Ictal SPECT in children with epilepsy: comparison with intracranial EEG and relation to postsurgical outcome


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Summary

In order to validate the ability of ictal single photon emission computed tomography (SPECT) to localize the epileptogenic zone (EZ) in children, we compared in 20 patients aged from 10 months to 17 years (mean 6.5 years) the topography of the area of increased ictal perfusion (IPA), determined on the basis of ictal minus interictal scan values, with that of the EZ determined by intracranial EEG recordings and assessed its relationship with the postsurgical outcome. Eighteen patients had symptomatic epilepsy and 10 had extra-temporal epilepsy. All patients except one had an ictal injection (mean time lag from clinical seizure onset was 18 s). Ictal and interictal SPECT images were successively co-registered, normalized, subtracted, smoothed and superimposed on MRI. All patients with ictal injection exhibited one or several IPAs. The topography of the ‘highest’ IPA, i.e. the maximal cerebral blood flow (CBF) change between ictal and interictal SPECT, significantly colocalized with the site of onset of the discharge, and that of the lower IPAs with that of the area of propagation (P < 0.0001). At a threshold of 30% of the maximal CBF change, the IPAs detected the onset of the discharge with a sensitivity of 0.80 and a specificity of 0.70. The highest IPA localized the EZ in 12 out of 15 patients. In the three others it missed the EZ and showed the area of propagation because of rapid seizure propagation or of infraclinical seizure onset. Among the patients with favourable surgery outcome, the highest IPA colocalized with the resected area in 70% of cases. Ictal SPECT could therefore plays an important role as a non-invasive presurgical method of investigation by optimizing the placement of intracranial electrodes, thus improving the postsurgery outcome of paediatric partial epilepsy.

Keywords: partial epilepsy; children; ictal SPECT; intracranial EEG; epilepsy surgery

Abbreviations: EZ = epileptogenic zone; CBF = cerebral blood flow; IPA = increased perfusion area; SISCOM = subtraction of ictal minus interictal co-registered to MRI; SPECT = single photon emission computed tomography

Introduction

Pharmacoresistant partial epilepsy in infants and children raises problems that are different from those in adults. The impact of intractable epilepsy on motor, sensorial and cognitive functions may be dramatic because these functions are still developing. However, the potential for recovery is greater than it is in adults, because of the remaining cerebral plasticity (Chugani and Muller, 1999). Ideally, children should therefore undergo surgical resection as soon as intractability has been established. However, surgery is technically difficult for several reasons. Ictal semiology is difficult to assess in terms of topography, and seizures often appear clinically and neurophysiologically as being generalized from onset (Nordli et al., 2001). Correlation between semiology and the topography of the discharge remains to be

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established. In a significant proportion of patients, structural imaging fails to demonstrate any brain lesion (Cukiert et al., 2001). The proportion of patients with extratemporal epilepsy, who are known to be relatively poor candidates for surgery, is higher in children than it is in adults (Kral et al., 2001).

Removing the epileptogenic zone (EZ), i.e. the area of seizure onset, has been shown to be an absolute requirement for seizure freedom, especially in children (Duchowny et al., 1998; Paolicchi et al., 2000). Non-invasive data, including video-EEG and MRI, are often enough to suggest the location of the EZ, but usually they fail to determine its extent. Occasionally they even fail to indicate any candidate area. The gold standard for the delineation of the EZ is the seizure record obtained by intracranial EEG, the only method proven to localize the site of seizure onset and propagation with sufficient precision to enable the limits of surgical resection to be drawn. The resection must involve the entire EZ to be effective: for this, the key question is to determine the optimal placement of the intracranial electrodes in order to investigate the entire EZ and to discriminate the EZ from the areas of propagation of the discharge.

Ictal single photon emission computed tomography (SPECT) has been shown to be effective, as it permits non-invasive disclosure of increased cerebral blood flow (CBF) in the areas affected by an epileptic discharge (Newton et al., 1995). Immediate postictal SPECT can show, in contrast, decreased CBF in the same areas (O’Brien et al., 1999). For temporal lobe epilepsy in adults, the sensitivity of ictal and postictal SPECT is 97 and 75% respectively (Devous et al., 1998). For extratemporal epilepsy, the sensitivity of peri-ictal SPECT is usually under 50% but can reach 80% when using the subtraction image processing method known as subtraction SPECT. Ictal SPECT is usually under 50% but can reach 80% when using the 1998 subtraction method known as subtraction SPECT. The first validation of ictal SPECT as a means of identifying the EZ was recently reported in adult patients on the basis of findings generated by intracranial EEG (Spanaki et al., 1999a,b). In children, peri-ictal SPECT has been shown to be feasible from the first year of life (Harvey et al., 1993a,b; Cross et al., 1995; Menzel et al., 1996; Packard et al., 1996; Chiron et al., 1999; Koh et al., 1999) and its sensitivity to reach 90% using SISCOM, in series in which extratemporal epilepsy accounts for two-thirds of the patients (O’Brien et al., 1998b; Vera et al., 1999). But these data still await proper validation with reference to intracranial recording.

The purpose of this study was to compare the ictal SPECT localizing data with those of intracranial EEG records and to assess their relationship with the postsurgical outcome in a paediatric population.

