Pathological assessments in patients with epilepsy

김 세 훈
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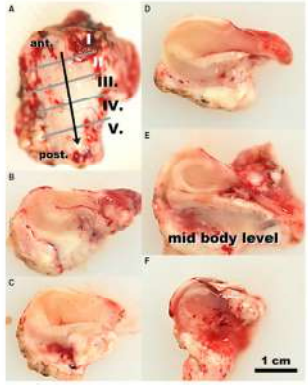
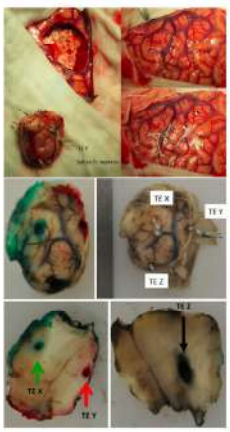
Pathologial assessments in patients with epilepsy

연세의대 병리학교실
김세훈

1. Pathological assessment
2. Limitations
3. Basic concept of Classification
4. Future


International recommendation for a comprehensive neuropathologic workup of epilepsy surgery brain tissue: A consensus Task Force report from the ILAE Commission on Diagnostic Methods





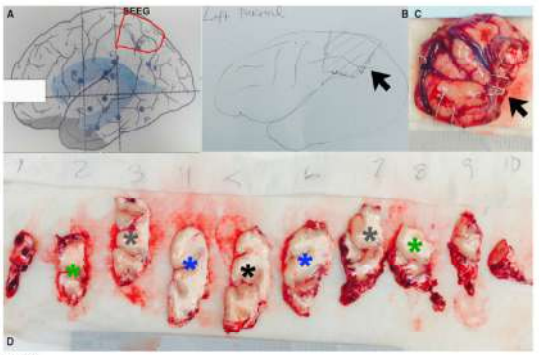
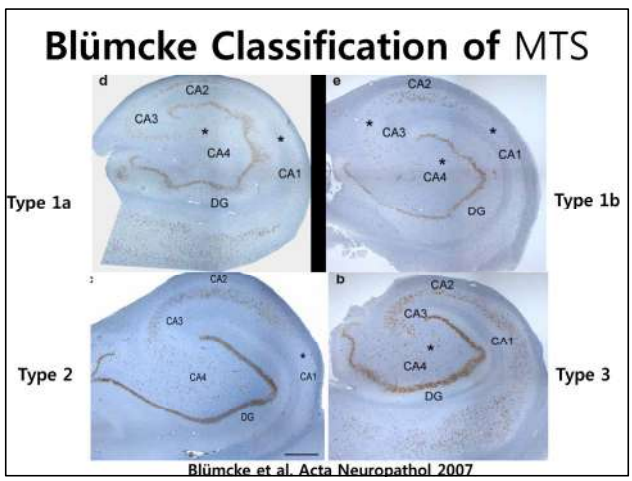


Figure 5.
Procurement of fresh cortical tissue (MRI-negative) following an anatomically intact surgical resection procedure. Identify the anterior-posterior axis of fresh sample from brain maps (**A, B**) and neurosurgical landmarks (**B, C**, staples indicating 3D orientation). (**D**) Dissect tissue specimen in 5-mm slabs at coronal plane in anterior-posterior direction. Document order (slab 1–10) and choose every second slice for histopathology (i.e., 1, 3, 5, 7, 9). Adjacent tissue can be used for tissue banking at −80°C (blue asterisks, slices 4 and 6) or other approved and consented research projects (green asterisks in slices 2 and 8). Slices 1, 9, and 10 represent the resection border and should be separately embedded into paraffin for systematic histopathologic examination. Taken from Blümcke I., Sarnat H.B., Coras R. (2015). Surgical Neuropathology of Focal Epilepsies: Textbook and Atlas, with permission from John Libbey Eurotext.
Epilepsia © ILAE

Limitations

1. Ability, Experiences and Skill of Pathologists
2. Lack of clinico-radio-pathologic correlation
3. Ambiguity of Pathological Classification
4. Inter-observer variation



