EPILEPSY

• Affects 1-2% of population
• WHO estimates 50 million affected worldwide
• Medically refractory cases common
  – Affects quality of life for patients and caregivers
  – Secondary psychological and cognitive consequences
  – Social stigma
  – High morbidity and mortality, including SUDEP
  – High health care costs
  – Skewed experience of surgeons/pathologists
  – Subset with anatomic explanations on pathology
Epilepsy Classification Schemes

- International League Against Epilepsy (ILAE) 2001 clinical scheme with 5 axes: ictal phenomenology; seizure type; syndrome; etiology; impairment
- Palmini 2004 scheme for cortical dysplasias
- ILAE 2010 clinicopathologic scheme
- ILAE 2011 modified scheme for cortical dysplasias
- Future schemes are a certainty as we learn more about what’s most relevant clinically and for therapy
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Epilepsies</th>
</tr>
</thead>
</table>
| **Neonatal period** | Benign familial neonatal epilepsy (BFNE)  
Early myoclonic encephalopathy (BFNE)  
Ohtahara syndrome |
| **Infancy** | Epilepsy of infancy with migrating focal seizures  
West syndrome  
Myoclonic epilepsy in infancy (MEI)  
Benign infantile epilepsy  
Benign familial infantile epilepsy  
Dravet syndrome  
Myoclonic encephalopathy in non-progressive disorders |
| **Childhood** | Febrile seizures plus (FS+) (can start in infancy)  
Panayiotopoulos syndrome  
Epilepsy with myoclonic atonic (previously astatic) seizures  
Benign epilepsy with centrotemporal spikes (BECTS)  
Autosomal-dominant nocturnal frontal lobe epilepsy (ADNFLE)  
Late onset childhood occipital epilepsy (Gastaut type)  
Epilepsy with myoclonic absences  
Lennox-Gastaut syndrome  
Epileptic encephalopathy with continuous spike-and-wave during sleep (CSWS)  
Landau-Kleffner syndrome (LKS)  
Childhood absence epilepsy (CAE) |
| **Adolescence-Adult** | Juvenile absence epilepsy (JAE)  
Juvenile myoclonic epilepsy (JME)  
Epilepsy with generalised tonic-clonic seizures alone  
Progressive myoclonus epilepsies (PME)  
Autosomal dominant epilepsy with auditory features (ADEAF)  
Other familial temporal lobe epilepsies |
| **Less specific age relationships** | Familial focal epilepsy with variable foci (childhood to adult)  
Reflex epilepsies |
| **Distinctive constellations** | Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE with HS)  
Rasmussen syndrome  
Gelastic seizures with hypothalamic hamartoma  
Hemiconvulsions-hemiplegia-epilepsy  
Epilepsies that do not fit these categories |
| **Epilepsies attributed to structural-metabolic causes** | Malformations of cortical development (hemi-megalencephaly, heterotopias etc.)  
Neurocutaneous syndromes (tuberous sclerosis complex, Sturge-Weber etc.)  
Tumour  
Infection  
Trauma  
Perinatal insults  
Stroke  
Vascular malformation |
| **Epilepsies of unknown cause** | Conditions with epileptic seizures that are not forms of epilepsy  
Benign neonatal seizures (BNS)  
Febrile seizures (FS) |

Table 1. Electroclinical syndromes and other epilepsies. This is taken from Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. (Berg, Berkovic et al. 2010). The syndromes are arranged by age of onset and do not reflect aetiology.
POSSIBLE PATHOLOGIC FINDINGS

- Mesial temporal (hippocampal) sclerosis
- Tumors (mostly low-grade)
- Malformative (e.g. cortical dysplasias)
- Inflammatory (e.g. Rasmussen’s)
- Infectious (e.g. cysticercosis)
- Syndromes (e.g. tuberous sclerosis)
- Adult or perinatal ischemic insults
- Trauma
- Vascular malformations
- Secondary effects: subpial/subcortical gliosis, neuronal loss, organizing electrode sites, chronic inflammation, cerebellar atrophy
Normal Hippocampus

CA1

CA4
CHICKEN OR EGG
the battle rages on

THE EGG
The egg came first; dinosaurs laid eggs, and chickens are descendants of the dinosaurs.

WOW
Who the hell takes a question like that seriously?
From: Greenfield’s 9th ed.

B. Malformations with activation of the mTOR pathway

- Growth factors
- Insulin signalling
  - Activation in sporadic FCD IIB
  - Mechanism?

