Focal cortical dysplasia – review

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Summary

Focal cortical dysplasia is a malformation of cortical development, which is the most common cause of medically refractory epilepsy in the pediatric population and the second/third most common etiology of medically intractable seizures in adults.

Both genetic and acquired factors are involved in the pathogenesis of cortical dysplasia. Numerous classifications of the complex structural abnormalities of focal cortical dysplasia have been proposed – from Taylor et al. in 1971 to the last modification of Palmini classification made by Blumcke in 2011. In general, three types of cortical dysplasia are recognized.

Type I focal cortical dysplasia with mild symptomatic expression and late onset, is more often seen in adults, with changes present in the temporal lobe.

Clinical symptoms are more severe in type II of cortical dysplasia usually seen in children. In this type, more extensive changes occur outside the temporal lobe with predilection for the frontal lobes.

New type III is one of the above dysplasias with associated another principal lesion as hippocampal sclerosis, tumor, vascular malformation or acquired pathology during early life.

Brain MRI imaging shows abnormalities in the majority of type II dysplasias and in only some of type I cortical dysplasias.

The most common findings on MRI imaging include: focal cortical thickening or thinning, areas of focal brain atrophy, blurring of the gray-white junction, increased signal on T2- and FLAIR-weighted images in the gray and subcortical white matter often tapering toward the ventricle. On the basis of the MRI findings, it is possible to differentiate between type I and type II cortical dysplasia. A complete resection of the epileptogenic zone is required for seizure-free life. MRI imaging is very helpful to identify those patients who are likely to benefit from surgical treatment in a group of patients with drug-resistant epilepsy.

However, in type I cortical dysplasia, MR imaging is often normal, and also in both types the lesion seen on MRI may be smaller than the seizure-generating region seen in the EEG. The abnormalities may also involve vital for life brain parts, where curative surgery will not be an option. Therefore, other diagnostic imaging techniques such as FDG PET, MEG, DTI and intra-cranial EEG are widely used to establish the diagnosis and to decide on management.

With advances in both genetics and neuroimaging, we may develop a better understanding of patients with drug-resistant epilepsy, which will help us to provide more successful pharmacological and/or surgical treatment in the future.

Key words: focal cortical dysplasia • FCD • epilepsy

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Background

Focal cortical dysplasia is not very well known and still rarely diagnosed in Poland. It is responsible for nearly half of intractable epilepsy cases in children and adults, and at the same time it is characterized by quite good treatment outcome. Focal cortical dysplasia was first distinguished from developmental malformations in 10 patients by Taylor and colleagues in 1971 and its classification has been subjected to several modifications ever since. The continuous improvement of neuroimaging techniques providing more precise assessment of pathological lesions creates a chance for good surgical treatment outcome. Rapid development of new branches of science, such as genetics and diagnostics, implicates the need for reconsideration of the disease, as nowadays treatment methods of this disease give patients hope for recovery.

Pathomorphology

Focal cortical dysplasia (FCD) forms a very heterogeneous group of cortical lesions. In the literature it is described as malformation of cortical development, cortical dysplasia, cortical dysgenesis or neuronal migration disorder. FCD encompasses multiple types of alterations: 1. Cortical architecture abnormalities – columnar disorganization (formation of vertically oriented microcolumns consisting of at least 8 neurons) and laminar disruption (alterations in 6-layered tangential composition of the cortex). 2. Cytological abnormalities: – hypertrophic neuron cells – outside typical location in layer V, – immature neurons – round or oval cells with large nucleus and thin rim of cytoplasm, absent in matured cortex, – dysmorphic neurons – with abnormal size and morphology of axons and dendrites, as well as increased accumulation of neurofilament proteins, – balloon cells – pathognomonic for Taylor-type dysplasia (described by Taylor for the first time in 1971) [1], usually large cells with ill-defined membrane, single or multiple eccentric nuclei and eosinophilic cytoplasm, demonstrating immunohistochemical features of neuronal and glial lineage [2].

