
New classification system of focal
cortical dysplasia;
application to practical diagnostic field

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New classification system of focal
cortical dysplasia;
application to practical diagnostic field

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ABSTRACT

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Malformation of cortical development (MCD) is a well-known cause of drug-resistant epilepsy and focal cortical dysplasia (FCD) is the most common neuropathological finding in surgical specimens from drug-resistant epilepsy patients. Palmini's classification proposed in 2004 is now widely used to categorize FCD. Recently, however, Blumcke et al. recommended a new system for classifying FCD in 2011. We applied the new classification system in practical diagnosis of a sample of 117 patients who underwent neurosurgical operations due to drug-resistant epilepsy at Severance Hospital in Seoul, Korea. Among 117 cases, a total of 16 cases were shifted to other FCD subtypes under the new classification system. Five cases were reclassified to type IIIa and five cases were categorized as dual pathology. The other six cases were changed within the type I category. The most remarkable changes in the new classification system are the advent of dual pathology and FCD type III. Thus, it will be very important for pathologists and clinicians to discriminate between these new categories. More large-scale research needs to be conducted to elucidate the clinical influence of the alterations within the classification of type I disease. Although the new FCD classification system has several advantages compared to the former, the correlation with clinical characteristics is not yet clear.

Key words: focal cortical dysplasia, malformation of cortical development, drug-resistant epilepsy

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I . INTRODUCTION

Malformation of cortical development (MCD) is a well-known cause of drug-resistant epilepsy. More specifically, focal cortical dysplasia (FCD), a localized form of MCD, is thought to be the most common neuropathological finding in drug-resistant epilepsy patients following attempted curative neurosurgery. FCD was first described by Taylor et al. in 1971¹, who delineated specific microscopic findings such as cortical disorganization, bizarre neurons, and balloon cells, among other features, in ten drug-resistant epilepsy patients. Since then, although many classification systems have been proposed by neuropathologists and clinicians²⁻⁵, the pathogenesis, etiology, and clinical characteristics of FCD are still relatively unclear.

Currently, Palmini's classification system, proposed in 2004, is widely used to categorize FCD. According to this system, cortical dyslamination is a common characteristic of FCD, regardless of subtype. Type Ia is defined as cortical dyslamination only, while the designation of types Ib, IIa, and IIb are given when additional cytoarchitectural abnormalities are present such as giant or immature neurons, dysmorphic neurons, and balloon cells⁴. Although

Palmini's system is commonly applied in diagnosis, it has inherent flaws. According to Palmini's system, the radiologic characteristics of FCD may be diverse even within a given subtype^{6,7}. Moreover, histologic examination cannot guarantee reliability in diagnosis, particularly when the FCD pathology is mild⁸.

In 2011, Blumcke et al. recommended a new classification system for FCD. The most striking change in the new classification system is the incorporation of a three-tiered system. FCD associated with other principal lesions is denoted to be type III and is further divided into four categories according to the associated principal lesions⁹. The principal lesions include hippocampal sclerosis, tumorous conditions such as glioneuronal tumors or dysembryoplastic neuroectodermal tumors, vascular malformations, and acquired lesions induced by trauma, ischemic injury, and encephalitis. In addition, the definition of FCD type I has been changed according to the new system. The cortical dyslamination that was used to describe FCD type I in Palmini's system is a vague definition, which can result in interpersonal communication errors. In contrast, Blumcke et al. divided cortical dyslamination into two subcategories: abnormal radial lamination and abnormal tangential lamination⁹. The former is classified as type Ia and the latter as type Ib. The diagnosis of type Ic can be made when both radial and tangential cortical dyslamination are detected

Herein, we will apply the new classification system of FCD to practical diagnosis.

II. MATERIALS AND METHODS

1. Case enrollment

Cases included 117 patients with cortical dysplasia who were histologically proven after neurosurgery due to drug-resistant epilepsy between May 2003 to March 2011 at Severance Hospital in Seoul, Korea. All clinical information was investigated by reviewing the electronic medical records of Severance Hospital.

