Multimodality imaging for focus localization in pediatric pharmacoresistant epilepsy


ABSTRACT – Multiple structural and functional imaging modalities are available to localize the epileptogenic focus. In pre-surgical evaluation of children with pharmacoresistant epilepsy, investigations with the maximum yield should be considered in order to reduce the complexity of the workup. Objective. To determine the extent to which PET, ictal/interictal SPECT and its co-registration with the patient’s MRI contributes to correct localization of the epileptogenic focus, surgical intervention and to the post surgical outcome in paediatric patients. Methods. The study population included children and adolescents with pharmacoresistant epilepsy (n = 50) who underwent preoperative evaluation, surgery and had postoperative follow-up for at least 12 months. Outcome was measured by postoperative seizure frequency using Engel’s classification. Results. Thirty-nine patients (78%) became completely seizure free after surgical intervention. The likelihood to benefit from surgical treatment was significantly higher if localization with more imaging modalities (MRI, PET, SPECT) were concordant with respect to the resected brain area (p < 0.01). Preoperative PET examination provided better localizing information in patients with extratemporal epilepsy and/or dysplastic lesions, whereas SPECT was found to be superior to PET in patients with temporal lobe epilepsy and/or tumors (p < 0.05). No significant difference was noted in the surgical outcome in younger or older age group, in children with or without special education needs. Conclusion. In paediatric epilepsy pre-surgical evaluation, the combined use of multiple functional imaging modalities for a precise localisation of the epileptogenic focus is worthwhile for both extratemporal and temporal lobe epilepsy, also when EEG and MRI alone are non-contributive, given the potential benefit of complete postoperative seizure control.

Key words: epilepsy, childhood epilepsy, co-registration, MRI, PET, SPECT, multimodality imaging, presurgical evaluation

About a 20-30% of patients with epilepsy continue to have seizures in spite of treatment with modern antiepileptic drugs. In two thirds of this patient population, the disease starts in childhood (Kim et al. 2000a, Rossi
Surgery has become an accepted method of treatment in properly selected patients with intractable focal epilepsy (Wyllie, 2000), aiming at a higher quality of life (Gilliam, 1997) and an increasing number of children with medically intractable seizures are now being referred for surgical management. For a successful outcome from epilepsy surgery, precise localization of the epileptogenic region in the brain is necessary (Snead, 2001). Many structural and functional imaging modalities are available to localise the epileptogenic brain tissue. Detailed magnetic resonance imaging (MRI) examinations, for which particular protocols have been proposed (Kuzniecky, 1999) contribute to the detection of structural brain abnormalities such as hippocampal sclerosis and malformations of cortical development which are often associated with medically refractory epilepsy (Dupont and Baulac, 2004, Goyal et al. 2004, Grant et al. 1997; Bronnen, 2002). Positron emission tomography (PET) has an established role in the non-invasive localization of epileptic foci being able to lateralize and regionalize potentially epileptogenic regions in particular in children and in patients who have normal MR imaging (Sood and Chugani, 2006, Juhasz and Chugani, 2003, Gaillard et al. 1995). Single photon emission computerized tomography (SPECT) is another useful adjunctive technique in the presurgical evaluation of children and adults with refractory partial epilepsy of diverse etiologies, if carried out in the ictal period and compared to an interictal examination (Lawson et al. 2000, O'Brien et al. 1998, Harvey and Berkovic, 1994, Chiron et al. 1999, Kaminska et al. 2003). Recent studies have shown that digital analysis i.e. subtraction SPECT co-registered to MRI (SISCOM) improves the yield of SPECT exams (O'Brien et al. 2004, O'Brien et al. 2000, Valenti et al. 2002, Vera et al. 1999). Multimodality imaging combines the structural imaging with coregistered functional imaging information, thereby improving the ability to detect and define the extent of epileptogenic lesions. Overall, the concordance of EEG onset with an abnormality on the MRI and corroborating localization by other modalities markedly increases the chances of surgical outcome in adults (Knowlton 2004, Lee et al. 2005).

In the paediatric population, optimal numbers of examinations should be addressed to reduce evaluation time and complexity of the presurgical exploration. While the yield of a particular imaging technique to localize the epileptic focus in children has been looked at in some pediatric studies (Hertz Pannier et al. 2001), no comparative study of MRI, PET and SPECT and co-registration of PET/SPECT with the patient’s MRI with respect to postoperative outcome has been reported so far in children. Moreover, it is not yet clear if the combination of all methods increases the yield of the single techniques in younger patients.

This study was done to determine if the comprehensive application of various imaging modalities to delineate the epileptic focus and their co-registration with MRI improves epileptic focus localization and whether this is related to a better surgical outcome in paediatric patients. The surgical outcome was studied to see whether the outcome differs according to the age group or cognitive status and if the yield of PET or SPECT differs with respect to the site of the epileptic focus (temporal versus extratemporal), across different type of surgical interventions or according to the underlying histopathological substrate.

