Epilepsy and malformations of the cerebral cortex

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ABSTRACT – Malformations of the cerebral cortex (MCC) are often associated with severe epilepsy and developmental delay. About 40% of drug-resistant epilepsies are caused by MCC. Classification of MCC is based on embryological brain development, recognising forms that result from faulty neuronal proliferation, neuronal migration and cortical organisation. Hemimegalencephaly, an enlarged dysplastic hemisphere, can present as early onset severe epileptic encephalopathy or as partial epilepsy. In focal cortical dysplasia (FCD), MRI shows focal cortical thickening and simplified gyration. Patients have drug-resistant, often early onset epilepsy. Complete surgical ablation of FCD is accompanied by remission in up to 90% of patients, but may be technically difficult. Tuberous sclerosis (TS) is a multisystemic disorder primarily involving the nervous system; 60% of patients having epilepsy, with 50% having infantile spasms. TS is caused by mutations in the *TSC1* and *TSC2* genes; 75% of cases are sporadic. *TSC1* mutations cause a milder disease. Bilateral periventricular nodular heterotopia (BPNH) consists of confluent and symmetric nodules of grey matter along the lateral ventricles. X-linked BPNH presents with epilepsy in females and prenatal lethality in most males. Most patients have partial epilepsy. *Filamin A* mutations have been reported in families and sporadic patients. Lissencephaly (LIS – smooth brain) is a severe MCC characterised by absent or decreased convolutions. Classical LIS is quite rare and manifests with severe developmental delay, spastic quadriparesis and severe epilepsy. *XLIS* mutations cause classical lissencephaly in hemizygous males and subcortical band heterotopia in heterozygous females. Thickness of heterotopic band and degree of pachygyria correlate well with phenotype severity. Schizencephaly (cleft brain) has a wide anatomo-clinical spectrum, including partial epilepsy in most patients. Polymicrogyria (excessive number of small and prominent convolutions) has a wide spectrum of clinical manifestations ranging from early onset epileptic encephalopathy to selective impairment of cognitive functions. Bilateral perisylvian polymicrogyria may be familial. Patients present with facio-pharingo-glosso-masticatory diplegia and epilepsy, which is severe in about 65% of patients.

KEY WORDS: epilepsy, cerebral cortex abnormalities, magnetic resonance imaging, genetics

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Malformations of the cerebral cortex (MCC) or of cortical development [1] are often associated with severe epilepsy, with onset during childhood, and developmental delay. However, prevalence and severity of epilepsy is variable in different malformations [2]. About 40% of children with drug-resistant epilepsy harbour a cortical malformation [3], and up to 50% of the pediatric epilepsy surgery operations are carried out in children with an MCC [4]. Diagnostic recognition of MCC *in vivo* has increased during the last ten years, especially through the use of magnetic resonance imaging.

Variations in distribution and depth of cortical sulci, cortical thickness, boundaries between gray and white matter, and signal intensity allow recognition of different malformation patterns. Abnormalities of any or all of these features may be restricted to discrete cortical areas or alternatively, be diffuse. Attempts at nosological subdivisions [1] and genetic linkage studies have led to the identification of several genes regulating brain development [5] *(table 1)*, which, when mutated, cause specific malformation patterns. Although it requires further investigation, some cortical malformations seem to be directly associated with particular epilepsy syndromes or seizure types.

Issues of classification and nomenclature of cortical malformations

Three distinct but overlapping processes are involved in the development of the cerebral cortex, namely neuronal and later, glial proliferation, neuronal migration and cortical organization. Any or all of these processes can be altered, resulting in cortical malformations. A classification system of cortical malformations, based on fundamental embryological and genetic principles and a combination of neuroimaging, gross pathological, and histological criteria, has been developed and subsequently up-dated [1, 6, 7] *(table 2)*. The framework of the classification system is based on the three major embryological processes namely, cellular proliferation, neuronal migration,

and cortical organization. Some malformations result from abnormalities that are restricted to one of these phases, while others imply prolonged action of a causative factor, involving different phases. In this case, classification is usually based on the earliest embryological abnormality.

Table 2. Classification of cortical malformations (modified from Barkovich *et al.*, 2001)

I. Malformations due to abnormal neuronal and glial proliferation or apoptosis
 A. Decreased proliferation/increased apoptosis: microcephalies
  1. Microcephaly with normal to thin cortex
  2. Microlissencephaly (extreme microcephaly with thick cortex)
  3. Microcephaly with polymicrogyria/cortical dysplasia
 B. Increased proliferation/decreased apoptosis (normal cell types): megalencephalies
 C. Abnormal proliferation (abnormal cell types)
  1. Non-neoplastic
   a. Cortical hamartomas of tuberous sclerosis
   b. Cortical dysplasia with balloon cells
   c. Hemimegalencephaly
  2. Neoplastic (associated with disordered cortex)
   a. DNET (dysembryoplastic neuroepithelial tumor)
   b. Ganglioglioma
   c. Gangliocytoma
II. Malformations due to abnormal neuronal migration
 A. Lissencephaly/subcortical band heterotopia spectrum
 B. Cobblestone complex
  1. Congenital muscular dystrophy syndromes
  2. Syndromes with no involvement of muscle
 C. Heterotopia
  1. Subependymal (periventricular)
  2. Subcortical (other than band heterotopia)
  3. Marginal glioneuronal
III. Malformations due to abnormal cortical organization (including late neuronal migration)
 A. Polymicrogyria and schizencephaly
  1. Bilateral polymicrogyria syndromes
  2. Schizencephaly (polymicrogyria with clefts)
  3. Polymicrogyria with other brain malformations or abnormalities
  4. Polymicrogyria or schizencephaly as part of multiple congenital anomaly/mental retardation syndromes
 B. Cortical dysplasia without balloon cells
 C. Microdysgenesis
IV. Malformations of cortical development, not otherwise classified
 A. Malformations secondary to inborn errors of metabolism
  1. Mitochondrial and pyruvate metabolic disorders
  2. Peroxisomal disorders
 B. Other unclassified malformations
  1. Sublobar dysplasia
  2. Others

Table 1. Genes responsible of malformation of cortical development (modified from Barkovich *et al*, 2001).

Syndrome	Locus	Gene	Protein
ILS^{DCX}	Xq22.3-q23	*DCX = XLIS*	DCX or doublecortin
SBH^{DCX}	Xq22.3-q23	*DCX = XLIS*	DCX or doublecortin
MDS	17p13.3	Several contiguous	PAFAH1B1 and others
ILS^{LIS1}	17p13.3	*LIS1*	PAFAH1B1
SBH^{LIS1}	17p13.3	*LIS1*	PAFAH1B1
LCH^{RELN}	7q22	*RELN*	reelin
FCMD^{FCMD}	9q31	*FCMD*	FCMD or fukutin
MEB	1p32	Unknown	Unknown
BPNH	Xq28	*FLN1*	filamin-1
TSC1	9q32	*TSC1*	hamartin
TSC2	16p13.3	*TSC2*	tuberin

ILS - isolated lissencephaly sequence; **SBH** - subcortical band heterotopia; **MDS** - Miller – Dieker syndrome; **LCH** – lissencephaly with cerebellar hypoplasia; **FCMD** - Fukuyama congenital muscular dystrophy; **MEB** - muscle – eye – brain disease; **BPNH** – bilateral periventricular nodular heterotopia.

In the following sections, several of the most common malformations of the cortex or of cortical elements will be reviewed.

Malformations related to abnormal proliferation of neurons and glia

Hemimegalencephaly

In hemimegalencephaly (HME), one cerebral hemisphere is enlarged and presents with thick cortex, wide convolutions and reduced sulci *(figure 2A)*. Although the abnormality is strictly unilateral in most cases [8], post-mortem examination shows minor abnormalities of the apparently unaffected hemisphere in some cases [9, 10]. Laminar organization of the cortex is absent, and gray-white matter demarcation is poor. There are giant neurons (up to 80 mµ in diameter) throughout the cortex and the underlying white matter. Large, bizarre cells, defined as 'ballon cells', are observed in about 50% of cases [9]. Hemimegalencephaly is probably a heterogeneous condition with an uncertain nosography. Localization of the abnormality to one cerebral hemisphere could indicate somatic mosaicism [8]. Hemimegalencephaly could also result from a fault in programmed cell death or apoptosis [11].