2. Pathologic approach

In cases where surgical specimens are taken from epilepsy patients, it is often difficult for pathologists to identify the margins of lesions. Therefore, all brain specimens submitted were reexamined on formalin-fixed, paraffin-embedded tissue cut perpendicular to the pia matter. Sections were dissected at intervals of four micrometers and stained with hematoxylin and eosin. All slides from the cases were independently reviewed by a neuropathologist and a general pathologist.

The initial diagnoses were reviewed according to the classification system of Palmini (table 1). Cases described before 2004, when Palmini first proposed the classification of FCD, were initially reclassified according to Palmini's classification system. For example, cases diagnosed as "neurons in white matter" or "presence of dysmorphic neurons" were reclassified as MCD type II and FCD type IIa, respectively. Pathological specimens were then reclassified

according to Blumcke's new classification system (table 2).

Table 1. Palmini's Classification System of Cortical Dysplasia

Type	Subtype	Main neuropathological features
Mild MCD*	Type I	Heterotopic/excess neurons in layer I
	Type II	Heterotopic/excess neurons outside layer I
FCD† type I	Type Ia	Cortical dyslamination only
	Type Ib	Cortical dyslamination + giant or immature neurons
FCD type II	Type IIa	Cortical dyslamination + dysmorphic neurons
(Taylor-type)	Type IIb	Cortical dyslamination + dysmorphic neurons and balloon cells

*MCD: Malformation of Cortical Development

†FCD: Focal Cortical Dysplasia

Table 2. Blumcke's Classification System of Focal Cortical Dysplasia

FCD* type I (isolated)			
FCD type Ia	FCD type Ib	FCD type Ic	
Focal cortical dysplasia with abnormal radial cortical lamination	Focal cortical dysplasia with abnormal tangential cortical lamination	Focal cortical dysplasia with abnormal radial and tangential cortical lamination	
FCD type II (isolated)			
FCD type IIa		FCD type IIb	
Focal cortical dysplasia with dysmorphic neurons		Focal cortical dysplasia with dysmorphic neurons and balloon cells	
FCD type III (associated with principal lesion)			
FCD type IIIa	FCD type IIIb	FCD type IIIc	FCD type IIId
Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis	Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor	Cortical lamination abnormalities adjacent to vascular malformation	Cortical lamination abnormalities adjacent to any other lesion acquired during early life, e.g., trauma, ischemic injury, encephalitis

*FCD: Focal Cortical Dysplasia

3. Terminology

“Dysmorphic neurons” are random in orientation and have abnormal dendritic processes and high Nissle substance concentrations (figure 1A) ⁴. “Balloon cells” are large cellular elements with glassy eosinophilic cytoplasm and eccentric nuclei (figure 1B) ⁴.

“Microcolumns” are defined by the vertical alignment of at least eight small neurons ¹⁰. The presence of microcolumns can be confirmed through NeuN immunohistochemistry. “Dual pathology” is applied when additional findings exist separately, unrelated to cortical dysplasia ⁹.

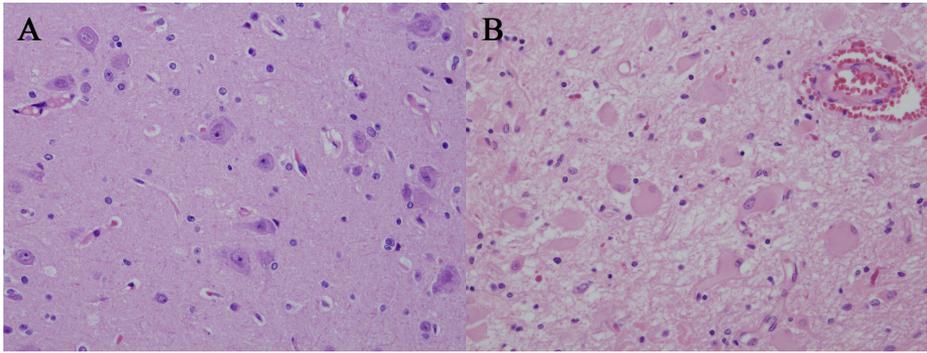


Fig 1. Dysmorphic neurons (A) and balloon cells (B) of focal cortical dysplasia, type IIa and IIb, respectively (hematoxylin and eosin, x200)

III. RESULTS

The patient sample consisted of 71 males and 46 females (M:F=1.54:1) with an age range of two months to 24 years. The mean age was 8.09 years.