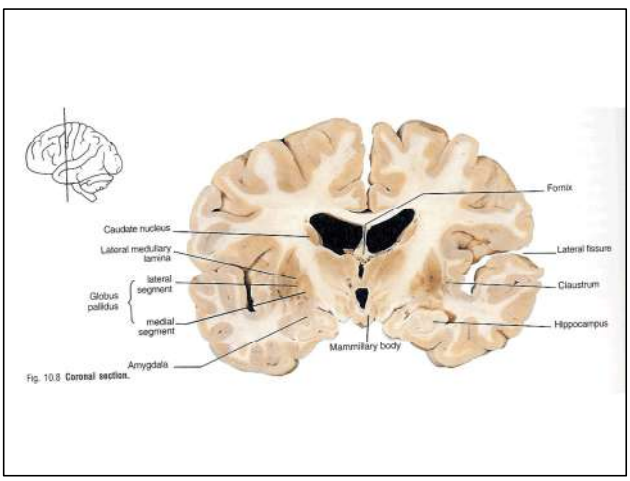
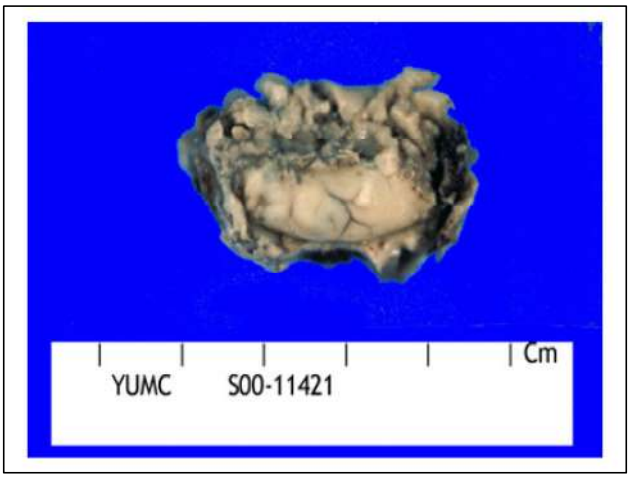
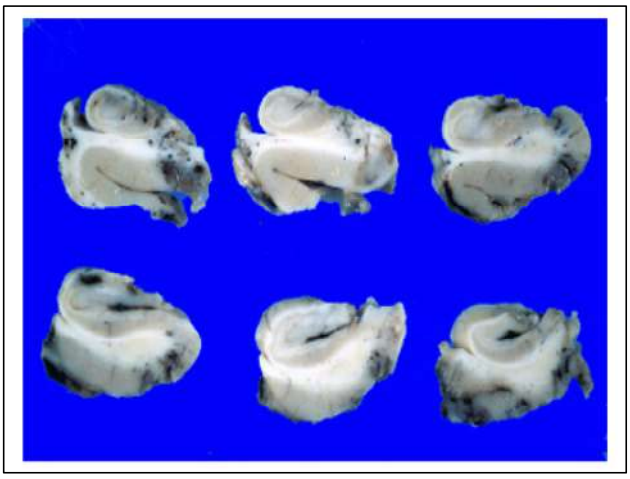


Fig. 10.8 Coronal section.





Limitations

- Fragmentation
- Longitudinal section
- surgical skill

Similar pathologic findings of FCD type II

- Hemimegalencephaly
- Tuberous sclerosis

Epilepsia, 52(1):158–174, 2011
doi: 10.1111/j.1528-1167.2010.02777.x

SPECIAL REPORT

The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission[1]

*[2]Ingmar Blümcke, †Maria Thom, ‡Eleonora Aronica, §Dawna D. Armstrong, ¶Harry V. Vinters, #Andre Palmini, **Thomas S. Jacques, ††Giuliano Avanzini, ‡‡A. James Barkovich, §§Giorgio Battaglia, ¶¶Albert Becker, ##Carlos Cepeda, ***[3]Fernando Cendes, †††Nadia Colombo, ‡‡‡Peter Crino, §§§J. Helen Cross, ¶¶¶Olivier Delalande, ###François Dubeau, ****John Duncan, ††††Renzo Guerrini, ‡‡‡‡Philippe Kahane, §§§§Gary Mathern, ¶¶¶¶Imad Najm, ####Çiğdem Özkara, *****Charles Raybaud, †††††Alfonso Represa, ‡‡‡‡‡Steven N. Roper, §§§§§Noriko Salamon, ¶¶¶¶¶Andreas Schulze-Bonhage, ######Laura Tassi, ******Annamaria Vezzani, and ††Roberto Spreafico

Palmini et al. 2004

Classification of cortical dysplasias in epilepsy

Dysplasia type	subtype	Main neuropathological type
Mild MCD	Type I	Heterotopic/excess neurons in layer I
	Type II	Heterotopic/excess neurons outside layer I
FCD type I	Type Ia	Cortinal dislamination only (±MCD features)
	Type Ib	Cortinal dislamination + giant or immature neurons
FCD type II	Type IIa	Cortinal dislamination + dysmorphic neurons
(Taylor-type)	Type IIb	Cortinal dislamination + dysmorphic neurons and balloon cells