### Patients (Table 1)

**Selection and characteristics**

From the 80 children who underwent peri-ictal SPECT in our department between the years 1995 and 2000 for refractory partial epilepsy and for whom surgery was planned, we selected those who met the following criteria: (i) ictal SPECT performed during a seizure type considered usual for this patient on the basis of previous video-EEG records; and either (iia) intracranial EEG localizing the onset of the epileptic discharge (the area of onset in this case was defined as that of suppression and disappearance of interictal spikes, or of the occurrence of tonic or rapid rhythmic spike activity) and recording of at least two seizures of the usual type, or (iib) focal resection and at least 1 year of follow-up. Twenty children, 10 girls and 10 boys, were included in the study. The most frequent causes of exclusion were intracranial EEG recordings unexpectedly showing multifocal seizures and insufficient postsurgery follow-up. The patients included were aged 10 months to 17 years (mean 6.5 years) when ictal SPECT was performed. All had had pharmacoresistant partial epilepsy, and the age of onset ranged from 2 weeks to 9 years (mean 2 years); it was symptomatic in 18 and cryptogenic in two. The topography of the lesion was frontal (5 patients), frontotemporal (1), parietal (2), occipital (2) or temporal (8, including one in whom the lesion was temporo-insular). Four children had tuberous sclerosis with multiple tubers, but presurgical evaluation suggested that only one was epileptogenic. Twelve children, including the four with tuberous sclerosis, had cortical dysplasia and four others had dysembryoplastic neuroepithelial tumour. For two children the lesion could not be classified neuropathologically.