Hemimegalencephaly has been associated with many different disorders *(table 3)*, but it can also occur in isolation. The clinical spectrum of hemimegalencephaly is wide, ranging from cases with severe epileptic encephalopathy beginning in the neonatal period [9], to patients with normal cognitive levels [12, 13] in whom the malformation is detected on MRI after seizure onset. The most typical presentation is with asymmetry of the skull and macrocrania, hemiparesis, hemianopia, mental retardation and seizures. Most patients have a severe structural abnormality and almost continuous seizures. Seizure intractability can be established within the first year of life. Hemispherectomy is indicated in the most severe cases [14]. Clinical features are fairly homogeneous, with partial motor seizures beginning in the neonatal period, infantile spasms and often a suppression burst pattern on sleep EEG [14, 15]. A high mortality rate is observed in the first months or years of life for patients with early onset, severe epilepsy, with status epilepticus being the most common cause of death [8, 16-18]. Survivors have severe cognitive and motor impairment [19]. Hemispherectomy may prevent either life-threatening seizures or long term, deleterious interference by the epileptogenic hemisphere on physiological functioning of the healthy hemisphere [18, 20]. There are indications that the operation should be performed early [21]. Transfer of functions to the "normal" hemisphere is greater in younger children. A higher degree of recovery of neuropsychological functions is achieved in subjects undergoing surgery at an early age. The milder extreme of the clinical spectrum in HME includes patients with well controlled seizures or no seizures at all [14].

Focal cortical dysplasia

In focal cortical dysplasia (FCD), histological abnormalities are restricted to one lobe or to a segment of a few centimeters. Extensive examination of brains with focal lesions may, however, show widespread minor dysplastic changes [22]. FCD was originally described in patients who were surgically treated for drug-resistant epilepsy [23]. Histological abnormalities include: local disorganization of laminar structure, large aberrant neurons, isolated neuronal heterotopia in subcortical white matter, balloon cells sharing histochemical characteristics of both neuronal and glial cells, giant and odd macroglia, and foci of demyelination and gliosis of adjacent white matter [24] *(figure 1)*. The abnormal area is not usually sharply delimited from adjacent tissue [8, 25].

One or more of the above components may not be present, so that three main subtypes of FCD are recognised, possibly corresponding to different stages of embryological development. Type 1 is characterised by abnormal cortical lamination and ectopic neurons in white matter, type 2 presents with giant, neurofilament-enriched neurons, in addition to altered cortical lamination, and type 3 corresponds to Taylor-type FCD with giant dysmorphic neurons and balloon cells associated with cortical laminar disruption [26]. MR images show focal areas of cortical thickening, with simplified gyration, rectilinear or blurred boundaries between gray and white matter [27], and

Table 3. Conditions associated with hemimegalencephaly

- Epidermal nevus syndrome
- Klippel-Trenaunay-Weber syndrome
- Proteus syndrome
- Neurofibromatosis
- Ito's hypomelanosis
- Focal alopecia
- Tuberous sclerosis
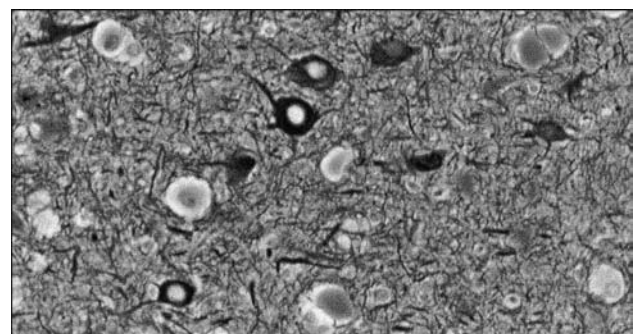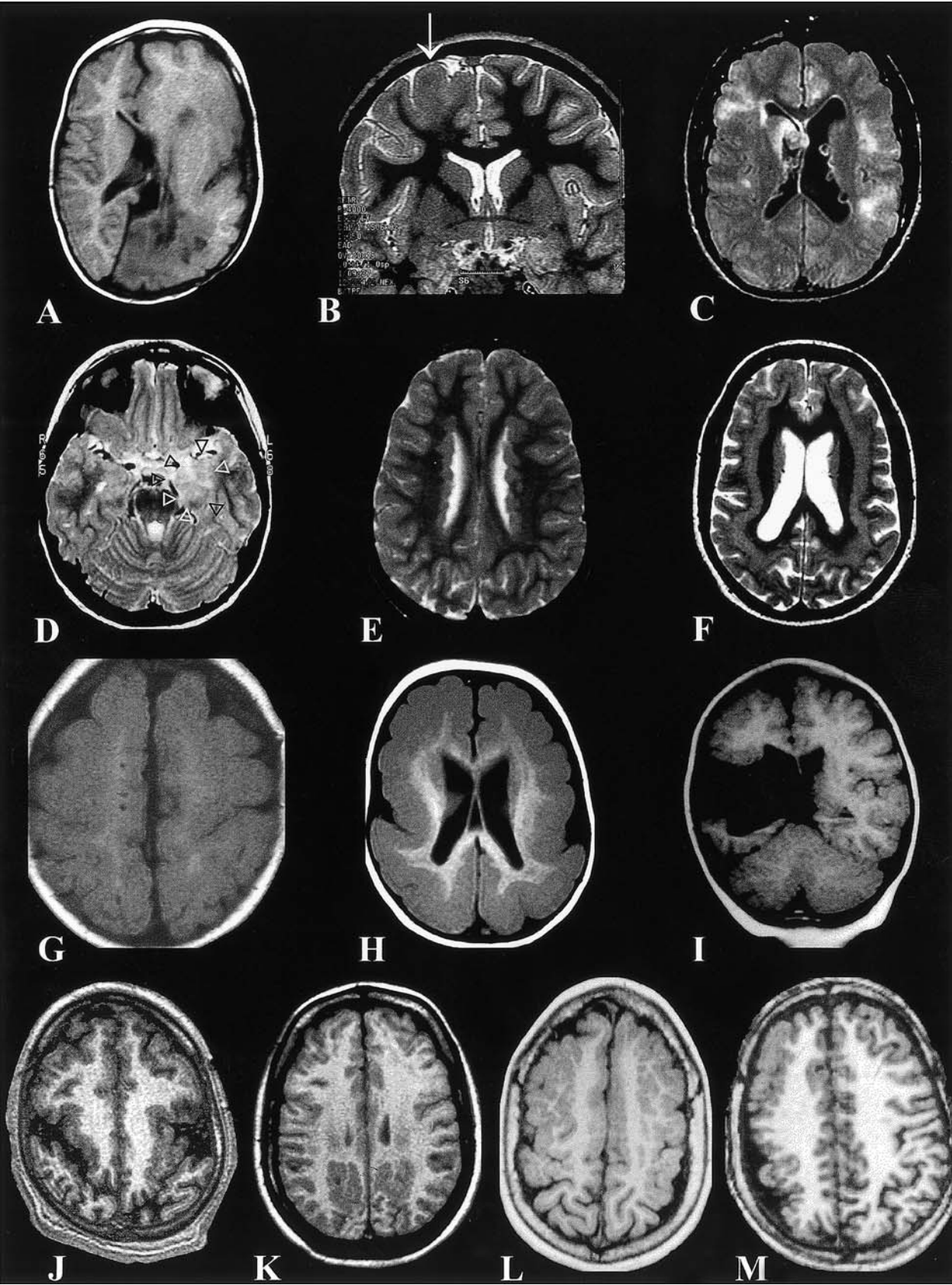- Dysembryoplastic neuroepithelial tumor

