

**E-Methods:**

Patient cohorts: The initial screen identified all patients with medically refractory epilepsy (failure of seizure control after more than three anti-epilepsy drugs in mono- or poly-therapy) and cortical dysplasia (CD) by histopathology that had undergone resective neurosurgery at the University of California, Los Angeles (UCLA) Epilepsy Surgery Programs (Adult and Pediatric) from January 2004 to December 2007. Excluded were patients with hemimegalencephaly (n=11), tuberous sclerosis complex (n=14), CD associated with tumors (e.g. DNET, ganglioglioma; n=5) or hippocampal sclerosis (n=4; dual pathology), and CD patients who had undergone previous resective surgery (n=4), leaving a final cohort of 45 patients. FDG-PET/MRI co-registration was a routine component of the presurgical evaluation during this interval. The same inclusion/exclusion criteria were used to identify a similar group of patients with CD from 2000 to 2003 (n=38) for comparison with the 2004 to 2007 cohort. FDG-PET/MRI co-registration had not been a regular part of the presurgical evaluation from 2000 to 2003. Informed consent was obtained to use clinical, neuroimaging, and histopathology data for research purposes, and the research protocols were approved by the Institutional Review Board (IRB) of UCLA.

2004 to 2007 protocol: The multimodality presurgical evaluation included history and neurological examinations, interictal and ictal scalp EEG-video recordings, structural MRI, FDG-PET scans, FDG-PET/MRI co-registration, and (when necessary) magnetic source imaging (MEG; n=7),<sup>1</sup> neuropsychological assessments and intracarotid amobarbital injections (Wada test) for evaluation of memory and speech representation.<sup>2-4</sup> At surgery, the scalp interictal EEG focus was confirmed using intraoperative electrocorticography (ECoG) to identify areas of persistent background slowing, frequent interictal epileptiform discharges and focal abnormal

fast frequencies.<sup>5</sup> If necessary, motor-sensory mapping with somato-sensory evoked potentials (SSEP) and language localization with direct cortical stimulation while awake was performed. With the exception of one CD patient who had a normal co-registration scan, the extent of the cortical and white matter resection was based on the anatomic borders as defined by FDG-PET/MRI co-registration studies that concurred with ECoG abnormalities. If ECoG findings were wide-spread, then the resection was based on the anatomic borders identified by FDG-PET/MRI studies. The one patient with the normal FDG-PET/MRI study had chronic intracranial electrode recordings to identify sites of ictal onsets.

*Study design:* Patients in the 2004 to 2007 cohort were classified into groups based on CD histopathology, initial MRI reports from outside and within UCLA, and initial gray-scale FDG-PET scans and compared with clinical variables including postoperative seizure outcomes. In addition, we measured abnormalities in FDG-PET uptake. The main goals of our study were to compare the 2000 to 2003 with the 2004 to 2007 cohorts, and within the 2004 to 2007 cohort patients with Type I and Type II CD.<sup>6,7</sup> Secondary analyses compared patients with Normal or Abnormal MRI reports from scans performed outside of UCLA; Normal, Subtle or Obvious lesions identified using UCLA MRI protocols; Positive and Negative initial FDG-PET reports; and Concordant or Non-Concordant pre-surgery assessments based on combining data from the scalp EEG and neuroimaging (MRI & FDG-PET). The criteria for these classifications are described below.

*Clinical variables:* Clinical variables were abstracted from the medical record and included age at seizure onset, age at surgery, gender, history of infantile spasms, number of anti-epilepsy drugs (AEDs) at the time of evaluation, side and brain location(s) of the surgical resection, extent of surgery (hemispherectomy, multi-lobar, or lobar/focal resections), and use of intracranial grids

or depth electrodes (Phase II studies). Epilepsy duration was calculated as the interval (in years) from age at seizure onset to surgery. Patient records were further reviewed to determine if MRI scans had been performed at an outside hospital or clinic prior to presurgical evaluation at UCLA, and whether they had been interpreted as Normal or Abnormal identifying the lesion as cortical dysplasia. After surgery, the brain tissue was processed for histopathology as previously described.<sup>8</sup> Cases were classified as Palmini Type I (mild without dysmorphic cells) or Type II (severe with dysmorphic cytomegalic neurons with or without balloon cells) CD.<sup>6,7</sup> Also recorded was whether patients were seizure-free postoperatively, the time since surgery of last follow-up (in years), and any surgical complications.

The inpatient scalp EEG-video reports were abstracted to determine seizure frequency and localization of abnormal findings. Seizure frequency was calculated as the average number of seizures per 24 hours during the time of inpatient EEG monitoring. All patients had at least three ictal events captured during scalp video-EEG telemetry. Interictal and ictal EEG findings were classified as Normal (no interictal abnormalities), Localized (intermittent interictal focal background slowing, focal spikes or ictal onsets recorded in up to three scalp electrodes in closest proximity to the eventual site of resection), Lateralized (if interictal and ictal EEG findings were ipsilateral to the side of the lesion) or Bilateral/Non-Focal (interictal discharges of nearly equal frequency over both hemispheres or ictal onsets non-lateralizing).