FCD: Focal cortical dysplaia MCD: malformation of cortical development
Child's Nerv Sys 22:821-826, 2006

ILAE Classification of FCD

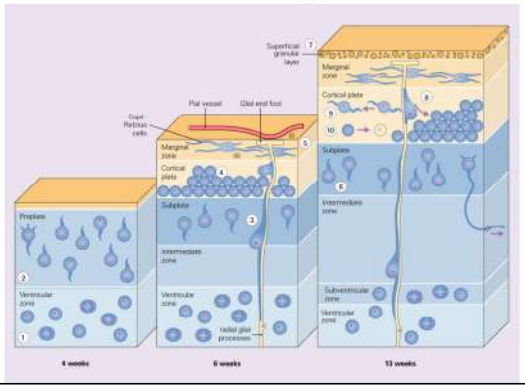
Table I. The three-tiered ILAE classification system of focal cortical dysplasia (FCD) distinguishes isolated forms (FCD Types I and II) from those associated with another principal lesion (FCD Type III).

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

FCD Type III (not otherwise specified, NOS): if clinically/radiologically suspected principal lesion is not available for microscopic inspection.
Please note that the rare association between FCD Types IIa and IIb with hippocampal sclerosis, tumors, or vascular malformations should not be classified as FCD Type III variant.

Epilepsia, 52(1):158–174, 2011

Neuronal Migration



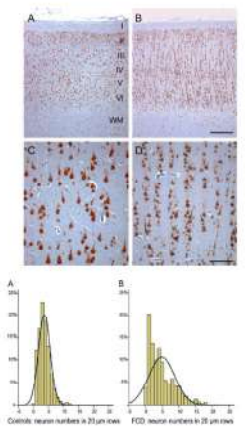
Acta Neuropathol (2005) 110: 1–11
DOI 10.1007/s00401-005-1016-6

REGULAR PAPER

Michelle Hildebrandt · Tom Pieper · Peter Winkler
Dieter Kolodziejczyk · Hans Holthausen
Ingmar Blümcke

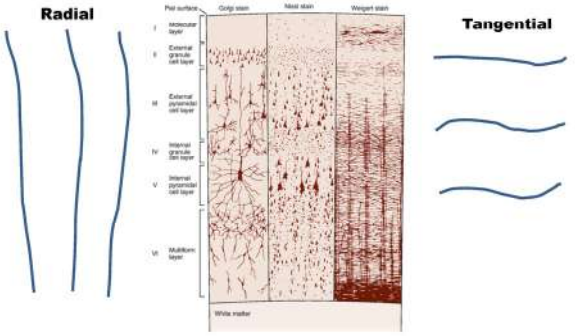
Neuropathological spectrum of cortical dysplasia in children with severe focal epilepsies

Received: 15 November 2004 / Revised: 16 February 2005 / Accepted: 16 February 2005 / Published online: 17 June 2005



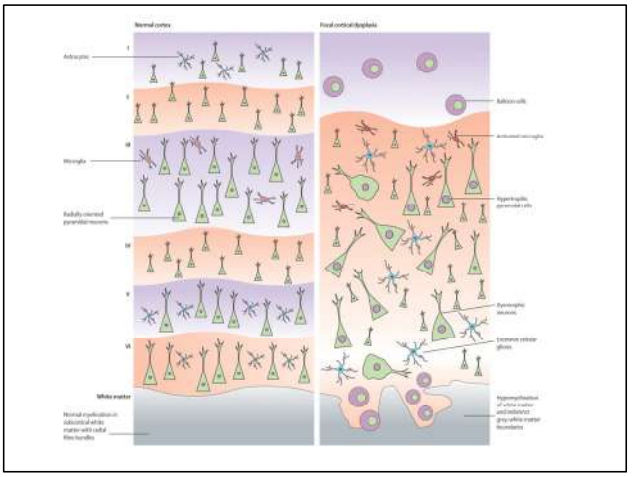
FCD type I

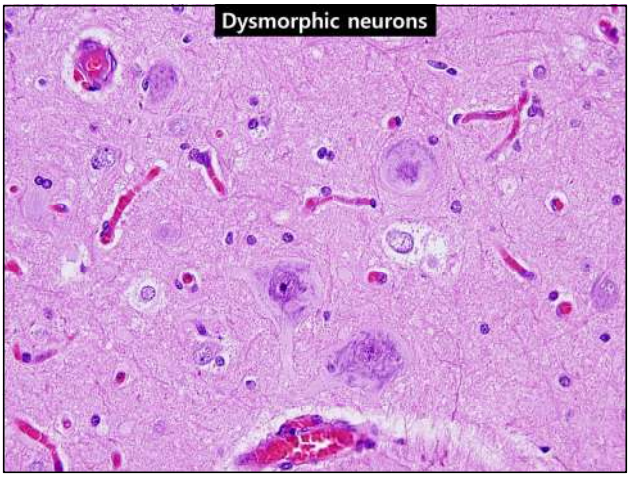
- Abnormal radial cortical lamination
- Abnormal tangential cortical lamination
- Abnormal radial and tangential cortical lamination