Patients and methods

Patients

Eighty-one children and adolescents were evaluated in the Geneva-Lausanne presurgical unit between 1996 and 2004. The cases of all patients who underwent surgical intervention (n = 50) were retrospectively reviewed. Before admission, all patients were at least on two antiepileptic drugs (AEDs); in most cases even more AEDs were tried. The patients in the current study had a neurological examination as well as long-term video-EEG monitoring, high resolution MRI, PET, an ictal and an interictal SPECT and neuropsychological examination (interictal and postictal) as part of their preoperative evaluation. The interictal neuropsychological examination included tests of verbal and visuospatial memory, attention and language. The postictal neuropsychological examination was done in the immediately postictal period. A subset of the tests used in the interictal neuropsychological examination was given in the postictal period (Pegna et al. 1998). In patients younger than six years, a developmental examination was done.

As part of the presurgical work up, nuclear imaging was used in order to determine bilateral or multifocal dysfunction. In all patients who had an ictal SPECT examination, SISCOM analysis was performed in order to identify the maximum perfusion abnormality and correlate with the MRI. Surgical decision was based on the combined results of the interictal EEG, ictal scalp EEG, MRI and the functional imaging findings as well as the neuropsychological workup. When the results of the workup were discordant, intracranial EEG (Phase 2 evaluation) was considered in order to determine and/or delineate the epileptic focus. Fifty patients between the ages of six months to 18 years had surgical intervention, including temporal lobectomy, unilobar extratemporal resections, multilobar resections, lesionectomy and hemispherectomy (table 1).

Post-surgical follow up

All patients except one had postoperative follow-up for at least 12 months (range: 12 months to 48 months; mean 21 months). The only patient without regular follow-up was referred to us by a human rights organization which also does the basic follow-up after the children return to their
home country. No persisting seizures in this patient were reported to our team.

In order to determine possible differences in the clinical characteristics and the yield of the comprehensive work-up (multimodal imaging) in younger versus older patients, we divided our patients into two groups, those who were younger or equal to 12 years (Group 1) and those who are older than 12 years (Group 2). We also examined if multimodal imaging is more contributive (or less) for focus localization and surgical intervention, in children with specialized education needs, with regard to postoperative seizure control.

Video-EEG recording

Scalp recordings of 32 channels, with a sampling frequency of 128 or 256 Hz, including ECG, during a mean of five days (range: 3-10 days) were carried out using either Deltamed® (Paris, France) or Biologic® (Mundelein, IL, USA) equipment. Medical and/or paramedical staff supervised the children during 24 hours/day, with or without the presence of one parent. EEG was recorded continuously throughout the investigation with a sampling rate of 256 Hz and filter settings between 0.1-100 Hz against FCz electrode as reference. Some patients had sphenoidal electrodes or additional anterior temporal electrodes.

Magnetic Resonance Imaging

All the patients had baseline MRI scans as part of the preoperative evaluation. The volumetric MRIs obtained for all patients in this study were acquired with a 1.5 T Eclipse scanner (Picker Inc., Cleveland, Ohio, USA). The MRI was performed according to a standardized seizure protocol (Coronal T2-weighted fast spin-echo (TR 3092; TE 11/100), Coronal and axial fluid-attenuated inversion recovery (FLAIR) TR11000; TE140; TI 2800, T2 0.9 x 0.9 x 6 mm/Flair 0.45 x 0.45 x 6 mm), sagittal 3D gradient echo T1 (TR 12, TE 4, voxel size 0.98 x 0.98 mm³, thickness 1 mm and diffusion sequences), coronal and axial MPR reconstructions were systematically done as well as T1 after gadolinium injection. Gadolinium injection was used only if an expansive lesion/tumour was suspected.

PET & SPECT studies

PET examination was done in all except one patient. The emission study (25 min) started 30 min after intravenous injection of approximately 222 MBq of fluorine-18 fluoro-deoxyglucose (FDG). All data sets were acquired in 3D on an ECAT ART PET scanner (CTI PET Systems, Knoxville, TN) upgraded to use collimated 137Cs single-photon point sources for TX scanning. Acquired projection data were pre.corrected for scatter using the latest numerical implementation of the single-scatter simulation algorithm supplied with the ECAT 7.2 software provided by the scanner manufacturer. The re-projection algorithm (3DRP) used routinely for reconstruction of clinical brain studies in our division was used (Ramp filter, cut-off frequency 0.35 cycles/pixel), resulting in 47 slices consisting of 128 x 128 matrices with a zoom factor of three (voxel size, 1.716 x 1.716 x 3.375 mm³). Areas with focal decreases (hypometabolism) were identified by visual analysis of the FDG activity images. The qualitative visual interpretation was done by experts in nuclear medicine (JPW and VM), who were blinded to other localizing information, especially the MRI. Each individual PET has been co-registered with MRI to enhance its spatial resolution and to allow proper analysis with respect to the resection site. Ictal SPECT was obtained in 41 patients. A single bolus of 740 megabecquerels (MBq) of ethylenecysteinate dimer (ECD) labelled with Technetium-99m (99mTc-ECD) was injected for each scan session. SPECT scans were obtained 20-60 minutes after injection on a 3-heads Toshiba CGA-9300 camera with fan beam collimators and simultaneous acquisition of the 153Gd-rod source for transmission and scatter correction. Data were acquired and reconstructed in a 128 x 128 matrix. The whole brain volume was covered. Scatter correction used a Shepp and Logan filter and transmission correction was applied using the 153Gd transmission scan.

