to evaluate the

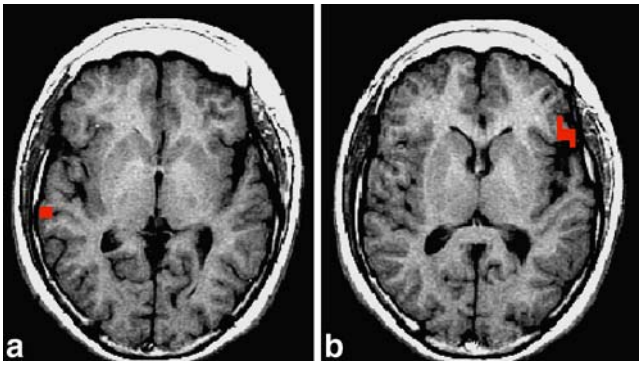

Fig. 1 Functional MR imaging. Language mapping. Boy, 15 years, persistent seizure disorder after resection of left temporal lobe tumor. fMRI shows mixed hemispheric dominance. Word repetition and listening to a story show language comprehension on the right side (**a**); object naming show expressive language on the left side (**b**)

thickness of the cortex, the blurring of the cortical–subcortical junction, etc. These methods are unfortunately not fully automated, time consuming, and difficult to use in clinical practice. Multimodal integration of the anatomic data from MRI, functional data from interictal PET or ictal/interictal SPECT, and electrophysiological data from cortical or stereo-EEG or from MEG may also help in identifying the epileptogenic focus with its underlying structural abnormalities.

Structural studies using the diffusion imaging approach, *fractional anisotropy* and *diffusion tensor imaging* [15] have allowed a really new approach of the epileptic brain, depicting the abnormalities of the white matter in addition to the conventional MR imaging that rather depicts the cortex. These methods are based on the fact that the fascicular organization of the white matter imposes preferential directions to the diffusion of the water molecules. Registering these preferential directions allows the reconstruction of the fiber tracts anatomy [15, 16] in normal subjects as well as, more recently, in focal cortical dysplasia (FCD) [17] and schizencephaly [18].

Functional MR imaging

The eloquent cortex needs to be spared during epilepsy surgery. In general, electrophysiological methods like EEG or MEG define underlying cortical events in real time (10–100 ms) but suffer from poor spatial resolution. PET evaluates metabolic and blood flow changes but is slightly more invasive and has a poorer temporal resolution. fMRI links the high spatial resolution to the temporal resolution of these techniques. Increased neuronal activity is associated with regional increase in blood flow, which has the paradoxical effect of increasing the oxyhemoglobin-to-deoxyhemoglobin ratio and of producing changes in T2* signal that can be detected by fast imaging techniques. This blood oxygen level dependent (BOLD) fMRI technique is a reasonably accurate method of detecting such changes in response to activation. It is noninvasive, making it possible to use more easily in children, provided that a complete immobility can be warranted, however. The primary sensory cortices (post-central, auditory, and visual) can be activated even under sedation. fMRI may be used to help in locating a focus in instances of infra-clinical or non-convulsive seizures by using the EEG activity to trigger the recording of the signal [19, 20]. However, this is still under methodological development. In fact, fMRI is widely used today mostly for mapping the main functional areas (language and memory) [20, 21].

Motor and sensory mapping is the most reliable and reproducible of fMR imaging paradigms. The motor strip may be identified by tongue wiggling, finger tapping, or toe/foot tapping. The sensory strip may be identified by brushing. Identifying these areas is useful when planning extratemporal neocortical frontal or parietal resections, for example, for cortical dysplasias in this area. Motor paradigms were the first to demonstrate that dysplastic cortex can sustain motor function. There is usually excellent agreement between fMRI findings and evoked potential or direct cortical stimulation.

Language mapping is used to replace the (really invasive) Wada test or intracarotid amobarbital test (IAT). With increasing experience, fMRI has been shown to be reliable, and good concordance with IAT is reported in approximately 90% of patients. Patients who show disparity tend to demonstrate bilateral language on fMRI. A number of paradigms are used to localize expressive and comprehensive language functions. Expressive language is well demonstrated in the inferior frontal gyrus (Broca's area), with word and verb generation. Language comprehension areas are usually localized along the superior temporal sulcus and are activated by tasks that stress phrase or sentence comprehension, such as listening to stories or reading stories or sentences. Tasks can be adapted for children, for example, by adding an auditory cue instead of using only a visual cue in a verb-generation task to ensure that the child completes the task. Language mapping is often more complex in patients with epilepsy. A high incidence of atypical language patterns such as mixed hemispheric dominance is noted, as well as a higher-than-usual incidence of right-sided dominance in right-handed children (Fig. 1).

Language lateralization is usually determined by region of index asymmetry. Regions of interest targeted to known language processing areas are usually used, and activation of voxels is compared with a pre-determined threshold of asymmetry (this can vary but 0.20 to 0.25 asymmetry index is usually used). Visual rating also works well and some centers rely on this to determine lateralization. There is usually good concordance between the Wada test and

fMRI, but there are some disorders in which physiology is altered and the BOLD response may not be as reliable. Postictal state may cause alterations in the normal BOLD response to activation. But, in spite of these limitations, fMRI is a reliable technique for language lateralization.

Presurgical imaging in generalized epilepsies

Any disorder of the brain may result in generalized epilepsy. Except for the Chiari malformations, all cerebral malformations (holoprosencephaly, commissural agenesis, and malformations of cortical development, MCD) or any metabolic disease that affects the neurons may be complicated by a partial onset or a generalized epilepsy. However, those diffuse disorders are typically not surgical indications. Specific infantile epileptic syndromes, however, might point to surgically curable disorders.

The *Ohtahara syndrome* (or early infantile epileptic encephalopathy with suppression–burst pattern) is the earliest of the three age-dependent epileptic encephalopathies. It occurs in the first weeks of life and is characterized by tonic spasms, in association with partial seizures and hemiconvulsions, and by the characteristic suppression–burst EEG pattern [22]. Evolution is toward death or severe mental impairment [22]. The main structural brain anomalies associated with this syndrome are a hemimegalencephaly (HME), an Aicardi syndrome (callosal agenesis with interhemispheric cysts and ocular dysplasia in a girl), a dentato-olivary dysplasia, or destructive lesions such as a porencephaly or a nonspecific "atrophy". According to some reports, HME, which is surgically treatable, may represent the most common causative lesion associated with this syndrome [22].

The *West syndrome* develops typically between 3 and 7 months (but occasionally also before and after up to 5 years). It is characterized by clusters of axial spasms, by a psychomotor deterioration ,and by the characteristic EEG pattern of hypsarrythmia. The prognosis is poor, with motor, sensory and mental defects, and persistent epilepsy [23]. Brain imaging is usually abnormal, the classical associated lesions being tuberous sclerosis (TSC), lissencephaly, HME, focal cortical dysplasia, schizencephaly, and callosal agenesis (Aicardi syndrome) [23]. Scars from hypoxic–ischemic encephalopathy (HIE) are also common [23]. But, even in cases of cryptogenic West syndrome, focal abnormalities with microdysgenesis accessible to surgery may be demonstrated [24].

The third age-dependent epileptic encephalopathy, the *Lennox–Gastaut syndrome*, has no specific associated brain malformation. The only surgical treatment would be an anterior callosotomy to help decrease the frequency of falls. Imaging is of little help except to show the midline brain anatomy in the patients for which this palliative procedure is considered.

Imaging epilepsy-associated tumors

Epilepsy-associated developmental tumors form an intriguing group of developmental lesions. In one surgical series [25], they represent up to two thirds of the epilepsy-associated tumors, involving mostly the temporal lobe (83%), the mesial temporal structures more than the neocortex. Even if it is biased due to the surgical indications, it reflects a general trend. Whereas these epilepsy-associated tumors present diverse histological patterns, they share many clinical and morphological features: all originate in and develop from the cerebral cortex, and all are clinically expressed by long-term refractory partial-onset epilepsy. The common features are intimate admixture of glial and neuronal elements, benign biological behavior, and low proliferation index [26]. Typically stable or only slow-growing tumors, well demarcated, and without associated edema, they make excellent indications for epilepsy surgery. Complete removal in general suppresses or, at least, greatly reduces the seizures. They affect mostly children and young adults. They may be, as a group, somewhat developmentally related to the focal cortical dysplasia [26], an assumedly malformative disorder with which they share their clinical expression. Features of cortical dysplasia with dysplastic neuronal elements are also characteristically present in the cortex surrounding the developmental tumors. Moreover, the CD34 antigen is expressed in a majority of gangliogliomas, in pleomorphic xanthoastrocytoma (PXA) [27] (and in pilocytic astrocytoma) as well as in focal cortical dysplasia [26, 28]. These lesions may all derive from the same precursor cells and the tumor might originate in the dysplastic tissue [26, 28]. The epileptogenicity that these developmental tumors share with cortical dysplasias has been postulated to relate to the dysplastic neurons; however, an abnormal homeostasis due to glial cell alterations or a dynamic synaptic, axonal, and neurotransmitter receptor reorganization may also alter the seizure threshold [26].

The epilepsy-associated developmental tumors are: (1) the ganglioglioma and its variants, including the desmoplastic infantile ganglioglioma, (2) the dysembryoplastic neuro-epithelial tumor (DNT) and what has been sometimes reported as a cortical oligodendroglioma (non-specific form of DNT), and (3) the pleomorphic xanthoastrocytoma.

Ganglioglioma

True gangliogliomas represent 4% of the pediatric CNS tumors, ten times more common in children than in adults,

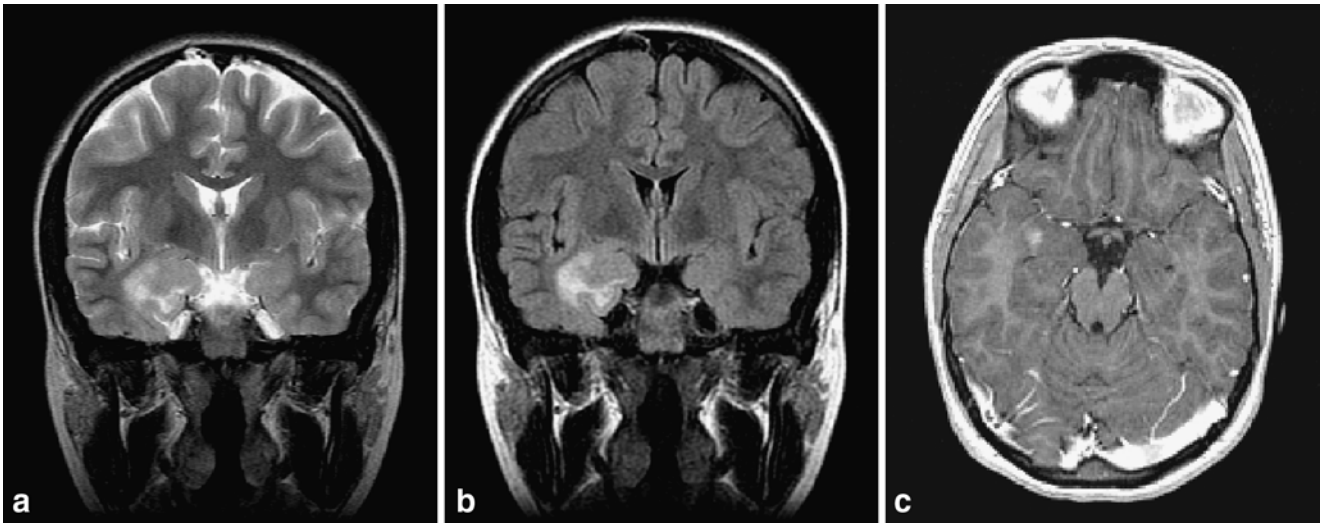

Fig. 2 Ganglioglioma. Girl, 13 years, long history of temporal lobe epilepsy. A right mesial temporal lesion is seen involving the amygdala and the adjacent white matter. High T2 (**a**) and more heterogeneous high FLAIR (**b**) signal of the lesion, which seems to spare the cortex and appears mildly swollen. Its lateral portion enhances after contrast administration (**c**)

and 40% of the epilepsy-associated tumors [26]. They are slightly more common in males, associated with a long-term epilepsy in 85% (no seizures in 6%), mostly temporo-mesial (50%) or temporo-lateral (29%), less commonly frontal (12%) or elsewhere [29]. Gangliogliomas histologically comprise two cellular populations, one neuronal and one glial. The neuronal component does not expand. The glial component is responsible for the evolution of the tumors. It may present diverse differentiations: WHO grade 1 (pilocytic) astrocytoma, the most common (93%); WHO grade 2 (fibrillary) astrocytoma, much less common (6%); and, exceptionally, the malignant anaplastic WHO grade 3 (1%) [29] or even WHO grade 4 (glioblastoma multiforme). The latter two are typically related to secondary degeneration that may occur in an estimated 6% of the cases [30].

