Focal cortical dysplasia: Molecular disturbances and clinicopathological classification (Review)

MONIKA SIEDLECKA[1], WIESŁAWA GRAJKOWSKA[2], RYSZARD GALUS[1], BOŻENNA DEMBOWSKA-BAGIŃSKA[3] and JAROSŁAW JÓŹWIAK[1]

[1]Department of Histology and Embryology, Center for Biostructure Research, Medical University of Warsaw; Departments of [2]Pathology and [3]Oncology, The Childrens' Health Institute, Warsaw, Poland

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Abstract. Focal cortical dysplasia (FCD) is one of the most important causes of drug-resistant epilepsy in paediatric patients, particularly in those below the age of 3. Even though over 40 years have passed since the first description of the entity by Taylor, the exact mechanisms causing these cortical abnormalities remain unelucidated. In this review, we summarise the current knowledge on clinical and histopathological aspects, taking into account the new classification system proposed by the International League Against Epilepsy. We focus on the clinicopathological associations and differences in post-surgical outcome among FCD subtypes, in particular isolated FCD vs. FCD associated with principal lesions, which have not been summarised to date. We also recapitulate genetic studies, pointing to the possible mechanisms of the cortical dysregulation and drug resistance, and summarise novel factors which may contribute to epileptogenesis in FCD. Furthermore, we compare FCD type IIB (FCDIIB) with brain tumours found in a neurocutaneous disorder, tuberous sclerosis, as we evaluate the hypothesis that FCD IIB may be a local form of this disease.

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Correspondence to: Professor Jarosław Jóźwiak, Department of Histology and Embryology, Center for Biostructure Research, Medical University of Warsaw, ul. Chalubinskiego 5, 02-004 Warsaw, Poland
E-mail: jaroslaw.jozwiak@gmail.com

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1. Introduction

Malformations of cortical development (MCDs) play a major role in the aetiology of epilepsy. One of the MCD subtypes, focal cortical dysplasia (FCD), is particularly important as a frequent cause of epilepsy resistant to drugs, as approximately one half (46.5%) of patients with epilepsy has some form of this pathology (1). The disorder is the result of neuronal migration, proliferation and differentiation disruption during brain development, leading to regional cortical lamination, neuronal maturation and differentiation abnormalities. The first description of FCD in resected specimens from 10 patients treated surgically for refractory epilepsy was made by Taylor *et al* in 1971 (2). Taylor described FCD as a malformative disorganisation and dyslamination of the neocortex with the presence of giant, dysmorphic neurones and bizarre 'balloon cells', similar to giant cells in tuberous sclerosis (TS). Since then, the classification of FCD has changed, distinguishing architectural dysplasias with or without the presence of dysmorphic neurons or balloon cells (Taylor cells). None of these, however, have met the requirements of clinical practice. Additionally, some neurodevelopmental studies have shed light on the possibility of postnatal neurogenesis failure due to various pathogenic states of the brain (dysmature cerebral developmental hypothesis) as the background of epileptogenesis (3). Against this background, an ad hoc Task Force of the International League Against Epilepsy (ILAE), the Diagnostic Methods Commission, have proposed a new clinicopathological classification system to help clinical practice (4). The ILAE consensus classification included both isolated and associated FCD variants (Table I) and its recent evaluation showed good inter- and intra-observer agreement (5).

2. Aetiology and pathophysiology

The aetiology and pathogenesis of FCD is still uncertain; however, many histopathological and molecular findings point to abnormal neuronal and glial proliferation and migration

processes (see below). Several hypotheses for FCD II have been proposed. The extrinsic damage hypothesis postulates that the damage to the developing brain is made by extrinsic factors, such as ischemia, hypoxia or toxins. Alternative somatic mutation hypothesis points to a mutant cortical progenitor cell to produce a clonal population of abnormal cells, forming FCD lesions (6). The latter hypothesis seems convincing, as FCD lesions have a characteristic funnel-shaped morphological distribution, typical of clonally-related neurons, as well as the co-expression of glial and neuronal antigens in different combinations, in balloon cells and dysmorphic neurons in FCD specimens (7). Some studies have also suggested that FCD lesions originate from the abnormal retention of pre-plate cells in the subplate and marginal zones, as the consequence of the partial failure of events during late corticogenesis (3,8).

The recent study by Rossini *et al* (9) on the layer-specific gene expression in FCD II, revealed the presence of hidden cortical laminations among normal-looking neurons, but not dysmorphic neurons or balloon cells, which may suggest that only selected precursor cells could be subjected to damage during cortical development.

Recently, a number of proteins involved in the regulation of cortical development has been observed to be deregulated and the cellular distribution alterations of these proteins have been found in FCD specimens. Among these proteins are: bone morphogenic protein-4, whose expression has been found to be reduced and altered in FCD IIB and cortical tubers from TS (10); the increased expression of doublecortin-like protein, found within the dysplastic cortex of FCD IIB and cortical tubers from TS (11); a study on the expression and distribution of interleukin-2 (IL-2), IL-2 receptors (IL-2R) and the downstream factors of the IL-2 signalling pathway revealed higher IL-2 and IL-2R levels in the FCD samples vs. the control and in FCD II vs. FCD I, as well as increased levels of Janus kinases 1 and 3 in FCD (12).