The epileptogenic activity during tracer caption of the PET and interictal SPECT was controlled with simultaneous EEG recordings and analyzed with respect to the presence of clinical or subclinical seizures. The presence of a subtle seizure would have influenced the interictal functional imaging, i.e. generating a hyper-rather than a hypoactivity.

### Table 1. Type of surgical intervention and% of correct focus localization with different investigative modalities in different subgroups.

<table>
<thead>
<tr>
<th>Operation (n = 50)</th>
<th>EEG</th>
<th>MRI</th>
<th>PET</th>
<th>SPECT</th>
<th>Patients with class I outcome (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporal lobe resection (16)</td>
<td>11 (69%)</td>
<td>13 (81%)</td>
<td>11 (69%)</td>
<td>12 (75%)</td>
<td>13 (81%)</td>
</tr>
<tr>
<td>Extra temporal (unilobar) resection (12)</td>
<td>10 (83%)</td>
<td>7 (58%)</td>
<td>9 (75%)</td>
<td>7 (58%)</td>
<td>7 (58%)</td>
</tr>
<tr>
<td>Multilobar resection (4)</td>
<td>4 (100%)</td>
<td>3 (75%)</td>
<td>3 (75%)</td>
<td>2 (100%)</td>
<td>3 (75%)</td>
</tr>
<tr>
<td>Lesionectomy (7)</td>
<td>6 (86%)</td>
<td>7 (100%)</td>
<td>5 (71%)</td>
<td>4 (57%)</td>
<td>6 (85%)</td>
</tr>
<tr>
<td>Hemispherectomy (11)</td>
<td>8 (80%)</td>
<td>10 (91%)</td>
<td>10 (91%)</td>
<td>6 (55%)</td>
<td>10 (91%)</td>
</tr>
</tbody>
</table>

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An interictal SPECT was performed only if an ictal SPECT was done, given that the yield of interictal SPECT alone is low (Spencer, 1994). Injection of the SPECT tracer during the seizure was done as quickly as possible (the average delay between seizure onset and injection of the tracer being 20 seconds), this was verified by review of the video-EEG recording and not considered as ictal if the injection was carried out after the electroencephalographic seizure pattern stopped. Intercital studies were performed after the patient had been seizure free for 24 hours. In some patients, the seizure frequency was > 10 seizures/day despite polytherapy, and the limit for being seizure free for 24 hours was lowered to 2 hours without seizures.

Subtraction study of ictal versus interictal SPECT
Nuclear medicine images were transferred on the dedicated image processing workstation in the papyrus format (Ratib et al. 1994). The images were then resampled in an isotropic set and then co-registered with the anatomical framework using AIR 5.2 software (Woods et al. 1998), a voxel based intensity algorithm avoiding the use of external markers with the possibility of intermodal misplacement. Once the interictal and ictal SPECT images were co-registered with MRI, sets of images were normalized and subtraction between these two sets (SISCOM) computed for each patient (O’Brien et al. 1999). For the purpose of the study, ictal SPECT analysis was considered alone in those cases where the discharges were too frequent or when clinical/subclinical seizures occurred during the interictal SPECT, i.e. a subtraction analysis would have provided inconclusive results.

Histopathological examination was done in all study patients. The findings were classified as malformations of cortical development (cortical dysplasia, tuberous sclerosis), tumor (e.g. DNET, ganglioglioma), gliosis, Rasmussen’s encephalitis and vascular malformations.

Analysis
Outcome in relation to seizure control was based on Engel’s classification of postoperative outcome (Engel et al. 1993). We assessed the relation between the surgical outcome and the concordance of the imaging results. For comparisons of the yield and correctness of a given investigation with the operated site, the result of the investigation was coded with respect to its indicated dysfunctional zone. Left and right frontal, temporal and posterior (i.e. parietal and occipital) as well as left, right hemispheric and multifocal-bihemispheric were differentiated. The localization by an imaging modality was defined as concordant with the operative site if the lesion/dysfunctional zone were uni focal, and when the imaging abnormality and the resection site were matched or largely overlapping. It was considered non-concordant if several lesions or dysfunctional zones were seen in a given exam or if the lesion was in another lobe than where the surgery was performed or despite being in the same lobe, the imaging abnormality and the resection site was not overlapping or was largely mismatched.

Significant deviation of the relative frequency from chance level was tested with the Chi-square test. Correlation analysis was performed using Spearman’s rank correlation. The significance level was set at p < 0.05. In order to calculate the yield of combining different imaging modalities (MRI, PET, SPECT) in localizing the dysfunctional zone, a co-registration score was calculated with one point for each concordant exam. A score of 3 was given if all 3 exams are concordant with the operation site, score 2 if 2/3 are concordant, score of 1 if 1/3 concordant and 0 if all exams provided ambiguous information (e.g. if MRI and PET were concordant, but not SPECT with the future operated site, a score of 2 was given).