Since the first description of this entity, several attempts have been made for the last 40 years to classify the huge variety of histopathological findings. The most widely accepted was the scheme according to Barkovich, recently modified in 2005 [3,4] classifying FCD among developmental malformations in group Ib – Non-neoplastic malformations due to abnormal neuronal and glial proliferation or apoptosis, and IIb – Malformations due to abnormal cortical organization. The most commonly used histopathological classification until now [2,5] distinguished two types of focal cortical dysplasia. Type I (benign) – characterized by isolated architectural abnormality – Ia or with additional abnormal cells (such as hypertrophic cells and immature neurons) – Ib. Type II (Taylor) – encompassing larger abnormalities with dislayering and additional presence of dysmorphic neurons – type Ia or balloon cells – type Ib. Focal cortical dysplasia was frequently found in hippocampal atrophy [6] or neoplastic developmental tumors (DNET, ganglioglioma) or in posttraumatic and postischemic patients (Table 1).

Several months ago, an international group of experts [7] modified the recent Palmini classification, distinguishing three types of focal cortical dysplasia:

Type I – malformation presenting with abnormal cortical layering as a result of abnormal radial migration and maturation of neurons (FCD Type Ia) or disruption of typical 6-layered tangential composition of the cortex with immature neurons (FCD Type Ib) or compromising both architectural abnormalities (FCD Type Ic).

Type II – malformation resulting from disrupted cortical lamination and specific cytological abnormalities, Type IIa with dysmorphic neurons and Type IIb with dysmorphic neurons and balloon cells.

Type III – malformation connected with different cortical dislamination and cytological abnormalities with main lesion within the same area/lobe. Type IIIa – cortical dislayering with hippocampal atrophy, IIIb – with glial or glioneuronal tumors (DNET, ganglioglioma), IIIc – with vascular malformations (as hemangiomas, arteriovenous malformations, telangiectasias, etc), IIId – acquired at early age (trauma, ischemia or perinatal hemorrhage, infectious or inflammatory diseases) and other non-classified (Table 2).

Genetics

Genetic aspects of focal cortical dysplasia are not fully investigated, mainly due to the limited number of cases and lack of proper experimental model. More extensive future studies will certainly shed more light on this problem. There are reports of familial FCD [8] with early onset.

Table 1. Palmini classification of focal cortical dysplasia.

| Type   | Characteristic features                                      |
|--------|-------------------------------------------------------------|
| Ia     | Heteropic neurons within white matter. Architectural distortion of cortical layer |
| Ib     | Heteropic neurons within white matter. Architectural distortion of cortical layer Giant neurons |
| IIa    | Heteropic neurons within white matter. Architectural distortion of cortical layer Giant neurons. Dysmorphic neurons |
| IIb    | Heteropic neurons within white matter. Architectural distortion of cortical layer Giant neurons. Dysmorphic neurons Balloon cells |
Focal cortical dysplasia may involve any part of the brain, may vary in size and location and may be multifocal [14]. Epilepsy is the main symptom of dysplasia, sometimes associated with mental retardation, particularly with early seizure onset. There are no significant neurological deficits despite large areas of brain tissue occupied by a lesion. Symptoms appear at any age, mostly in childhood, but also occur in adults. Epilepsy is usually drug-resistant.

In patients with FCD type II manifest earlier onset comparing to type I [2,15]. Similarly, earlier onset is observed in patients with a larger focus on brain MRI as compared to patients with smaller lesions. According to the literature, focal cortical dysplasia type I is related to temporal lobe seizures [5,16]. In patients with FCD type II, multilobar lesions are found, involving hemisphere, often with extratemporal location and mainly in the frontal lobe. Therefore seizures with early onset in neonatal period or childhood are more likely FCD type II with multilobar or hemispheric lesion, while FCD type I with a small focus, usually in the temporal lobe, predominates in adults [15,17].

The regular, surface EEG recording is characterized by low specificity for focal cortical dysplasia.

### Neuroimaging

**Magnetic Resonance Imaging**

Most commonly used imaging technique for assessing brain pathology in focal cortical dysplasia is MRI. It is performed as a whole-brain study, transverse T2-weighted, coronal T2-weighted TSE, coronal FLAIR and coronal IR T1-weighted sequences. In most of the patients volume 3D-FSE T1 is also performed. If necessary, sagittal T2 and FLAIR sequences are obtained. Other techniques, well-defining the white matter – gray matter junction are also helpful, as well as the automatic computed methods like morphometry, allowing the assessment of atrophy and ill-defined lesions of increased signal intensity within cortex [18,19]. Occasionally, lesions within temporal lobe are examined – transverse images parallel and coronal images perpendicular to the long axis of hippocampus. In some patients, an i.v. contrast medium can be used if tumor is suspected, but it is not required for diagnosis [5,20].