The gangliogliomas observed are reported to be macroscopically up to eight times larger in children than in adults [31]. They present as a solid mass in 43%, as a cyst in 5%, and as mixed lesion in 52% [30]. They are typically located at the periphery of the hemisphere, involving the cortex; they may remodel the adjacent bone there. Other locations not associated with epilepsy are the thalami and basal ganglia, the pineal region, the cord, and even the anterior optic pathways, presumably from neurons of the hypothalamus [30]. Gangliogliomas of the cerebellum, on the contrary, do generate epilepsy [32]; together with the hypothalamic hamartomas, they are the only extracortical disorders to do so.

On CT, gangliogliomas may present as hypo-attenuating (38%), iso-attenuating (15%), hyperattenuating (15%), or mixed masses (32%). Calcification is common, but less so in purely solid masses. On MR, the tumor is shown to involve the cortex and often to broaden the gyrus. A cystic appearance does not necessarily reflect a real cyst [30]. Ganglioma is typically hypo- or iso-intense to gray matter on T1w sequences and hyper-intense on T2w sequences. Some tumors may demonstrate a spontaneous high T1 signal [30]. Enhancement after contrast agent infusion is common but variably appreciated [30], maybe up to about 60% of cases [33]; it is variable, from faint to massive. It may rarely demonstrate a leptomeningeal involvement [30]. Whereas most gangliogliomas have the appearance of a low-grade glioma, they rarely present with malignant features including hemorrhages and surrounding edema (Figs. 2 and 3).

On MR spectroscopy, most gangliogliomas display the features of a low-grade glioma with decreased NAA and increased choline peaks (Fig. 3).

Gangliocytoma is uncommon, affecting more often older children and young adults. It is a purely neuronal variant of ganglioglioma without any glial component. It presents as a cortical mass, with no significant mass effect and no edema, with low T1, low or high T2 signals [30, 34, 35], usually both cystic and solid, often calcified, and commonly enhanced by contrast agents.

The *desmoplastic infantile ganglioglioma* is a rare tumor, likely congenital, that develops in infants. It is usually huge, more often supra-sylvian. It is partly cystic and partly solid; the solid portion incorporates the cortex and is diffusely attached to the dura. The infant typically presents with macrocephaly, neurological deficits, and seizures in about half of the cases. The solid portion is strongly desmoplastic, and this, together with the age of the patient, characterizes the tumor. Two infantile desmoplastic tumors were initially described, the desmoplastic infantile astrocytoma and the desmoplastic infantile ganglioglioma [36]. Further pathological studies have established that both were variants of a

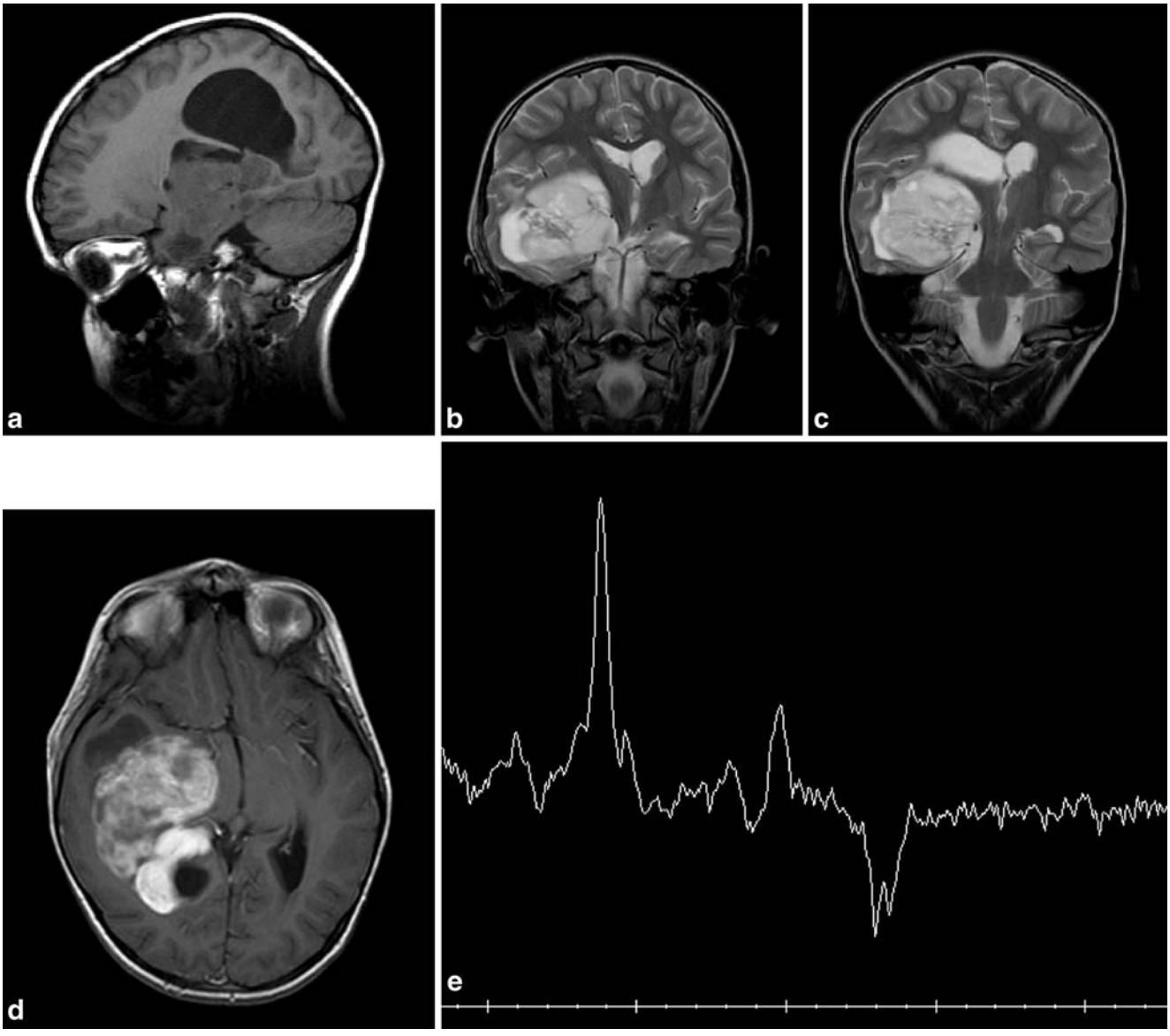

Fig. 3 Ganglioglioma. Girl, 7 years, history of seizures with recent neurological deterioration. Large right temporal mass, apparently centered on the mesial structures, both solid and cystic. The solid component has an iso-to-low signal on T1 and a high signal on Flair and T2 (*b* and *c*) and is markedly enhanced after contrast administration (*d*). MRS (144 ms) displays a pattern consistent with a glioma: increased Cho, low NAA, lactate peak. The final diagnosis was ganglioglioma with juvenile pilocytic astrocytoma (WHO grade 1) differentiation

single entity [37]. The imaging features are relatively specific when observed in an infant: huge cystic and solid mass involving more often the frontal and parietal lobes, less commonly the temporal lobe, associated with a cranial asymmetry and an expansion of the vault. The solid portion, attached to the dura, is mildly hyperattenuating on CT and may be calcified [38]. The cystic portion extends toward the midline. On MR images (Fig. 4), the solid portion is iso-intense to gray matter on T1w sequences and hyper-, iso-, or hypo-intense on T2w sequences, usually heterogeneously. Enhancement of the solid portion is intense on both modalities after administration of contrast agents and extends to the dura. The walls of the cysts are not enhanced [38]. In spite of the spectacular appearance of the tumor, the prognosis is good if it is appropriately removed [38, 39].

Dysembryoplastic neuroepithelial tumor

In children, *DNT* (14%) is much less common than ganglioglioma (43%) as an epilepsy-associated tumor

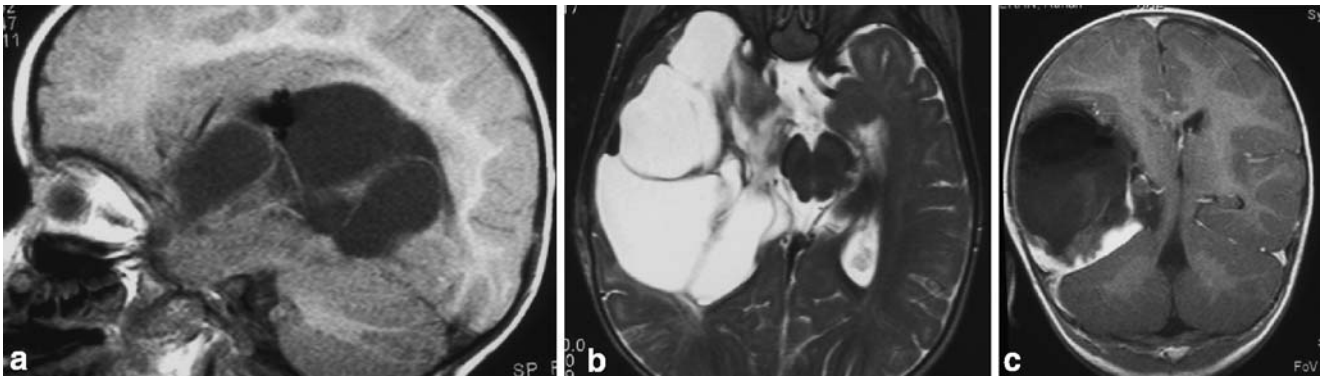

Fig. 4 Desmoplastic infantile ganglioglioma. Infant boy, 11 months, new onset of seizures, macrocephaly. Huge right temporal mass, with a solid portion involving the infero-medial cortex and a multi-cystic component developed in the white matter. The cortical solid portion shows a moderately low T1 (**a**) and a high T2 (**b**) signal. Post-contrast imaging demonstrates marked enhancement of this solid portion and of the adjacent meninge but not of the walls of the cysts (**c**)

[25]. The first description was published in 1988 by Daumas-Duport et al. [40, 41]. They described an indolent, highly epileptogenic cortical tumor with a characteristic histological appearance: multinodular architecture with nodules composed of variants resembling astrocytomas, oligodendrogliomas, or oligoastrocytomas; foci of dysplastic cortical disorganization; and a distinctive columnar structure perpendicular to the surface, made of bundles of axons attached by cell processes of small oligodendrocytes (the "specific glioneuronal element") with neurons floating in the interstitial fluid [41]. Further studies have shown that besides this characteristic "complex form" of DNT, a "simple form" with the unique specific glioneuronal element could be described, also cortical and with the same clinical expression, as well as a "nonspecific" form, actually the most common, resembling various types of gliomas but still cortical, stable and strongly epileptogenic [41]. In one later report from the same group [42], the complex form represents 26% of cases (14 of 53), the simple form 11% (6 of 53), and the nonspecific form 62% (33 of 53).