Figure 1. *Focal cortical dysplasia. Silver-stained section showing irregular arrangement of large neurons and 'balloon cells'.*

increased signal intensity in the cortex and subcortical white matter on T_2, FLAIR, or PD-weighted images *(figure 2B)*. Histological and image characteristics of Taylor-type FCD are reminiscent of tubers of tuberous sclerosis. Recently, a significant increase in the frequency of sequence alterations of the *TSC1* gene was found in DNA samples from microdissected dysplastic lesions containing ballon cells from 48 patients undergoing surgical treatment. These findings suggest a common pathogenetic mechanism for Taylor-type FCD and the cortical tubers of tuberous sclerosis [28]. Some cases present the involvement of an entire lobe (so-called partial hemimegalencephaly). Normal brain MRI has been reported [29, 30]. FCD usually presents with intractable partial epilepsy, starting at a variable age, but generally before the end of adolescence. Since lesions may be located anywhere in the brain, any type of focal seizure can be observed and focal status epilepticus has been frequently reported [29, 31, 32]. However, infantile spasms may be the first manifestation [33] *(figure 3)*. Location in the precentral gyrus is often complicated by epilepsia partialis continua [34-37]. Unless the dysplastic area is large, patients do not suffer from severe neurological deficits. Interictal EEG shows focal, rhythmic epileptiform discharges in about half of the patients [38].

These EEG abnormalities are highly specific of FCD, are located over the epileptogenic area and are related to the continuous epileptiform discharges recorded during electrocorticography (EcoG) [31, 39]. ECoG seizure activity shows spatial co-localization with the lesion. At follow-up, most patients with complete resection of the tissue producing the ictal ECoG discharges were seizure-free or had over 90% reduction in major seizures. None of the patients with persistence of discharging tissue had a favourable outcome.

Dysplastic tissue seems to produce epileptiform activity, as demonstrated by *in vitro* studies [40, 41]. The mechanisms underlying the epileptiform activity remain to be elucidated. In the abnormal cortical multilaminar organization typical of FCD, neurons are prevented from establishing normal synaptic connections with their neighbours and are dysfunctional. Intracellular recordings have revealed no abnormalities in the membrane properties of single dysplastic neurons [42]. However, a dysfunction of synaptic circuits seems to be responsible for the abnormal synchronization of neuronal populations underlying the epileptiform activity. Abnormalities in the morphology and distribution of local-circuit GABAergic inhibitory neurons have been observed using immunocytochemistry [35, 43]. Such abnormal circuitry could play an important role in the origin and maintenance of the epileptiform activity.

Most of the clinical and electrophysiological features reported in FCD and HME are probably biased because they are likely to be typical of the most severe cases, recruited in epilepsy surgery centers, the only places where histological diagnosis, electrocorticography and experimental electrophysiology studies can be carried out. Our experience indicates that there are some patients, with well controlled seizures, in whom MRI shows FCD [44].

Tuberous sclerosis

Tuberous sclerosis or tuberous sclerosis complex (TSC) is a multisystemic disorder involving primarily the central nervous system, the skin, and the kidney [45]. A prevalence of 1:30 000 – 50 000 has been reported. In the brain, the characteristic features are cortical tubers, subependymal nodules and giant cell tumors. Cortical tubers are more directly related to epileptogenesis. They are identified by their nodular appearance, firm texture, and variability in

Figure 2. A – *Hemimegalencephaly involving the left hemisphere. MRI, T1-weighted axial section. The architecture of the whole left hemisphere is severely impaired. Note the enlarged appearance of the hemisphere, bulging across the midline, with thickened and smooth cortex and blurred boundaries between gray and white matter, especially in the frontal lobe.* **B** – *Right frontal focal cortical dysplasia in a 14-year-old girl with intractable focal epilepsy. Coronal MRI scan. The cortex presents thickened gyri and is not clearly separated from the underlying white matter.* **C** – *Tuberous sclerosis in a 22-year-old male patient with symptomatic generalised epilepsy and mental retardation. PD weighted axial MRI scan. Several subependymal calcified nodules are present along the ventricular walls. At least three hyperintense, subcortical lesions are clearly visible, one in the right and two in the left frontal lobe. They represent cortical tubers. A fourth lesion (tumoral) involves the right thalamus.* **D** – *MRI, T2 weighted axial section. Left temporal DNET, visible as an area of enhanced signal is in the anteriomedial aspect of the left temporal lobe (arrows) in a six-year-old boy with drug-resistant, complex partial seizures.* **E** – *MRI, T2-weighted axial section. Bilateral periventricular nodular heterotopia. Nodules of gray matter, presenting the same signal as the normal cortex, are lining the lateral ventricles.* **F** – *Subcortical band heterotopia. MRI T2-weighted axial slice showing a thick, diffuse band of heterotopic cortex. Twenty-year-old woman with drug-resistant partial epilepsy and DCX gene mutation.* **G** – *XLIS lissencephaly. T1-weighted axial section. A simplified gyral pattern with severely thickened cortex is observed with a prominent frontal involvement.* **H** – *LIS1 lissencephaly. T1-weighted axial section showing a simplified gyral pattern and a thick cortex that is completely smooth particularly in the posterior brain.* **I** – *Unilateral open lip schizencephaly. T1-weighted coronal MRI. A large cleft in the right hemisphere spans from the subarachnoid space to the lateral ventricle.* **J** – *Bilateral perisylvian polymicrogyria. T1-weighted axial section showing open sylvian fissures overlaid by an irregular and thick cortex. A sixteen-year-old male patient with facio-pharingo-glosso-masticatory diplegia, mild mental retardation and Lennox-Gastaut syndrome.* **K** – *Bilateral parasagittal parieto-occipital polymicrogyria. T1-weighted MRI showing irregular thickening and infolding of the cortex at the mesial parieto-occipital junction.* **L** – *Bilateral frontal polymicrogyria. MRI, T1-weighted axial section. Polymicrogyric cortex with a irregular, bumpy aspect involves all the gyral pattern anterior to the precentral gyri. A 10-year-old boy with spastic quadriparesis, moderate mental retardation and partial epilepsy. Seizures have been in remission for some years.* **M** – *Unilateral polymicrogyria. MRI, T1-weighted axial section. The right hemisphere is smaller than the left and the subarachnoid space overlying the right hemisphere is enlarged. The cortex on the right is irregular, with areas of thickening. An eight year-old boy with left hemiparesis, moderate mental retardation, atypical absences and partial motor seizures.*
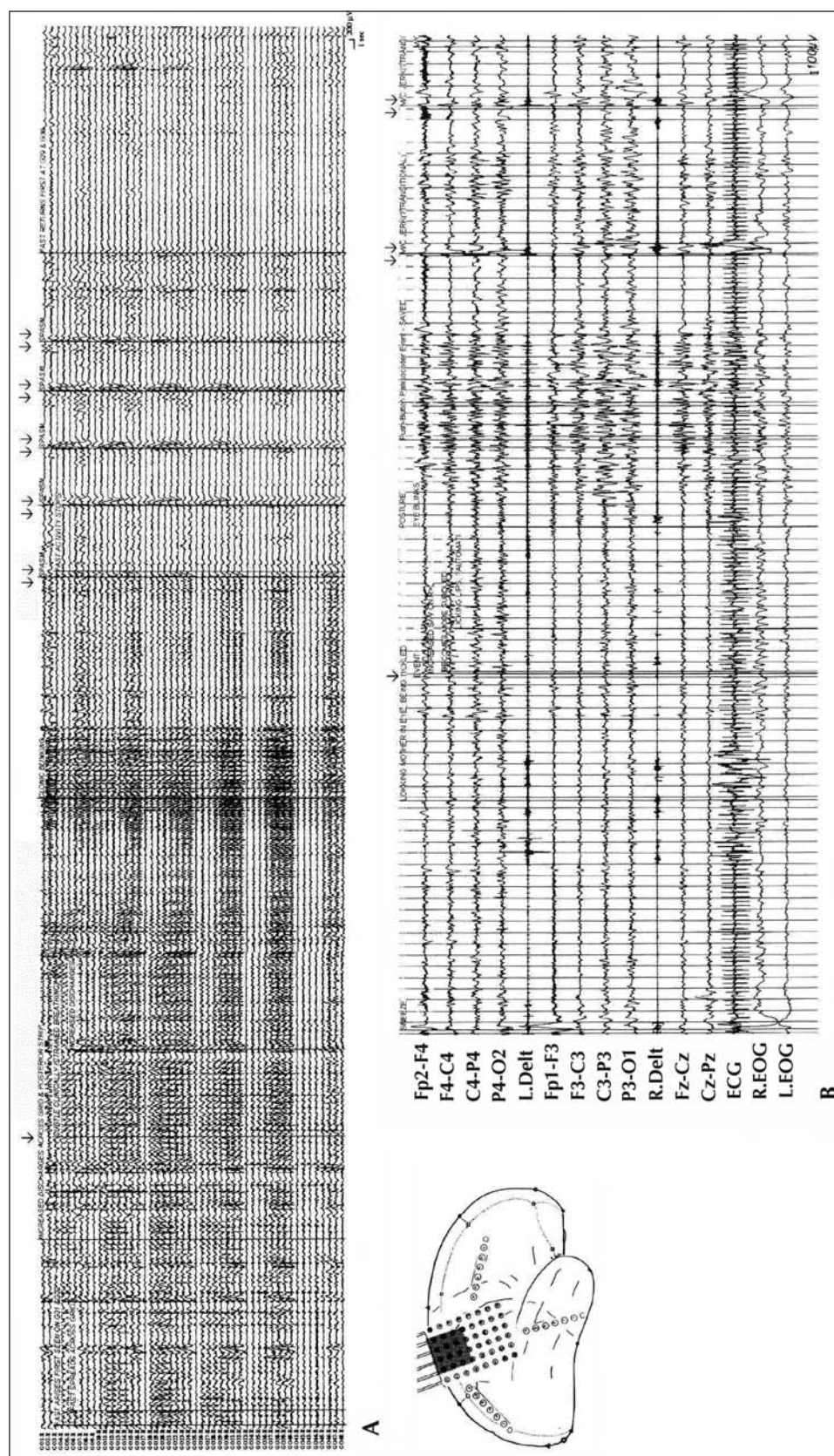
Figure 3. **A** – *Intracranial subdural recording from a 48-contact grid in a one-year-old boy suffering from symptomatic partial epilepsy due to focal cortical dysplasia involving the right parietal lobe. The drawing in the inset shows the position of the 48-contact grid overlying the right parietal lobe. Three additional six-contact strips overlay the right frontal lobe, the right temporal lobe and the right parieto-occipital junction. A 'hypomotor' seizure characterised by behavioural arrest starts at the time indicated by the single arrow. This is followed by a cluster of asymmetric spasms indicated by the double arrows. EEG shows a build-up of a rhythmic fast activity starting in the grid contacts that are shadowed in the schematic drawing.*
B – *A similar seizure is recorded in the same patient with scalp EEG. The electrical onset of the seizure is difficult to pin-point on surface recording. An arrow indicates the clinical onset of the seizure. A clear cut build – up of diffuse theta activity with a prominent sharp component on the parieto-occipital areas, bilaterally, is observed approximately 14 seconds after seizure onset. A cluster of asymmetric spasms, of which two are indicated by a double arrow, follows the initial 'hypomotor' episode. Each line represents a second (time).*
Delt. = deltoid muscle; **EOG** = electro-oculogram; **L.** = left; **R** = right.