According to Palmini's classification system, 44 patients were classified as having MCD, six as FCD type Ia, eight as FCD type Ib, 36 as FCD type IIa, and 23 as FCD type IIb. When reclassified by Blumcke's new classification system, 7 (15.91%) of 44 MCD cases, 5 (83.33%) of 6 FCD type Ia cases, 1 (12.50%) of 8 FCD type Ib cases, 2 (5.56%) of 36 FCD type IIa cases, and 1 (4.35%) of 23 FCD type IIb cases were reclassified to other subtypes (Table 3).

Table 3. The Proportion of Reclassified Cases

Previous diagnosis	Number of cases	Mean age (yrs)	Sex (M:F)	Number of remainders (A)	Number of reclassified cases (B)	Proportion (B/(A+B)) (%)
MCD*	44	8.46	1.18:1	37	7	15.91
FCD†Ia	6	7.22	2:1	1	5	83.33
FCD Ib	8	9.80	5:1	7	1	12.50
FCD IIa	36	7.88	1.85:1	34	2	5.56
FCD IIb	23	7.39	1.5:1	22	1	4.35
Total	117	8.09	1.54:1	101	16	13.68

*MCD, malformation of cortical development

†FCD, focal cortical dysplasia

Among the 16 reclassified cases, MCD was found to be the most common initial diagnosis. Most cases were reclassified to FCD type IIIa, which is associated with hippocampal sclerosis. Two of seven MCD cases and three type II FCD cases were redesignated to dual pathology due to the presence of separately located hippocampal sclerosis, tumors, and vascular malformation. The clinical characteristics of the reclassified cases and factors influencing reclassification are summarized in Table 4.

Table 4. Clinical Information of Reclassified Cases and Causes of
Reclassification

Case	Age	Sex	Previous diagnosis	Reclassified diagnosis	Causes of reclassification
1	12y	M	MCD*	FCD†IIIa	Hippocampal sclerosis
2	15y 7m	M	MCD	FCD IIIa	Hippocampal sclerosis
3	12y 10m	M	MCD	FCD IIIa	Hippocampal sclerosis
4	16y 4m	M	MCD	FCD IIIa	Hippocampal sclerosis
5	5y 1m	M	MCD	FCD IIIa	Hippocampal sclerosis
6	12y 1m	M	MCD	Dual pathology	Meningioma
7	17y	F	MCD	Dual pathology	Cavernous hemangioma
8	6y 8m	M	FCD Ia	FCD Ib	By definition
9	1y 10m	M	FCD Ia	FCD Ib	By definition
10	2m	M	FCD Ia	FCD Ib	By definition
11	6y 1m	M	FCD Ia	FCD Ib	By definition
12	10y 5m	F	FCD Ia	FCD Ib	By definition
13	1y 8m	M	FCD Ib	FCD Ia	By definition
14	11y 3m	M	FCD IIa	Dual pathology	Hippocampal sclerosis
15	5y 11m	M	FCD IIa	Dual pathology	Ganglioglioma
16	10m	F	FCD IIb	Dual pathology	Hippocampal sclerosis

*MCD, malformation of cortical development

†FCD, focal cortical dysplasia

IV. DISCUSSION

FCD is the most common cause of drug-resistant epilepsy. Thus, neuropathologists and clinicians have proposed many classification systems for FCD²⁻⁵. We applied the new classification system suggested by Blumcke in 2011 to practical diagnosis and considered its advantages and limitations.

MCD was found to be the most commonly recategorized subtype by the new classification system, accounting for seven out of 16 cases. However, two out of seven cases were reassigned to dual pathology, rather than only recategorized.

As the definitions of type I FCD in two classification systems differ from each other, the proportion of recategorized cases within this group (42.86%) is substantial. This may be explained, as Blumcke et al. subdivided cortical dyslamination into two detailed categories. However, as the subdivision is purely based on morphologic criteria, it is unclear whether the change in FCD type I has any clinical significance. Furthermore, giant neurons and immature neurons are no longer incorporated into grouping criteria. Nevertheless, those characteristics should not be disregarded because there are no established clinical data associated with the presence of giant and immature neurons. Notably, FCD type Ib comprised a large proportion of the reclassification of FCD type I. This may be rooted in the narrow definition of microcolumns, which are necessary to diagnose FCD type Ia. Despite immunohistochemical support, microcolumnar arrangement is difficult to find.