DNTs have a quite characteristic appearance on imaging (Figs. 5, 6 and 7) [30, 40–42, 43, 44–46]. They affect mostly the temporal lobe, then the frontal lobe. Subcortical locations exist (basal ganglia, brain stem, and cerebellum) but are unusual [30]. Epileptogenic DNTs develop in the cortex (100%) and extend in the subjacent white matter, sometimes with multiple discrete nodules extending to the ventricle (personal observation). The lesion may be clearly demarcated (50%) or its margins may be somewhat blurred [44]. The tumor is classically described as devoid of mass effect, but some effacement of the adjacent sulci, compression of the ventricular lumen, and "swelling" of the involved gyrus may be observed in more than half of the cases [44], especially the cystic ones [28]. Moreover, whereas the lesion is described as stable over the years by most authors, in a few instances, a significant increase in size has been documented [44] (personal observation) (Figs 6 and 7). A remodeling of the vault overlying the mass is seen in 44% of the cases [42]. There is characteristically no surrounding edema, but this also has been reported in one case [44]. On CT, the tumor is hypo-attenuating, often cyst-like looking

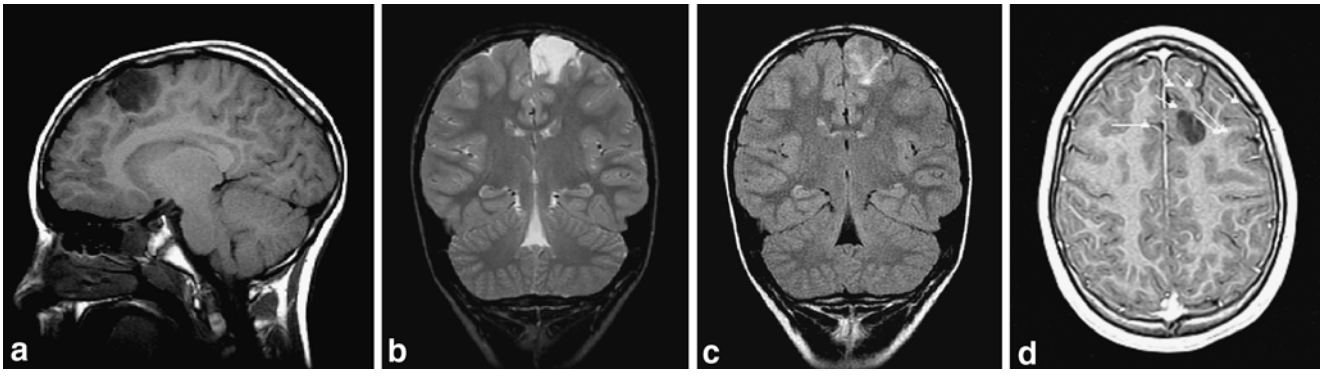

Fig. 5 DNT. Girl, 9 years, long-standing seizure disorder. Imaging shows a well-demarcated lesion of the left superior frontal gyrus with low T1 (**a**), high T2 (**b**), moderately high FLAIR with bright rims (**c**), and no enhancement (**d**). MEG demonstrates multiple spikes distributed over the possibly cortex surrounding the tumor (**d**)

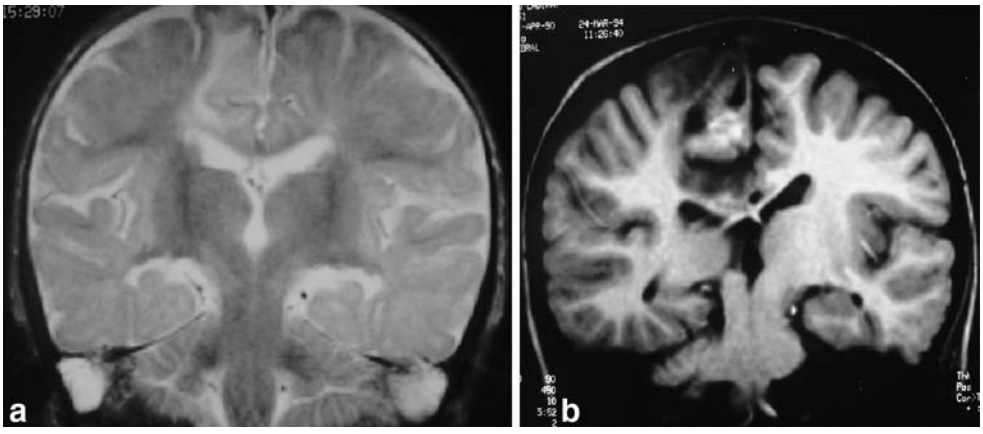

Fig. 6 DNT. Girl, at 11 months (**a**) and 4 years (**b**), intractable partial seizures. Imaging at 11 months shows an apparently poorly myelinated lesion of the right medial frontal lobe suggesting a FCD, although the cortex itself is heterogeneous (**a**). Three years later, imaging demonstrates a clearly demarcated lesion, heterogeneous and more bulky with significant mass effect (**b**)

[43]. Calcification is reported in 20 to 36% of cases [25, 42]. On MR imaging, the lesion is low T1, high T2, heterogeneous, and often with a single or multi-cystic appearance [44]. Spontaneous hemorrhages have been reported in DNTs [45], in one case possibly due to head trauma [44]. They may be explained by the pattern of vascularity present in these tumors [45]. Contrast enhancement is observed from 21 [42] to 36 [30] to 50% [44] of the cases. Although DNTs are said to be stable tumors, their appearance may change with time: increase in size as noted above (Fig. 6) or secondary appearance of contrast enhancement in an otherwise pathologically typical tumor [46] (personal observation) (Fig. 7). Malignant transformation of a DNT has been reported in one case [47].

It is somewhat frustrating that no real correlation was made in most reports between the histopathological type of the lesion (complex, simple, and nonspecific forms) and the imaging features, except in one preliminary description [41]. It is also frustrating that, whereas it is recognized that the recurrence of intractable seizures after surgery is likely due to the persistence of a dysplastic cortex around where the tumor was [48], there is no MR imaging method so far to identify the presence and the extent of this abnormal cortex pre-operatively, even with the help of MEG.

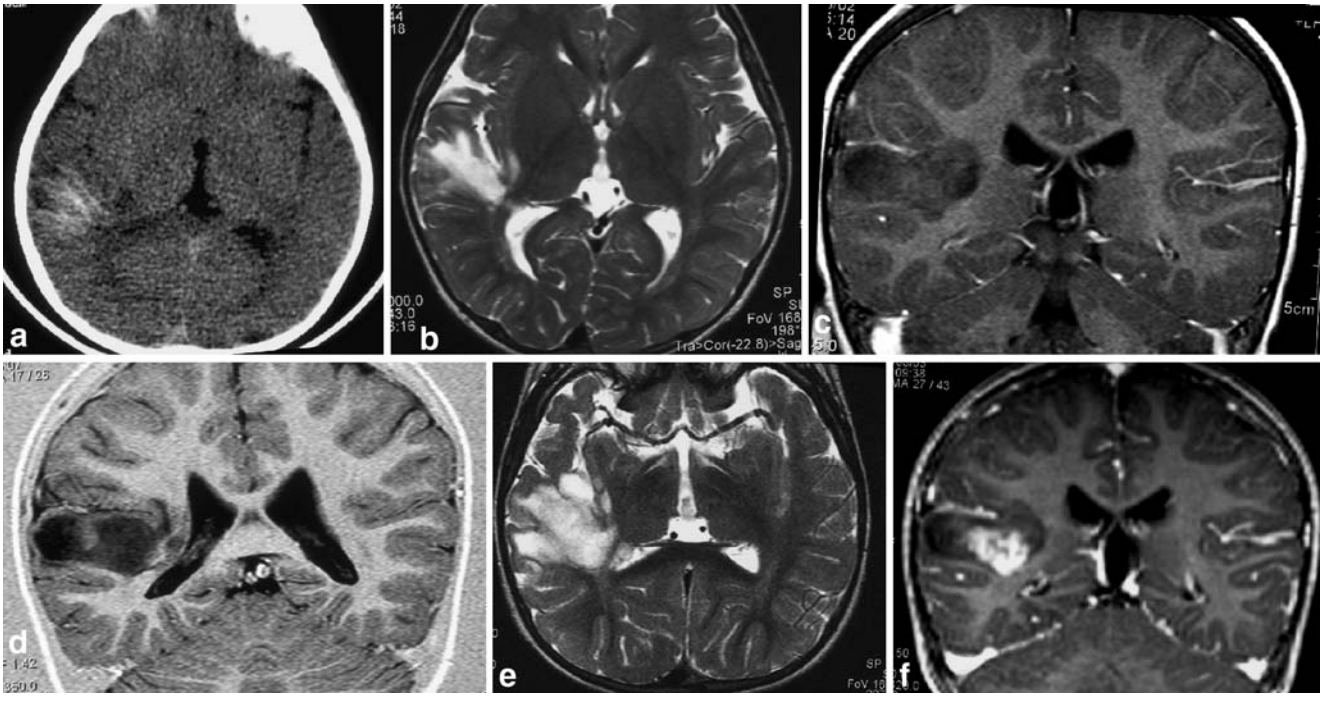

Fig. 7 DNT. Boy, at 3 years (**a**–**c**) and a year later (**d**–**f**), refractory partial epilepsy. CT demonstrates a calcified lesion of the superior portion of the right temporal lobe, extending to the ventricle (**a**). On MR, the lesion appears high T2, well demarcated; it extends to the ventricle and the posterior insular cortex (**b**). Coronal post-contrast imaging shows that the lesion sits in the superior temporal gyrus and does not enhance (**c**). Parents deferred surgery until a year later. Pre-surgical imaging again demonstrates a mildly expanding lesion (**d**, **e**), now bulging more into the ventricle (**e**), more heterogeneous on T2 (**e**), and now strongly enhancing with contrast (**f**)

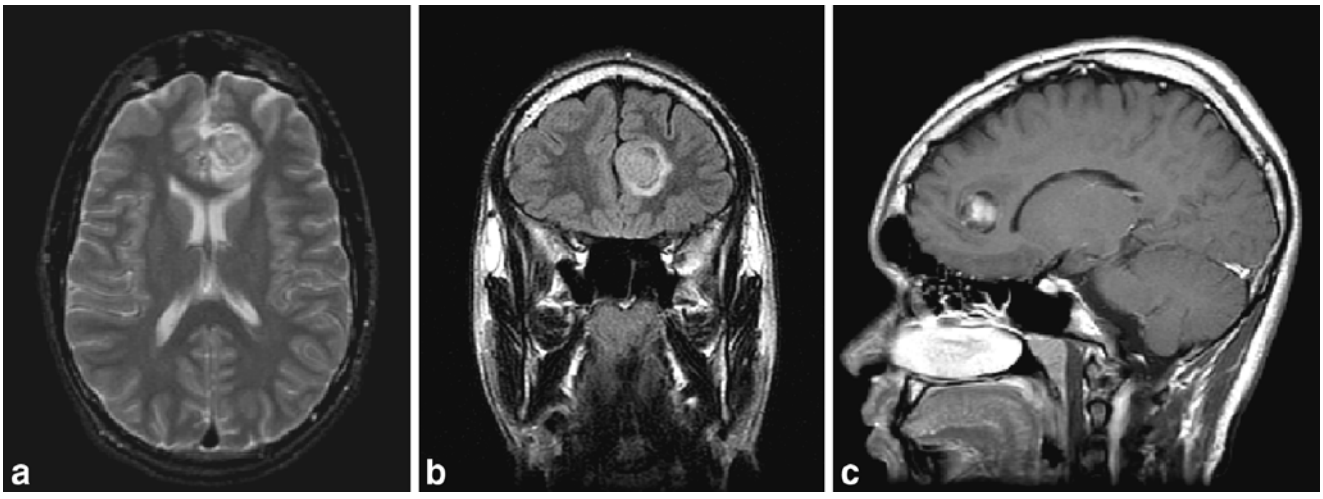

Fig. 8 PXA. Cortex-centered heterogeneous mass developed into the left cingulate gyrus. Mass effect is apparent on T2 imaging, with poor demarcation and a rim of surrounding edema extending to the corpus callosum (**a**). FLAIR imaging shows the central heterogeneity well (**b**). Contrast administration demonstrates irregular enhancement of the core of the lesion (**c**). Apart from the cortical location, this appearance is nonspecific

The differential diagnosis of DNTs is usually said to include gangliogliomas, low-grade gliomas, and purely malformative focal cortical dysplasias. The mild mass effect often present in DNTs is not found in FCD; also, FCD never enhances. Gangliogliomas usually have more mass effect, but they share with DNTs the same topography and the same clinical features. Moreover, in one report, an association of both tumor types is described [49]. MR spectroscopy is reported to be normal in DNTs [50], while high choline and low NAA are observed in gliomas/gangliogliomas.