- PI3K
- PTEN
- Akt
- mTORC2
  - Rapamycin insensitive
  - Loss of function mutations in TSC

- TSC1/TSC2

- AMPK pathway
- Rheb
- Raptor
- mTORC1

- mTOR
  - p70S6 K1
  - pS6
  - eIF4G
  - elf4E
  - Protein synthesis
  - Cell growth
  - Cell proliferation

- p4E-BP-1/ elf4E

- Promotion of epileptogenic mechanisms
  - Hamartoma formation
  - Developmental lesions e.g. FCDII, Tuber, SEGA
The clinicopathologic spectrum of focal cortical dysplasias: A consensus classification proposed by an ad hoc Task Force of the ILAE Diagnostic Methods Commission

*2Ingmar 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, ####Fernando Cendes, †††Nadia Colombo, ††††Peter Crino, †††§J. Helen Cross, †††‌†Olivier Delalande, ###Francois Dubeau, ####John Duncan, †††††Renzo Guerrini, ††††‌Philippe Kahane, §§§Gary Mathern, †††††Imad Najm, ††††††Çigdem Özkara, *****Charles Raybaud, ††††††Alfonso Represa, †††††Steven N. Roper, §§§§Noriko Salamon, †††††††Andreas Schulze-Bonhage, ††††††Laura Tassi, ††††††Annamaria Vezzani, and ††Roberto Sprefico

*Department of Neuropathology, University Hospital Erlangen, Erlangen, Germany; †Department of Neuropathology, Institute of Neurology, University College London, London, United Kingdom; ‡Department of Neurology, Academic Medisch Centrum, Amsterdam, The Netherlands; §§Formerly Baylor College of Medicine and Texas Children's Hospital, Houston, Texas, U.S.A.; ¶Departments of Pathology and Laboratory Medicine (Neuropathology) and Neurology, UCLA Medical Center and David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.; §§§Molecular Neuroanatomy and Pathogenesis Unit, IRCCS Foundation Neurological Institute “Carlo Besta,” Milan, Italy; ††Department of Neuroradiology, University of California at San Francisco, San Francisco, California, U.S.A.; §§§Molecular Neuroanatomy and Pathogenesis Unit, IRCCS Foundation Neurological Institute “Carlo Besta,” Milan, Italy; †††Department of Neuropathology, University Hospital Bonn, Bonn, Germany; ††††IDDRG, Semel Institute, UCLA Medical Center, Los Angeles, California, U.S.A.; ††††Department of Neurology, University of Campinas, Campinas, Brazil; †††††Department of Neuroradiology, Ospedale Niguarda, Milan, Italy; ††††††PENN Epilepsy Center, University of Pennsylvania, Philadelphia, Pennsylvania, U.S.A.; ††††††The Prince of Wales’ Chair of Childhood Epilepsy, UCL-Institute of Child Health, Great Ormond Street Hospital for Children and National Centre for Young People with Epilepsy, London, United Kingdom; †††††††Fondation Ophthalmologique Rothschild, Service de Neurochirurgie Pediatrique, Paris, France; ††††††††Montreal Neurological Institute, McGill University, Montreal, Quebec, Canada; ††††††Department of Clinical and Experimental Epilepsy, Institute of Neurology, University College London, London, United Kingdom; ††††††Pediatric Neurology Unit and Laboratories, Children's Hospital A. Meyer, University of Florence, Firenze, Italy; ††††††Neurology Department and INSERM U836, Grenoble University Hospital, Grenoble, France; ††††††Departments of Neurosurgery, Psychiatry and Behavioral Sciences, David Geffen School of Medicine at UCLA, Los Angeles, California, U.S.A.; ††††††Cleveland Clinic, Neurological Institute, Cleveland, Ohio, U.S.A.
<table>
<thead>
<tr>
<th>FCD Type I (isolated)</th>
<th>Focal cortical dysplasia with abnormal radial cortical lamination (FCD Type Ia)</th>
<th>Focal cortical dysplasia with abnormal tangential cortical lamination (FCD Type Ib)</th>
<th>Focal cortical dysplasia with abnormal radial and tangential cortical lamination (FCD Type Ic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FCD Type II (isolated)</td>
<td>Focal cortical dysplasia with dysmorphic neurons (FCD Type IIa)</td>
<td></td>
<td>Focal cortical dysplasia with dysmorphic neurons and balloon cells (FCD Type IIb)</td>
</tr>
<tr>
<td>FCD Type III (associated with principal lesion)</td>
<td>Cortical lamination abnormalities in the temporal lobe associated with hippocampal sclerosis (FCD Type IIIa)</td>
<td>Cortical lamination abnormalities adjacent to a glial or glioneuronal tumor (FCD Type IIIb)</td>
<td>Cortical lamination abnormalities adjacent to a vascular malformation (FCD Type IIIc)</td>
</tr>
<tr>
<td>FCD Type III (not otherwise specified, NOS); if clinically/radiologically suspected principal lesion is not available for microscopic inspection.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*