Many authors tried to define specific MRI features for focal cortical dysplasia [5,7,16,20–27]. The characteristic findings are as follows: cortical thickening, blurring of white matter – gray matter junction with abnormal architecture of subcortical layer, altered signal from white matter with or without the penetration through cortex (transmantel sign), altered signal from gray matter, abnormal sulcal or gyral pattern and segmental and/or lobar hypoplasia/atrophy.

In each type of FCD, images are as follows:

- FCD type I – significant segmental or lobar hypoplasia/atrophy often coexistent with reduced volume of
subcortical white matter, which may reveal moderately increased signal on T2-weighted images, significantly increased on FLAIR and decreased on T1, 3D volume GE T1, and significantly decreased on T1 IR. Slight blurring...
of GM/WM junction and abnormal sulcal and gyral pattern may be observed as well. Focal cortical dysplasia type I is frequently found in the temporal lobe with coexistent hippocampal atrophy according to Palmini et al. (2005), while Blumcke et al. (2011) distinguished a new type – IIIa (Figure 1).

There are no essential differences between MR images of type Ia and type Ib. However, type Ib is more often located outside the temporal lobe (for this reason, it is difficult to differentiate it from FCD type II) (Figure 2).

- FCD type II is characterized by cortical thickening, marked blurring of GM/WM junction, and in some patients with a slight increase of white matter signal on T2-weighted images, significant increase on FLAIR, decrease on T1, 3D volume GE T1 and significant decrease on T1 IR images. Altered white matter signal is often extended towards the ventricle (transmantle sign), which is observed exclusively in FCD type II. As a rule, blurring of GM/WM junction is usually more evident than in type I. Abnormal sulci and gyri are often found, clearly visualized by surface 3D. Perivascular space may also be enlarged (Figures 3,4).

The increased signal from gray matter on T2-weighted images is more evident in type II than type I. Nevertheless cortex remains more hypointense than white matter. There are no features distinguishing type IIa and IIb despite more evident demarcation of type IIb lesion comparing to other types.

FCD type II is more often found in extratemporal locations with predilection towards frontal lobe.

Lesions in FCD associated with developmental tumors, such as DNET or ganglioglioma, are currently classified as IIIb according to Blumcke et al. 2011 and characterized by a positive mass effect, cystic component, various calcifications and contrast enhancement. Dysplastic lesions are usually located peripherally in relation to tumor. However they may be located within the main lesion (Figure 5).

Occasionally, FCD may remain invisible on MRI, usually in type I [28]. Moreover, the affected area of the brain can be larger than lesion revealed by MRI, which can be a possible cause of poorer postoperative outcomes if surgery is based on the MRI data solely [29,30]. For that reason, despite MRI visualization of FCD, other methods of precise preoperative selection of patients are required.

**FDG-PET**

As it turned out, patients with unrevealing MRI and EEG show reduced metabolism within the areas affected by dysplasia [32–34] (Figure 6).
Additionally, in recent years this method has been improved by FDG-PET/MR fusion technique that has resulted in higher sensitivity (up to 98%) for FCD, especially in patients with benign FCD type I and normal MRI [35]. FDG-PET study has become a useful tool for preoperative FCD detection in patients with intractable epilepsy and normal or less specific findings on MRI. It has resulted in better surgery outcomes and longer seizure-free periods postoperatively [36].

There are also reports suggesting that ictal SPECT may localize a dysplastic focus in patients with normal MRI [37].

**Magnetoencephalography (MEG)**

Non-invasive technique showing electric activity of brain by registration of the magnetic field induced by cortex has been used intraictally for brain mapping in order to find and assess the size of epileptogenic focus. In addition, the data obtained by MEG can be fused with MR images helping to localize abnormal discharges in patients with intractable epilepsy and normal results in other examinations. Some reports point that this method may also allow to differentiate FCD type I and II [38].

Moreover, MEG localizes anatomically the functional areas: sensory, motor and speech [39], which could be spared during operation in order to improve the quality of life after surgical treatment.