The new theory of FCD pathogenesis, based on HPV16 infection and HPV16 oncoprotein E6 expression in the developing foetal brain, has been postulated by Chen *et al* (13). They demonstrated for the first time the presence of HPV16 E6 oncoprotein in FCD IIB specimens and in the human brain in general. The 100% association of HPV16 infection with FCD IIB in 50 samples resected from patients with intractable epilepsy was demonstrated; however, the authors did not find the presence of HPV16 in other types of FCD, as such an association was found only in balloon cells. In addition, the functional correlation between HPV16 E6 oncoprotein expression and focal cortical malformation development associated with enhanced mammalian target of rapamycin (mTOR) complex 1 (mTORC1) signalling in an animal model was demonstrated. A similar study by Liu *et al*, detecting HPV16 and three other viral species: cytomegalovirus, herpes simplex virus, and human herpes virus in FCD IIA, seems to support these data (14). Furthermore, it is already known that all the above-mentioned viruses are able to activate the mTOR pathway (15), which is also implicated in FCD pathogenesis. In spite of these findings, whether we can classify FCD as a viral pathology, remains uncertain, particularly, as some data contradicting this hypothesis have been published (16). It is generally known that extensive cortical malformations can be caused by prenatal infections (e.g., TORCH spectrum syndromes); however, whether more localised malformation, such as FCD may result from intrauterine infections, warrants further investigation.

3. Molecular and genetic studies

The most convincing data point to mTOR cascade abnormalities, as the cause of FCD. Some authors have suggested TS complex 1 (*TSC1*) gene involvement in FCD pathogenesis. Amino acid polymorphisms of hamartin (*TSC1* gene product), involving exons 5 and 17, and silent base substitution in exons 14 and 22, are more frequent in FCD in comparison to controls. In addition, the loss of *TSC1* heterozygosity has been reported. Hamartin, forming a complex with tuberin encoded by the TS complex 2 (*TSC2*) gene, is a negative regulator of mTOR. *TSC1*/*TSC2* mutations, or sequence alterations, lead to the loss of hamartin/tuberin protein complex activity which, in consequence, enables mTOR cascade activation, cell growth and proliferation, in response to diverse external or intracellular signals (17,18) (Fig. 1). The activation of upstream signalling pathways, e.g., protein kinase B or AKT (PKB) and exracellular signal-regulated protein kinase (ERK) pathways, results in mTOR upregulation; there are some reports on AKT pathway activation in balloon cells and, recently, one study on ERK hyperactivation in FCD IIB has been published (19-21). It has also been recently suggested that FCD may be caused by *de novo* somatic mutations of mTOR occurring during brain development (22).

It is unlikely that FCD could be connected with only one gene mutation. The alterations of Notch and Wnt pathway proteins, which are involved in neurogenesis, neuroglial cell fate determination, neuronal migration and neural tube development, have been shown to be altered as well. The study by Cotter *et al* found elevated levels of disheveled and adenomatous polyposis coli (APC) proteins, the absence of Notch-1 protein and alterations in β-catenin levels, with decreased levels of nuclear β-catenin in balloon cells (23) (Fig. 2).

As only polymorphysms or allelic *TSC* variants have been shown in FCD, and no disease-causing mutations of *TSC* genes, as well as no signalling pathway alterations specific for FCD, it is currently unjustifiable to use histopathological staining in FCD diagnoses. Such studies, however, could extend our knowledge on genetic disturbances in FCD, bringing new diagnostic options in the future.

4. Cytopathology and epileptogenesis

Balloon cells in FCD IIB have glial features and seem to arise from radial glial stem cells (3). For this reason, there is a supposition of the aberrant differentiation of these cells or possible pluripotency, with the abnormal destination of the cell (10). In addition, cell markers indicating immaturity and developmental abnormality, such as glial fibrillary acidic protein (GFAP), nestin, vimentin, CD133, CD34 are all expressed in balloon cells (7,24). Moreover, dysmorphic neurons exhibit a strong expression of phosphorylated and non-phosphorylated neurofilament proteins, maturity markers, including NeuN, as well as cell markers pointing to cell immaturity or abnormalities in development or survival (7,8,25). The above-mentioned data support the idea that the neuronal as opposed to the glial differentiation of these cells is disrupted.

Table I. Characteristics of FCD types in the ILAE classification system (25).