A so-called c*ortical oligodendrogliomas* (WHO grade II) have been reported as an epilepsy-associated tumor [25]. In opposition with the deep oligodendrogliomas, this peripheral tumor has a good prognosis [51, 52]. Presenting on imaging as a "DNT-like" tumor [51], it is labeled either as a *oligodendroglioma grade II* or a *nonspecific DNT*, the latter label reflecting the clinical and biological features better. It is again an intra-cortical hemispheric tumor, presenting with isolated epilepsy without neurological deficit nor increased intracranial pressure, without surrounding edema or mass effect. One report [51] describes it as a triangular cortical lesion with septa, low T1 and high T2 signals, and no enhancement. The prognosis is excellent after total removal, with no recurrent seizures or tumor.

Pleomorphic xanthoastrocytoma

PXA is a rare tumor affecting children and young adults. Like the other developmental tumors, it is slow growing, located in the cortex, and highly epileptogenic. Although prominently glial, it also contains neuronal elements [53, 54], is associated with cortical dysplasia [54, 55], and expresses the CD34 antigen [27, 28]. It may develop as a composite tumor in association with other neuronal/neuronoglial tumors [55, 56].

In most of the cases (71%), long-standing epilepsy is the presenting symptom [57]. The tumor is supratentorial in 98%, mostly temporal (49%) and less commonly parietal, frontal, and occipital [57]. Although the prognosis is generally good, it may recur and malignant degeneration occurs in 20% [57]. The mass appears circumscribed but infiltration of the surrounding brain and Virchow–Robin spaces is common, as well as attachment to the dura, as seen in 71% [30, 58]. The tumor is cortical in location, classically cystic but solid tumors are actually more common (52%). It is hypo- and iso-attenuating on CT, hypo- or iso-intense to gray matter on T1, and hyper- to iso-intense on T2 sequences. Calcification is rare and peritumoral edema uncommon [30, 58]. Hemorrhages have been reported. A well-demarcated enhancement of the solid portion is usual [30, 58]. Except for the cortical location, the appearance is nonspecific (Fig. 8) and the differential includes glial (benign and malignant) tumors as well as meningiomas.

Imaging focal cortical dysplasia

The first histologic description of the focal cortical dysplasia was that of Taylor et al. who coined the term in 1971. They described a specific cortical abnormality found in patients who presented with refractory partial epilepsy and were cured by excision of the affected cortical area [59]. The dysplastic cortex was characterized by disorganization, the presence of ill-oriented

"bizarre neurons", and by giant dysmorphic "balloon cells". Later, better imaging modalities with more frequent recognition of the various cortical abnormalities have led to some terminological confusion. To correct this, efforts are being made to have these various malformations of cortical development better identified and classified on clinical, morphological, developmental, and genetic grounds [60]. In this classification, depending on whether the dysplastic cortex includes dysmorphic/balloon cells or not, the lesion is considered as resulting from an early disorder of the proliferation/differentiation or from a late disorder of the organization, respectively [60]. A tentatively agreed upon classification and uniform nomenclature for the FCD themselves has been recently proposed [61]. At the cellular level, it differentiates between the dysmorphic neurons and balloon cells on one hand and the giant and immature neurons on the other hand, the former being truly dysplastic cells. This classification is the following:

1. *Mild MCD* (formerly described as microdysgenesis and not detectable by current MRI techniques)
   - Type I: ectopic neurons in or adjacent to layer 1
   - Type II: microscopic neuronal heterotopias outside layer 1
2. *FCD*
   - FCD type I (non-Taylor): no dysmorphic neuron or balloon cell and mostly temporal
     - Type IA: isolated architectural abnormalities (dyslamination plus mild MCD)
     - Type IB: isolated architectural abnormalities plus giant or immature, but not dysmorphic, neurons (cytoarchitectural dysplasia)
   - FCD type II (Taylor): mostly extra-temporal
     - Type IIA: architectural abnormalities with dysmorphic neurons without balloon cells
     - Type IIB: architectural abnormalities with dysmorphic neurons and balloon cells

Mild MCD can be clinically related to epilepsy but has been observed also in autism, schizophrenia, and dyslexia [61]. On the contrary, FCD are mostly associated with long-standing severe partial epilepsy, typically without neurological deficit. Depending on the extent of the abnormalities and on the severity of the epilepsy, psycho-developmental delay and/or personality changes may develop, however.

Different pathophysiological processes have been proposed to explain the FCDs. For the FCD IIA/B (Taylor's type), it has been generally assumed that they result from a defective differentiation of the neurono-glial progenitors at the time of the migration from the germinal zone to the cortical plate, as the abnormal balloon cells retain the characters of both neuronal and glial cells [62, 63]. Other authors, however, stipulate that the dysmorphic neurons would be abnormally retained cells of the normally transient sub-plate and of the pool of Cajal–Retzius cells and that the balloon cells would be the persisting cells of the radial glia [64]. Genetic studies seem to indicate a pathogenic link between FCD IIB and tuberous sclerosis [65]; this was already suggested by the similarities between the cortical tubers and the lesions of FCD and between the balloon cells and the so-called "giant astrocytes". Therefore, *tuberous sclerosis* is considered a syndromic form of FCD. Besides, pathological studies have shown that *hemimegalencephaly* is different from FCD only by the extent of the involvement of the hemisphere, and it is thus considered a giant variant of FCD.

How FCD IA/B form is still less clear. Several reports suggest that the typical histopathological appearance of FCD with giant neurons but without dysmorphic neurons and balloon cells may, at least in certain cases, be attributed to lesions acquired in the late gestation, in the premature, and the term neonate [66–70]. Appearances of dysplastic cortex with abnormal circuitry and giant neurons have been described in the context of severe peri-natal injury following ventricular hemorrhages in the premature [66], white matter hypoxic–ischemic injury of the premature [67], or of the term neonate [68], as well as a complication of early perinatal closed head injury [69] or of the shaken infant syndrome [70]. These reports suggest that a histological appearance of FCD with giant neurons without dysmorphic neuron or balloon cell may be secondary to the disruption of the normal connectivity in the cortex or the subjacent white matter, with a secondary adaptation and re-organization of the neurons and of the neuronal networks.

Whereas it is generally agreed that FCD are intrinsically epileptogenic, the exact mechanism of the epilepsy is still debated: abnormal firing from the dysplastic neurons rather than from the balloon cells [71], dysfunction of synaptic circuits with abnormal synchronization of the neuronal population, and abnormal organization of the inhibitory interneurons [72] are common hypotheses. Besides, the FCD IA/B dysplastic cortex may be integrated in the normal synaptic pathways [73], although this has been contested for the FCD IIA/B [74].

Specific imaging features of FCD

In the past decade, especially since the development of the FLAIR sequence, many reports have described the typical features of FCD [75–80]. The frontal lobe is more often

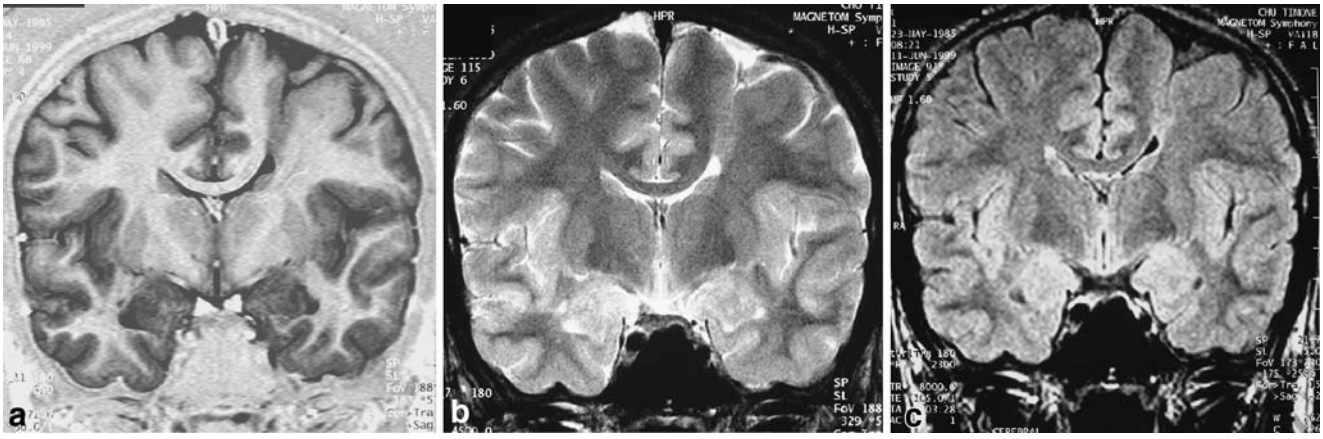

Fig. 9 FCD with transmantle dysplasia (Taylor type). Girl, 8 years, intractable partial complex epilepsy. Radial band of abnormal signal extending from the depth of the superior frontal sulcus to the angle of the ventricle. The signal of this white matter abnormality is similar to that of the cortex on T1 (**a**) and T2 (**b**) imaging but different on FLAIR (**c**). Therefore, it can be differentiated from a trans-cerebral gray matter heterotopia. The cortex lining the sulcus is thick, and its margin is blurred. This pattern is generally felt to be specific for FCD IIB (Taylor type, with balloon cells). Note that the radial band of transmantle dysplasia follows the radial migration pathway from the periventricular germinal matrix to the cortex; it is interposed between the corpus callosum and the caudate nucleus that appears displaced, and the ventricle is focally enlarged

involved, as well as the parieto-occipital lobe and the central region. It has been reported that, in half of the cases (11 of 22), two adjacent gyri are involved, and less commonly (4 of 22 each) one gyrus or the depth of a sulcus [79]. Two discrete FCD may be found in the same patient [77, 79].

The main features of the FCD are, above all, the *thick cortex*, the *blurring* of the cortical–subcortical junction, and the *abnormal signal* of the white matter. A gyral involvement is associated with focal macrogyria (but the adjacent subarachnoid spaces are often slightly prominent), a sulcal involvement, with a deep sulcus (Figs. 9 and 10). The cortex commonly presents a mildly high T1 and low T2 signal. The underlying white matter presents with a strand of low T1, slightly high T2, and clearly high FLAIR tissue that typically extends to and tapers toward the ventricle [76] (Fig. 9). This has been called a trans-mantle dysplasia [81]; it corresponds to the cellular migration pathway and could be specific for FCD IIB. When the trans-mantle dysplasia is in the frontal lobe at the depth of the superior frontal sulcus, it may be associated with a displacement of the head of the caudate nucleus and a focal enlargement of the ventricle (personal observation) (Fig. 9). Calcification may occur [76]. Some contrast enhancement has been reported [76, 79].