**Diffusion Tensor Imaging (DTI)**

Analyzing the diffusion process of free water molecules in brain using MRI, we may assess a cerebral microstructure (diffusion is restricted due to crossing fibers, large number of cells, demyelination or gliosis) and track the fibers – tractography – (the perpendicular water diffusion is more restricted than parallel diffusion along the fibers orientation). Therefore DTI can be used for assessing the extension of cortical dysplasia (with disrupted white matter structure, abnormal myelination, gliosis and increased number of cells, such as heterotopic neurons) which often appears larger than lesion revealed by conventional MRI and in patients with normal MRI [40,41]. There is no possibility to differentiate between other abnormalities of cortical development, neither to assess the histopathological correlation between particular FCD types. It is also uninformative, whether revealed lesions are primary – causing dysplasia, or occurring as result of repeating seizures locally and along the epileptic network.

The second method, tractography, allows the neurosurgeon to plan the operation basing on the assessment of anatomical relations between dysplastic focus and fiber bundles of eloquent centers.
DWI technique is helpful in determining the microstructure of affected brain and fiber tracts. However, more a precise connection with histopathology of the lesion must be elaborated.

**Intracranial EEG (electrocorticography)**

Intracranial EEG can be performed if methods described above are insufficient to determine the epileptogenic focus. Intracranial electrodes are implanted registering an ictal or interictal activity in order to find epileptogenic zone. This method is also used intraoperatively allowing a precise selection of tissue for resection.

**Surgical Treatment**

Epileptic seizures in focal cortical dysplasia are difficult to control with pharmacological treatment and often intractable. Hence, the surgical treatment appears to be a next therapeutic procedure. The resection of lesion, lobectomies and even hemispherectomies are performed. More limited surgeries are performed in elderly patients, usually due to FCD type I, usually located within the temporal lobe [44]. Younger patients usually have FCD type II, with more extensive lesions and extratemporal location, predominantly in the frontal areas. In these cases operation includes lobectomy/ies or even hemispherectomy [25]. There is no prove for gender or side predilection [45].

According to the literature, 60–80% of patients remain seizure-free after surgery, depending on the study center [25]. Most favorable prognostic factor is a total resection, defined as the resection of lesion visible on MRI or epileptic focus determined by intracranial EEG. Unfortunately, according to different authors, subtotal resection is seen in approximately 30% of patients [17,46] with seizure relapsing after only 6 months [45].

The most frequent cause of unsuccessful surgical treatment is lesions invisible on MRI or located within vital and neurologically important structures – sensomotoric or speech-related [47]. Poorer outcome is also observed in extratemporal location of the lesion, ill-defined epileptic focus, secondarily generalized tonic-clonic seizures, intracranial electrodes application and extensive resections [45,46,48]. Postoperative mortality for these surgeries is low. The most common transient postoperative complications include small neurological deficits and infections.

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**Figure 5.** Focal cortical dysplasia type Ib associated with dysembryoplastic neuroepithelial tumor (DNET) in a 3-year-old boy by Blumcke IIIb. MR coronal TSE IR TWI (A,B); coronal TSE FLAIR T2WI (C,D) and coronal TSE T2WI (E,F). Histology slides (G,H). Diffuse abnormal hyperintensity of white matter in the right temporal lobe, with blurring of the cortical-white matter junction on T1WI which shows sharper demarcation on T2WI. Within the uncus-amygdala, some locations hypointense on T1WI (white arrow, A) and hyperintense on T2WI (white arrow, C); these proved to be islands of cystic DNET (black arrows, G,H) surrounded by dysplastic cortex. *Courtesy of dr Norico Salamon. Epileptic Disorders, 2009; 11, 194–205.*
Permanent deficits such as new deficits or hydrocephalus are rarely seen. Complications are comparable in both FCD type I and type II. Reoperations with good outcome are also performed [17,27].

Some of the initial reports suggest a preferable mental development in children operated on early in lifetime due to focal cortical dysplasia [49].

Conclusions

Despite well-developed methods of neuroimaging and quite effective surgical techniques, focal cortical dysplasia remains underdiagnosed. An issue emerges, how many patients with intractable epilepsy reveal unspecific changes on EEG with normal brain MRI, having no chances of surgical treatment. The hope for the future is MR imaging using magnetic field of higher intensity – 3T, the development of DTI technique, dynamic perfusion MRI, fMRI and computed analysis of white and gray matter abnormalities, as well as the new PET ligands and modified EEG using a higher number of electrodes.

Further studies regarding epileptogenesis in dysplasia may contribute to the development of new pharmacological therapies. A huge step forward in surgical treatment would be the possibility of removing the lesions from vital brain centers.

The rapid development and improvement in various fields of medicine provides hope that many of these issues may find their solution in the future.

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