Distinguishing between dual pathology and type III FCD may be unclear at times. When the cortical dyslamination is subtle and principal lesions are located within the same lobe (mostly temporal), type III can be preferred over

dual pathology. In contrast, when obvious pathologic findings such as dysmorphic neurons or balloon cells are noted, type III should not be considered without evidence of distinct association. Gangliogliomas are brain tumors that are commonly associated with cortical dysplasia. In the case with a ganglioglioma, however, we could not include the case as type III because the tumor was small (about 2cm) and an incidental finding. Similarly, cases with meningioma and cavernous hemangioma were categorized as dual pathology since the lesions were unrelated to cortical dysplasia. As discrimination between dual pathology and type III is critical to the clinical approach, pathologists must differentiate between the two subtypes.

Hippocampal sclerosis was the leading cause of reclassification. Most cases with hippocampal sclerosis were diagnosed as FCD type IIIa, except for two cases that were considered dual pathology. Significant clinical and radiological differences were found between isolated FCD type I and FCD type I associated with hippocampal sclerosis or tumor¹¹. Thus, it was important that cases shifted classification to FCD type IIIa as the presence of hippocampal sclerosis is likely meaningful.

There were several cases of patients with congenital neurodevelopmental disorders such as Sturge-Weber syndrome and tuberous sclerosis. They were not included in FCD type IIIc, since the subtype can only be diagnosed when acquired events are present. Thus, patients with congenital syndromes might be overlooked with this classification. There were cases with encephalomalacia, leukomalacia, gliosis, and mild hypoxic damage, most of which suspect the category of FCD type IIIc. If there are any perinatal or acquired histories

available, we could have put them in type IIIId.

In this study, there were no cases categorized as type Ic, IIIb, IIIc, or IIIId. As we only analyzed 117 cases from a single institute, further large-scale studies are required to establish the proportion of those subtypes.

V. CONCLUSION

Not inconsiderable number of cases were reclassified to other subtypes in this study. The most remarkable change of the new classification system is the advent of dual pathology and FCD type III. As referred to earlier, it is important for pathologists to discriminate between two entities. The clinical influence by the change of FCD type I should be validated later. Even though the new classification system suggests detailed subcategories of FCD type III, it cannot encompass specific congenital conditions. For investigation of rare subtypes, further surveys with a large population should be required. Although the new FCD classification system has several advantages compared to the former, the correlation with clinical characteristics is not yet clear.

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ABSTRACT(IN KOREAN)

Focal Cortical Dysplasia의 새로운 분류체계;
실제 진단 영역으로의 적용

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예로부터, malformation of cortical development는 많은 약물불응성 뇌전증 (drug-resistant epilepsy) 의 원인으로 알려져 왔다. Focal cortical dysplasia (FCD)는 그 중 가장 흔히 관찰할 수 있는 신경병리학적 소견이다. 2004년 Palmini가 제시한 분류체계가 비교적 널리 사용되고 있는 시점에서 최근 2011년 Blumcke가 focal cortical dysplasia의 새로운 분류체계를 제시하였다. 이에 저자는 8년 10개월 간 신촌세브란스병원에서 약물불응성 뇌전증으로 수술 받은 117명의 환자를 대상으로 새로운 분류체계를 적용해 보았다.

총 117명의 환자 중 16 증례가 다른 아형으로 분류되었다. 6 증례는 type III FCD로, 3증례는 dual pathology로 재분류되었다. 나머지 증례의 대부분은 type I FCD내에서 변화를 보였다.

새로운 분류체계의 가장 괄목할만한 변화는 dual pathology와 type III FCD의 등장이다. 그 둘의 감별은 병리의사와 임상 의사 모두에게 매우 중요할 것이다. Type I FCD의 경우 그 변화가 갖는 임상적 의미에 대해서 더 연구해야 할 필요가 있다. 이전의 분류체계에 비해

새로운 분류체계가 갖는 이점이 있지만 임상적으로 얼마나 영향력이 있을 지는 아직 불확실하다.

핵심되는 말: focal cortical dysplasia, malformation of cortical development, 약물 불응성 뇌전증