Besides this typical MRI appearance of Taylor FCD IIA/B found mostly in the extra-temporal cortex, it has been suggested that non-Taylor FCD IA/B might also have specific features [80]: small lobe, poorly developed white matter, mildly increased signal of the white matter, more diffuse, ill limited abnormalities, mostly located in a temporal lobe (Fig. 11). In more than half of the cases in a non-pediatric series, these abnormalities have been found to

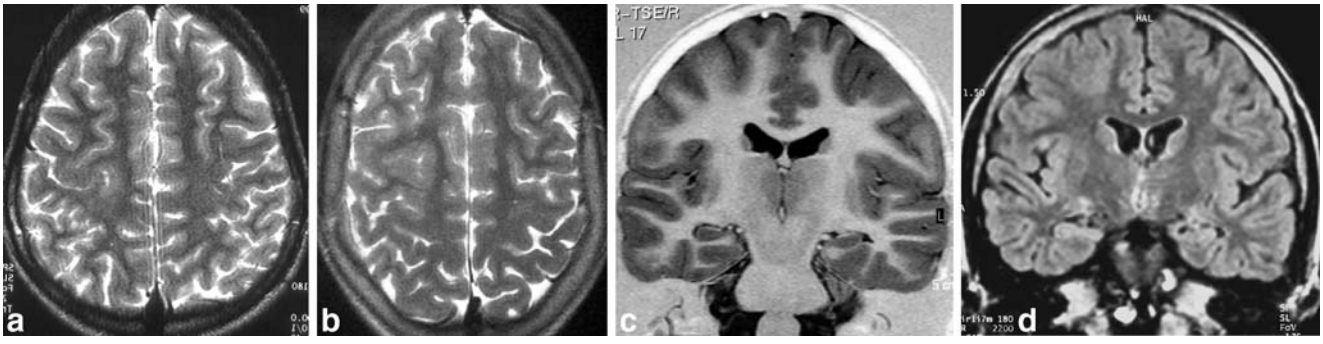

Fig. 10 FCD with thick, blurred cortex but normal white matter. Girl, 14 years, long-standing partial epilepsy. The cortex at the crossing of the superior frontal and the central sulci on the right appears thick and its junction with the white matter is blurred on the T2w axial images (**a**, **b**). Coronal T1 (IR) shows that the blurring extends to the operculum, with a cortical T1 signal higher than that in the normal contralateral cortex (**b**). FLAIR imaging, however, demonstrates no signal abnormality in the white matter (**c**)

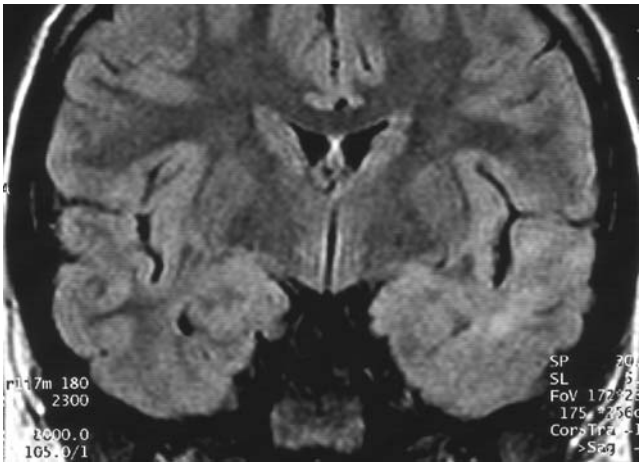

Fig. 11 FCD, non-Taylor type. Girl, 11 years, temporal lobe seizures with some implication of language. Diffusely high FLAIR signal of the temporal white matter on the left, with loss of the gray/white demarcation

be associated with hippocampal sclerosis (HS, dual lesion) [80], and they were previously thought to represent atrophy and gliosis consecutive to the hippocampal epilepsy.

MR appearance of FCD may change with brain maturation

The abnormal signal of the white matter is not always found in FCD (Fig. 10), and it has actually no clear explanation. It may be caused by an abnormal cellularity as well as by an abnormal myelination, for example, by lack of fibers, therefore of myelin [75]. Longitudinal MR studies in infants with FCD have shown that, whereas the initial study might be normal, later imaging showed the delayed appearance of the high T2 signal in the white matter, as well as the high T1 signal in the cortex and the blurring of the cortical/white matter junction [75]. This supports the hypothesis that the high signal results from a poor myelination that would only become apparent in the mature brain. It also implies that, in the case of normal study with normal cortical thickness, normal white matter signal, and normal junction in an infant with refractory partial epilepsy or a West syndrome, a repeated study may be needed after a few months [24, 75].

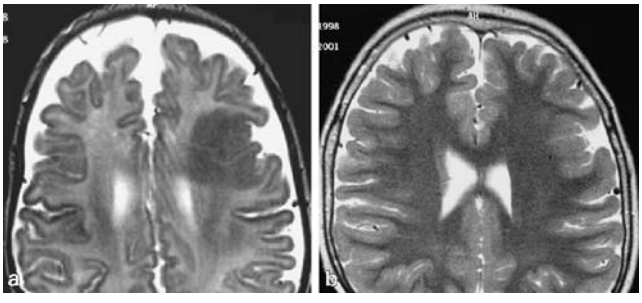

Fig. 12 FCD, white matter changes. Boy, imaged at 4 months and at 4 years. Intractable partial epilepsy. Imaging at 4 months shows a somewhat atrophic brain and a large area of low T2 signal extending from the ventricle to the cortex in the lateral aspect of the left frontal lobe; the overlying cortical pattern is unusual (**a**). Imaging at 4 years shows the same abnormality of the cortical pattern, cortical thickening and cortical blurring, but the underlying white matter now appears evenly low signal, consistent with normal myelination for the age. The evolution of the images suggests an initially accelerated myelination focally, possibly related to the repetition of epileptic discharges

Yet, a fully opposite picture may be observed. An early study in an infant may show a clear abnormality of the white matter, with a low T2 signal, that will disappear on subsequent studies [82] (personal observation) (Fig. 12). Such an evolution suggests an accelerated myelination instead of a hypomyelination. An experimental study in the mouse has shown that repeated neuronal electrical activity (such as that which occurs in repeated seizures) induces myelination [83]. Repeated seizures in those infants may possibly induce an early myelination in the white matter that would not be apparent anymore when the whole brain becomes myelinated. A similarly accelerated myelination observed in Stürge–Weber disease (SWD) [84] has been recently related to venous congestion [85]: the effect of repeated seizures might be considered as well. Finally, it must be noted also that the white matter MR abnormality in FCD may be related to calcification clearly apparent on CT (personal observation).

MRI appearance of the FCDs does not always correlate with histopathology

Few reports have focused on specific MR features of FCD Taylor type vs FCD non-Taylor type. However, both subgroups may be clearly divided if one considers the clinical, surgical, and prognostic implications [86]. A pre-surgical identification of the FCD subtype on imaging would therefore be useful [61]. Colombo et al. have attempted such an identification [80]. Besides the typical "Taylor" appearance (cortical thickening, cortical blurring, and high T2/FLAIR signal of the white matter) assumed to reflect the FCD (Taylor's) IIA/B, they have postulated that a different, more diffuse abnormality ("non-Taylor": focal brain hypoplasia, white matter core atrophy and more diffuse, and mild white matter hyperintensity on T2) could represent the FCD IA/B (architectural dysplasia and cytoarchitectural dysplasia). They actually found that the correlation was poor:

- Among 15 cases with documented FCD Taylor's type IIA/B, 9 of 15 presented the typical "Taylor" appearance, but 5 of 15 presented a normal imaging and 1 of 15 presented a "non-Taylor" appearance in the temporal lobe. Among 28 cases with documented non-Taylor architectural dysplasia, 15 of 28 presented the expected "non-Taylor" appearance, but 2 of 28 presented typical "Taylor" MR features and 11 of 28 were fully normal.

– From another point of view, 19 of 49 cases presented with normal MRIs, and among those, 5 of 19 had a FCD IIA/B (Taylor) and 14 of 19 had a FCD IA/B (non-Taylor) histology. A group of 13 of 49 presented with a typical "Taylor" MR appearance, but only 9 of 13 were real Taylor FCD IIA/B and 4 of 13 were not. The last 17 of 49 presented with the "non-Taylor" MR appearance and, among them, 16 of 17 were "non-Taylor" FCD IA/B and one was a Taylor's FCD IIA/B.

MRI does not display the real extent of the cortical dysplasia

MRI certainly has transformed the surgical approach to the FCD-associated epilepsy. However, the results of the surgery of FCD are not as good [87–91] as those of the tumor-associated epilepsy [25, 87]. In most cases, this can be explained by the fact that the surgical resection did not involve the full extent of the cortical dysplasia, either because the full resection was prevented by the proximity of eloquent cortex or because the resection was limited to the MRI-apparent abnormalities. histologically proved FCD dysplasia has also been demonstrated at surgery in the case of status epilepticus with normal MR imaging [92]. The surgical results are improved when the extent of the resection is determined by electrophysiological means [89, 93, 94] and the resection specimens typically demonstrate that the dysplastic cortex is much more extended than the apparent abnormalities on MRI.

Could the sensitivity of MRI be improved to show more of the cortical malformation? Several paths can be explored. As the physical–chemical structure of the FCDs (with the poor cortical–subcortical segregation, the abnormal cellularity, the abnormal connectivity, and the often-abnormal myelination) is always somewhat different from the surrounding normal brain, any factor that increases the sensitivity of MRI may improve the detection rate of dysplastic tissues. Technological advances with the most recent coils improve the signal to noise ratio (*S*/*N*), as do higher magnetic field magnets; the convexity cortex can be exquisitely depicted by the combination of 3T clinical magnets and appropriate coils [18].

In one report, a *computer-aided structural analysis* using the cortical thickness, the cortical T1 signal, and the evaluation (gradient) of the blurred cortical–subcortical junction as parameters correlated them with post-surgical histopathological findings. Results are promising as a FCD was correctly identified not only in the 16 cases in which the MRI was diagnostic but also in seven more cases in which the MRI was considered normal [95].

Although *MR proton spectroscopy* has been occasionally reported to be normal in FCD [77], its potential use to appreciate the extent of the cortical lesion has been evaluated at 4.1 T [96] as well as on a more conventional clinical magnet at 1.5 T [97]. In the first study, the ratio of Cr to *N*-acetylated compounds and of Cho to *N*-acetylated compound were increased (decreased NAA) in most cases of FCD. The correlation with the histopathological abnormalities or with the interictal discharge was poor, but there was a positive correlation with the frequency of seizures [96]. This again demonstrates that MRS abnormalities reflect the functional anomalies more than the structural lesion [6]. In the second report, it was demonstrated that the NAA/Cr ratio was decreased in the structural malformation, as defined by MRI, and beyond it into the normal-appearing brain as well. This again likely reflects the functional disorder.

Magnetization transfer imaging has proved to be extremely contributive to demonstrate the parenchymal abnormalities in tuberous sclerosis [98–100]. Based on the interaction between free and bound water protons, the method consists in saturating the bound protons with an off-resonance frequency, thus decreasing the signal of the mobile protons. The magnetization transfer ratio is determined by the magnetic field and the imaging parameters and mostly by the concentration of macromolecules. Any alteration in the macromolecular structure of the tissue may be enhanced [98, 99]. Very efficient in the evaluation of TSC (Fig. 13), its use is restricted to a few centers because the sequence is not implemented by all constructors. As FCD (Taylor) seems to be closely related physiopathologically as well as histopathologically to TSC, this approach needs to be investigated.

In the recent years, the techniques of diffusion tensor imaging have been considerably developed, notably *fractional anisotropy* and *tractography*. If one assumes that a disorganization of the white matter may logically be associated with the cortical dysplasia, identifying it might help in locating the lesion and would therefore enhance the detection power of MR imaging. Two somewhat contradictory reports on the use of DTI in FCD have been published recently. One states that tractography depicted a decreased volume of white matter bundles in every case of FCD, including those with normal T2 signal of the white matter [17]. The other, on the contrary, states that DTI abnormalities were found in patients with T2 signal abnormalities only [101]. This research has to be developed further to reach valid conclusions.