Results
The age of the patients ranged from six months to 18 years (mean 10.2 +/- 5.3 years). Mean age of onset of seizures was 4.3 years (+/- 4.2; median: 3 years). The average preoperative duration of epilepsy was 5.7 (+/- 4.2; median: 5 years). There was no difference for boys and girls in any of the above variables. Group 1 (children) was composed of thirty patients equal to or younger than 12 years (14 boys and 16 girls; group I). Group 2 (adolescents > 12 years) comprised 20 patients, including more girls (n = 13) than boys (n = 7). The mean age of epilepsy onset in Group 1 was 2.0 years (one month to 9 years) compared to 7.7 (3 months to 14 years) in Group 2. The duration of epilepsy was shorter in Group 1 (4.7 vs 5 years in Group 2) although this did not reach significance (p = 0.07). In the patient group as a whole, 62% patients (n = 31) needed specialized schooling or kindergarten. There was a significant difference between the need for specialized education between two patient subgroups: 77% (n = 23) patients in Group 1 were enrolled in special assistance programs, as compared to 40% (n = 8) in Group 2 (p = 0.009).

Preoperative evaluation
In 39 patients, unifocal onset was noted in the ictal EEG while multifocal or diffuse EEG onset was found in 11 patients. Continuous Video-EEG recording provided concordant results with respect to the future operation site, in 32 (64%) patients. MRI provided localisation, concordant to the operation site in 41 (82%) patients, PET in 38 (78%) patients and SPECT in 31 (76%) patients. Intracranial EEG monitoring was done in 5 (10%) patients.
Surgical outcome

Thirty-nine patients (78%) had class I outcome, four patients had class II and four patients had class III outcomes respectively, and in two patients surgery did not lead to worthwhile improvement (class IV). Overall, 86% (n = 43) benefited significantly from surgical treatment (i.e. class I and II).

There was no significant difference regarding the postoperative seizure outcome, between the younger and the older children, i.e. patient subgroups 1 and 2: 82% (n = 24) patients and 75% (n = 15) were seizure-free postoperatively. The same was true for children with and without special education needs, 84% (n = 16) of children with normal schooling were seizure free versus 77% (n = 23) of those with special education needs.

Duration of epilepsy

Ninety percent (n = 9) of the patients who were operated within two years of epilepsy onset had a seizure free outcome compared to 74% (n = 28) patients operated after 2 years of epilepsy onset (mean duration of epilepsy seven years, range 2.8 – 13.7 years) with a seizure free outcome, p = 0.2. All patients except one who had less favorable seizure outcome (class III and IV) were operated after the duration of five years after epilepsy onset.

Comparing the postoperative outcome in patients who had different types of surgical intervention, more than 75% of the patients who had temporal lobectomy, lesionectomy, multilobar resection and hemispherectomy had complete seizure-freedom (Engel’s class I) while 58% of patients with unilobar extra-temporal resection had class I outcome (p = 0.06).

Concordance of MRI, PET and SPECT

The concordance of the preoperative focus localization using different imaging modalities with the operation site was examined in relation to the seizure outcome (table 2). Concordance of focus localization by all three imaging modalities (MRI, PET and SPECT) with the operation site (co-registration score 3) was seen in 19/41 patients and 95% (n = 18) of these patients have a seizure free outcome. Focus localization with both PET as well as SPECT were concordant with the operative site (co-registration score 2) in 25/41 (61%) patients; 92% (n = 22) of these patients have a seizure free outcome.

There was a marked association between the calculated co-registration score and operation results: the chances of postoperative seizure freedom were higher if localization with more imaging modalities were concordant with respect to the resected brain area (r = -0.55, p = 0.003, figures 1 and 2). This was true for both patients with temporal and extratemporal epilepsies.

Concordance of the focus localized with PET and the future operation site turned out to be of prognostic significance: in the patient group with class I and II (favorable outcome), it was concordant in 84%, compared to 33% in patients with class III and IV (p < 0.001). Ictal/interictal SPECT comparison (or SISCOM) alone did not differentiate between the better and less good outcome groups: the focus localized by SPECT/SISCOM corresponded to the future operation site in 75% (class I and II) and 67% (class III and IV), respectively (not significant).

Yield of the PET and SPECT imaging in patients whose MRI was non-contributive

In those patients whose MRI was not contributive for focus localization (n = 9), PET was concordant with the operated site in 4/9 (44%) and two of them were completely seizure free (table 3). SPECT was concordant with the operated site in 8/9 (89%) and three of them were completely seizure free. Both PET and SPECT were concordant with the operated site in 4/9 (44%) patients. Among them, one patient had temporal lobe resection and is completely seizure free. The other three had extratemporal resections, two of them have significant reduction of seizures (class I and class II).