doi: 10.1111/j.1528-1167.2010.02777.x
FULL-LENGTH ORIGINAL RESEARCH

Interobserver and intraobserver reproducibility in focal cortical dysplasia (malformations of cortical development)

*Wendy A. Chamberlain, †Mark L. Cohen, ‡Kymberly A. Gyure, §Bette K. Kleinschmidt-DeMasters, ¶Arie Perry, #Suzanne Z. Powell, **Jiang Qian, ††Susan M. Staugaitis, and *Richard A. Prayson

*Department of Anatomic Pathology, Cleveland Clinic, Cleveland, Ohio, U.S.A.; †Department of Pathology, Case Western University, Cleveland, Ohio, U.S.A.; ‡Department of Pathology, West Virginia University, Morgantown, West Virginia, U.S.A.; §Department of Pathology and Immunology, Washington University School of Medicine, St. Louis, Missouri, U.S.A.; ¶Department of Pathology, The Methodist Hospital, Houston, Texas, U.S.A.; #Department of Pathology and Laboratory Medicine, Albany Medical College, Albany, New York, U.S.A.; and ††Department of Neurosciences, Lerner Research Institute and Department of Anatomic Pathology, Cleveland Clinic, Cleveland, Ohio, U.S.A.

SUMMARY

Purpose: Malformations of cortical development (MCD) (cortical dysplasias) are well-recognized causes of intractable epilepsy. Although a histologic classification system for MCD has been proposed by Palmini et al. (Neurology 2004; 62:S2), studies to date have not assessed reproducibility. The purpose of this study was to analyze inter- and intraobserver agreement among eight experienced neuropathologists (NPs) with respect to this classification system.

Methods: Sections from 26 epilepsy resections were selected to represent the range of pathologies described by Palmini et al. Recuts of single sections from each case were sent to the NPs to classify. The slides were resent at a later date for reclassification. Kappa analysis for both inter- and intraobserver concordance was performed.

Results: Interobserver agreement was moderate (κ = 0.350–0.753) with the greatest concordance being 0.743. Of the 26 cases, the greatest concordance was present when making focal cortical dysplasia (FCD) type IIA/B classifications (12 of the 14 cases with ≥75% consensus). Mild MCD (types I/II) and FCD types I/II classifications were the least reproducible, and used most frequently in cases without consensus. Interobserver concordance was moderate to very good (range κ = 0.465–0.8504). The category with the fewest classification changes made on reevaluation was FCD type IIB (4.2%), whereas that with the most changes was mild MCD (types I/II) (52.9%).

Discussion: Interobserver concordance using this approach was moderate. The classification categories with the greatest concordance were FCD type IIA/B, and the least, mild MCD and FCD types I/II. In addition, difficulty in differentiating Mild MCD/FCD type I lesions from normal and/or gliotic tissue was noted.

KEY WORDS: Cortical dysplasia, Classification, Interobserver variability, Intraobserver variability, Malformation of cortical development.
LONG-TERM EPILEPSY ASSOCIATED TUMOR (LEAT)

• Glioneuronal
  – Dysembryoplastic neuroepithelial tumor (DNET), WHO I
  – Ganglioglioma (GG), WHO I (or PGNT)
  – Mixed GG/DNET, WHO I
  – Uncertain types

• Gliomas
  – Diffuse astros/oligos, WHO II
  – Pilocytic astro, WHO I
  – Pleomorphic xanthoastrocytoma (PXA), WHO II

• Others: angiocentric glioma, meningioma, ependymoma, astroblastoma, etc.
DNET (WHO I)

- LEAT of children/young adults
- Temporal lobe
- Benign/surgically curable
- Tumor vs. hamartoma
- Simple, complex, ‘non-specific’ variants
- BRAF-V600E in 20-30%; mIDH-, 1p19q codeletion-
EXAMPLE CASE