Hemimegalencephaly

HME is considered a giant variant of FCD [102], although it may be a heterogeneous disorder. It is clinically sporadic [103] but commonly associated with neurocutaneous syndromes [103, 104]: epidermal nevus syndrome/linear

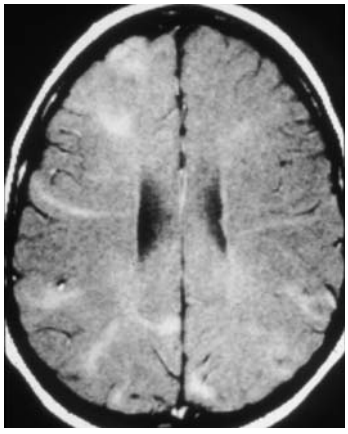

Fig. 13 Magnetization transfer imaging and TSC. Adolescent girl. MT imaging shows poor anatomic details, but it nicely depicts the cortico–subcortical tubers with their radial extension toward the ventricular wall

nevus sebaceous syndrome, hypomelanosis of Ito, Proteus syndrome, Klippel–Trenaunay syndrome, and encephalocraniocutaneous lipomatosis. Its association with TSC is a matter of nosology, as both may be variants of the same disorder [105]. In NF1, a large hemisphere probably has a different pathogenesis, without the histopathological features of FCD.

In one report, nearly two thirds of the cases of HME were on the right side [103]. The malformation is commonly unilateral, but both hemispheres may be affected asymmetrically. Even in unilateral cases, the "normal" hemisphere also seems actually to be abnormal and smaller than in normal individuals [106]. The cortex presents an abnormal gyration, a dyslamination with cortical–subcortical blurring, giant neurons in both gray and white matter, and in 50% of cases, balloon cells. Abnormal myelination is common. The clinical picture is usually severe [103] with an early onset and refractory epilepsy or an epileptic encephalopathy such as the Ohtahara syndrome [22]. Mental retardation, hemiparesis, and hemianopia are common. Because of recurrent seizures and progressive deterioration, the usual treatment is hemispherectomy [107], often early, either anatomic or functional.

On imaging [108, 109], one hemisphere is large, with an expanded calvarium and usually, but not always, a large lateral ventricle. The hemispheric enlargement may be mild. On CT, calcifications of the white matter may be seen. There is often a peculiar appearance of the frontal horn [108] associated with a dysplasia of the anterior corpus callosum and of the septum pellucidum, which may appear "pulled" toward the dysplastic hemisphere. The cortex is usually thick, with broadened gyri; it may occasionally be agyric or on the contrary irregularly polymicrogyric (Fig. 14). The white matter often has a low T1 and high T2 irregular signal with calcifications and possible microcystic changes. The basal ganglia may be abnormal, too. In infants, signal changes may suggest an early myelination [110], possibly related to the seizure activity [83]. HME may extend to the cerebellum [111] or, on the contrary, be restricted to a portion of the hemisphere, usually its posterior portion [112]. Over time, because of recurrent seizures or refractory status epilepticus, the initially enlarged hemisphere may become atrophic and smaller than the normal one [113].

Tuberous sclerosis complex

Tuberous sclerosis may be considered a syndromic variant of FCD and the two diseases may actually be genetically related [65]. The "giant astrocyte" that characterizes the brain lesions of TSC corresponds to the "balloon cell" of FCD (Taylor) IIA/B. The diagnosis of the brain lesions of TSC is radiologically easy in most of the cases. The multiple, asymmetrically distributed cortical/subcortical tubers are characterized by broad gyri, thick cortex, and

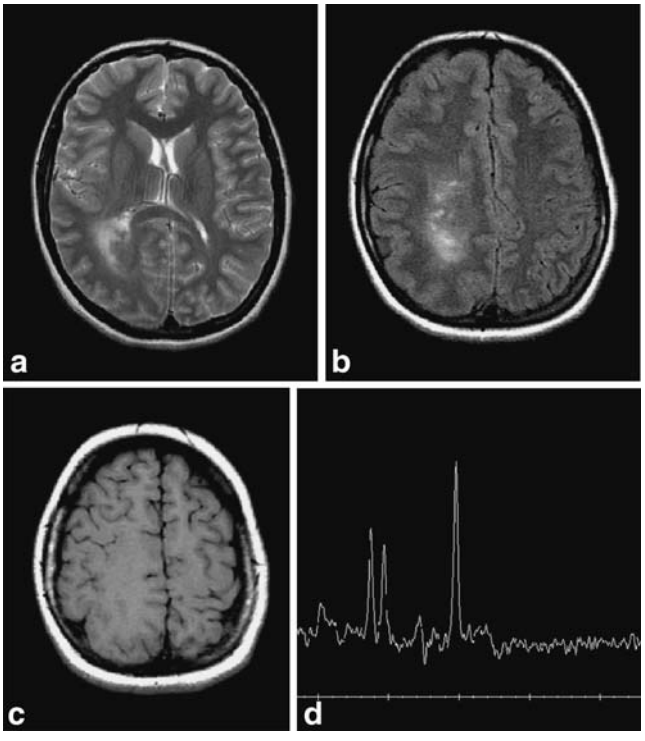

Fig. 14 HME. Girl, 16 years, generalized tonic–clonic seizures. T2 imaging shows ill-limited white matter abnormalities in the right hemisphere and dysplastic appearance of the septum pellucidum "pulled" to the right (**a**). FLAIR imaging confirms the heterogeneous high-signal abnormalities in the right centrum semi-ovale (**b**). Abnormal pattern of the overlying cortex is apparent on FLAIR (**b**) and T1 imaging (**c**), together with cortical thickening and cortical blurring. The patient had been referred for brain tumor but MRS (144 ms) shows an essentially normal spectrum (**d**) more consistent with HME

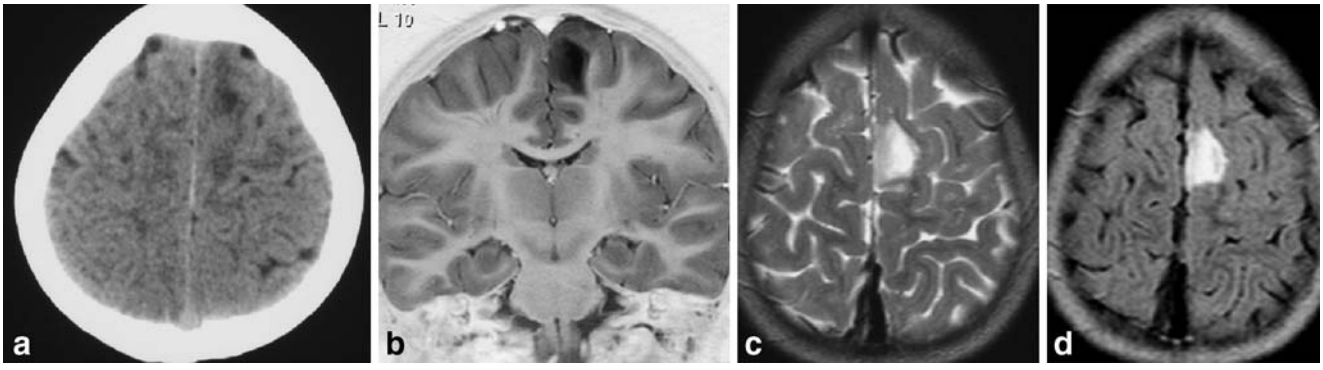

Fig. 15 FCD: "solitary tuber", FFTS. Girl, 13 years, severe partial epilepsy. CT shows an area of low attenuation in the left parasagittal frontal lobe, similar to what can be seen with CT in TSC. Low T1 (**b**), high T2 (**c**) and high FLAIR (**d**) demonstrate the abnormal signals of both the cortex and the white matter of this clearly demarcated lesion

bright subcortical gray matter. The ventricles are lined with multiple, often-calcified nodules. At the foramen of Monro and adjacent structures, subependymal nodules may grow slowly to constitute the tumor known as the "giant cell astrocytoma". In the posterior fossa, the cerebellar cortex is often dysplastic. The patients commonly have moderate to severe epilepsy, often as infancy (West syndrome), and the multiplicity of the brain lesions would typically preclude a surgical treatment. However, there are instances in which neuro-imaging may disclose TSC-related lesions that are surgically accessible: the solitary tubers; the large, discrete tubers of the infant; the large hemimegalencephalic dysplasia of one hemisphere; and a tuber identified as a constant epileptogenic focus.

Solitary tubers present as cortical–subcortical lesions in patients with severe epilepsy. They show a focal gyral broadening, with a thick, possibly high T1 cortex and low T1, high T2 white matter, sometimes with trans-mantle signal abnormalities [114, 115]. In young infants, the signal pattern is reversed [114], which is true also in the complete form of the disease. Most solitary tubers are found in the frontal lobe (Fig. 15). Calcification is reported as well as, rarely, contrast enhancement. Other stigmata of the TSC (ocular, cutaneous, renal, cardiac, pulmonary, and pancreatic) and the other usual brain lesions are missing, but clinical follow-up might see cutaneous stigmata appearing years after the removal of the cortical tuber. These solitary tubers have been classified either as forme fruste of tuberous sclerosis (FFTS) or as FCD IIA/B, and it is now accepted that both entities are variants of the same disorder. A surgical removal of the lesion, like in classical FCD, cures the epilepsy. It must be noted that multiple tubers may also occur without other stigmata of TSC [115].

An investigation of severe epilepsy in an infant may occasionally disclose the presence of a large, discrete cortical dysplasia characterized on CT by diffuse calcification and on MR by an extensive area of high T1 and low T2 signal corresponding to the dysplastic white matter [116] (personal observation). Other tubers and subependymal nodules are usually observed in association. The dysplasia may also affect the posterior portion of the hemisphere, with a deformity of the ventricle, like a lobar form of hemimegalencephaly (personal observation). Whole hemispheric hemimegalencephaly may rarely occur as well [105]. The efficacy of surgery depends on whether or not the large lesion is solely responsible for the epilepsy.

Even in the classical form of TSC with multiple dispersed tubers, the epileptic activity may be focused in one or two tubers, and surgically removing those tubers may therefore cure the epilepsy. However, the identification of the epileptogenic lesions rests upon functional imaging (PET and SPECT) or electrophysiological methods [117, 118], not on structural imaging.

Other malformations of cortical development

Besides the FCD, MCD include the *micrencephalies with simplified gyral pattern* (proliferation disorder), for which epilepsy, when it occurs, is only a part of globally severe condition: the nodular and the laminar *heterotopias* (migration disorders), the polymicrogyrias (organization disorder), and the schizencephalies (more uncertain classification) [119].