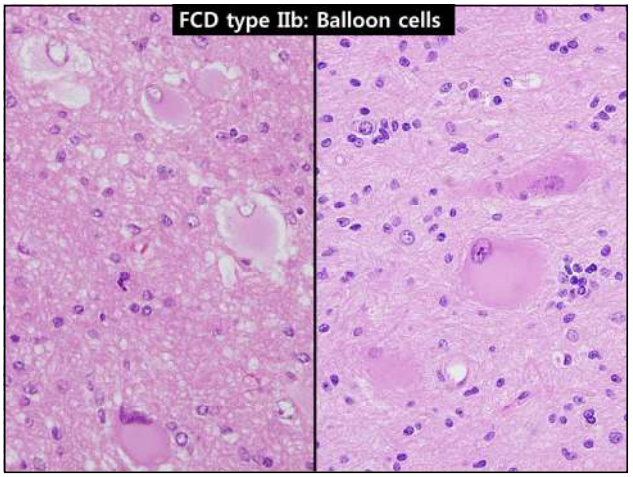


FCD Type II

- Abnormal Cortical lamination
- **Dysmorphic neurons**
- **Balloon cells**







Journal of Clinical Neuroscience 23 (2016) 68–72

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Clinical Study

Clinical characteristics and post-surgical outcomes of focal cortical dysplasia subtypes

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[b] Pediatric Epilepsy Center, Peking University First Hospital, Peking University, No. 1 Xi'an Men Street, West District, Beijing 100034, China

Table 3
Clinical characteristics of FCD type I, IIa and IIb patients

n (%)	I	IIa	IIb	*p* value*
Patients	47	16	8	N/A
Focal MRI	8 (17)	8 (50)	4 (50)	0.014
Transmantle sign	0 (0)	3 (21.4)	5 (62.5)	N/A
EEG				0.055
Localize	11 (23)	7 (44)	5 (63)	N/A
Regional	22 (47)	8 (50)	3 (38)	N/A
Bilateral	14 (30)	1 (6)	0 (0)	N/A
Site of surgery				0.001
Temporal lobe	18 (38)	4 (25)	0 (0)	
Frontal lobe	9 (19)	5 (31)	3 (38)	
Parietal lobe[a]	10 (21)	5 (31)	5 (63)	
Occipital lobe	3 (6)	1 (6)	0 (0)	
Multiple lobe resection	7 (15)	1 (6)	0 (0)	
Seizure free	20 (43)	10 (63)	6 (75)	0.133

Weak points

- FCD type I especially Ic
- mMCD is not included
- Problems of FCD type III

FCD type Ic

tangential cortical lamination. Histopathologic hallmarks are identical to those specified in Histopathologic findings. This FCD variant is diagnosed only as an isolated lesion and not in combination with any other pathology. It has to be clarified in the future, however, whether such lesions occur within patients with more widespread abnormalities linked to mental retardation and/or multiple congenital abnormality syndromes.

Palmini et al. 2004

Table 1 Classification of cortical dysplasias in epilepsy

Focal 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 dislamination only (±MCD features)
	Type Ib	Cortical dislamination + giant or immature neurons
FCD type II	Type IIa	Cortical dislamination + dysmorphic neurons
(Taylor-type)	Type IIb	Cortical dislamination + dysmorphic neurons and balloon cells

FCD Focal cortical dysplasia and *MCD* malformation of cortical development

Heterotopic neurons in outside layer I

accumulation of neurofilament proteins. There are no balloon cells present (to be confirmed by immunohistochemistry). Discrimination of individual cortical layers is almost impossible (with the exception of layer 1). Other cortical layer abnormalities are frequently encountered and should not be separately classified, including abnormal isocortical layer organization adjacent to the main lesion, as well as heterotopic neurons in layer 1 or white matter.

mild MCD

tially) epileptogenic lesions (FCD Type III). We propose in addition that mild forms of cortical malformations (mMCDs) should be included in the classification, although their clinical impact will need further clarification (see below). Notwithstanding, any classification system using histopathologic examination will rely on sufficient and representative surgical tissue as well as standardized laboratory protocols (see Supporting Information).