Yield of the PET and SPECT imaging in temporal versus extratemporal epilepsy

We analyzed patients with temporal and extratemporal epilepsy separately in terms of the yield of the PET and SPECT imaging. In patients with class I and II outcome, PET was more often correct in extratemporal epilepsy (94%) as compared to temporal lobe epilepsy (69%).

<table>
<thead>
<tr>
<th>Imaging modalities</th>
<th>Concordant (Engel’s class I)</th>
<th>Non-concordant (Engel’s class I)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI, PET &amp; SPECT</td>
<td>19/41</td>
<td>11/22 (50)</td>
<td>0.002</td>
</tr>
<tr>
<td>PET &amp; SPECT</td>
<td>25/41</td>
<td>10/16 (63)</td>
<td>0.05</td>
</tr>
<tr>
<td>PET and MRI</td>
<td>34/49</td>
<td>8/15 (53)</td>
<td>0.003</td>
</tr>
<tr>
<td>PET alone</td>
<td>38/49</td>
<td>5/11 (45)</td>
<td>0.001</td>
</tr>
<tr>
<td>SPECT and MRI</td>
<td>22/41</td>
<td>10/18 (56)</td>
<td>0.003</td>
</tr>
<tr>
<td>SPECT alone</td>
<td>31/41</td>
<td>7/10 (70)</td>
<td>NS</td>
</tr>
</tbody>
</table>
Pat. 1. Left posterior temporal epilepsy with dysplasia

Pat. 2. Right parietooccipital epilepsy, polymicrogyria on MRI

Pat. 3. Left temporal epilepsy, MRI normal

Pat. 4. Right frontal epilepsy, cavernoma frontal right

Figure 1. Multimodal integration of imaging techniques in epilepsy – figure showing four different patients for whom MRI, PET and SISCOM/SPECT show different results. PET is shown in yellow and SISCOM in red (maximum) and green (isosurface projected on the 3D rendering of the brain). Axial views are shown in A, C, E, G, H and 3D reconstruction (lateral view) are displayed in B, D, and F. Patient 1 is a four year old girl, who suffered from left posterior temporal epilepsy; MRI showed dysplasia in the left temporal lobe, PET presented a hypometabolism in the temporal lobe. SISCOM indicated maximum perfusion changes in the same area (A, B), co-registration score 3, she was operated and is seizure free (Engel’s class I). Patient 2 is nine years old boy who suffered from right parieto-occipital epilepsy. MRI showed a polymicrogyria in the right parieto-occipital area, the PET suggested hypometabolism and SISCOM showed activation in the same area (C, D) co-registration score 3, he was operated and is seizure free (Engel’s class I). Patient 3 is six year old boy who suffered from left temporal epilepsy, MRI did not show any abnormality, PET was indicative of temporal hypometabolism and the SISCOM showed a clear temporal hypersignal (E, F), co-registration score 2. He was operated on, histopathologic examination showed cortical dysplasia with balloon cells, he is seizure free (Engel’s class I). Patient 4 is 16 year old girl, she suffered from right frontal epilepsy, MRI showed multiple cavernomas, the biggest in the right frontal area (G). PET was suggestive of hypometabolism in the right occipital area and SISCOM showed hypersignal in the right occipital area (H), co-registration score 1, she was operated (resection of the frontal cavernoma) and is seizure free (Engel’s class I).
The reverse pattern seems to be true for ictal/inter-ictal SPECT comparisons: it was found to be concordant with the future operation site in 90% of patients with temporal lobe epilepsy, and in 69% with extratemporal epilepsy (p = 0.014, figure 3).

Concordance of the focus localized with MRI, PET and SPECT and intracranial EEG

Five patients had intracranial EEG recordings (Phase 2 evaluation) to determine the ictal onset zone. MRI was non-contributive in four of them. In two of these patients, functional imaging findings (both PET and SPECT) correlated with the invasively determined ictal onset zone. Only one of these two patients is completely seizure free, the other patient has a moderate reduction of seizures (class 3). In the other two, localization by SPECT correlated with the intracranial EEG localization (MRI and PET did not show any abnormality in one patient and showed multifocal abnormalities in the other). One of these two patients has a class III outcome; the other patient had no improvement at all after surgery (table 3). The fifth patient had a left temporo-occipital lesion on the MRI, but multifocal abnormalities on the PET and SPECT, intracranial EEG monitoring showed a clear occipital focus, he was operated and is seizure free.

Table 3. Yield of the PET and SPECT imaging in patients whose MRI was non-contributive.