### Methods

**SPECT examination and image acquisition**

Patients’ parents gave informed consent. The study was approved by the Ethics Committee of each institution. The ictal injection was performed and then monitored by video-EEG, as soon as possible after the appearance of clinical features. For each ictal SPECT examination we measured the time lag between the clinical onset, the administration of the tracer and the overall duration of the seizure. SPECT was performed ictally for 19 children, and the time lag from the clinical onset of the seizure to the injection ranged from 4 to 80 s (mean 18 s). For the patient who had the latest injection (Patient 3), the SPECT was performed postictally; the tracer was administered 20 s after the onset of a seizure that had lasted 5 s. Ictal SPECT was followed by interictal SPECT and 3D MRI 48 h later, as described previously (Vera et al., 1999). Both SPECTs involved the intravenous injection of technetium 99m ethyl cysteinate dimer (99mTc-ECD). The dose to be administered was scaled on a body surface area basis of 740 MBq (20 mCi) for 1.73 m². For the subsequent image acquisition, patients were sedated if necessary with rectal pentobarbital (5 mg/kg), which was administered after the tracer. Ictal and interictal SPECT acquisitions were performed ~1 h after the 99mTc-ECD injection using a double-head rotating gamma-camera (DST-XL, General Electric Medical System, Bue, France) equipped with ultra-high-
<table>
<thead>
<tr>
<th>Patient no./age (years)</th>
<th>Seizure [injection time/duration (s)]</th>
<th>MRI lesion (aetiology)</th>
<th>Intracranial EEG: onset of discharge</th>
<th>Ictal SPECT: highest cortical IPA</th>
<th>Surgical resection (Engel class)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/4</td>
<td>Asymmetrical tonic posturing then clonic seizure of left limbs (10/80)</td>
<td>R frontal (cortical dysplasia)</td>
<td>R frontal</td>
<td>R central</td>
<td>R anterior frontal (III)</td>
</tr>
<tr>
<td>2/3</td>
<td>‘Psychomotor’ seizure with automatic hand movements (10/44)</td>
<td>R frontal (cortical dysplasia)</td>
<td>R orbital and polar frontal</td>
<td>R orbital, polar and mesial frontal</td>
<td>R anterior frontal (IV)</td>
</tr>
<tr>
<td>3/5</td>
<td>Brief generalized tonic seizure (20/5)</td>
<td>L frontal (atypical)</td>
<td>L orbital and mesial frontal</td>
<td>No IPA</td>
<td>L anterior frontal (III)</td>
</tr>
<tr>
<td>4/2</td>
<td>Jerk of upper limbs then tonic contraction of the left upper limb (15/47)</td>
<td>R mesial frontal (cortical dysplasia, TS)</td>
<td>R mesial frontal</td>
<td>R mesial frontal</td>
<td>R mesial and lateral frontal (IV)</td>
</tr>
<tr>
<td>5/1.5</td>
<td>Clonus of the right labial commissure then swallowing and atonic fall (13/63)</td>
<td>R operculum frontal (cortical dysplasia + DNET)</td>
<td>R anterior parietal (astrocytoma)</td>
<td>R anterior parietal</td>
<td>R anterior parietal (Ib)</td>
</tr>
<tr>
<td>6/6</td>
<td>Paraesthesia of the left hand then tonic contraction of the upper limbs (10/14)</td>
<td>R mesial parietal (cortical dysplasia, TS)</td>
<td>R mesial parietal</td>
<td>R mesial parietal and central, L central, R parietal</td>
<td>R mesial parietal (Ib)</td>
</tr>
<tr>
<td>7/12</td>
<td>Paraesthesia then clonus of the left foot and vertigo (21/122)</td>
<td>R occipital (cortical dysplasia)</td>
<td>L occipital</td>
<td>L occipital</td>
<td>L occipital (Ia)</td>
</tr>
<tr>
<td>8/2 (Fig. 3A)</td>
<td>Strabismus then oculoclonus (50/70)</td>
<td>R occipital-temporal (cortical dysplasia, TS)</td>
<td>L occipital</td>
<td>L occipital</td>
<td>L occipital (IV, infectious complication)</td>
</tr>
<tr>
<td>9/0.8</td>
<td>Oculoclonus (15/80)</td>
<td>L occipital (cortical dysplasia)</td>
<td>L occipital</td>
<td>L occipital</td>
<td>L occipital (Ia)</td>
</tr>
<tr>
<td>10/10</td>
<td>Staring, rotation of the trunk and head to the right, mouthings, automatisms, screaming (10/70)</td>
<td>R polar temporal (cortical dysplasia)</td>
<td>R lateral temporal and temporo-parieto-occipital</td>
<td>R polar and lateral and temporo-parieto-occipital</td>
<td>R polar and lateral temporal (III)</td>
</tr>
<tr>
<td>11/12.5</td>
<td>Staring, head deviation to the right, tonic flexion of upper limbs, crying (5/35)</td>
<td>R polar and mesial temporal (cortical dysplasia)</td>
<td>R polar temporal</td>
<td>R polar temporal</td>
<td>R anterior temporal (Ia)</td>
</tr>
<tr>
<td>12/17 (Fig. 3B)</td>
<td>Staring and concomitant tonic deviation of the head, eyes and trunk to the right, mouthings, crying with asymmetrical tonic flexion of the upper limbs (38/60)</td>
<td>R mesial and lateral temporal (DNET)</td>
<td>R polar and lateral temporal</td>
<td>R mesial frontal</td>
<td>R temporal (Ia)</td>
</tr>
<tr>
<td>13/5</td>
<td>Staring, rotation of the trunk and head to the right, clonus of the right eyelid (14/54)</td>
<td>R polar temporal (cortical dysplasia)</td>
<td>Not done</td>
<td>R polar temporal</td>
<td>R polar temporal (Ia)</td>
</tr>
<tr>
<td>14/13 (Fig. 2)</td>
<td>Staring then asymmetrical tonic contraction and extension of the limbs with grimace and crying (12/31)</td>
<td>R mesial and lateral temporal (DNET)</td>
<td>Not done</td>
<td>R mesial, lateral, polar temporal, R insula</td>
<td>R temporal (Ia)</td>
</tr>
<tr>
<td>15/2.5</td>
<td>Covers her face with her hands (4/16)</td>
<td>R polar temporal (cortical dysplasia + hippocampus sclerosis)</td>
<td>Not done</td>
<td>R polar temporal</td>
<td>R temporal (Ia)</td>
</tr>
<tr>
<td>16/2.5</td>
<td>Staring, deviation of the head and eyes to the right, then tonic clonic generalization (7/60)</td>
<td>R insular and temporal (DNET)</td>
<td>Not done</td>
<td>R insular and temporal</td>
<td>R temporal (IV)</td>
</tr>
<tr>
<td>17/4</td>
<td>Staring, looking around, rotation of the eyes and head to the left (9/23)</td>
<td>L, temporal, parietal frontal (multifocal cortical dysplasia, TS)</td>
<td>L temporal, parietal, frontal</td>
<td>L temporal, parietal</td>
<td>L temporal parietal, frontal (IIb)</td>
</tr>
</tbody>
</table>
resolution fan-beam collimators. For each ⁹⁹mTc-ECD SPECT scan, 64 angular views of 60 s were obtained through a 360° circular orbit (32 angular views by head). The SPECT scans were reconstructed from projection data using the filtered back-projection algorithm with a Hann filter with cut-off frequency 0.5 cycle per pixel and a software zoom of 2 (matrix 128 × 128, mode word, 128 slices, voxel size 1.7 mm).

**Intracranial EEG**

Sixteen patients underwent intracranial EEG. Fourteen were investigated with subdural grids and depth electrodes, and two with only stereo EEG (Patients 12 and 19). Grids and electrodes were implanted in the neurosurgery department, their location covering the areas of onset and propagation of the seizure judged from the non-invasive presurgical data, including video-EEG, MRI and SPECT. However, since the localizing value of SPECT has still not been validated in children, the site for the intracranial EEG implantation was chosen primarily from video-EEG and MRI data. SPECT images were used as additional data either to confirm the site when they were concordant or to extend it when they disclosed more widespread perfusion changes.

**Postsurgery outcome**

Nineteen children received surgery, 15 after intracranial recording and four without intracranial EEG (Patients 13, 14, 15 and 16). All four presented with an epileptogenic lesion in the temporal lobe. Patient 19 (with cryptogenic epilepsy) did not undergo surgery because the EZ was multifocal. Postsurgical follow-up ranged from 1.5 to 5 years (mean 3.5 years).