site, number and size. Microscopically, the tubers consist of subpial glial proliferation with orientation of the glial processes perpendicular to the pial surface, and an irregular neuronal lamination with giant multinucleated cells that are not clearly neuronal or astrocytic. The junction between gray and white matter is indistinct and may be partly demyelinated. These pathological changes are similar to those seen in FCD. Cortical tubers are usually well visualized by MRI as enlarged gyri with atypical shape and abnormal signal intensity, mainly involving the subcortical white matter [46] *(figure 2C)*. In the newborn, they are hyperintense with respect to the surrounding white matter, on T1-weighted images, and hypointense on T2-weighted images. Progressive myelination of the white matter in the older infant gives the tubers a hypointense center on T1 and high signal intensity on T2. In the adult, the lesions tend to become isointense, with the white matter on T1-weighted images, but maintain hyperintensity on T2. Tubers may have a tendency to calcify, which increases with age.

TSC is transmitted as an autosomal dominant trait, with variable expression seen within families. Recurrence in siblings of non-affected parents has rarely been reported and is thought to be related to low expressivity or gonadal mosaicism. There is no clear evidence of nonpenetrance for TSC. Therefore, careful clinical and diagnostic evaluation of apparently unaffected parents is indicated before counseling the families. Between 50 to 75% of all cases are sporadic. Linkage studies have allowed the identification of two loci for TSC, mapping to chromosome 9q34 *(TSC1)* and 16p13.3 *(TSC2)* [47]. About 50% of the familial cases are linked to *TSC1* [48]. A classical positional cloning approach has led to the isolation of the *TSC1* gene [49], encoding for a predicted protein, named "hamartin". A mutation in the *TSC1* gene has so far been identified in about 80% of the families and linked to chromosome 9q34 [50]. The identification of a second gene mapping to 16p13.3 has been facilitated by the presence of interstitial deletions in 5, unrelated TSC patients [51]. A gene (*TSC2*) was found to be disrupted by all the deletions and was demonstrated to harbor intragenic mutations in other non-deleted TSC patients [51]. Clinical assessment indicated that sporadic patients with *TSC1* mutations had, on average, a milder disease than did patients with *TSC2* mutations, including a lower frequency of seizures, moderate to severe mental retardation, fewer subependymal nodules and cortical tubers, less severe kidney involvement, no retinal hamartomas, and less severe facial angiofibroma [52]. Both germline and somatic mutations in the *TSC2* gene have been demonstrated in tumors derived from patients with TS.

Epileptic seizures are frequent in TS. They usually begin before the age of 15, mostly in the first 2 years of life: 63.4% before one year [45], 70% before two years. Infantile spasms are the most common manifestation of epilepsy in the first year of life, sometimes preceded by partial seizures [53]. In their study of 126 patients, Roger *et al.* [54] found 63 (50%) with infantile spasms and 63 (50%) with other types of epilepsy (35 partial, 11 Lennox-Gastaut syndrome, four symptomatic generalized, six occasional seizures and seven unclassifiable). Forty-two of the latter 63 patients had their first seizure before two years of age and the prognosis was strongly related to this early onset. Almost all patients were cognitively impaired, and the course of epilepsy was severe in about one third. MRI studies have established that there may be a correlation between tubers and epilepsy. In children with partial epilepsy or with infantile spasms, the largest tuber was found in the area corresponding to the main EEG focus [55]. However, MRI may fail to show all the tubers in infants if myelination is not complete [46]. Patients with TS must be carefully investigated in order to determine whether there is a single epileptogenic area, as its surgical removal can yield good seizure control [56, 57].

Gangliogliomas and dysembryoplastic neuroepithelial tumors (DNET)

This group of highly heterogeneous lesions include supratentorial tumours resembling gliomas, but characterised by a benign evolution and a distinct cortical topography. Association between these epilepsy-related neoplasms and areas of dysplasia in the same patients has suggested a maldevelopmental basis for their origin [58, 59]. The typical clinical presentation is of drug-resistant partial epilepsy with onset before age 20 [59]. In large series of patients with surgically-treated, drug-resistant epilepsy due to neoplastic lesions, gangliomas and DNET represent the majority (50 – 75%) of histopathologically diagnosed lesions [59-62]. Any lobe can be affected, but temporal lobe locations appear to be far more frequent for both gangliogliomas and DNET [59] *(figure 4)*. Neuroradiological studies typically show a hypodense lesion on CT scan, with possible associated hyperdense calcified lesions. Overlying skull can be deformed in superficially located lesions [59]. A cystic component is frequently observed. MRI scans show a hyperintense T1 lesion, that is usually peripherally enhanced after gadolinium administration. Gray and white matter are both involved [59]. A well-demarcated, multilocular appearance is typically seen *(figure 2D)*.