ILAE consensus classification system for FCDs	
FCD I: Cortical dyslamination	FCD IA: FCD with abnormal radial cortical lamination • Abundant microcolumnar organization FCD IB: FCD with abnormal tangential cortical lamination • Failure to establish a six-layered tangential composition of the isocortex • Less clear demarcation of white/grey matter transition • Cellular abnormalities (immature neurons, hypertrophic pyramidal neurons outside layer 5, disoriented dendrites) FCD IC: FCD with abnormal radial and tangential cortical lamination
FCD II: Cortical dyslamination with dysmorphic neurons	FCD IIA: FCD with dysmorphic neurons, without balloon cells • Dysmorphic neurons • Cortical dyslamination (only layer 1 is identifiable) • Usually blurred grey/white matter transition FCD IIB: FCD with dysmorphic neurons and balloon cells • Balloon cells • Dysmorphic neurons • Intermediate cells (cells of glial and neuronal features) • Cortical dyslamination • Blurred grey/white matter transition • Usually reduced myelin content in the underlying white matter
FCD III: Cortical lamination abnormalities related to additional pathology (in the adjoining area)	FCD IIIA: Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis • Patient with hippocampal sclerosis (HS; Ammon's horn sclerosis) plus: • Alterations of cytoarchitectural composition or temporal lobe sclerosis FCD IIIB: Cortical lamination abnormalities (dyslamination, hypertrophic neurons, cortical hypoplasia) adjacent to a glial or glioneuronal tumor FCD IIIC: Cortical lamination abnormalities adjacent to vascular malformation FCD IIID: Cortical lamination abnormalities adjacent to any other lesion acquired during early life (e.g., traumatic brain injury, glial scarring after ischaemia or haemorrhage, inflammatory or infectious diseases, which were not included in types IIIA-C) FCD III NOS (not otherwise specified): Focal cortical dysplasia associated with clinically suspected principal lesion, but lesion not available for histopathological examination

ILAE, International League Against Epilepsy; FCD, focal cortical dysplasia; HS, hippocampal sclerosis.

The specific morphology of balloon cells may be a result of uptriggered cellular pathways. mTOR, the central regulator of the cellular state, is a kinase responsible for the production of even 5-10% of all proteins in the cell. mTOR upregulation has been consistently found in balloon cells, which may contribute to their volume. A similar phenomenon has also been described in seemingly identical giant cells found in TS, where mTOR upregulation results usually from ERK hyperactivity (26).

Balloon cells are unable to generate epileptic discharges. They lack dendritic spines and axons, and have a very high input resistance. The newest findings suggest even their protective anti-seizure role by glutamate neutralisation, as glutamine synthetase immunopositivity in these cells, but not in dysmorphic neurons, was shown (27). On the other hand, cytomegalic neurons exhibit very low input resistance and atypical hyperexcitable properties of the intrinsic membrane, which allows the cells to generate repeated spikes after reaching firing threshold (28,29).

Several mechanisms leading to neuronal hyperexcitability and epilepsy in FCD have been postulated. There is evidence of both decreased inhibition and increased stimulation states, including the overexpression of NMDA and AMPA receptor subunits in FCD neurons, the loss of GABAergic neurons, differential composition of GABA receptor subunits, altered GABAA responses in paediatric cortical dysplasia (similar to immature cortex), as well as the dysfunction of the synaptic inhibition of pyramidal neurons due to disordered migration and the maldistribution of interneurons (3,30,31). In addition, the deregulation of cation-chloride cotransporter expression: Na^+-K^+-$2Cl^-$ cotransporter (NKCC1) and K^+-Cl^- cotransporter (KCC2), has been observed in FCD tissue (32), while other studies point to post-translational voltage potassium channel (Kv4.2) modifications (33). The authors suggested that the abnormal expression of these cotransporters in neuronal and glial cells may contribute to increased network excitability, as their distribution is comparable to the immature cortex. It is, however, not certain as to