Post-surgical outcome was evaluated according to Engel’s classification: Ia, neither seizures nor aura following surgery; Ib, only auras; Ic, a few seizures following surgery but none thereafter; IIa, initially no seizure, then late recurrence of a small number of seizures; IIb, rare seizures following surgery (<2/year); III, clinically relevant improvement; IV, no improvement. Postsurgery results were as follows: class Ia, six cases; class Ib, one case; class IIa, one case; class IIb, two cases; class III, three cases; class IV, six cases. In two of the class III patients and one of the class IV patients, the resection was deliberately incomplete in order to preserve motor and language functions (Patients 1 and 10). One patient suffered from postsurgery meningitis, which generated a new epileptogenic lesion in the contralateral hemisphere (Patient 9).

**Image processing**

The MRI-SPECT co-registration procedure comprised the following seven steps (Vera et al., 1999). (i) Intercital and ictal SPECT and MRI images were transferred to the same computer. (ii) Each child’s interictal and ictal perfusion scans
were registered to the same child’s MRI scan, using a computer 3D registration program. Discrete representations of the head surface were extracted automatically from the SPECT and MRI images. Then a shape-independent surface-matching algorithm was used to give a rigid-body transformation which permitted the transfer of information between the two modalities. Finally, the MRI images were co-registered to the SPECT images using a rotation matrix and a translation vector. (iii) Extracted MRI boundaries were visualized on the interictal and ictal perfusion scans to verify the accuracy of co-registration. (iv) The co-registered ictal and interictal perfusion scans were normalized according to the mean pixel counts in the brain. (v) Normalized ictal and interictal scans were subtracted from each other to obtain ictal – interictal difference images, which were computed. (vi) These subtraction images were smoothed with a 3D Deriche filter (alpha = 1). (vii) Five subtraction images were obtained using five thresholds of 10, 20, 30, 40 and 50% of the maximum pixel value of the difference image (Fig. 1). These five ictal – interictal subtraction images were superimposed successively on the MRI. They showed increased perfusion areas (IPAs) during the seizure. Lower thresholds therefore corresponded to higher IPAs and higher thresholds to lower IPAs (the highest IPA corresponded to a threshold of 10%) (Vera et al., 1999).

For each threshold, we studied the number of IPAs and localized them as frontal (central, dorsolateral, polar, medial, orbital, operculum), temporal (medial, lateral, polar, basal), parietal (anterior, posterior, medial, operculum), occipital (lateral, medial, polar), temporo-parieto-occipital, insular or cingulate (anterior or posterior gyrus). The topography of the subcortical IPAs (lenticular nucleus, thalamus, caudate nucleus, cerebellum) and that of the areas of ictal decreased perfusion were also studied.

**Intracranial EEG records**

For each patient, we selected one recorded seizure that was typical of and of the same type as that studied during ictal SPECT. On this epileptic discharge, we determined the sites of onset and propagation and we localized them within the regions defined above for ictal SPECT. One discharge could occasionally disclose more than one site of onset. The time lag from the onset of the epileptic discharge on intracranial EEG to the clinical onset was measured for each recorded seizure.
Surgical resection areas
For each patient, the topography of the remote area was determined visually on the postsurgical MRI according to the regions defined above for ictal SPECT and intracranial EEG records.

Data analysis
The analysis of SPECT images and intracranial EEG records was performed blindly by one reviewer for SPECT and another reviewer for EEG. Data analysis focused on the relationships between (A) SPECT and intracranial EEG findings, and (B) SPECT and surgical outcome findings. For (A), we examined (i) the association between the presence or absence of an IPA (whatever the threshold) and the presence or absence of an epileptic discharge (onset or propagation), (ii) the relationship between IPAs at different thresholds and the onset of the discharge, and (iii) the relationship between IPAs at different thresholds and the propagation of the discharge. For (B) we examined the surgical outcome according to whether the highest IPA colocalized with the resection area. Simple statistical tests were used ($\chi^2$ test and Fisher’s exact test). Then, data for individual patients were examined carefully, especially for patients showing discrepancy between SPECT and intracranial EEG data and for those with an unfavourable outcome.

Results
Ictal SPECT images (Table 1)
One or several IPAs were identified in all 19 patients with ictal SPECT, depending on which threshold was selected (Fig. 2).

Fig. 2 Patient 14. Subtraction (ictal minus interictal) SPECT images at a threshold of 40% of the maximum of CBF changes, superimposed on MRI. Injection 12 s after the onset of a right temporal seizure with frontal propagation. Notice the highest IPA (red, 10% threshold) in the temporal lobe and right insula; the frontal, temporoparietal and contralateral cerebellum IPAs are visualized only at thresholds of 30–40% (green, blue) and correspond to lower IPAs.
The inferior thresholds to calculate threshold, we used all the IPAs observed at this threshold and at epileptic discharge recorded on intracranial EEG. For each using only the number of IPAs corresponding to the onset of the epileptic discharge, the columns represent the number of the IPAs corresponding to the regions of the onset or propagation or absence of the epileptic discharge recorded on intracranial EEG (lines) at each threshold studied. The column 10% shows the number of IPAs observed at this threshold compared with the immediately inferior threshold. The columns 20% to 50% show the numbers of additional IPAs observed at the given threshold compared with the immediately inferior threshold.