Gray matter heterotopia

Gray matter heterotopias are masses of apparently normal gray matter located in abnormal places. They are assumed to be disorders of migration. They are epileptogenic because they are made of active neurons with abnormal connections between themselves as well as with the overlying cortex. This overlying cortex is also somewhat dysplastic, typically in proportion to the size of the

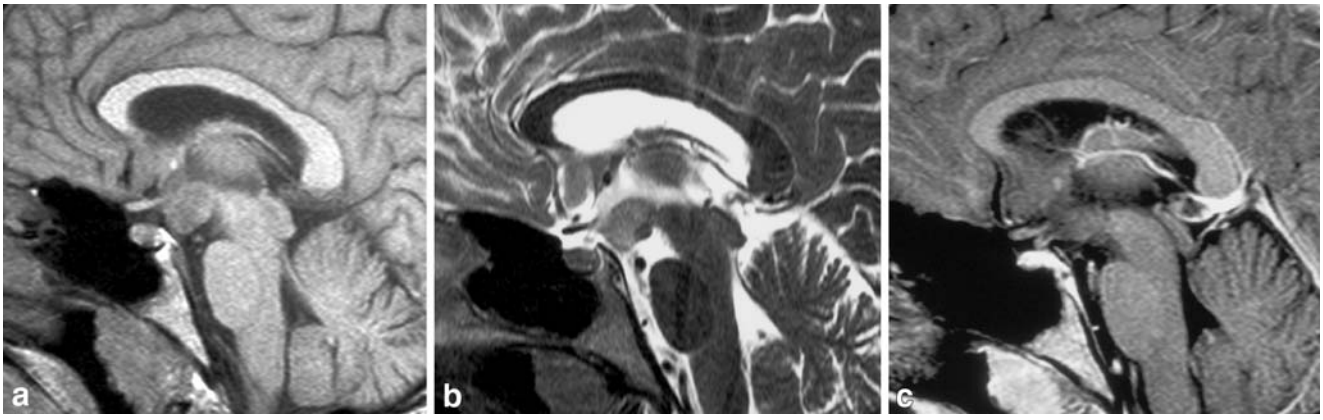

Fig. 16 Hypothalamic hamartoma. Boy, 13 years, gelastic seizures since infancy with progressive mental deterioration. Imaging shows a mass in tuber cinereum, bulging into both the third ventricular lumen and the inter-peduncular cistern (**a**, **b**). The mamillary bodies are clearly displaced downward (**b**); this feature is characteristic for an epileptogenic hypothalamic hamartoma. The T1 signal is similar to that of the cortex (**a**), but the T2 signal is higher (**b**). There is no enhancement after contrast administrations (**c**), which differentiates this dysplasia from the usual tumors of the hypothalamus (gliomas and craniopharyngiomas mostly)

heterotopia. The diagnosis can be made from the fact that, whatever the sequence used, they have the same signal as the central or cortical gray matter. Depending on their location, they are designated as *periventricular nodular heterotopia* (*PNH*) (isolated, multiple, or diffuse; never on the basal ganglia nor the corpus callosum), *subcortical nodular heterotopia* (often huge and transcerebral), and *subcortical laminar heterotopia* (or band heterotopia). A classification of PNH in five groups with clinical implications has been proposed recently [120]:

- Group 1: bilateral and symmetrical, diffuse PNH; patients are intellectually and neurologically normal but present a non-surgical partial refractory epilepsy
- Group 2: bilateral single-nodule PNH; patients are in poor mental and neurological condition, with a non-refractory epilepsy
- Group 3: bilateral asymmetrical PNH, clinically with bi-hemispheric, non-surgical epilepsy
- Group 4: unilateral PNH; the patients have a partial epilepsy potentially surgically curable
- Group 5: single unilateral PNH extending to the cortex; partial epilepsy potentially surgically curable

Subcortical laminar heterotopias (or band heterotopias) are variants of the agyria–pachygyria spectrum. They result from the same genetic disorders: DCX for the predominantly anterior form and LIS1 for the predominantly posterior form. Whereas the nodular heterotopias may present with relatively late epilepsy, the subcortical laminar heterotopias tend to present with early, severe epilepsy.

Most cases of heterotopia are not indications for epilepsy surgery. Pachygyria and still more agyria are severe forms of laminar heterotopias. They are not surgical indications either.

Micropolygyria and schizencephaly

Both are classified as late organization disorders of the cortex [60]. Both may be sporadic, infectious (then mostly due to fetal infection with cytomegalovirus, CMV), or familial. Both are predominantly peri-insular, unilateral, or bilateral, and when they are bilateral, they are typically asymmetrical. Both present with neurological deficits mostly, and epilepsy in approximately 50% of cases.

MPG is characterized by the multiplicity of small gyri, often hidden below a continuous superficial cortical layer. The cortex is otherwise of normal thickness. The sulcal pattern in the affected area is fully disorganized with aberrant sulci [121]. The lesion is usually located in the peri-insular area, with a variable extent toward the hemispheric convexities [119, 121]. It may be unilateral or bilateral, but then not absolutely symmetrical. The involved portion of the brain that is affected is atrophic, and this appears also in the brainstem [119, 121]. The subcortical white matter may present areas of high T2 signal suggestive of previous CMV infection. The sub-arachnoid spaces are locally enlarged, and sometimes dysplastic veins are apparent. The abnormal cortex is typically still functional, and it is the surrounding normal-appearing cortex that often is epileptogenic [122], probably because of abnormal connectivity [122–125]. For these reasons and

its usually large extent, PMG is a poor indication today for epilepsy surgery, except for hemispherectomy.

Schizencephaly associates features suggesting a focal growth defect of the cerebral mantle, a migration disorder sometimes (heterotopias), and a destructive lesion (PMG). It is characterized by a trans-cerebral cleft lined with the polymicrogyric cortex covered itself with pia (and vessels) joining the ependymal lining ("pial–ependymal seam"). The cleft may be small or large and unilateral or bilateral, but then not perfectly symmetrical. The septum pellucidum is missing when the cleft is frontal or central. By analogy with PMG, it is assumed that the epileptogenic cortex might be the normal-looking cortex surrounding the defect. There are several reports on successful surgery of closed lip schizencephaly [126–128]; in one of these, the epileptogenic cortex surrounding the cleft was very dysplastic and contained giant neurons [127]. This could be related with the observation of cortical dysplasia with giant neurons after severe neonatal hypoxic–ischemic encephalopathies or early-occurring brain trauma [66–70]. Surgical indications for schizencephaly-associated epilepsy are nevertheless uncommon.

Hypothalamic hamartoma

"Epileptogenic hypothalamic hamartomas are malformations of the mammillary region of the hypothalamus and are invariably attached to one or both mammillary bodies" [129]. The clinical manifestations of hypothalamic hamartoma are epilepsy, characterized mostly by refractory gelastic seizures, at least in the initial stage of the disease, and by central precocious puberty. The epilepsy is severe and generates cognitive deterioration and behavioral problems over time. A morphologic distinction of the hypothalamic hamartoma has been proposed by Arita et al. [130] between the intra-hypothalamic hamartomas that encroach upon the third ventricle and would be characterized by the early occurrence of epilepsy and the para-hypothalamic hamartomas pedunculated or sessile but not encroaching upon the third ventricle, which would be characterized by a central precocious puberty. Freeman et al. [129], studying the displacement of the white matter bundles and the mammillary bodies, have further demonstrated that the epilepsy-associated hypothalamic hamartoma are invariably located behind the post-commissural fornix, in front of the mammillo-thalamic tract and above the mammillary bodies.

Epileptogenic hypothalamic hamartoma therefore presents as an intra-hypothalamic mass that encroaches upon the third ventricle. Its signal on T1 SPGR is mildly inferior to that of the central gray matter (74%), its signal on T2 is superior to that of central gray matter (93%), and the FLAIR signal is always high [129]. This might reflect some degree of gliosis related to the seizure activity [129]. It can be used to demarcate the lesion from the surrounding brain on MR imaging [129]. There is no enhancement and no calcification. Cystic components are sometimes observed [129, 131]. The mass never increases in size over the years, but one case of decrease in size during the first months of life has been reported [129]. Small epileptogenic lesions are typically intraventricular, while large lesions extend both into the ventricular lumen and the interpeduncular fossa; strictly inferior masses are rarely epileptogenic. The mass may splay the cerebral peduncles apart and displace the basilar artery. Epileptogenic hypothalamic hamartoma always involve the mamillary bodies and, in 90%, the tuber cinereum as well (Fig. 16). Less commonly, they involve the chiasm (22%) up to the lamina terminalis (17%) or the pituitary stalk (20%; central precocious puberty is then associated) [129]. The mass is bilateral symmetrical in 37% and predominantly or fully unilateral in 63%; the mammillary bodies are distorted on one side only in 68% and on both sides in 19%; an intraventricular expansion is usual [129]. MR spectroscopy shows increased *myo*-inositol and decreased NAA as compared with the thalami or the frontal lobes. This again correlates well with the mild gliosis that is found histopathologically [129].

In 25% of the cases, other brain abnormalities are found. MCD (heterotopia and FCD) are rare. High signal of the anterior temporal white matter and blurring of the cortical/subcortical junction are seen in 16% of the cases on the side of the hamartoma when it is lateralized or bilateral otherwise. This again seems to reflect epilepsy-related gliosis rather than dysplasia [129]. Ammon's horn sclerosis was never observed in this report, but a dysplastic appearance of the hippocampus was seen in four cases. "Arachnoid" cysts were observed in relation with the hypothalamic hamartoma in four cases also. This and other similar reports [131] make one wonder whether they are really arachnoid cysts. They might actually be predominantly cystic hamartomas. Figure 1 in [131] shows that the hamartoma sits on the lower aspect of the cyst, away from the ventricular floor. Ependymal remnants have been observed in otherwise solid hypothalamic hamartoma [130], and closed suprasellar cysts without apparent hypothalamic hamartoma are occasionally observed in patients who present with refractory epilepsy and/or precocious puberty (personal observation).

The only possible treatments for epilepsy-associated hypothalamic hamartoma are surgical disconnection or radiosurgery. Careful imaging can demonstrate the specific location of the epileptogenic hypothalamic hamartoma in relation to the forniceal–mammillary–anterior thalamic system, and show the demarcation of the lesion vis-à-vis the normal hypothalamus.

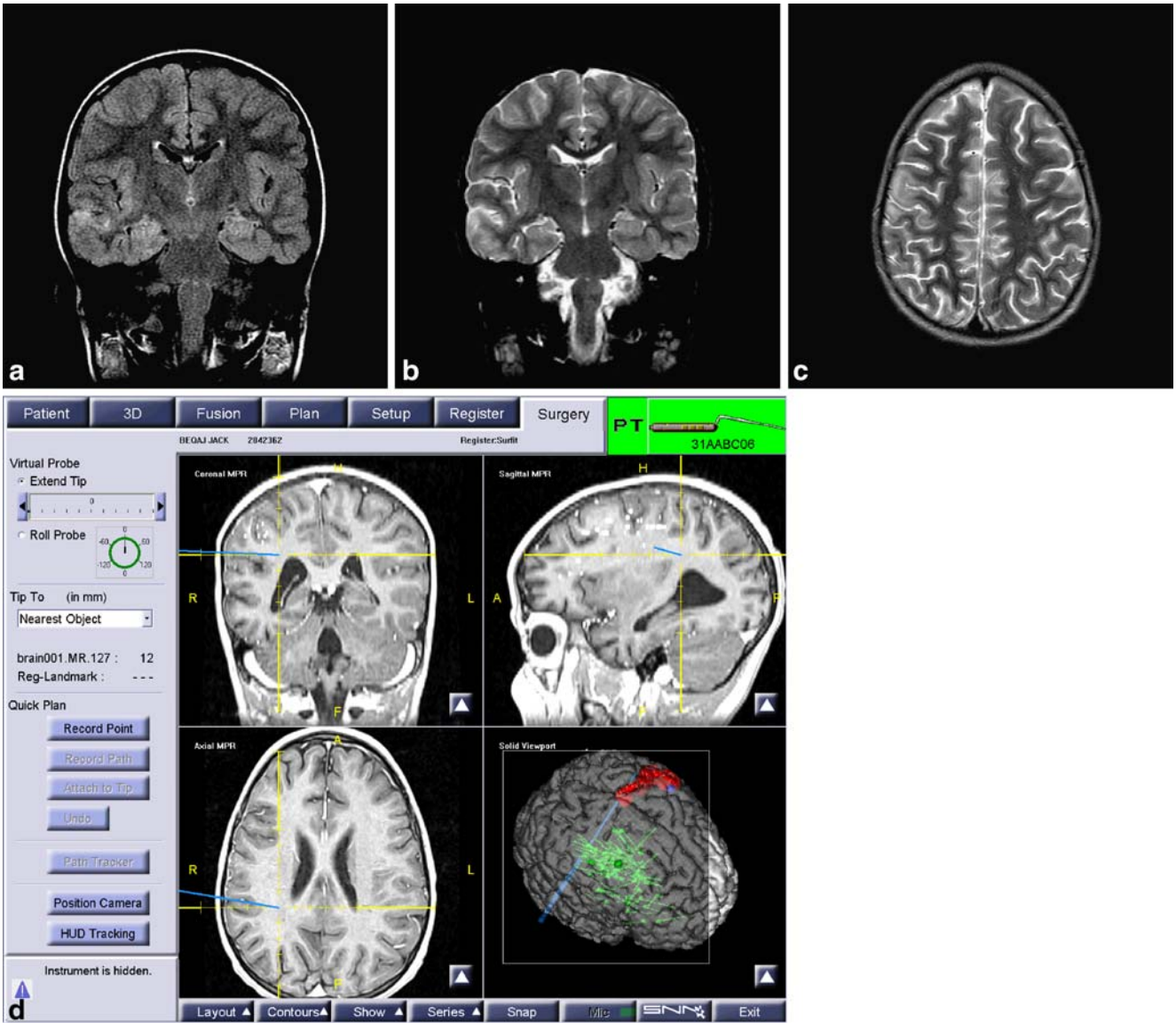

Fig. 17 Rasmussen's encephalitis. Boy, 5 years, new onset (1 month) of intractable focal seizures. Initial FLAIR (**a**) and T2 imaging (**b**) demonstrate high signal in the right temporal cortex (**a**), but the frontal cortex is unremarkable. One month later, a new imaging demonstrates a significant edema in the cortex of the right central area indicating a suprasylvian extension of the inflammatory process (**c**). MEG for pre-surgical planning shows numerous, diffusely distributed spikes over the fronto-central cortex on the right side (**d**)