- 20-year-old man
- Right occipital cystic lesion with enhancing nodule
- Followed for a couple of years; originally non-enhancing, but increased in size over time and became ring enhancing
GANGLIOGLIOMA (WHO I)

- Most common LEAT
- Children/young adults
- Temporal lobe
- Benign/surgically curable
- Anaplasia rare: definition?
  - WHO grade III (grade II eliminated in 2007)
- BRAF-V600E in roughly half
GANGLIOGLIOMA (WHO I)
GANGLIOGLIOMA (WHO I)
ANA GG, WHO GRADE III
ANA GG, WHO GRADE III
Brain Pathol 24 (2014) 52–66

RESEARCH ARTICLE

BRAF V600E Mutation Is Associated with mTOR Signaling Activation in Glioneuronal Tumors

Avanita S. Prabowo; Anand M. Iyer; Tim J. Veersema; Jasper J. Anink; Antoinette Y. N. Schouten-van Meeteren; Wim G. M. Spliet; Pieter C. van Rijen; Cyrille H. Ferrier; David Capper; Maria Thom; Eleonora Aronica

Departments of (Neuro)Pathology and Pediatric Oncology, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. Departments of Neurosurgery, Neurology, Pathology and Clinical Neurophysiology, Rudolf Magnus Institute for Neuroscience, University Medical Center Utrecht, Utrecht, The Netherlands. Department of Neuropathology, Ruprecht-Karls-Universität Heidelberg, Heidelberg, Germany. Clinical Cooperation Unit Neuropathology, German Cancer Research Center (DKFZ), Heidelberg, Germany. Neuropathology Department, University College London Institute of Neurology, London, UK. Stichting Epilepsievastelling Nederland (SEIN), Heemstede, The Netherlands. Swammerdam Institute for Life Sciences, Center for Neuroscience, University of Amsterdam, Amsterdam, The Netherlands.

Keywords
BRAF, immunohistochemistry, inflammation, long-term epilepsy associated tumors, mTOR, sequencing.

Corresponding author:
Eleonora Aronica, MD, PhD, Department of (Neuro)Pathology, Academic Medical Center, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands (E-mail: e aronica@amc.uva.nl)

Received 5 June 2013
Accepted 25 July 2013
Published Online Article Accepted 14 August 2013

Disclosure: D.C. has applied for a patent on the diagnostic use of BRAF V600E mutant-specific antibody VE1. All terms are being managed by the German Cancer Research Center in accordance with its policy on financial conflicts of interest.

Abstract
BRAF V600E mutations have been recently reported in glioneuronal tumors (GNTs). To evaluate the expression of the BRAF V600E mutated protein and its association with activation of the mammalian target of rapamycin (mTOR) pathway, immunophenotype and clinical characteristics in GNTs, we investigated a cohort of 174 GNTs. The presence of BRAF V600E mutations was detected by direct DNA sequencing and BRAF V600E immunohistochemical detection. Expression of BRAF-mutated protein was detected in 38/93 (40.8%) gangliogliomas (GGs), 2/4 (50%) desmoplastic infantile gangliogliomas (DIGs) and 23/77 (29.8%) dysembryoplastic neuroepithelial tumors (DNTs) by immunohistochemistry. In both GGs and DNTs, the presence of BRAF V600E mutation was significantly associated with the expression of CD34, phosphorylated ribosomal S6 protein (pS6; marker of mTOR pathway activation) in dysplastic neurons and synaptophysin (P < 0.05). In GGs, the presence of lymphocytic cuffs was more frequent in BRAF-mutated cases (31 vs. 15.8%; P = 0.001). The expression of both BRAF V600E and pS6 was associated with a worse postoperative seizure outcome in GNT (P < 0.001). Immunohistochemical detection of BRAF V600E-mutated protein may be valuable in the diagnostic evaluation of these glioneuronal lesions and the observed association with mTOR activation may aid in the development of targeted treatment involving specific pathogenic pathways.
PXA, WHO II-III
PXA, WHO GRADE II
PXA, WHO GRADE II
ANA PXA, WHO GRADE III
ANA PXA, WHO GRADE III

Ki-67
PXA, WHO II VS. GBM WHO IV

LightCycler PCR assay

V600E

WT

MOL12-1447 POSITIVE