Table 2 Correspondence between intracranial EEG and ictal SPECT data in 15 children and 102 regions recorded on intracranial EEG

<table>
<thead>
<tr>
<th>IPA ranges*</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial EEG</td>
<td>≤10%</td>
</tr>
<tr>
<td>Onset</td>
<td>27</td>
</tr>
<tr>
<td>Propagation</td>
<td>5</td>
</tr>
<tr>
<td>No discharge</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
</tr>
</tbody>
</table>

The columns represent the number of the IPAs corresponding to the regions of the onset or propagation or absence of the epileptic discharge recorded on intracranial EEG. For each threshold, we used all the IPAs observed at this threshold and at the inferior thresholds to calculate χ², specificity, sensitivity and per cent correct; sensitivity = number of IPAs at one threshold/number of onsets of the epileptic discharge recorded on intracranial EEG on the corresponding cerebral region; specificity = number of regions without IPA/number of regions with no epileptic discharge recorded on intracranial EEG.

χ², specificity, sensitivity and per cent correct were calculated using only the number of IPAs corresponding to the onset of the epileptic discharge recorded on intracranial EEG. For each threshold, we used all the IPAs observed at this threshold and at the inferior thresholds to calculate χ², specificity, sensitivity and per cent correct; sensitivity = number of IPAs at one threshold/number of onsets of the epileptic discharge recorded on intracranial EEG on the corresponding cerebral region; specificity = number of regions without IPA/number of regions with no epileptic discharge recorded on intracranial EEG.

The analysis involved the 15 patients with intracranial EEG and at least one IPA (16 had intracranial EEG but Patient 3 had no change on SPECT images). The highest IPA was inside the area recorded on intracranial EEG in all 15 patients, but two patients also disclosed an additional highest IPA outside this area [either in the contralateral hemisphere (Patient 7) or in another lobe on the same side (Patient 20)]. The highest IPA co-localized with the onset of the discharge in 12 children (80%). In another patient (Patient 11), the highest IPA included both the onset and the immediate propagation areas. In the two remaining patients, the highest IPA co-localized with the immediate propagation, but not with the EZ, which corresponded to lower IPAs (Patient 12) or no IPA (Patient 7).

Correspondence between ictal SPECT increased perfusion areas and intracranial EEG

The analysis involved the 15 patients with intracranial EEG and selected in the 15 patients, a total of 102 regions were explored. Eighty-two of them were involved by an epileptic discharge (42 onsets and 40 propagations). Ictal SPECT showed an IPA in 62 of them and there were only two false-positive IPAs [χ²(1) = 29.6, P < 0.0001] (Table 2). The topography of these two false-positive IPAs was near the EZ (Patients 4 and 7). Among the 20 regions with epileptic discharge but without any IPA on ictal SPECT, six corresponded to the onset of the discharge (Table 2). In all these six regions, the highest IPA was located in the same lobe (Patients 7, 17, 18, and for Patient 1 in three regions). Overall, the sensitivity of ictal SPECT in detecting an epileptic discharge was 0.76 (62/82) and the specificity 0.90 (18/20).

Table 3 Ability of the IPAs on ictal SPECT to detect the onset of the discharge at different thresholds

<table>
<thead>
<tr>
<th>IPA threshold*</th>
<th>≤10%</th>
<th>&lt;20%</th>
<th>&lt;30%</th>
<th>&lt;40%</th>
<th>&lt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>χ² value</td>
<td>36</td>
<td>27</td>
<td>25.5</td>
<td>20.9</td>
<td>16</td>
</tr>
<tr>
<td>Sensitivity‡</td>
<td>0.64</td>
<td>0.73</td>
<td>0.8</td>
<td>0.85</td>
<td>0.86</td>
</tr>
<tr>
<td>Specificity§</td>
<td>0.92</td>
<td>0.78</td>
<td>0.7</td>
<td>0.6</td>
<td>0.53</td>
</tr>
<tr>
<td>Per cent correct</td>
<td>0.8</td>
<td>0.76</td>
<td>0.74</td>
<td>0.70</td>
<td>0.66</td>
</tr>
</tbody>
</table>

χ², specificity, sensitivity and per cent correct were calculated using only the number of IPAs corresponding to the onset of the epileptic discharge recorded on intracranial EEG. For each threshold, we used all the IPAs observed at this threshold and at the inferior thresholds to calculate χ², specificity, sensitivity and per cent correct; sensitivity = number of IPAs at one threshold/number of onsets of the epileptic discharge recorded on intracranial EEG on the corresponding cerebral region; specificity = number of regions without IPA/number of regions with no epileptic discharge recorded on intracranial EEG.

They involved the brain cortex in all cases. Subcortical IPAs were also identified in 16 children and involved the lenticular nucleus (10 cases), cerebellum (11 cases), thalamus (five cases) or caudate nucleus (two cases). The highest IPAs involved a single hemisphere in all children except one, who exhibited bilateral central location (Patient 7). In 14 children the highest IPAs involved a single lobe, and in the five others 2 lobes. In 14 of the 18 symptomatic children, the highest IPA colocalized with the lesion. In three others, it was either in the same lobe near the lesion, or in another lobe. In the only patient with postictal SPECT (Patient 3), subtraction images failed to disclose any CBF changes.

Areas of ictal decreased perfusion were observed in 10 cases. They were multifocal and most often involved the hemisphere contralateral to the IPAs (eight cases). In seven cases, hypoperfusion mirrored the highest IPA, with a coronal or sagittal axis of symmetry.