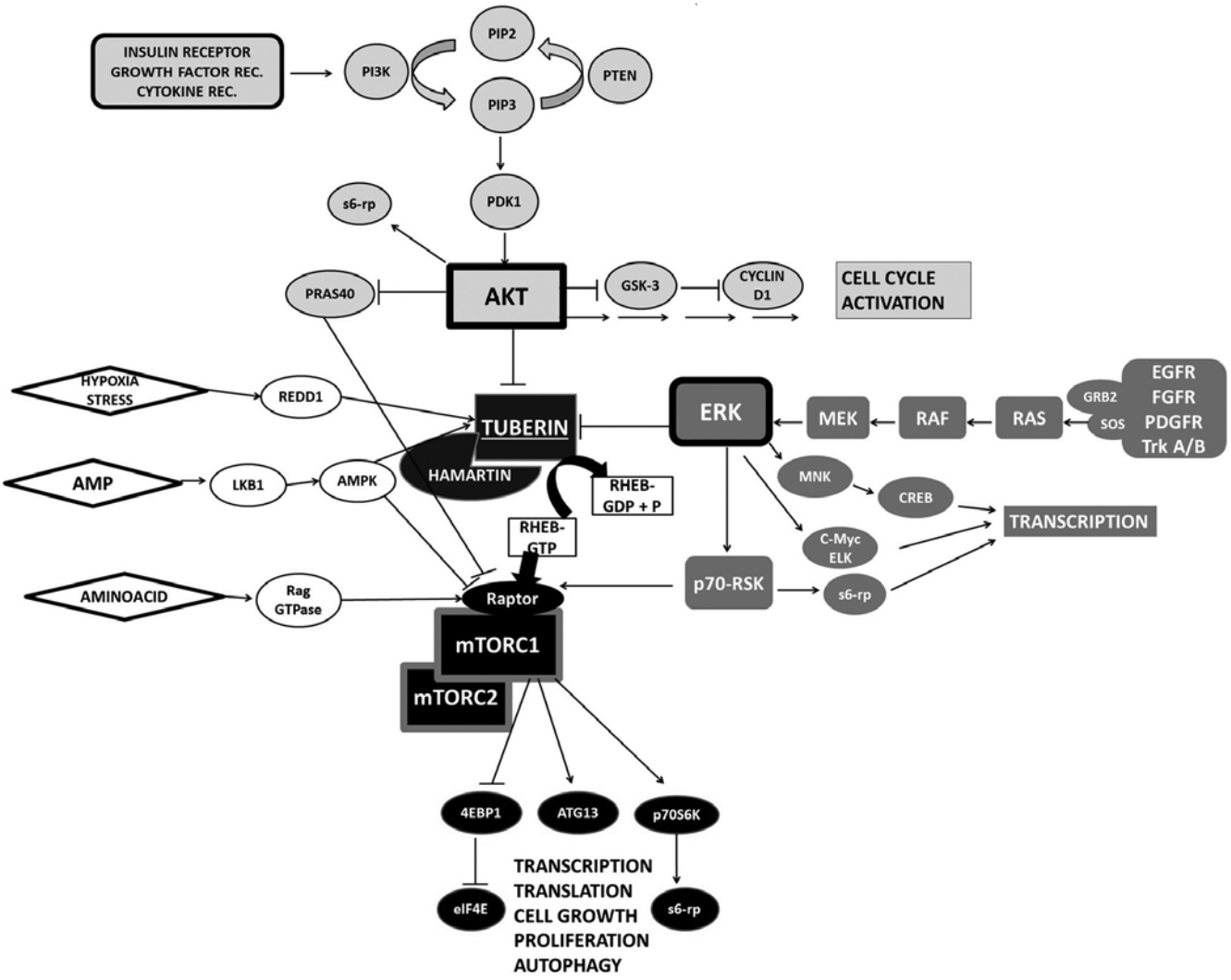

Figure 1. Upstream and downstream mammalian target of rapamycin (mTOR) regulation. Growth factor control plays a crucial role in mTOR regulation. Two main kinase cascades, AKT and exracellular signal-regulated protein kinase (ERK), mediate signal leading to phosphorylation and inhibition of tuberous sclerosis complex 2 (TSC2) which, subsequently, upregulates the mTOR activator, Rheb. mTORC1 activates S6K and inhibits 4EBP1, accelerating translation. PI3K, phosphatidylinositol 3-kinases; PIP3, phosphatidylinositol (3,4,5)-triphosphate; PDK1, 3-phosphoinositide dependent protein kinase 1; GSK-3, glycogen synthase kinase 3; Mek, mitogen-activated protein kinase kinase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; PDGFR, platelet-derived growth factor receptor; RSK, ribosomal s6 kinase; s6-rp, S6 ribosomal protein; Rheb, Ras homolog enriched in brain; Raptor, regulatory-associated protein of mTOR; AMPK, 5'AMP, activated protein kinase; 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; eIF4E, eukaryotic translation initiation factor 4E; p70S6K, ribosomal protein S6 kinase β-1; ATG13, autophagy-related protein 13.

whether this finding actively contributes to epileptogenesis in FCD and other malformations of cortical development. Finally, the activation of various inflammatory pathways connected with cells of microglial/macrophage lineage has been observed in FCD as well (34).

5. Clinical presentation

In recent years, as the entity recognition increased, rare, as it was thought, FCD became one of the most frequent pathologies in paediatric patients undergoing surgical treatment (35). It is the most prevalent lesion found in paediatric patients undergoing epilepsy surgery and is one of the three most common lesions in adult patients undergoing epilepsy surgery (35,36). Its prevalence in patients with epilepsy patients has not been ascertained. In a summary prepared by Spreafico and Blümcke, based on the European Epilepsy Brain Bank and German Reference Center for Epilepsy surgery, among 748 patients with intractable epilepsy or histopathologically confirmed MCDs, FCDs constitute >75%, with FCD IIB being the most frequent (>39%) (37).

FCDs may affect any part of the brain cortex, varying in size and location. Clinically, the most frequent symptom of FCD is drug-refractory epilepsy, beginning in most cases, in early childhood. Adult-onset epilepsy in most studies is limited to several cases (38,39). Seizures are generally of high frequency, up to dozens a day (40) and can be localised or generalise secondarily. A recent study comparing the characteristics of patients with FCD and epilepsy onset in the first year showed that the presence epileptic spasms is connected with the frontal lobe localisation of the lesion (41). The same study also found that patients with focal seizures and epileptic spasms have an earlier epilepsy onset compared to those with only partial seizures. The early onset of seizures is also