N ENGL J MED 377;17 NEJM.ORG OCTOBER 26, 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Histopathological Findings in Brain Tissue Obtained during Epilepsy Surgery

I. Blumcke, R. Spreafico, G. Haaker, R. Coras, K. Kobow, C.G. Bien, M. Pfäfflin, C. Elger, G. Widman, J. Schramm, A. Becker, K.P. Braun, F. Leijten, J.C. Baayen, E. Aronica, F. Chassoux, H. Hamer, H. Stefan, K. Rössler, M. Thom, M.C. Walker, S.M. Sisodiya, J.S. Duncan, A.W. McEvoy, T. Pieper, H. Holthausen, M. Kudernatsch, H.J. Meencke, P. Kahane, A. Schulze-Bonhage, J. Zentner, D.H. Heiland, H. Urbach, B.J. Steinhoff, T. Bast, L. Tassi, G. Lo Russo, C. Özkara, B. Oz, P. Krsek, S. Vogelgesang, U. Runge, H. Lerche, Y. Weber, M. Honavar, J. Pimentel, A. Arzimanoglou, A. Ulate-Campos, S. Noachtar, E. Hartl, O. Schijns, R. Guerrini, C. Barba, T.S. Jacques, J.H. Cross, M. Feucht, A. Mühlebner, T. Grunwald, E. Trinka, P.A. Winkler, A. Gil-Nagel, R. Toledano Delgado, T. Mayer, M. Lutz, B. Zountsas, K. Garganis, F. Rosenow, A. Hermsen, T.J. von Oertzen, T.L. Diepgen, and G. Avanzini, for the EEBB Consortium*

Table 2. Summary of the 10 Most Common Histopathological Diagnoses among 9523 Patients Who Underwent Epilepsy Surgery.*

Diagnosis	Category	Patients with Condition (N = 9523)	Age at Onset of Seizures	Duration of Epilepsy	Localization†	
		no. (%)	years		lobe	%
Hippocampal sclerosis	Hippocampal sclerosis	3463 (36.4)	11.3±10.1	22.5±12.7	Temporal	100.0
Ganglioglioma	Tumor	986 (10.4)	12.1±10.3	11.4±10.4	Temporal	82.5
Focal cortical dysplasia type II	Malformation of cortical development	859 (9.0)	5.6±6.9	14.0±11.7	Frontal	51.6
No lesion	No lesion	738 (7.7)	13.0±10.6	15.4±10.6	Temporal	67.7
Dysembryoplastic neuroepithelial tumor	Tumor	565 (5.9)	14.0±10.9	12.0±10.7	Temporal	68.1
Glial scar	Glial scar	461 (4.8)	10.7±10.3	14.8±11.1	Temporal	37.1
Cavernous angioma	Vascular malformation	431 (4.5)	25.4±13.0	12.3±11.2	Temporal	74.7
Mild malformation of cortical development	Malformation of cortical development	279 (2.9)	9.6±10.0	13.7±11.5	Temporal	49.1
Focal cortical dysplasia type I	Malformation of cortical development	268 (2.8)	7.4±9.6	9.3±8.1	Temporal	35.1
Focal cortical dysplasia not otherwise specified	Malformation of cortical development	206 (2.2)	8.0±8.0	13.4±11.5	Temporal	45.1
Total		8256 (86.7)	11.6±10.8	17±12.6	Temporal	71.9

* Plus–minus values are means ±SD. A full list of diagnoses is provided in Table S2 in the Supplementary Appendix.
† Data are the lobe in which surgery was most commonly performed for each condition and the percentage of cases in which surgery was performed in that lobe.

Epilepsia, 53(8):1341–1348, 2012
doi: 10.1111/j.1528-1167.2012.03508.x

FULL-LENGTH ORIGINAL RESEARCH

Good interobserver and intraobserver agreement in the evaluation of the new ILAE classification of focal cortical dysplasias