Intracranial EEG records (Table 1)

In nine patients (Patients 1, 5, 6, 7, 8, 9, 10, 11 and 12) the onset of the epileptic discharge preceded the onset of clinical features by a period ranging from 10 s to 1 min, and for three of them (Patients 10, 11 and 12) clinical features appeared when the discharge had already reached all the electrodes. Regarding the 14 patients with symptomatic epilepsy, the onset of the discharge co-localized with the lesion and also involved the nearby areas in two of them. Patient 17 had several distant areas of onset (frontal, temporal and parietal) related to three tubers, and all three were involved during the seizures.

Correspondence between intracranial EEG and ictal SPECT

The analysis involved the 15 patients with intracranial EEG and at least one IPA (16 had intracranial EEG but Patient 3 had no change on SPECT images). The highest IPA was inside the area recorded on intracranial EEG in all 15 patients, but two patients also disclosed an additional highest IPA outside this area [either in the contralateral hemisphere (Patient 7) or in another lobe on the same side (Patient 20)]. The highest IPA co-localized with the onset of the discharge in 12 children (80%). In another patient (Patient 11), the highest IPA included both the onset and the immediate propagation areas. In the two remaining patients, the highest IPA co-localized with the immediate propagation, but not with the EZ, which corresponded to lower IPAs (Patient 12) or no IPA (Patient 7).

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The analysis involved the 15 patients with intracranial EEG and at least one IPA (16 had intracranial EEG but Patient 3 had no change on SPECT images). The highest IPA was inside the area recorded on intracranial EEG in all 15 patients, but two patients also disclosed an additional highest IPA outside this area [either in the contralateral hemisphere (Patient 7) or in another lobe on the same side (Patient 20)]. The highest IPA co-localized with the onset of the discharge in 12 children (80%). In another patient (Patient 11), the highest IPA included both the onset and the immediate propagation areas. In the two remaining patients, the highest IPA co-localized with the immediate propagation, but not with the EZ, which corresponded to lower IPAs (Patient 12) or no IPA (Patient 7).

For the 15 seizures recorded on intracranial EEG and selected in the 15 patients, a total of 102 regions were explored. Eighty-two of them were involved by an epileptic discharge (42 onsets and 40 propagations). Ictal SPECT showed an IPA in 62 of them and there were only two false-positive IPAs [χ²(1) = 29.6, P < 0.0001] (Table 2). The topography of these two false-positive IPAs was near the EZ (Patients 4 and 7). Among the 20 regions with epileptic discharge but without any IPA on ictal SPECT, six corresponded to the onset of the discharge (Table 2). In all these six regions, the highest IPA was located in the same lobe (Patients 7, 17, 18, and for Patient 1 in three regions). Overall, the sensitivity of ictal SPECT in detecting an epileptic discharge was 0.76 (62/82) and the specificity 0.90 (18/20).
For the 82 regions in which an epileptic discharge was present, IPAs on ictal SPECT were detected more frequently for sites of discharge onset (86%, 36/42) than for sites of discharge propagation (65%, 26/40) $[\chi^2(1) = 4.8, P = 0.03]$ (Table 2).

For the 62 regions with both an epileptic discharge and an IPA, the IPA was higher if it was the site of onset of a discharge [10% threshold, 84% (27/32); 20–30% threshold, 39% (7/18); 40–50% threshold, 17% (2/12)] than if it was at a propagation site (16, 61 and 83% for thresholds of 10, 20–30 and 40–50%, respectively) $[\chi^2(2) = 20.3, P < 0.0001; \text{linear tendency } \chi^2(1) = 19.3, P < 0.0001]$ (Table 2).

Finally, considering again all 102 regions investigated with intracranial EEG, we examined the ability of ictal SPECT to detect the site of onset of the discharge according to various IPA thresholds (Table 3). The most restrictive threshold (10%) led to few false positive results (8%) but failed to detect the site of onset in 36% of the regions. The most permissive threshold (50%) failed to detect the site of onset in 14% but led to false-positive results in 47% of the regions. A threshold of 30% led to 20% false-negative and 30% false-positive results.

**Correspondence between ictal SPECT and surgery outcome**
The analysis involved 17 children (Patient 19 did not have surgery), Patient 9 had complications and Patient 3 had no IPA on SPECT images. The relationship between the extent of surgical resection, the IPAs and surgery outcome is shown in Table 4.

### Table 4 Correspondence between ictal SPECT (highest IPA) and resection and surgical outcome

<table>
<thead>
<tr>
<th>Engel I and II</th>
<th>Resection colocalized with the highest IPA</th>
<th>Resection not colocalized with the highest IPA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>7 (5, 6, 8, 13, 14, 15, 17)</td>
<td>3 (7, 11, 12)</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Engel III and IV</td>
<td>3 (2, 4, 18)</td>
<td>4 (1, 10, 16, 20)</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are number of patients (identification numbers of individual patients).

Engel classes III and IV (seven cases)
Among the seven patients with unfavourable surgery outcome, the highest IPA co-localized with the site of surgical resection in three cases (Patients 2, 4 and 18). Since ictal SPECT was consistent with the intracranial EEG findings in the three patients, it must be assumed that both SPECT and intracranial EEG partly missed the EZ. In the remaining four children (Patients 1, 10, 16 and 20), the highest IPA co-localized only partly with the site of surgical resection.