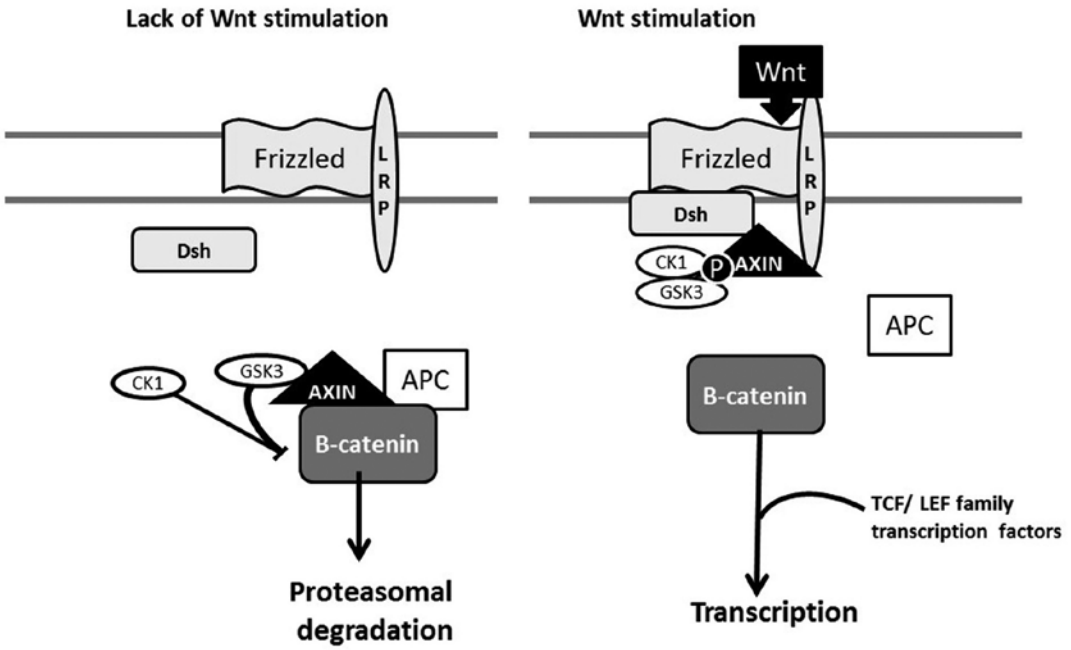

Figure 2. Wnt/β-catenin sygnaling pathway: 'off' and 'on' states. Wnt presence activates the receptor complex, leading to 'destruction complex' (APC, axin and GSK3) disassembling, axin binding to the receptor complex and β-catenin translocation to the nucleus, where it performs a variety of functions. LRP, lipoprotein receptor-related protein; Dsh, dishevelled; GSK3, glycogen synthase kinase 3; APC, adenomatous polyposis coli protein; CK1, casein kinase 1; P, phosphate.

presumed to be associated with the posterior localisation of the lesion, compared to other sitings (42). A recent FCD II subgroup analysis pointed out that FCD IIB patients have an earlier epilepsy onset in comparison with FCD IIA patients. Subtype IIB was observed predominantly in the frontal lobe and subtype IIA was more often observed in the temporal lobe (40). In cases where cortical lamination abnormalities co-exist with the principal lesion, such as glial or glioneuronal tumours (FCD IIIB), the frequency of seizures reaches 100%, particularly when the tumour is slow-growing (43). In addition, male predominance and a higher seizure frequency in tumours associated with FCDs compared to solitary tumours has been noted (44).

The clinical consequences of FCD are also congnitive impairment and neurological deficits, as well as a decrease in intelligence quotient (IQ) in the majority of patients (42). It is thought that the grade of this deficit and the clinical manifestations of the disorder correlate with lesion localisation, size as well as subtype. In the study by Widdess-Walsh *et al*, cognitive impairment was observed more often in FCD II (42). Moreover, the study by Krsek *et al* showed that 96% of FCD I patients had mental retardation, with 55% of patients retarded severely (IQ <35), while in FCD II, the proportion was 67 and 27%, respectively (45). Patients with FCD I also exhibit higher maladaptive scales, whilst behavioural disorders due to brain dysfunction are not observed in FCD II patients at all. Psychiatric features have been observed to be connected with the early onset and the posterior localisation of the lesion. A minor delay in development and normal development are associated with patients with more circumscribed lesions. Early onset is more frequently associated with mild to severe mental retardation and more often leads to adverse outcomes in comparison with adult-onset seizures (46).

6. Imaging

Magnetic resonance imaging studies allow the separation of FCD IIB from other cortical dysplasias. The indicative features are local cortical thickening, blurring of the white-grey matter interface and the focally increased signal of the subcortical white matter on T2-weighted imaging, often tapering toward the underlying ventricle ('transmantle sign'-nearly unique for FCD IIB) (47).

As the neuroimaging techniques became more advanced and precise, the identification of the lesion is more prevalent and classification is easier. Still, however, there are cases with pathologically proven FCD without any abnormalities in neuroimaging studies.