Special clinical contexts of epilepsy in children

Catastrophic epilepsy

Catastrophic epilepsies are epilepsies that cannot be controlled and result in severe neurological and cognitive deterioration. Most of them are not surgical (malignant epileptic encephalopathies of infancy and childhood), but sometimes an epileptogenic focus or at least a strict lateralization can be demonstrated and surgery then becomes an option. Typical examples are Rasmussen's encephalitis (RE), Stürge–Weber angiomatosis, hemimegalencephalies, and cases of intractable status epilepticus.

Rasmussen's encephalitis

RE is devastating. Despite recent advances, no medical treatment has been shown to stop the disease, and hemispherectomy is still the most efficient approach, at the cost of a hemiparesis. Such a radical treatment implies that the diagnosis would be reasonably secure, however, even in the early stage of the disease.

A report on serial MRI of ten patients with RE shows a pattern that is fairly suggestive of the disease [132]. All MRI demonstrated focal or unilateral abnormalities, whatever the stage. At a given point of the brain, the disease evolves in several consecutive stages

reflecting the brain pathology, with marked inflammatory changes in the early stages followed by gliosis and atrophy in the later stages. The longitudinal sequence is as follows:

Stage 0: normal appearance

Stage 1: swelling of the cortical ribbon and high T2/FLAIR signal

Stage 2: normal thickness of the cortical ribbon and high T2/FLAIR signal

Stage 3: focal atrophy and high T2/FLAIR signal

Stage 4: ongoing atrophy and normal signal

The disease is initially focal. Its starting point is commonly in the temporo-insular cortex and the fronto-temporal cortex, which correlates the early psychomotor or partial motor seizures well. From this initial point, it extends throughout the hemisphere, each newly affected area developing the same longitudinal sequence so that the global MRI picture is a composite image of different stages of evolution at different places (Fig. 17). Another report [133], although using a less systematic longitudinal approach, corroborates these findings and describes also a progressive atrophy of the head of the caudate, of the contralateral cerebellar hemisphere, and of the ipsilateral hippocampus.

Other catastrophic epilepsies

It is generally agreed upon that the intellectual and neurological development of children suffering from *Stürge–Weber disease* depends on the occurrence of repeated seizures. If the medical treatment fails, severe status may need hemispherectomy. The absence of contralateral involvement should therefore be ascertained. The characteristic brain MR imaging features of SWD is the diffuse enhancement of the surface of one hemisphere, typically over its posterior portion, reflecting the pial angioma. To better demonstrate it against both the brain and the CSF, a contrast-enhanced FLAIR sequence is to be used rather than the conventional T1 contrast-enhanced sequence [134]. If a T1 sequence is used, a fat saturation should be applied as well to increase the contrast and show the associated abnormalities of the calvarium. Other usual findings are a large choroid plexus in the ipsilateral ventricle and prominent, DVA-like trans-medullary veins. Hemispheric swelling from prolonged seizure activity may be demonstrated. Acute ischemia may also occur, with focal edema, and possibly bleed. In infants, the white matter may present with a low T2 signal [84] that has been tentatively explained by the venous congestion [85], but early myelination induced by seizure activity [83] may be considered an alternative explanation. Calcification is unusual in infants. The angiomatous hemisphere may already show atrophy, presumably due to previous seizure activity rather than to the perfusion defect, although this is controversial.

Another instance of catastrophic epilepsy in which hemispherotomy may have to be performed early is *hemimegalencephaly*.

Finally, refractory *status epilepticus* also may need urgent surgical treatment. MRI may help not only in showing a structural epileptogenic lesion but also even in generalized seizures or status, in showing a focal cortical edema that allows, together with the electrophysiological data, the locating of the epileptogenic area; changes in the cornu ammonis on one side (swelling and/or high T2-FLAIR) indicates that the seizures originate from the ipsilateral hemisphere [135, 136].

Temporal lobe epilepsy in children

In the adult population, temporal lobe epilepsy is usually related to hippocampal sclerosis. Although HS develops in young children, it does not typically become clinically apparent until in the second decade, and temporal lobe epilepsy in children is more often related to developmental dysplasias or tumors than to HS. This is apparent in a medical series in which 55% of patients did not demonstrate any abnormality on MRI and 27% exhibited either a tumor or a dysplasia, but only 17% presented with isolated HS [137]. Because of the surgical bias, the ratios are different in surgical series, but the predominance of tumors and dysplasia is demonstrated also. One surgical series of 42 patients [138] reveals 33% tumors (7 of 14 gangliogliomas, 2 of 14 DNTs, and 5 of 14 conventional tumors) and 20% FCD/TSC, but only 20% isolated HS. Another series of 35 patients [139] presents a relatively large group of HS with 40%, but still 19% are DNT and oligodendroglioma (unexpectedly, there is no ganglioglioma) and 34% are cortical dysplasias. Nonspecific gliosis and scarring/porencephaly are not uncommon either.

Other causes for partial epilepsy in children

Refractory epilepsy and epileptic encephalopathies are common complications of destructive brain lesions. These may be nonspecific (atrophy) or specific (porencephalies and focal scars). They typically relate to late gestational, perinatal, or early infantile events such as hemorrhages, ischemia, infection, trauma, HIE-related ulegyria [140], and even hypoglycemia [141]. The scar itself is obviously devoid of neurons and does not generate epilepsy, but as it occurs in a developing brain, abnormal neuronal networks may develop in the surrounding preserved cortex.

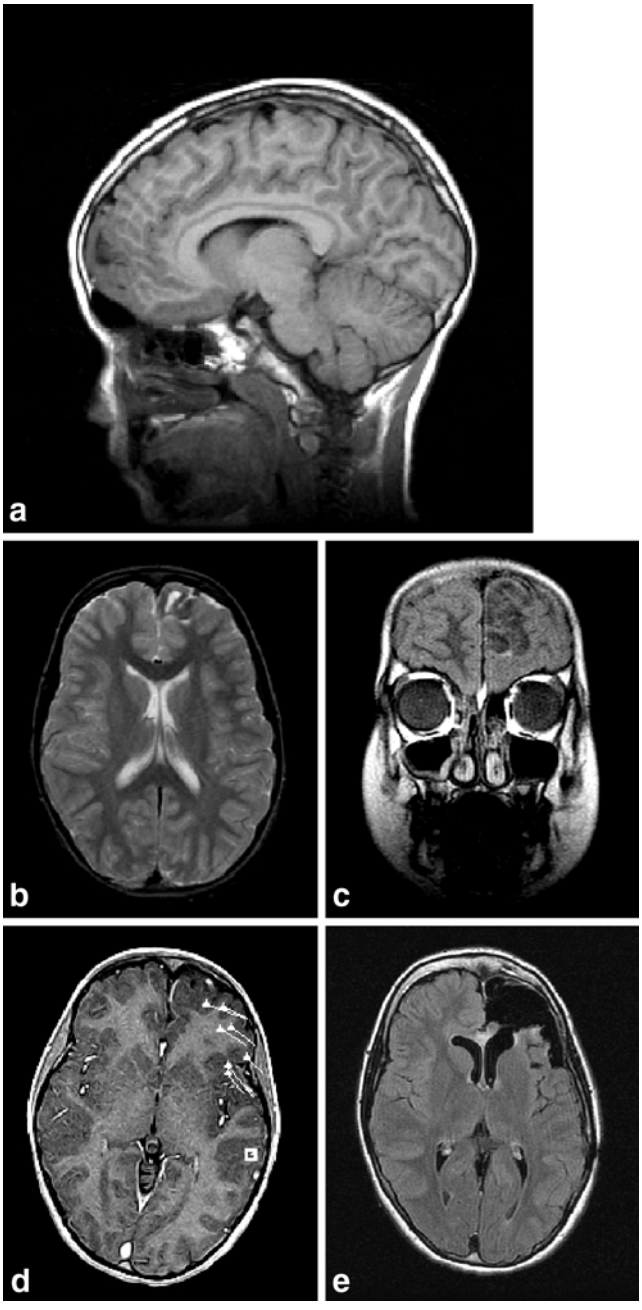

Fig. 18 Meningioangiomatosis. Girl, 8 years, complex partial seizures. Dysplastic lesion of the left frontal pole (**a**). The cortex is thick and has a clear demarcation from the white matter on T2 (**b**) with some low T2 signal probably related to calcification; the white matter appears bright. On FLAIR (**c**), the lesion appears well demarcated, the cortex is not distinct from the white matter, and the signal is globally low, somewhat heterogeneous with some septation. No contrast enhancement of the brain but faint enhancement of the pia (**d**). It was not surprising that a diagnosis of DNT was made. Pre-surgical MEG shows diffuse spikes over the adjacent frontal cortex (**d**). Surgery was performed accordingly (**e**) and it revealed that the dysplastic lesion was related to a meningioangiomatosis

Arterio-venous malformations are usually not epileptogenic in children, except for the large ones. Cavernomas are often located at the cortical–subcortical junction and may be epileptogenic; they may be small, and they are best depicted on T2 GE imaging which should always be done when no other cause is found for partial seizures. Stürge–Weber angiomatosis is typically epileptogenic. The rare meningioangiomatosis, sporadic or associated with neurofibromatosis type 2, is characterized by meningovascular proliferation and calcification [142]; the underlying brain tissue may appear dysplastic and may be intrinsically epileptogenic, as well as the perilesional cortex [142] (Fig. 18). Surgical removal of the affected tissue is curative in a limited number of cases however [142].

Conclusion

The efficacy of MRI in the detection and the assessment of the epilepsy-associated focal lesions of the brain has considerably improved over the last two decades, thanks to technical developments with better signal-to-noise, better definition, and sensitized sequences such as FLAIR. The field of MRI also has extended beyond structural imaging as MR spectroscopy helps in differentiating tumor from dysplasia and functional MRI in identifying eloquent areas. While MR imaging is reasonably efficient in detecting and identifying epilepsy-associated developmental tumors, its contribution to the diagnosis of FCD is still uncertain. The lesion is obviously not detected in a significant number of cases. When it is detected, its true extent may be larger than what appears on the images: hopefully, DTI will provide an additional structural approach. It is not always possible either to identify the subtypes of the dysplasia from their appearance, and there is still controversy on whether a given appearance (loss of gray–white matter definition) reflects a cortical dysplasia or some gliotic changes [143]. The whole concept of FCD actually may need to be reassessed as the previously accepted pathophysiological processes leading to the lesions have been contended in recent reports.

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