<table>
<thead>
<tr>
<th>Patient</th>
<th>MRI</th>
<th>PET</th>
<th>SPECT</th>
<th>Phase 2 (EEG onset)</th>
<th>Operation*</th>
<th>Pathology</th>
<th>Outcome (Engel’s class)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal</td>
<td>Temporal</td>
<td>Temporal</td>
<td>-</td>
<td>TLR</td>
<td>Dysplasia</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>Multifocal</td>
<td>Multifocal</td>
<td>Temporal</td>
<td>-</td>
<td>TLR</td>
<td>Gliosis</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Multifocal</td>
<td>Multifocal</td>
<td>Temporal</td>
<td>Temporal</td>
<td>TLR</td>
<td>Gliosis</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>Normal</td>
<td>Frontal</td>
<td>Frontal</td>
<td>Frontal</td>
<td>UELR</td>
<td>Gliosis</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>Normal</td>
<td>Normal</td>
<td>Frontal</td>
<td>Frontal</td>
<td>UELR</td>
<td>Gliosis</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>Multifocal</td>
<td>Frontal</td>
<td>Frontal</td>
<td>Frontal</td>
<td>UELR</td>
<td>Gliosis</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>Multifocal</td>
<td>Multifocal</td>
<td>Frontal</td>
<td>-</td>
<td>UELR</td>
<td>Tuberous sclerosis</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Multifocal</td>
<td>Multifocal</td>
<td>Multifocal</td>
<td>-</td>
<td>UELR</td>
<td>Cicatrix (ancient stroke)</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>Multifocal</td>
<td>Parieto-occipital</td>
<td>Parieto-occipital</td>
<td>-</td>
<td>MLR</td>
<td>Tuberous sclerosis</td>
<td>2</td>
</tr>
</tbody>
</table>

* TLR = temporal lobe resection, UELR = unilobar extratemporal lobe resection, MLR = multilobar resection, Phase 2 = intracranial EEG monitoring.
Yield of the PET and SPECT imaging across different types of surgical intervention

Among the patients who had temporal lobe resections (n = 16), PET provided correct localization in 11/16 (69%) and SPECT in 12/16 (75%) (table 1). In two of these patients, MRI was not contributive but PET and/or SPECT were contributive (figure 1E, F). They are both seizure free after the resection. Among the patients who had unilobar extra-temporal resections (n = 12), PET provided correct localization in 9/12 (75%) and SPECT in 7/12 (58%). In one of these patients, MRI was non-contributive, but PET and SPECT contributed to focus localization. This patient is seizure free after the surgery. Four patients had multilobar resections, three of them had lesions on MRI that were concordant with PET and/or SPECT, and they were all seizure free postoperatively. In the fourth patient, MRI showed multiple lesions in both hemispheres, PET and SPECT showed left parieto-occipital dysfunction; she was operated and has a class II outcome (table 3). Among the patients who had hemispherectomy (n = 11), MRI showed unilateral hemispheric involvement in 10 patients; this was concordant with the findings on PET and/or SPECT and 9 of them are seizure free. In another, MRI showed evidence of a left parieto-occipital lesion while PET as well as SPECT showed diffuse left hemispheric dysfunction. This patient had a hemispherectomy and is seizure-free.

Histopathology

Gliosis (n = 17) and dysplasia (n = 12) were the two most frequent histopathology findings. Dysplastic lesions were more often found in the younger patient group (Group 1), whereas no clear age predominance was noted for the other pathologies. The best surgical outcome was found for patients in whom the histopathological analysis revealed a tumor lesion (DNET, ganglioglioma), Rasmussen’s encephalitis and cortical dysplasia with balloon cells (table 4).

Yield of the PET and SPECT imaging in different pathologies

PET provided an excellent localization tool in dysplastic lesions, i.e. focus localized with PET was concordant with the operated site in 91% patients with dysplasia who had favorable (class I and II) outcome, in gliotic lesions, PET localization was concordant in 80%. Localization with ictal/interictal SPECT was also useful, although the concordance rates were somewhat lower in these two histopathology groups (70% for dysplastic lesions and 69% for gliotic lesions). The higher yield of PET versus SPECT for the localization of dysplastic lesions was highly significant (p < 0.001), while in tumor lesions, SPECT analysis yielded correct localization in all cases (5/5), compared to 4/5 (80%) for the PET.

Discussion

The main goal of epileptic focus localization with multimodality imaging is more effective presurgical evaluation and, consequently, better selection of patients for surgery. Bringing multiple imaging modalities together allows the utilisation of newer imaging techniques to guide and thus reduce the need for invasive procedures in the surgical procedure.
treatment of focal epilepsies. This requires the fundamental task of co-registration that aligns image information to the same anatomical coordinate space used before and during surgery (Knowlton, 2004). The synergistic use of imaging modalities, optimally applied using image co-registration, allows to overcome the intrinsic limitations of each modality and to enhance the specific advantages of the different approaches as it leads to increased spatial anatomical-functional precision.

In the present study, we addressed the utility of multimodality imaging in pediatric patients who were evaluated with video-EEG and modern imaging tools including co-registration of preoperative MRI, PET and SPECT and their correlation with operative and pathological findings. The primary goal of complete seizure control was achieved in the majority of the selected patients in whom surgery was undertaken; therefore only few patients were found in class III and IV (i.e. less favorable outcome). Our experience suggests that multimodality imaging improves our ability to detect and define the extent of epileptogenic lesions. However, with certain pathologies SPECT imaging seemed to be redundant in retrospective, (e.g. Rasmussen’s encephalitis) or other uni-hemispheric processes; similar to PET imaging in tumoral lesions in the temporal lobe.