**Patient 1** had a large frontal dysplasia. Intracranial EEG showed a large EZ involving both prefrontal and primary motor areas. SPECT failed to show frontopolar, orbital and intraslesional frontal (depth electrode) onset of epileptic discharge, but it showed frontocentral, mesial and dorsolateral IPAs, all being involved in the lesion. However, the resection was incomplete, in order to preserve motor function.

**Patient 10** had a right temporal lesion. Intracranial EEG showed the EZ in the entire lateral temporal area with rapid propagation to the temporo-occipital area. Ictal SPECT...
showed the highest IPA in temporal and temporo-occipital areas, consistent with intracranial EEG (Fig. 3C). However, the resection was limited to the anterior part of the temporal lobe in order to preserve language because both the Wada test and functional MRI had demonstrated right speech dominance in this left-handed patient.

Patient 16 had a temporo-insular lesion and was operated on without intracranial EEG. Ictal SPECT showed the highest IPA in the temporo-insular region, but only the temporal lobe was removed.

Patient 20 had cryptogenic epilepsy. The areas investigated with intracranial EEG did not cover the whole of the...
Discussion

This is the first series comparing in children with epilepsy the findings of ictal SPECT with those of reference methods of localizing the epileptogenic zone (EZ) and the intracranial EEG and assessing these data in relation to the postsurgical outcome. The topography of the IPAs correlates highly with that of the epileptic discharge (onset and propagation). The sensitivity of ictal SPECT is better for detecting the site of onset than that of propagation, the highest IPA significantly co-localizing with the site of onset of the discharge and the lower IPAs with that of propagation. The sensitivity and specificity of detected IPA in identifying the site of onset of the discharge varied with the threshold used, the best specificity being at 10% and the best sensitivity at 50%. The highest IPA (at 10%) localized the EZ in 12 patients out of 15. Finally, among the patients with favourable surgery outcome, the resected area co-localized with the highest IPA in 70% of cases. ictal SPECT could therefore play an important role as a non-invasive presurgical method of investigation in order to optimize the placement of intracranial electrodes in children and thus to improve the postsurgery outcome of paediatric partial epilepsy.

The main factor determining freedom from seizures after surgery is total removal of the EZ, both in adults and children (Duchowny et al., 1998; Chassoux et al., 2000; Paolicchi et al., 2000). Localizing the EZ is often difficult in extratemporal epilepsy, which is the form seen most frequently in children. Lesions are usually included in the EZ, but may not overlap it: the cortex near the site of a dysembryoplastic neuroepithelial tumour or ischaemic lesions is frequently the site of onset of the discharge (Chassoux et al., 2000). Even if the lesion is very likely to include the EZ, its anatomical limits may be impossible to determine on the basis of MRI. This is particularly the case for focal cortical dysplasia (Palmini et al., 1991; Chassoux et al., 2000). Determining the extent of the EZ by intracranial EEG recording improves considerably the postoperative course in extratemporal epileptogenic lesions in adults, since the percentage of seizure-free patients increases from 20% (Palmini et al., 1991) to 64% (Chassoux et al., 2000) using this technique. The same applies to children, 77% of whom have a good outcome when the resection of the EZ is complete according to intracranial EEG (Paolicchi et al., 2000). In other paediatric surgical series, the comparison is more difficult since they include large resections which do not require intracranial EEG, such as hemispherectomy (Chugani et al., 1993; Wyllie et al., 1998). Among the 14 patients of our series who had an identifiable structural lesion and who underwent intracranial EEG, there were only three (Patients 5, 6 and 13) in whom the EZ was superimposed on the lesion and restricted to it and for whom removing only the lesion resulted in favourable surgery outcome: they were the patients with dysembryoplastic neuroepithelial tumour. For all other patients the EZ would not have been identified properly, either because the lesion was poorly delineated (the seven cases with focal cortical dysplasia) or because the EZ exceeded the lesion or was multifocal (the four cases with tuberous sclerosis).

The number of intracranial electrodes that can be inserted in a given patient is limited, but the electrodes must cover the whole EZ and the propagation pathways of the discharge. The area to be removed is usually restricted to the EZ in order to spare the healthy cortex. It may, however, be necessary to include the immediate propagation pathways if they are constantly and very quickly involved in the discharge (Chassoux et al., 2000). Electroclinical and neuroradiological data play a major role in the placement of electrodes, but this source of information may not be sufficient. ictal SPECT provides precious additional information. SPECT subtraction analysis is more accurate than any other non-invasive procedure for the localization of epileptogenic regions and has 86% sensitivity and 75% specificity compared with the localization generated by intracranial EEG, which is the standard method used in adults (Spanaki et al., 1999a). SISCOM findings have also been shown to be predictive of good outcome after resective surgery in extratemporal epilepsy (O’Brien et al., 2000). In children, the location of CBF changes detected with ictal SPECT has good concordance with that of EZ detection based on the non-invasive presurgical work-up (Harvey et al., 1993a, b; Cross et al., 1995; O’Brien et al., 1998b; Chiron et al., 1999; Koh et al., 1999; Vera et al., 1999). ictal SPECT provides useful additional localization that may be used as a guide for intracranial implantation, especially in children with cryptogenic epilepsy (Lawson et al., 2000). However, only two paediatric patients were reported to have undergone both ictal SPECT and intracranial EEG (Koh et al., 1999). In addition, no attempt had been made to distinguish the EZ properly from the areas of propagation.