The presurgical EEG and neuroimaging information was classified as Concordant or Non-Concordant without consideration of the FDG-PET/MRI co-registration studies. Information was considered Concordant if the ictal scalp EEG showed Localized or Lateralized findings congruent with Subtle or Obvious MRI lesions and Positive FDG-PET scans. Patients were considered Non-Concordant if the MRI was Normal (even if FDG-PET was Positive), if the MRI

was Subtle with a Negative FDG-PET even if the scalp EEG was Localized, or if the initial ictal EEG was Bilateral/Non-Focal with a Subtle MRI and Positive FDG-PET scan.

*Neuroimaging:* MRI images were acquired on a 1.5-T Siemens Sonata scanner (Siemens Medical Systems, South Iselin, NJ). The structural MRI protocol included T1 sagittal (TR/TE 400/14, matrix 256x192, 5mm thickness), 3D T1 coronal Magnetization Prepared Rapid Gradient Echo sequence (MPRAGE) ( TR/TE 25/9, TI 8, matrix 256x256, 1.8 mm thickness), T2 axial (TR/TE 3000/80, matrix 256x192, 4mm thickness), FLAIR axial (TR/TE 8000/108, TI 2000, matrix 256x192, 4mm thickness), FLAIR coronal (TR/TE 8000/18, matrix 256x192, 4mm thickness), and T2 coronal (TR/TE 4000/85, matrix 256 x 192, 4mm thickness). The structural MRI scans were initially reviewed without knowledge of the FDG-PET scans and EEG data, and the MRI results were abstracted from those reports to determine if a lesion consistent with cortical dysplasia was identified. MRI scans within UCLA were classified as Normal, Subtle (not easily identified cortical dysplasia), or Obvious (should be identified by most radiologists) by the neuroradiologist (NS).

The FDG-PET scan was performed using the CTi/Siemens whole body positron tomography system with 15cm FOV and 3.0mm slice thickness using a standard protocol.<sup>9</sup> The gray scale FDG-PET scans were internally scaled relative to the basal ganglia, and initially interpreted qualitatively without knowledge of the structural MRI or EEG results. From the initial FDG-PET reports, the results were classified as Negative or Positive if an area of interictal hypometabolism that corresponded to the eventual site of surgical treatment was identified. In this surgical cohort, there were no patients in whom the localization of the FDG-PET abnormalities did not overlap with MRI findings if a MRI lesion existed.

FDG-PET and MRI image co-registration was performed using Fusion 7 software (Mirada) with Vitrea 3D workstation (Vital image). Automatic alignment was performed without fiducial markers. Fused images were displayed as multi colored images. Each color change corresponded to approximately a 15% difference of the FDG uptake. The borders of the area of PET hypometabolism were determined based on the asymmetry of uptake comparing the two cerebral hemispheres. The sequence in assessing the co-registration scans was as follows: A) The fusion scans were created with color coded grading (white as highest metabolism followed by red, orange, yellow, green, and blue as lowest). B) By visual assessment asymmetric areas of hypometabolism were identified. Most of the cases showed red to blue or red to green areas of asymmetry. Thus, the areas of hypometabolism were very different from normal cortex with normal metabolism and could be easily defined. C) When the visual asymmetry was red to yellow or yellow to green, which is more subtle hypometabolism we supplemented the visual assessment using the Bq/ml ratio (see below) to define if an area was abnormal. We accepted a difference of 10% as significant and suspicious for CD. However, we found that there was usually more than a 15% difference in patients with cortical dysplasia. D) The MRI and PET pictures were interchangeable using the fusion program. Thus, the areas of decreased FDG uptake could be directly compared with possible abnormalities on structural MRI.

Semi-quantitative measurement of the FDG signal was obtained using standard uptake value (SUV) which was defined as the ratio of activity (in  $\mu\text{Ci/mL}$ ) divided by the decay-corrected activity injected into the patient (in  $\text{mCi/Kg}$ ). This was calculated automatically in the fusion program.<sup>10</sup> The corresponding areas of gray matter over the contralateral cerebral hemisphere were chosen as control sites, and one region per patient measured. If the area of hypometabolism involved large multi-lobar regions, the area of the opposite cerebral hemisphere

corresponding to the region of greatest hypometabolism was chosen as the control site. Body surface area correction was applied and venous blood glucose levels were obtained in all patients.

Statistical analyses: CD histopathology classification (Type I, Type II), initial UCLA MRI classification (Normal, Subtle, Obvious), initial gray scale UCLA FDG-PET reading (Negative, Positive), outside MRI classification (Normal, Abnormal), presurgical classification (Concordant, Non-Concordant), clinical variables, and SUV measures of FDG-PET uptake were entered into a database and analyzed using a statistical program (StatView 5; SAS Institute, Inc., Cary, NC, USA). Differences between Normal (contralateral areas for FDG-PET) and patients with Type I and Type II CD, Normal, Subtle, and Obvious MRI lesions, Negative and Positive FDG-PET scans, Normal and Abnormal outside MRI reports, and Concordant and Non-Concordant presurgery classification were statistically compared using analysis of variance (ANOVA), t-tests, and Chi-square where appropriate. All tests were two-tailed. Given the number of planned statistical comparisons, the threshold for significance was set a priori at  $P < 0.01$ .

**References for Methods**

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