We found that an excellent surgical outcome was more likely if more imaging modalities agreed with respect to the operative location. Thus, the application of several investigations might be worthwhile in the context of presurgical evaluation given the potential benefit of complete seizure control post-operatively, although the logistical and medical expenditure are significant, particularly in young children. MRI, PET and ictal SPECT each have their strengths, but also their shortcomings with respect to precise focus localization. The presence of a plausible epileptogenic lesion on the MRI more or less determines the structure to be resected. However, MRI may not show abnormalities despite their existence (e.g. in dysplasias) (Pasquier et al. 2002), and on the other hand, may show abnormalities, which are transient and unrelated to a persistent and operable lesion (Lazeyras et al. 2000, Bauer et al. 2006) or might show multiple areas with abnormalities as in tuberous sclerosis. PET has an established role in the diagnosis of epilepsy, although the extent of hypometabolism may exceed the extent of the epileptogenic zone (Juhasz and Chugani, 2003). This is particularly true for epilepsy related to hippocampal sclerosis. In patients with extratemporal epilepsy in the present study, PET often showed very circumscribed metabolic changes concordant with the epileptogenic area. Whenever possible, the hypometabolic area as shown by PET was resected, provided that vital cortex was not harmed. Ictal SPECT and subtraction analysis have also been found to be useful; however, since seizures are a dynamic phenomenon, areas of hyper-perfusion may indicate propagation areas (Huberfield et al. 2006). Thus, comparison of several exams in terms of concordance may increase the likelihood of determination of the dysfunctional zone.

If EEG, PET and/or SPECT were concordant with the MRI, it added to the certainty of the localisation and therefore supported the decision for a surgical treatment or, as pointed out above, aided in the determination of the extent of resection. However, in nine patients (18%) MRI provided no localizing information (either no abnormality or presence of multiple focal abnormalities) with respect to the epileptogenic zone, necessitating additional information from other imaging tools (PET, SPECT) which was successfully provided in five patients (56%). While we cannot make definite predictions based on one patient in our study with normal MRI and PET and SPECT concordance, who had a temporal resection and an excellent outcome, we found that in extratemporal resections, when the MRI is non-contributive, PET and SPECT are definitely contributive.

Of the five patients in our patient group who had intracranial EEG recordings to determine the ictal onset zone, three showed concordance of PET and SPECT and two of them were ultimately seizure free. In the other two patients without localizing MRI and PET (and unclear scalp EEG), only the zone localized by SPECT correlated with the

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Frequency (n = 50)</th>
<th>Group I (n = 30)</th>
<th>Group II (n = 20)</th>
<th>Class I outcome (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical dysplasia</td>
<td>12</td>
<td>10</td>
<td>2</td>
<td>11/12 (92%)</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>0/2</td>
</tr>
<tr>
<td>Tumor (DNET, ganglioglioma)</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>5/5 (100%)</td>
</tr>
<tr>
<td>Gliosis</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>12/17 (71%)</td>
</tr>
<tr>
<td>Gliosis + vasculopathy</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Chronic inflammation + gliosis + Fascia dentata bilam</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>Sturge Weber</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1/1 (100%)</td>
</tr>
<tr>
<td>Rasmussen’s encephalitis</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td>2/2 (100%)</td>
</tr>
<tr>
<td>Vascular (cavernous angioma, capillary angioma)</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2/3 (67%)</td>
</tr>
<tr>
<td>Cicatrix cerebrale</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3/5 (60%)</td>
</tr>
</tbody>
</table>

Table 4. Histopathological findings and postoperative outcome.
intracranial localization. In these patients, no major improvement was seen after surgical intervention. Although these are small numbers we assumed that localization by SPECT alone should be interpreted with caution. In these two patients, not even intracranial evaluation improved the postsurgical outcome (class III and IV). Thus, intracranial EEG monitoring does not appear to provide better results in terms of surgical outcome, despite its invasive nature. In our current clinical practice, we try to apply comprehensive structural, functional and EEG source imaging (Sperli et al. 2006) whenever possible and reserve intracranial monitoring for those cases where a solid hypothesis can be formulated on the basis of thorough phase-I-investigations.

Several pediatric studies examined the yield of either SPECT (Lawson et al. 2000, Kaminska et al. 2003, Kaibori-boon et al. 2002, Adams et al. 1992) or PET (Juhasz and Chugani, 2003, Gaillard et al. 1995, Ollenberger, 2005) for epileptic focus localization. Ictal SPECT and interictal SPECT were reported as equally sensitive and reliable techniques in localizing the epileptogenic focus in adult patients (mean age 31 years) with temporal lobe epilepsy (Markand et al. 1997). A high yield of PET and interictal SPECT (86% with PET and 80% with SPECT) was reported by another group in pediatric temporal lobe epilepsy (Lee et al. 2005). While our results for the SPECT in the TLE group (90%) are comparable or even higher, the localizing properties of the PET were found to be somewhat lower (70%). The differences could be due to: a) different study populations, i.e. the mean age of our patients being lower (10 ± 5 years) compared to the mean age of their patients (15 ± 3 years); b) PET as well as SPECT analyzed with statistical parametric analysis in their study (our study did not utilize SPM). Further (prospective) studies are needed to determine the yield of PET and SPECT analysis with SPM; while one study showed some usefulness in patients with suspected frontal epilepsy (Plotkin et al. 2003), Lee et al. (2005) were unable to show clear benefit of SPM over visual assessment.