The recent study by Colombo *et al*, reviewing retrospectively MR images of 118 FCD II patients, showed that the MRI abnormalities were present in 79% of cases, whilst the correct diagnosis of FCD II, made on the basis of abnormal MRI scans, was made in 89% of patients. A strong correlation between the transmantle sign and FCD IIB was emphasised (48). Recently, Mühlebner *et al* pointed to some quantitative parameters, which may be useful for the higher sensitivity of MRI evaluation in patients with drug-resistant focal epilepsy (49). Other recent studies have demonstrated the predominance of morphometric MRI analysis as more sensitive for FCD II detection than conventional visual analysis alone (50). Lately, the Arterial Spin Labeling MRI technique, evaluating the cerebral perfusion abnormalities during interictal periods, turned out to be helpful in the evaluation of epileptic zones in FCD patients (51). Furthermore, novel techniques of ShearWave elastography and magnetoencephalography have been demonstrated to detect MRI-negative FCD lesions, facilitating presurgical evaluation (52). Finally, in uncertain situations, functional

neuroimaging techniques, including ictal SPECT or FDG-PET, are used.

7. Treatment

FCD treatment depends on individual patient presentation and remains mainly symptomatic, including cognitive and neurological deficit therapy, as well as epilepsy management. As epilepsy in FCD is commonly pharmacoresistant, and the basis of the resistance seem to be multifactorial, anti-epileptic treatment is particularly challenging, and should reflect different therapeutic strategies.

One of these strategies involves well-known mediators of drug resistance: multidrug resistance gene-1 P-glycoprotein (MDR1) and multidrug resistance-associated protein 1 (MRP1). These participate in the formation of blood-cerebrospinal fluid (CSF) and blood-brain barriers, and in FCD lesions they have been found to be overexpressed in many brain tissue components of the epileptogenic zone (53). They have been found to be most frequently expressed in glial fibrillary acidic protein-positive balloon cells (glial type) and microtubule-associated protein 2-positive balloon cells (neuronal type) (54). In addition, major vault protein, a protein associated with drug resistance, was found to be upregulated in dysmorphic neurons in FCD (55). Therefore, in order to design the treatment for drug-resistant seizures, specific knowledge on the above-mentioned proteins seems to be of uttermost significance.

Secondly, mTOR pathway inhibitors may be a novel targeted therapeutic option for epilepsy in FCD. Due to mTOR signalling dysregulation, FCD is sometimes termed 'mTORopathy'. As the mTOR pathway is involved in protein synthesis, its activity abnormalities may promote neurotransmitter receptor or ion channel alterations and, consequently, neuronal hiperexcitability, leading to epileptogenesis (at least in animal models) (56,57). mTOR inhibitors, such as rapamycin or everolimus, are used in the treatment of another 'mTORopathy', TS. Their potential anti-epileptogenic and disease-modifying effects have been described and their learning deficit-reversing activity has been demonstrated in a mouse model (58,59). Finally, other recent studies, pointing to the link between FCD and HPV16, may also, potentially, identify some novel therapeutic strategies for the prevention of FCD (13). Molecular and genetic studies, however, are still required and should bring new concepts of efficient therapies.

At the moment, the treatment of choice for epileptogenic, drug-resistant lesions, is surgical resection. Its long-term efficacy and safety in certain ILAE classification subgroups is evaluated in order to determine the associations between pathological subtypes and clinical relevance and prognosis. Particularly, type III FCD and its post-surgical outcome needs to be evaluated according to the new classification, as it was not specified previously.

Surgical resection of the epileptic lesion may not only liberate patients from seizures, but also has a positive effect on cognition and intellectual outcomes, improving full-scale IQ (60). Early surgical intervention in children with complete resection of the epileptogenic lesion seems to be of particular importance. If accomplished before two years of seizure duration, it not only leads to better seizure control, but it also improves cognitive function development and quality of life (61).

Failure to achieve a seizure-free state is often due to incomplete cortical resection. However, a recent study by Wagner *et al* showed that subcortical hyperintense zone resection is not essential for a positive post-operative outcome, which may reduce the risk of surgery (62), whilst according to the study by Mühlebner *et al*, complete resection of the lesion is the only predictor of surgical outcome, irrespective of the ILAE subtype (63). Other predictors of surgical outcome are also pre-operative seizure frequency, pre-operative ability of epileptogenic focus localisation in imaging techniques, multilobar lesion and dual pathology presence (64).

8. Clinicopathological associations and outcome

As a series of factors affects epilepsy surgery outcomes, it is hard to compare particular studies to one another. The probability of being free from seizures ranges in different studies, and on average, seizure recurrence affects approximately one half of patients treated surgically (65-68). Seizure outcome depends, however, on the time after surgery, and Kapplan-Meier curves (in the above-mentioned and other similar studies) analysis points at the highest epilepsy recurrence frequency within the first 3 years after surgery. A recent study by Ryzi *et al* (69) showed however, that approximately 30% of patients with seizure recurrence within one year after surgery remained seizure-free in a long term observation (at least 5 years) and the next 18% has auras only. Such data are, though, only general predictions for the patient, and recently, Jehi *et al* elaborated some nomograms for individualised predictions of post-surgical seizure outcome (66).