Gangliogliomas are histologically characterised by a glioma component intermixed with an atypical neuronal or ganglion cell component [63]. Atypical neuronal or ganglion cells are frequently binucleate. Cell proliferation studies show that the tumour growth rate is slow [63]. DNET are similar to gangliogliomas, but cytological atypia are more rare. Dysplastic neurons frequently lie adjacent to the neoplastic lesions [59, 63].

Clinical presentation is with a drug-resistant, partial epilepsy. In a population of 89 patients with DNET, partial seizures were the first clinical signs in 75%, while only 9%
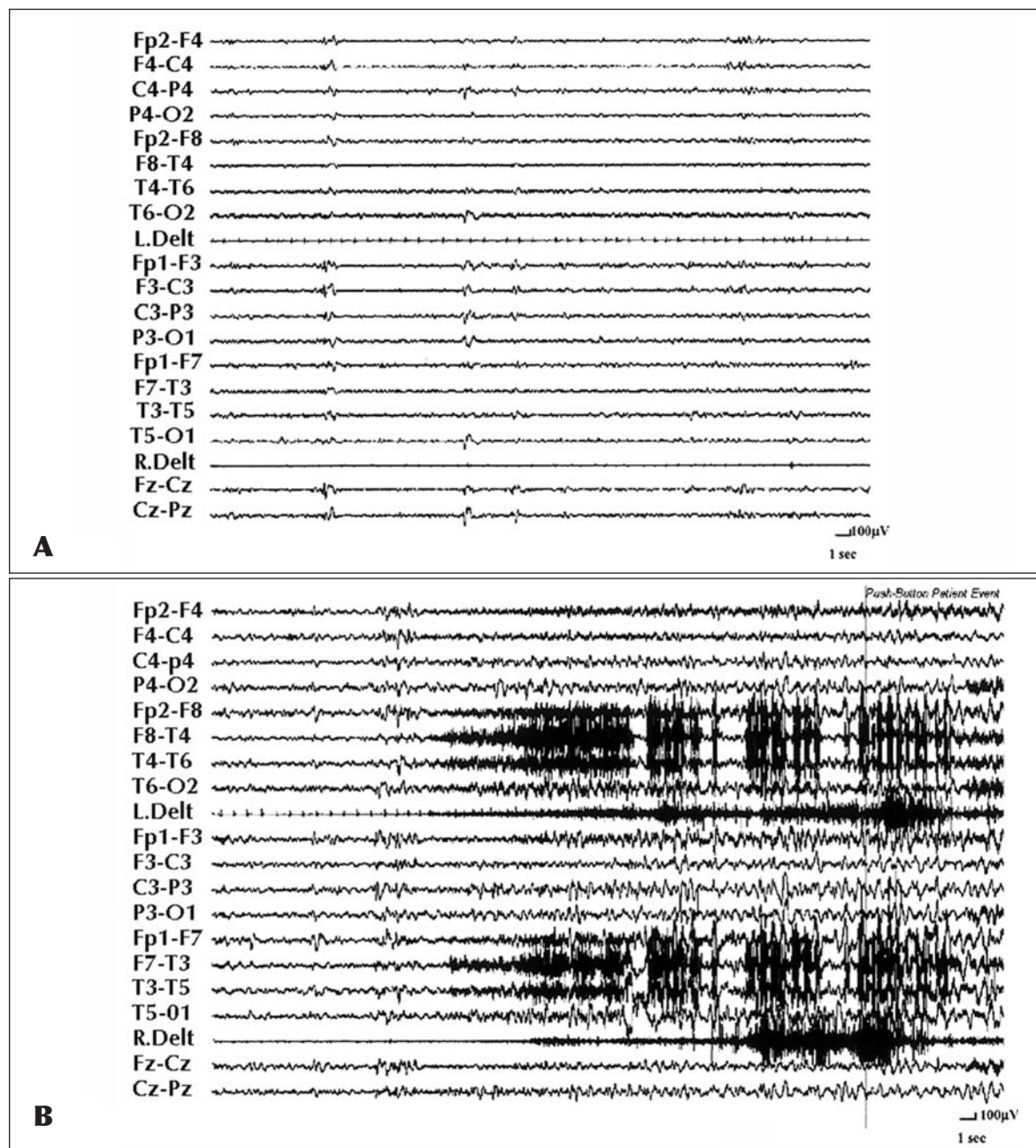
Figure 4. A – *Interictal recording during sleep in a 6-year-old boy with drug-resistant partial epilepsy and a left temporal DNET. The same patient as in figure 2D. Frequent left posterior sharp and slow waves that occasionally spread to the contralateral homologous regions.* **B** – *Ictal recording in the same patient. This seizure is characterized by behavioral arrest and retching. At onset, a diffuse, ill-defined, sharp and slow wave complex is observed; this is followed by rhythmic activity in the theta range that initially involves the posterior quadrants on both sides. However, sharper components are seen on the left.*

had neurological deficits consisting of quadranopsia. Epilepsy started at a mean age of nine years (range 1-20 years) and proved resistant to different antiepileptic medications. Complete surgical removal of the lesion was associated to remission of epilepsy in all patients [59].

Malformations due to abnormal neuronal migration

Isolated neuronal cells, or their agglomerates, in an abnormal site represent gray matter heterotopia. Heterotopic

neurons are normal in morphology, but lack normal synaptic connections [64]. Scattered and rare heterotopic neurons are occasionally found in subcortical white matter of normal subjects, but a density exceeding eight neurons per 2 mm^2 is considered neuronal heterotopia [65], while a density visible to the naked eye is considered gray matter heterotopia [66]. The most common type of heterotopia is nodular heterotopia located in either a subependymal or subcortical location. Other minor forms of heterotopia include leptomeningeal neuronal heterotopia [11], subpial neuronal heterotopia, and ectopic neurons scattered throughout the molecular layer. Gray matter heterotopia can be diagnosed with MRI, showing the same signal as the normal cortex at every impulse sequence used. On FDG-PET imaging, heterotopias have the same metabolic activity as normal gray matter [67]. Gray matter heterotopia can be diffuse or localized. Diffuse forms include subcortical band (or laminar) heterotopia [68] and extensive forms of bilateral periventricular nodular heterotopia. Localized forms can be subependymal, unilateral or bilateral, subcortical (nodular, laminar), unilateral, or may extend from the subependymal region to the subcortex unilaterally.

Bilateral periventricular nodular heterotopia (BPNH)

BPNH consists of confluent and symmetric subependymal nodules of gray matter located along the lateral ventricles *(figure 2E)*. Extent of the heterotopia and associated clinical symptoms are heterogeneous. BPNH is far more frequent in females, resulting in the syndrome of X-linked BPNH, with prenatal lethality in almost all males [69] and a 50 per cent recurrence risk in the female offspring of women with BPNH. Heterozygous females show epilepsy and coagulopathy. X-linked BPNH and BPNH occurring sporadically in women, has been associated with mutations of the *filamin A gene* [*FLNA*] [70-72]. Other unidentified genes may cause bilateral periventricular heterotopia in both sexes, with slightly different anatomical characteristics. Female patients with *FLNA* mutations usually have normal intelligence to borderline mental retardation, and epilepsy of variable severity. Only two living male patients are on record, both have features comparable to females [71]. Several syndromes featuring BPNH and mental retardation have been described as always occurring sporadically, almost exclusively in boys [73-75]. About 88% of patients with BPNH have epilepsy [76] beginning at any age. Seizure intractability is frequently observed.