To our knowledge, there are no studies that investigate specifically the comparative yield of PET and ictal SPECT in extra-temporal epilepsy in pediatric patients. On the basis of our results in all the 50 patients, PET and SPECT seemed to be complementary in focus localization: overall, PET gave a better yield in extra temporal lobe epilepsies, whereas the yield of SPECT was higher for temporal lobe epilepsy. This complementarity (Knowlton, 2006) also explains why their combination is even more powerful, given that it is often not clear beforehand if the child suffers from temporal or extra temporal epilepsy.

Both younger (Group 1) and older (Group 2) patients benefited equally from surgery, thus “young age” per se is not a prerequisite for better seizure outcome. However, “early surgery” in terms of short duration of epilepsy until surgery, i.e. intervention within two years after onset, is strongly associated with a favorable outcome. Thus, our study underlines the necessity of a thorough evaluation of the epilepsy disorder during the first two years with respect to the possibility of surgical treatment, both in younger and older children, in order to achieve seizure control and prevent the detrimental effects of frequent seizures on their psychomotor development and quality of life.

We did not find evidence that pediatric patients with a need for special education (reflecting cognitive impairment) are less likely to benefit from surgery. Other studies have also found that postoperative seizure outcome did not always depend on the preoperative intellectual disability level (Gleissner et al. 2006, Freitag et al. 2005). It has been reported that in certain distinct pathologies like tuberous sclerosis, mental retardation represents an increased risk of failure of surgical treatment (Chou and Chang, 2004, Romanelli et al. 2004). Our numbers are too small to allow the investigation of psychomotor retardation as a risk factor for each distinct pathology. In the “dysplasia” group, more patients needed specialized education, but most of these children had an excellent outcome in terms of postoperative seizure control. Specialized schooling was more frequent in the younger patient group as has been reported in other studies on patients with focal cortical dysplasia (Bast et al. 2006). Thus, the impact of seizures or of the lesion itself, on cognitive functions is more critical during early years and this relationship needs to be addressed in further studies that combine high quality neuroimaging studies with developmental assessment and neuropsychological evaluation.

However, psychomotor retardation per se should not be considered as a contraindication for surgery. Histopathological findings in the surgical specimens from our patients are similar to other reported series of surgical pathology of drug resistant epilepsy (Pasquier et al. 2002, Bocti et al. 2003, Sinclair et al. 2001). In our study we found a significantly higher yield of PET compared to SPECT for the localization of dysplastic lesions, while SPECT gave excellent yield in tumoral lesions. It has been reported that in patients with focal cortical dysplasia, cortical hypometabolism of the lesion was revealed on FDG-PET in 88% cases and the extent of the cortical abnormality was larger on PET than on MRI in 65% cases (Kim et al. 2000b). Ictal SPECT on the other hand provided localizing information in only 8/15 children (53%) (Gupta et al. 2004). Thus PET may give a more correct estimate of the abnormal dysplastic region than SPECT or even MRI and therefore has a major role in the exact identification of the abnormal zone. Including this dysfunctional zone in the resection (as we tried to do whenever possible) may have increased the yield of the intervention. In our patients, the hypometabolism was often well circumscribed, i.e. suggesting localized dysfunction, which is in contrast to diffuse and widespread PET hypo-metabolism described in patients with unilateral temporal epilepsy due to hippocampal sclerosis (Chassoux et al. 2004).
Post-surgical results from our center are similar to those reported in other larger series, i.e. better outcome seen with acquired well-defined lesions as opposed to developmental pathology (Mathern et al. 1999, Edwards et al. 2000, Doring et al. 1999). The best postoperative seizure freedom in pediatric epilepsy surgery patients has been reported in temporal epilepsy with mass lesions, followed by cortical dysplasia, gliosis, and tuberous sclerosis (Leiphart et al. 2001). Seizure-free outcome has been seen in all our patients with tumor as the pathology. Postsurgical results of our patients with dysplastic lesions (92% seizure free) are superior to those previously reported, which are between 50-73% seizure free (Hader et al. 2004, Kloss et al. 2002, Francione et al. 2003, Cohen-Gadol et al. 2004). However, in all these studies including ours, the follow-up period can be considered relatively short (<4 years). Ten-year postoperative seizure freedom rates were reported in 32% of a cohort of children with cortical dysplasia (Hamiwka et al. 2005). Further follow-up of our patients will enable us to determine if the rigorous use of multimodal imaging methods is also pertinent for the long-term results.

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