*Roland Coras, †Onno J. de Boer, ‡Dawna Armstrong, §Albert Becker, ¶Thomas S. Jacques, #Hajime Miyata, **Maria Thom, ††Harry V. Vinters, ‡‡Roberto Spreafico, §§Buge Oz, ¶¶Gianluca Marucci, ##Jose Pimentel, ***Angelika Mühlebner, †††Josef Zamecnik, ‡‡‡Anna Maria Buccoliero, §§§Fabio Rogerio, ¶¶¶Nathalie Streichenberger, ###Nobutaka Arai, ****Marianna Bugiani, ††††Silke Vogelgesang, ‡‡‡‡Rob Macaulay, §§§§Carolin Salon, ¶¶¶¶Volkmar Hans, #####Marc Polivka, *****Felice Giangaspero, †††††Dyah Fauziah, ‡‡‡‡‡Jang-Hee Kim, §§§§§Lei Liu, ¶¶¶¶¶Wang Dandan, ######Jing Gao, ******Benjamin Lindeboom, *Ingmar Blümcke, and ******Eleonora Aronica

Good interobserver and intraobserver agreement in the evaluation of the new ILAE classification of focal cortical dysplasias, Eleonora Aronica et al. (2012) Epilepsia, 53(8):1341–1348

Table 2. Interobserver agreement in the first, second, and third evaluation rounds per FCD types (κ values)

Round	FCD Ia	FCD Ib	FCD Ic	FCD IIa	FCD IIb	FCD IIIa	FCD IIIb	FCD IIIc	FCD IIId	No FCD	Mean
1	0.4821	0.3877	0.1319	1.0000	1.0000	0.8314	0.4869	0.7685	0.6963	0.3746	0.6192
2	0.7284	0.4287	−0.004[a]	1.0000	0.9565	0.7962	0.5113	0.6435	0.5465	0.4164	0.6202
3T	0.3252	0.1917	0.1509	0.4239	0.8045	0.5822	0.4407	0.6109	0.1800	0.2409	0.4060
3A	0.4220	0.4323	0.3438	0.5252	0.7838	0.7195	0.6101	0.7023	0.2951	0.2606	0.5056
3B	0.3185	0.1071	0.1608	0.4311	0.8555	0.5063	0.4451	0.5981	0.0517	0.2586	0.3884
3C	0.3763	0.0778	0.2137	0.3307	0.7136	0.4911	0.2171	0.4718	0.1955	0.1270	0.3265

3T, summary of third evaluation round including all 21 neuropathologists; 3A, neuropathologists with level A access to >40 epilepsy surgery cases/year; 3B, neuropathologists reviewing 10–40 cases/year; 3C, neuropathologists seeing <10 cases/year.
Kappa values were scored as follows: <0.2, poor agreement; 0.2–<0.4, fair agreement (yellow boxes); 0.4–<0.6, moderate agreement (purple boxes); 0.6–<0.8, good agreement (green boxes); 0.8–1.0, very good agreement (blue boxes).
[a]Kappa values can be negative in rare situations indicating that the observers agreed less than expected by chance.

Table 3. Intraobserver reproducibility in the ILAE classification system

NP	Unchanged diagnoses	Changed diagnoses on reevaluation	κ
1	23/25	2/25	0.8571
2	16/25	9/25	0.5849
3	19/25	6/25	0.7180
4	20/25	5/25	0.7657
5	23/25	2/25	0.8899
6	19/25	6/25	0.7268
7	25/25	0/25	1.0000
8	14/25	11/25	0.4991
9	25/25	0/25	1.0000
Summary	183/225	42/225	0.7824 (mean)

NP, neuropathologist.
Kappa values were interpreted as follows: <0.2, poor agreement; 0.2–<0.4, fair agreement; 0.4–<0.6, moderate agreement; 0.6–<0.8, good agreement; 0.8–1.0, very good agreement.

Intraobserver: good agreement (k= 0.7824, 0.4991 to 1.000). (09' k=0.5062)
Interobserver: moderate~ low, reflected by the level of experience (k= 0.5056 to 0.3265) (09' k= 0.4654–0.8504)

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MINI-SYMPOSIUM: Etiologies of Focal Epilepsy

Long-Term Epilepsy-Associated Tumors

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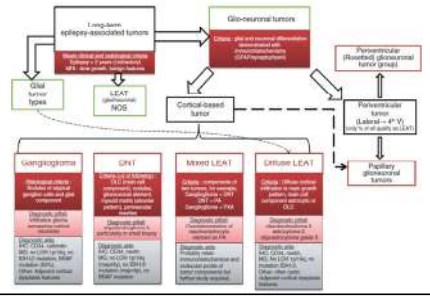
[2] Department of Neuropathology, University Hospital Erlangen, Erlangen, Germany.
[3] Department (Neural Pathology, Academisch Medisch Centrum, Amsterdam.
[4] SEIN-Epilepsy Institute in the Netherlands Foundation, Heemstede, The Netherlands.