Classical lissencephaly
and subcortical band heterotopia
(the agyria-pachygyria-band spectrum)

Lissencephaly (smooth brain) is a severe abnormality of neuronal migration characterized by absent (agyria) or decreased (pachygyria) convolutions, producing a smooth

cerebral surface [77]. Although there are several types of lissencephaly [78], we will refer here to the most frequent forms: lissencephaly caused by mutations of the *LIS1* gene [79] and lissencephaly caused by mutations of the *XLIS* (or *DCX*) gene [80, 81]. Subcortical band heterotopia (SBH) comprises the mild end of this group of malformations, which may accordingly be called the agyria-pachygyria-band spectrum [69]. In SBH, the gyral pattern is usually simplified with broad convolutions and increased cortical thickness. Just beneath the cortical ribbon, a thin band of white matter separates the cortex from a heterotopic band of gray matter of variable thickness and extension [82] *(figure 2F)*. In general, the thicker the heterotopic band, the higher the chances of finding a pachygyric cortical surface [68].

Pathological studies of both lissencephaly and SBH demonstrate incomplete neuronal migration. In classical lissencephaly, the cerebral cortex is abnormally thick. The cytoarchitecture consists of four primitive layers, including an outer marginal layer, a superficial cellular layer which corresponds to the true cortex, a variable, cell-sparse layer, and a deep cellular layer composed of heterotopic neurons [77]. It is not known whether LIS1 and XLIS lissencephaly have distinctive histological findings. SBH consists of symmetric and circumferential bands of gray matter, which show regional predominance in many patients. The cortex overlying the bands appears either normal or pachygyric. Pathological study of the brains of three women with SBH [64] revealed that the cerebral cortex had normal cell density and laminar organization. Neurons in the heterotopic band were either arranged haphazardly or organized in a pattern suggestive of columnar organization. Several malformation syndromes associated with classical lissencephaly have been described. The best known of these is Miller-Dieker syndrome, which is caused by large deletions of *LIS1* gene and contiguous genes [83]. The most frequent form, the X-linked dominant lissencephaly and SBH, consists of classical lissencephaly in hemizygous males and SBH in heterozygous females.

The *DCX* gene is located on chromosome Xq22.3-q23 [81, 84-86]. Mutations of the coding region of *DCX* were found in all reported pedigrees [87] and in 38 to 91% of sporadic, female patients [82, 85, 88]. Maternal germline or mosaic *DCX* mutations may ocurr in about 10% of cases of either SBH or XLIS [89]. SBH in rare, affected boys has been associated with missense mutations of *DCX* or *LIS1* [90]. The genetics and function of *DCX* are discussed extensively by Gleeson in a recent review [91]. *LIS1* (approved gene symbol *PAFAH1B1*) is the gene responsible for Miller-Dieker lissencephaly. This gene maps to chromosome 17p13.3 [79]. Approximately, 65% of patients with ILS show a mutation involving the *LIS1* gene. Among patients with ILS, 40% exhibit a deletion involving the entire gene [92], and 25% show an intragenic mutation [93]. In general, in patients with missense mutations

Table 4. Grading system for lissencephaly and SBH (agyria-pachygyria-band spectrum)
modified from Dobyns and Truwit, 1995.

Grade	Description
1	Agyria only
2	Agyria with limited frontotemporal pachygyria
3	Mixed agyria and pachygyria
	a. Frontal pachygyria and posterior agyria
	b. Frontal agyria and posterior pachygyria
4	Pachygyria only
	a. Diffuse pachygyria only
	b. Frontal pachygyria and posterior normal gyri
	c. Frontal normal gyri and posterior pachygyria
5	Mixed pachygria and subcortical band heterotopia
	a. Pachygyria with subtle band
	b. Pachygyria with clear band
	c. Pachygyria with thin cortex and band
6	Subcortical band heterotopia
	a. Thick band
	b. Medium band
	c. Thin band
	d. Thin partial frontal band
	e. Thin partial posterior band

the malformation is milder (lissencephaly grade 3 through grade 6, according to the 'Lissencephaly grading system', where grade 1 is the most severe) [94] (table 4) than in patients with truncating/deletion mutations [93].

Classical lissencephaly appears to be quite rare with a prevalence of 11.7 per million births (1 in 85 470) [95]. Affected children have early developmental delay and eventual profound mental retardation and spastic quadriparesis. Some children with lissencephaly have lived for more than 20 years, but life span may be much shorter in other patients. Seizures occur in over 90% of children, with onset before six months in about 75%. About 80% of children have infantile spasms, although the EEG may not show typical hypsarrhythmia. Later, most children have mixed seizure disorders including persisting spasms, focal motor and generalized tonic seizures [12, 96-98], complex partial seizures, atypical absences, atonic and myoclonic seizures. Many children with lissencephaly have characteristic EEG changes, including diffuse high amplitude fast rhythms [99], which is considered to be highly specific for this malformation [100]. Awareness that children with XLIS have anteriorly predominant lissencephaly *(figure 2G)* and children with LIS1 have posteriorly predominant lissencephaly *(figure 2H)* [92] will facilitate more specific morphological-electroclinical correlative studies.

The main clinical manifestations of SBH are mental retardation and epilepsy. Cognitive levels range from normal to severe retardation, and correlate with MRI parameters,

above all band thickness and overlying pachygyria [68]. Patients with pachygyria have more severe ventricular enlargement and thicker bands [68]; patients with pachygyria and more severe ventricular enlargement have significantly earlier seizure onset. The more severe the pachygyria and the thicker the heterotopic band, the greater are the chances of developing Lennox-Gastaut syndrome or some other form of generalized symptomatic epilepsy. Very early seizure onset is uncommon. Overall, 65% of the patients studied had intractable seizures, often with the characteristics of Lennox-Gastaut syndrome. Using depth electrodes, Morrell *et al.*, [101] demonstrated that epileptiform activity may originate directly from the heterotopic neurons, independently of the activity of the overlying cortex. Persistent seizures causing drop attacks have been treated with callosotomy in a few patients [102, 103], with worthwhile improvement.

Autosomal recessive lissencephaly with cerebellar hypoplasia

In a recent report, Hong *et al.* [104] described two recessive pedigrees with three affected siblings each, showing moderately severe pachygyria and severe cerebellar hypoplasia. Affected children in one family had congenital lymphedema, hypotonia, severe developmental delay and generalized seizures that were controlled by drugs. Severe hypotonia, delay and seizures were also reported in the other pedigree. A splice acceptor site mutation and a deletion of exon 42 in the *reelin* gene [approved gene symbol *RELN*] were reported for these families, respectively.

Malformations due to abnormal cortical organization

Aicardi syndrome

Aicardi syndrome [105, 106] is observed in females, with the exception of two reported males with two X chromosomes [107]. It is possibly caused by an X-linked gene with lethality in the hemizygous male. Familial occurrence has been reported in one family with two affected sisters [108]. The clinical picture includes severe mental retardation, infantile spasms, chorioretinal lacunae and agenesis of the corpus callosum. Eye abnormalities and agenesis of the corpus callosum are frequently associated with translocations involving Xp22.3, suggesting a possible linkage of Aicardi syndrome to the short arm of chromosome X. The estimated survival rate is 75% at 6 years and 40% at 15 years [109]. Neuropathological findings include: 1) a thin, unlayered cortex, 2) diffuse, unlayered polymicrogyria with fused molecular layers, 3) nodular heterotopias in the periventricular region and in the centrum semiovale [110, 111]. No laminar organization is recognizable in the cortex. Additional, less frequent, malformations include

agenesis of the anterior commissure, the fornix, or both, choroid plexus cysts, colobomata, and vertebral and costal abnormalities. Specific features of Aicardi syndrome include early onset of infantile spasms and partial seizures. Spasms have been the only seizure type in 47% of 184 reported patients. In 35% of patients, spasms were associated with partial seizures [112]. Hypsarrhythmia is observed in only about 18% of patients [107]. Interictal EEG abnormalities are typically asymmetric and asynchronous (split brain EEG) with or without suppression bursts during wakefulness and sleep. Seizure and EEG patterns change little, if any, over time and seizures are almost always resistant.