The seizure-free post-operative outcome rate in FCD varies in different reports and the proportion ranged from approximately 50 to 83% in a recent study by Tassi *et al* (70). The meta-analysis by Rowland *et al* (71) presented freedom from seizures in 58% of patients out of a group of over 2,000 patients with FCD-related epilepsy. The result is not, however, stable in time. According to Mrelashvili *et al* (65) about one third of patients has early seizure recurrence (<3 months), with a median recurrence time of 38 months.

As far as FCD subtypes associated with principal lesions are concerned, their clinical presentation seems to have similar characteristics to epilepsy associated with isolated principal lesions, as well as at least similar (and often better) outcomes, in comparison to isolated FCD I cases (44,72-76). According to the most recent study by Fauser *et al* (77), there are no statistical differences in the outcome in FCD I, II and IIIA patients. The rate of (Engel's) class I post-operative results (i.e., patient free of disabling seizures) in this largest FCD patient cohort reported to date, was 65% after one year, and remained stable over time. The authors also noted higher numbers of febrile seizures and auras in FCD IIIA, compared to FCD I and II, which is also supported by the literature (72,76).

In another recent study by Giulioni *et al* (75), patients with hippocampal sclerosis associated with FCD I (i.e., FCD IIIA) showed a similar seizure outcome to patients with isolated hippocampal sclerosis (84 vs. 82%, respectively) and had better seizure outcome than patients with isolated FCD I (63%). FCD IIIA was also the most common pathology. Aforegoing and other similar findings [e.g., Thom *et al* (80) or Tassi *et al* (78,79)] are in contrast with the controversial results obtained recently

by Johnson *et al* (81). In the study by Johnson *et al*, FCD IIIA had the poorest seizure outcome, compared to major pathologies: isolated hippocampal sclerosis (HS) and isolated tumours, and similar to temporal FCD I. The presented data contradict the ILAE classification. However, there was similar electroclinical presentation between FCD IIIA and HS, taking into account e.g., the frequency of seizures, the age of epilepsy onset or the presence of auras. In the letter to the editor, Giulioni *et al* commented on this study critically (73).

Other associated FCD subtypes also seem to have a good prognosis. Santos *et al* (75) pointed to a very good seizure outcome of FCD IIIB (Engel I rate of 87%) following appropriate surgical resection. In their study, a better outcome was connected with the extended resection of the tumour and the whole area of epileptogenicity. Another study by Cossu *et al* (44) compared the outcome between associated and isolated forms of FCD, finding that the solitary FCD I outcome is worse than FCD IIIB or FCD II associated with tumours (47 vs. 83 vs. 76%, respectively). The clinical characteristics and outcome in tumour-associated FCDs in that study was more similar to the cases of solitary tumour than FCD I, which is consistent with results obtained by the above-mentioned authors (74,78-80).

There is not much information on the outcome in FCD IIIC and FCD IIID subtypes. One of the latest studies suggests that FCD IIIC differs from the other FCD III subtypes (76). In that study, the mean age of epilepsy in FCD III C was higher than in other FCD III types and was similar to that of vascular malformations in the temporal lobe. The duration of epilepsy in FCD III B and III C was shorter than that in other associated types. The characteristics of epilepsy in these subtypes were similar to the seizures associated with isolated principal lesions.

Little is known about the clinicopathological associations of FCD IIID. In one study (76) on a group of FCD IIID patients, six had traumatic brain injury, three patients had glial scarring after perinatal ischaemic injury, and two patients underwent infections. The mean age of epilepsy onset in this group was 14 years and the seizure frequency was not higher than in other subtypes. There is, unfortunately, no information on seizure outcome in these patients.

As far as FCD I and II is concerned, there is much literature on prognosis in these subtypes, as it had been present in previous classifications. The study by Simpson and Prayson, taking into consideration the ILAE classification, including the new FCD IC subtype, did not reveal any differences in Engel I rate after surgery, which was 48%, in all three FCD I subtypes (82). The outcome in FCD II cases is better, it fluctuates between 50-88% (40,71). There is a higher seizure outcome in FCD IIB, compared to FCD IIA, and there is no correlation between outcome and age at onset or the duration of epilepsy (71).

To sum up these findings, FCD III outcome is rather similar to that in isolated principal lesions connected with particular subtypes and seems distinct from FCD I and II. In particular, the difference between a relatively good seizure outcome in FCD IIIA and a worse outcome in isolated FCD I suggests that in FCD III, the principal lesion is a very important factor of the outcome. A summary of the largest recent studies on the post-surgical seizure outcome in epilepsy due to FCD and other causes is presented in Table II.

9. FCD IIB: local form of tuberous sclerosis?

Taylor *et al* observed a histological similarity between FCD and TS, and postulated it to be an attenuate or atypical form of TS (2). Nowadays, after over 40 years, this issue is still under investigation, and it is sometimes assumed that FCD IIB may be a local form of TS (83,84).