ILAE Task Force for Neuropathology: LEAT study group First round

38 Raters were invited to review 30 LEAT cases from EEBB (Erlangen, Germany)
25 Raters have responded within given time frame of 6 weeks
12 Tumors (40%) reached above/equal 75% agreement (> 19 raters)
18 Tumors (60%) had less than 75% agreement (< 19 raters)
WHO grading was also inconsistent (i.e. from 1° to 3° for same sample)

Agreement cases included
6 DNET (WHO 1°) with specific glio-neuronal element
6 Gangliogliomas (WHO 1°) with distinct neuronal component

Conclusion

Agreement for the microscopic diagnosis of LEAT needs improvement

URGENTLY

Proposal for a new terminology use for long-term epilepsy associated brain tumors

Every fourth patient submitted to epilepsy surgery suffers from a brain tumor. Microscopically, these neoplasms present with a wide-ranging spectrum of glial or glio-neuronal tumor subtypes. Gangliogliomas (GG) and dysembryoplastic neuroepithelial tumors (DNT) are the most frequently recognized entities accounting for 65% of 1551 tumors collected at the European Epilepsy Brain Bank (n=5842 epilepsy surgery samples). These tumors often present with early seizure onset at a mean age of 16.5 years, with 77% of neoplasms affecting the temporal lobe. Relapse and malignant progression are rare events in this particular group of brain tumors. Surgical resection should be regarded, therefore, also as important treatment strategy to prevent epilepsy progression as well as seizure- and medication-related comorbidities. The characteristic clinical presentation and

Table 3: Terminology proposal for long-term epilepsy associated tumors

WHO	ILAE[1]	CD34	MAP2 glial	MAP2 neuronal	IDH1
ANET[2]	ANET[2]	-	+/-	Preexisting	-
GG[3]	BNET*	+	+/-	Dysplastic	-
DNET[4]	CNET[4]	f.c.t.c.	f.c.t.c.	f.c.t.c.	-
DNET[5]	DNET[5]	-	+/-	floating neurons	-
-	ENET*	-	+/-	+/-	t.b.d.
GG[3]	GNET*	-	-	Dysplastic	-
A II[6]	INET*	-	-	Preexisting	-

ILAE Task Force for Neuropathology: LE AT study group Second round

25 (same as round 1) Raters were invited to review 30 LEAT cases from EEBB (Erlangen, Germany)
20 Raters have responded within given time frame of 6 weeks
14 Tumors (47%) reached above/equal 75% agreement
18 Tumors (53%) had less than 75% agreement

Conclusion

Agreement for the microscopic diagnosis of LEAT slightly improved (>>> CD34 positive tumors), but still needs improvement !!

Third LEAT agreement round to be envisaged

ILAE Classification of Focal Cortical Dysplasia

ILAE classification of Focal Cortical Dysplasia - an update (ILAE survey from the FCD Task Force)

The Diagnostic Methods commission of the ILAE released a first international consensus classification of Focal Cortical Dysplasia (FCD) in 2011. Since that time, the FCD classification has been widely used in clinical diagnosis and research. A new Task Force was launched in September 2017 to critically review the current FCD classification and to identify areas in need of a revision or update. As eminent examples, there are recent discoveries in molecular-genetics in FCDs that may require clarification for use in clinical practice; also, electro-clinical-imaging phenotypes and surgical outcomes have been further defined or validated.

We need you to help us identify areas in need for an update or revision of the FCD classification to better serve its clinical purpose. Please take a few minutes to answer the 16 questions of our survey below. Be assured that all answers will be strictly kept anonymous.

1. 1. Do you use the ILAE classification of FCD (2011) in your clinical practice and/or research projects?

- ◯ No (please proceed to Q9)
- ◯ Yes (please help us to better understand subtype frequencies by answering all questions)

2. Please estimate % of FCD subtypes from all FCD I and II patients in your practice (i.e. 2017). One answer per row.

	<20%	20 - 50%	>50%
FCD Type I	◯	◯	◯
FCD Type II	◯	◯	◯

3. Please estimate % of FCD I subtypes in your practice. One answer per row.

	virtually never	<20%	20 - 50%	>50%
FCD Type Ia	◯	◯	◯	◯
FCD Type Ib	◯	◯	◯	◯
FCD Type Ic	◯	◯	◯	◯

4. Do you recommend genetic testing from blood and brain samples for the diagnosis of FCD?

- ◯ Yes
- ◯ No

5. Do you classify associated FCD III according to the ILAE classification 2011?

- ◯ Yes
- ◯ No

6. Please estimate % of principal lesions associated with FCD III in your practice. One answer per row

	virtually never	<20%	20 - 50%	>50%
FCD IIIa (HS)	◯	◯	◯	◯
FCD IIIb (tumor)	◯	◯	◯	◯
FCD IIIc (vascular)	◯	◯	◯	◯
FCD IIId (other)	◯	◯	◯	◯

7. Do you use the diagnosis of mild malformations of cortical development (mMCD as defined by the Palmini classification 2004 and ILAE classification 2011)?