Schizencephaly

Schizencephaly (cleft brain) consists of a unilateral or bilateral full thickness cleft of the cerebral hemispheres with consequent communication between the ventricle and pericerebral subarachnoid spaces *(figure 2I)*. The walls of the clefts may be widely separated and thus be called open-lip schizencephaly or closely adjacent and known as closed-lip schizencephaly. The clefts may be located in any region of the hemispheres, but are most often found in the perisylvian area [113]. Bilateral clefts are usually symmetric in location, but not necessarily in size. Septo-optic dysplasia (agenesis of the septum pellucidum and optic nerve hypoplasia) is seen in up to one third of patients [114]. Schizencephaly is a malformation that is difficult to classify. At the basis of this disorder could be regional absence of proliferation of neurons and glia. However, schizencephalic clefts are covered by polymicrogyric cortex, and unilateral clefts are often accompanied by contralateral polymicrogyria, which could indicate a disorder of cortical organization [78]. Recent reports indicate that familial occurrence [115] and a specific genetic origin due to germline mutations in the homeobox gene *EMX2* (human), are possible in some cases [116, 117]. Severe mutations (frameshift or splicing mutations) were associated with severe bilateral schizencephaly, whereas missense mutations were associated with a milder cortical abnormality [118]. These genetic data await confirmation.

Since schizencephaly has a wide spectrum of anatomical presentations, the associated clinical findings likewise cover a broad range. Patients with bilateral clefts, usually have microcephaly and severe developmental delay with spastic quadriparesis [113, 119]. Open lip clefts result in more severe impairment. Seizures, present in most patients, usually begin before 3 years of age. Unilateral clefts are accompanied by a much less severe clinical phenotype. Small, unilateral, closed lip clefts may be discovered on MRI performed after the onset of seizures in otherwise normal individuals [113]. Epilepsy is estimated to occur in 81% of patients, in equal proportion with unilateral or bilateral clefts [119]. Seizure onset before the age of 3 years and seizure intractability are more frequent when

the malformation is bilateral (81% *versus* 63% and 50% *versus* 27%, respectively). All reported patients had partial epilepsy, with no distinctive electroclinical patterns.

Polymicrogyria

The term polymicrogyria designates an excessive number of small and prominent convolutions spaced out by shallow and enlarged sulci, giving the cortical surface a lumpy aspect [77]. On MRI, it may be difficult to recognize polymicrogyria since the microconvolutions are often packed and merged [32]. Cortical infolding and secondary, irregular, thickening due to packing of microgyri are quite distinctive MRI characteristics of polymicrogyria [78, 120]. Microscopically, two types of polymicrogyria are recognized. In *unlayered polymicrogyria*, the external molecular layer is continuous and does not follow the profile of the convolutions, and the underlying neurons have radial [or vertical] distribution, but no laminar organization [121]. Its aspect suggests an early disruption of normal neuronal migration with subsequent disordered cortical organization. By contrast, *four-layered polymicrogyria* is believed to result from perfusion failure, occurring between the 20th and 24th weeks of gestation. This would lead to intracortical laminar necrosis with consequent late migration disorder and postmigratory overturning of cortical organization [122]. The two types of polymicrogyria may co-occur in contiguous cortical areas [123]. The extent of polymicrogyria varies greatly, and with it the spectrum of clinical manifestations, which includes children with severe encephalopathies and intractable epilepsy, or normal individuals with selective impairment of cognitive functions [124]. Several malformation syndromes featuring bilateral polymicrogyria have been described, including bilateral perisylvian polymicrogyria (BPP) [125], bilateral parasagittal parieto-occipital polymicrogyria [126], bilateral frontal polymicrogyria [127] and unilateral perisylvian or multilobar polymicrogyria [32]. Several distinct entities might exist with regional distribution, in which contiguous, non-overlapping areas of the cerebral cortex are involved, possibly under the influence of regionally expressed developmental genes. Consistent familial recurrence has been reported only for bilateral perisylvian polymicrogyria [128, 129].

Bilateral perisylvian polymicrogyria (BPP)

This malformation involves the gray matter bordering the sylvian fissure bilaterally, which is almost vertical and in continuity with the central or postcentral sulcus *(figure 2J)*. Neuropathological studies have been performed in 4 sporadic cases, showing four-layered polymicrogyria in three [125, 130] and unlayered polymicrogyria in one [131]. Several families with several affected members have been reported, indicating genetic heterogeneity with possible autosomal recessive [129], X-linked dominant [132] and X-linked recessive [133] inheritance. Recently, a locus for X-linked BPP was mapped to Xq28 [134]. Some cases of

polymicrogyria, including BPP, and deletion at 22q11.2 have been reported [135-137]. However, most patients with 22q11.2 deletion do not show a brain abnormality [138]. BPP has also been reported in children born from monochorionic biamniotic twin pregnancies, which were complicated by twin-twin transfusion syndrome [139, 140], indicating causal heterogeneity. Patients with BPP have facio-pharingo-glosso-masticatory diplegia [125] with dysarthria. Most have mental retardation and epilepsy. Seizures usually begin between 4 and 12 years of age and are poorly controlled in about 65% of patients. The most frequent seizure types are atypical absences, tonic or atonic drop attacks and tonic-clonic seizures *(figure 5)*, often occurring as Lennox-Gastaut-like syndromes [125, 141]. A minority of patients [26%] have partial seizures.

Bilateral parasagittal parieto-occipital polymicrogyria

This malformation was detected using MRI in a series of patients with partial epilepsy [126], most of whom had seemingly normal CT scans. The abnormal cortex extended posteriorly to involve the occipital lobe just below the parieto-occipital sulcus and anteriorly to immediately behind the precuneus and superior parietal lobule *(figure 2K)*. IQs ranged from average to mild retardation. Several patients presented deficits in neuropsychological tasks requiring performance-under-time constraints, suggesting that this malformation may result in cognitive slowing. In the reported patients, seizures had started between the ages of 20 months and 15 years (mean 9 years), and were intractable in most. Complex partial seizures were frequently seen, sometimes preceded by sensory symptoms. Automatisms were not a prominent feature of seizure semiology.

Bilateral perisylvian and parieto-occipital polymicrogyria

Some patients have bilateral perisylvian polymicrogyria extending posteriorly. The sylvian fissure is prolonged across the entire hemispheric convexity up to the mesial surface. The posterior portion of this malformation therefore bears strong similarity to parasagittal parieto-occipital polymicrogyria, and the anterior portion to perisylvian polymicrogyria. Most patients have severe epilepsy [142], the characteristics of which are similar to the bilateral perisylvian syndrome, or they may have partial epilepsy with parieto-occipital seizure-onset.

Bilateral frontal polymicrogyria

In a series of patients with bilateral frontal polymicrogyria [127] *(figure 2L)*, almost all were initially brought to medical attention because of early developmental delay or spastic quadriparesis, impaired language development and mental retardation. Epilepsy, present in about half of the patients, was mainly accompanied by complex or simple partial seizures and atypical absences, which could be controlled by drugs in most. The malformation was sporadic in all patients, but occurred in the offspring of consanguineous parents in two unrelated families, suggesting possible autosomal recessive inheritance. A form of bilateral fronto-parietal polymicrogyria with recessive inheritance has recently been mapped to chromosome 16q12.2-21 [143].

Unilateral polymicrogyria

Unilateral polymicrogyria may affect the whole hemisphere or part of it. Large malformations are associated with hypoplasia of the affected hemisphere *(figure 2M)*. Multilobar forms are most frequently located in the perisylvian cortex. Polymicrogyria apparently shown to be unilateral on MRI, may turn out to be bilateral, although asymmetric, on microscopic examination of the brain [32].