Histomorphologically, balloon cells found in FCD and giant cells in TS are similar (85). Common TS brain lesions, subependymal giant cell tumour (SGCT), subependymal nodules and cortical tubers, as well as FCD IIB lesions express both neuronal and glial characteristics (7,86). This suggests that the above lesions originate from progenitor, undifferentiated cells, which either remain undifferentiated or tend to pursue one of three possible directions: differentiation as neuronal cells, glial (astrocytic) cells or cells of mixed glio-neuronal features (24,86). Immunohistochemical studies on balloon and giant cells have shown the expression of the same markers (e.g., CD34, nestin, wimentin, GFAP and doublecortin) (86,87). In addition, a strong MDR-1 and MRP-1 immunoreactivity was shown to be present in giant and other tuber cells of TS epileptogenic lesions, which (similarly to FCD), can possibly explain the drug resistance of epilepsy (88).

Apart from immunohistochemical markers, there are other molecular and morphological similarities between brain tumours in TS and FCD IIB. It is already known that mutations or genetic alterations of *TSC1* and *TSC2* suppressor genes are involved in the pathogenesis of both TS and FCDIIB (17,89). Both TS and FCD are mTORopathies, as the development of balloon and giant cells probably results from mTOR activation. Recent studies point also to apoptosis signalling pathways and the activation of neurodegeneration in both FCD II and TS (90), as well as at the defect in autophagy, both in balloon cells in FCD and TS cells, connected with abnormal mTOR activation and reversible by mTOR inhibition (91,92). Indeed, mTOR is responsible for the control over protein translation, and mTOR activation leads to hypertrophy of the cell (93). Thus, morphological similarity between balloon and giant cells may be a sign of mTOR activation.

The recent study by Kotulska *et al* also revealed the clinical association between TSC presentation and FCD presence. Patients with FCD have more severe epilepsy with higher drug-resistance as well as more severe mental retardation (94).

The above similarities suggest that both TS and FCD IIB may be pathogenically identical malformations, with FCD IIB being focal form of TS in CNS. However, in order to make a consistent statement, further molecular and genetic studies are required.

10. Conclusions

In the present review, we discuss different forms of FCD, specifying the similarities and differences between them. In light of recent findings, we also describe the molecular mechanisms leading to the development of the lesion e.g., the most convincing data point to mTOR cascade abnormalities, as the cause of FCD. As far as clinicopathological associations and outcome are concerned, we review current data, while focusing on the outcome data for FCD III, which has not been summarised to date, at least to the best of our knowledge. Finally, we describe

Table II. Post-surgical seizure outcome in epilepsy due to FCD and other causes, in recent studies (40,44,64,67,68,70,71,75,87-90).

	Post-surgical seizure outcome in FCD (regarding FCD subtype)	
Authors/(Refs.)	Surgical outcome Engel I class: % of PTS	Follow-up data
Fauser *et al* (77)	Total: 65 FCD I: 61 FCD II: 67 FCD IIIA: 65	5-year follow-up; outcome stable over time
Simpson and Prayson (82)	FCD I: 48	Median follow-up: 63 months (32-93 months); Total follow-up of all the patients: 58 months
Yao *et al* (40)	FCD IIA: 50 FCD IIB: 75	Mean follow-up: 2.5 years
Santos *et al* (75)	FCD IIIB: 87	5-year follow-up
Cossu *et al* (44)	FCD I: 47 FCD II: 84 FCD II + tumour 76 FCD IIIB: 83	No data on mean follow-up available
Giulioni *et al* (74)	FCD I: 63 HS: 82 FCD IIIA: 84	Mean follow-up: 6 years
Tassi *et al* (70)	Total: 83 FCDIIA: 74 FCD IIB: 88	Mean follow-up: 81 months; very rare seizure recurrences
Tassi *et al* (78)	Isolated FCD I: 46 FCD I + HS: 82 FCD I + tumour: 82	At least 2-year follow-up
	General post-surgical seizure outcome in epilepsy	
Authors/(Refs.)	Surgical outcome: %	Follow-up and other information
Jehi *et al* (66)	Baseline risk of seizure freedom: 0.52 at 2 years, 0.4 at 5 years; Baseline risk of Engel I score: 0.69 at 2 years, 0.62 at 5 years.	27% of studied patients had MCD-related epilepsy; Median follow up: 3.3 years
Mrelashvili *et al* (65)	Engel I: 53 Engel I/II: 21 Engel III/IV: 26 Early recurrence: 32 Median recurrence: 38 months	FCD-related epilepsy; Median time to last follow up: 13.5 months;
Simasathien *et al* (68)	Engel I: 57 Overall seizure-free probability: After 1 year: 66 After 2 years: 52 After 5 years: 33	59% of studied patients had MCD-related frontal lobe epilepsy; mean follow up: 4.3 years;
Bulacio *et al* (67)	Ovarall seizure-free probability: After 1 year: 61 After 5 years: 42 After 10 years: 33	Various causes of epilepsy were taken into consideration Comparable results in the group with cortical dysplasia only

FCD, focal cortical dysplasia; HS, hippocampal sclerosis; MCD, malformation of cortical development; PTS, patients.

why FCD IIB is sometimes known as the local form of TS, and what are the similarities between the two entities.

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