- ◯ Yes
- ◯ No

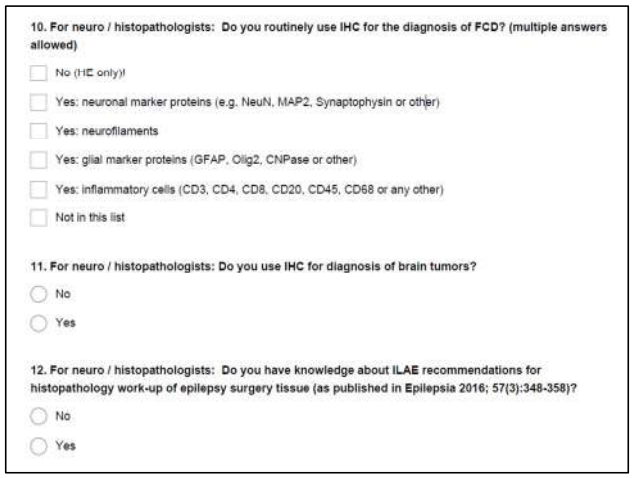
8. How often do you classify mMCD (in comparison to FCD)?

- ◯ Less often than FCD
- ◯ Same as FCD
- ◯ More often than FCD

9. Which topic(s) of the FCD classification do you think require revision (multiple answers allowed and please feel free to tell us any further thoughts or comments)?

- ☐ FCD I
- ☐ FCD II
- ☐ FCD III
- ☐ mMCD
- ☐ Genetics

Do you have any further thoughts or comments about any of your choices above?



10. For neuro / histopathologists: Do you routinely use IHC for the diagnosis of FCD? (multiple answers allowed)

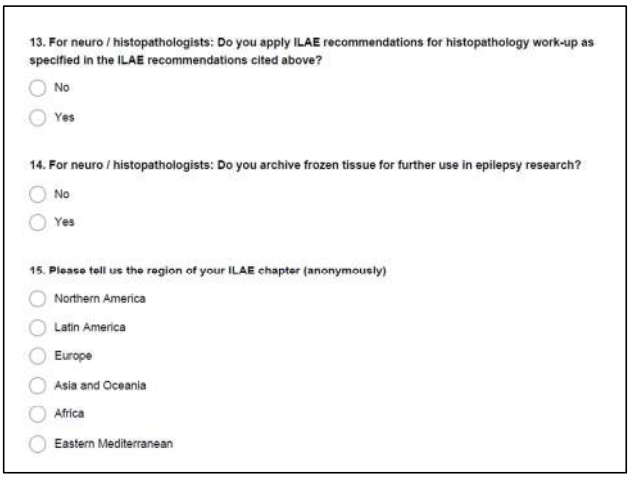
- [ ] No (HE only)!
- [ ] Yes: neuronal marker proteins (e.g. NeuN, MAP2, Synaptophysin or other)
- [ ] Yes: neurofilaments
- [ ] Yes: glial marker proteins (GFAP, Olig2, CNPase or other)
- [ ] Yes: inflammatory cells (CD3, CD4, CD8, CD20, CD45, CD68 or any other)
- [ ] Not in this list

11. For neuro / histopathologists: Do you use IHC for diagnosis of brain tumors?

- ◯ No
- ◯ Yes

12. For neuro / histopathologists: Do you have knowledge about ILAE recommendations for histopathology work-up of epilepsy surgery tissue (as published in Epilepsia 2016; 57(3):348-358)?

- ◯ No
- ◯ Yes



13. For neuro / histopathologists: Do you apply ILAE recommendations for histopathology work-up as specified in the ILAE recommendations cited above?

- ◯ No
- ◯ Yes

14. For neuro / histopathologists: Do you archive frozen tissue for further use in epilepsy research?

- ◯ No
- ◯ Yes

15. Please tell us the region of your ILAE chapter (anonymously)

- ◯ Northern America
- ◯ Latin America
- ◯ Europe
- ◯ Asia and Oceania
- ◯ Africa
- ◯ Eastern Mediterranean