Clinical characteristics of lateralized polymicrogyria have been studied in a series of 20 patients [144]: 75% had seizures and mild to moderate hemiparesis, 70% had mild to moderate mental retardation. Hemiparesis was associated with mirror movements of the affected upper limb. This feature has been attributed to ipsilateral cortical representation of the sensorimotor hand area [145]. In patients with motor seizures, hemiparesis became more apparent as interictal discharges or seizures increased. Age at seizure onset and epilepsy severity are quite variable [144]. The most commonly reported seizure types are partial motor seizures (73%), atypical absences (47%), generalized tonic-clonic seizures (27%) and complex partial seizures (20%). Epilepsy could be classified as partial in 80% of patients and generalized in 20%. Interictal EEG findings in most patients suggested greater cortical involvement than expected from MRI. Coexistence of multiple seizure types, inclusion of the motor cortex in the epileptogenic zone, and poor delimitation of the abnormal cortex make most patients with intractable seizures and polymicrogyria unlikely candidates for epilepsy surgery.

Multilobar polymicrogyria has been observed in children with epilepsy with electrical status epilepticus during sleep (ESES), or continuous spike and waves during slow sleep - (CSWS) [141, 144, 146]. Patients with this syndrome have both partial motor and atypical absence seizures, and both focal and generalized interictal discharges. Sleep recordings show continuous generalized SW complexes during slow-wave phases. The condition is usually detected between 2 and 10 years of age and may last for months to years. The generalized spike and wave EEG pattern in ESES seems to be due to age-related, secondary bilateral synchrony [147, 148].

Seizures usually remit completely before adolescence. However, neuropsychological impairment, often emerging during the period of ESES, may persist indefinitely [149, 150]. It is likely that the extent of eventual neurop-
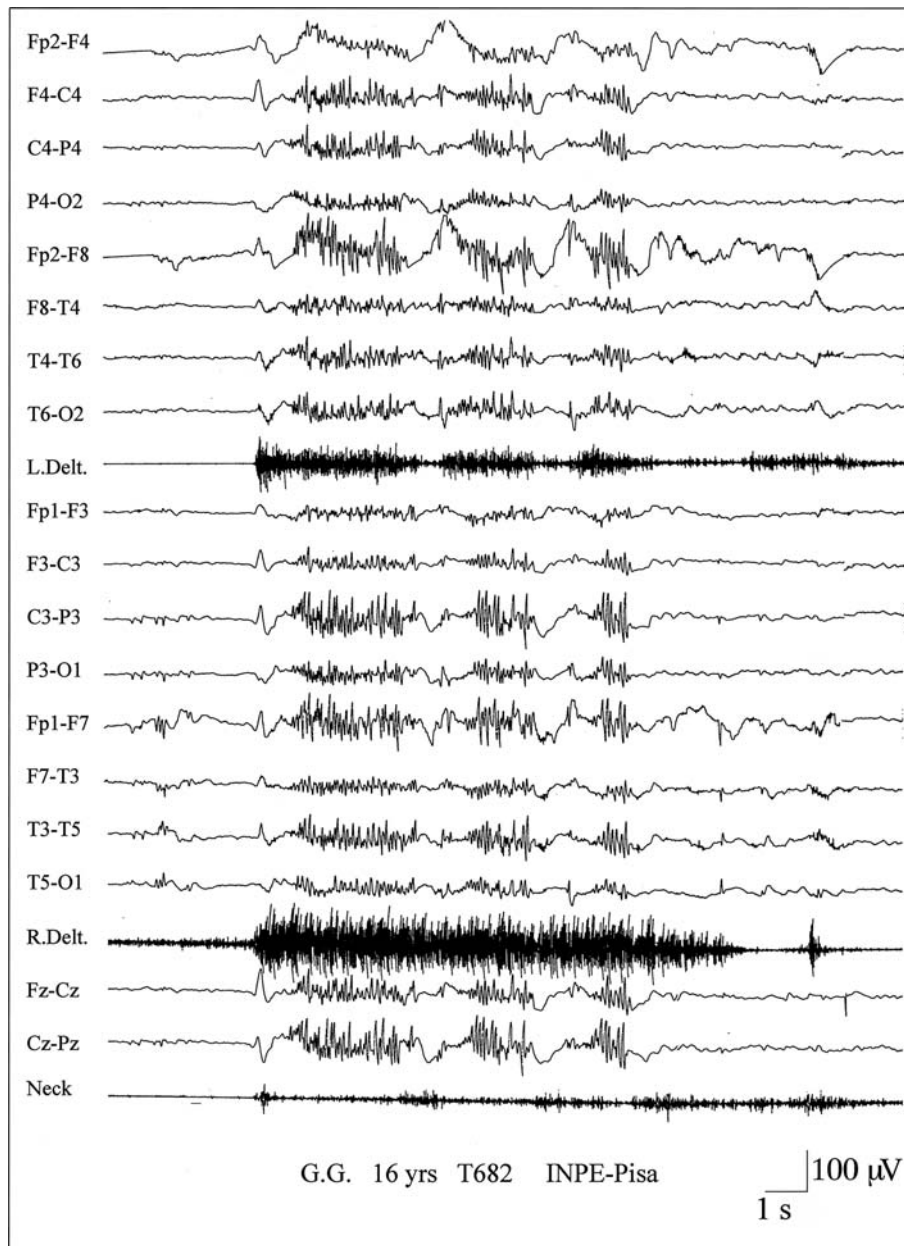
Figure 5. – *Polygraphic recording in a 16-year-old boy with bilateral perisylvian polymicrogyria and Lennox-Gastaut syndrome. The same patient as in figure 2J. A generalized tonic seizure is recorded. The EEG shows an initial sharp, diffuse complex that is followed by electrodecremental activity, rapidly evolving to a discharge of polyspikes. EMG from bilateral deltoids shows a tonic contraction starting at approximately the same time on both sides.* **Delt.** *= deltoid muscle;* **L.** *= left;* **Neck** *= neck muscles;* **R** *= right.*

sychological impairment is a function both of the underlying structural abnormality and duration of the ESES period. Although epilepsy with ESES is infrequent, its occurrence in patients with localized polymicrogyria is not rare [141, 146]. The ESES/CSWS syndrome has never been reported to date in patients with other forms of cortical malformations. In a series of nine patients whose follow-up periods extended beyond cessation of ESES,

seizure outcome was consistently good [141]. Although none of the patients exhibited demonstrable cognitive deterioration after ESES compared with pre-ESES evaluation, cognitive assessment was carried out with different methods and in different centers, which may have biased the procedures.

Although the role of resective surgery in epilepsy with ESES has not been specifically addressed, it has been

hypothesized that surgery may be effective when an underlying focal abnormality is identified [151]. However, the usually good prognosis of associated epilepsy and the inconstant association with a demonstrable, acquired neuropsychological deficit should discourage early surgical procedures in patients with ESES and polymicrogyria. Multiple subpial transections [152, 153] with selective interruption of intracortical horizontal fibres could represent a rational option in patients with unremitting ESES and incipient cognitive deterioration.

Conclusions

The clinical spectrum of epilepsy associated with malformations of the cerebral cortex is broad. Although some of the most severe forms of childhood epilepsy are caused by such malformations, intractable epilepsy is not the rule [44].

Early onset severe epilepsy seems to significantly reduce the potential for children with cortical malformations to develop an independent life [6]. Seizure improvement is possible, but long lasting remission of an intractable form of epilepsy associated with cortical dysplasia is exceptional [44, 141].

Although the advent of MRI has enabled epileptologists to discover how frequent these malformations are, structural neuroimaging still only provides limited evidence of their presence or full extent. Some electrographic patterns are highly suggestive of an underlying area of cortical dysplasia, and possibly result from high intrinsic epileptogenicity of the abnormally connected neurons. Co-localization of the structural abnormality and epileptogenic activity may help considerably in planning the area of resection. If surgical treatment is planned, the relationships between the macroscopic abnormality, microscopic changes and area of seizure origin may be very complex and depth electrode studies may be preferred in some cases. Recognition and study of cortical malformations over the last 10 years has had a major impact on the way we understand and, in part, treat non-idiopathic childhood epilepsy. □

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