The present study attempted to fill these gaps by the use of rigorous methods. (i) It involved a non-selected and representative paediatric population with pharmacoresistant epilepsy, which was mostly extratemporal (61% of our cases) and malformative (focal cortical dysplasia, tuberous sclerosis) or due to low-grade congenital tumour. (ii) Sufficient postsurgical follow-up was required since relapse after 1 year has been reported in children. (iii) In all children, ictal SPECT was performed with video-EEG and during their usual type of seizure. (iv) Ictal injection was performed very soon after seizure onset, usually during the first half of it. A single paediatric study reporting two patients also showed a very short time lag to injection (Kuzniecky et al., 1993), whereas in most other studies the injection was performed postictally (O’Brien et al., 1998b). However, the localizing value of SPECT is better when performed ictally than postictally, and
for injections performed during the first half of the seizure than during the second half (Devous et al., 1998; Kahane et al., 1999). (v) We used the subtraction technique, which significantly increases the sensitivity of ictal SPECT in both adults and children (O’Brien et al., 1998a; Vera et al., 1999). This method was validated recently in adults with reference to intracranial EEG (Spanaki et al., 1999b). The subtraction technique permits comparison of two examinations since it normalizes the ictal and interictal images to global blood flow. The amount of radioactivity delivered to the brain is indeed different from one examination to the next, even if the total dose administered is the same, and this is a real challenge (Zubal et al., 1995; Vera et al., 1999). In addition, analysing subtraction images at different thresholds is the only means of recognizing differences in ictal perfusion changes with ‘higher’ and ‘lower’ increased perfusion areas. In several patients in this study, lower IPAs disclosed hyperperfusion areas consistent with propagation pathways, subcortical areas, or even the EZ.

Nevertheless, some methodological issues remain. (i) In our series, ictal SPECT was not performed at the same time as intracranial EEG recording, which was the case in the adult series in which spontaneous and provoked seizures were reported (Kahane et al., 1999; Spanaki et al., 1999b). In order to overcome this difficulty, we selected seizures that were clinically and electrographically similar for the two methods (ictal SPECT and intracranial EEG). (ii) SPECT and intracranial EEG were not truly independent methods of localizing the EZ, since ictal SPECT imaging results were among the data we used to decide the site of intracranial EEG implantation in some patients of our series. SPECT data received lighter weighting than video-EEG or MRI, but greater weighting for the last patients than for the first ones, because the images proved their usefulness progressively. It was therefore ethically impossible to plan randomization for the placement of intracranial electrodes, with or without SPECT data. In addition, the patients operated on before the SPECT era could not be used as controls because our EEG technique changed from intra-operative to chronic presurgical when the SPECT era began. Taking SPECT into account in the placement of intracranial electrodes may therefore have introduced a bias in some patients in the present study, particularly those for whom video-EEG, MRI and SPECT missed the EZ; these patients continued to have seizures in spite of the concordance of intracranial EEG and ictal SPECT, because the EZ was not completely covered by intracranial electrodes and not completely removed. (iii) SPECT has the advantage of visualizing the entire brain, including subcortical and subtentorial structures, whereas both scalp and intracranial EEGs investigate restricted areas of the brain. Areas of hyperperfusion within the insula, subcortical areas or the cerebellum were observed in our series and in others, but they could not be validated by intracranial EEG since the subcortical regions are usually not recorded (Harvey et al., 1993a, b; Vera et al., 1999). (iv) The subtraction method we used did not permit quantitative assessment, as it does in adult series (Zubal et al., 1995; O’Brien et al., 1998a; Spanaki et al., 1999b), but provided relative values of CBF increase for each patient in the range of 10–50% of the maximum change between ictal and interictal CBF. Changes were studied at every threshold and 30% was the most reliable with respect to both sensitivity and specificity: it detected the onset of the discharge in 80% of cases but failed to distinguish the onset area from the propagation area in 30% of cases.

The maximum CBF change between ictal and interictal SPECT examinations (the ‘highest’ IPA) proved to be relevant since 70% of the patients with a good postsurgical outcome had a co-localization between the highest IPA and the resected area in the present series. The risk of the hyperperfused area missing the EZ and disclosing the propagation area was in the same range as that in a series of extratemporal epilepsy in adults (20% compared with 19%) (Noachtar et al., 1998). In our series, it was not due to late ictal injection but to rapid propagation of the discharge or the lack of clinical features at seizure onset (in nine patients the epileptic discharge preceded the onset of clinical features by 10 s to 1 min). The latter are two limiting factors for ictal SPECT. Another limitation is short seizure duration, 10 s being the lower limit in our experience. It must also be taken into account that ictal SPECT investigates a given seizure at a given time in the course of the epilepsy. For all these reasons, the topography of the area to be removed cannot be based only on SPECT data, even if it is early ictal.

**Conclusion**

This study validates the ability of ictal SPECT in children to localize the EZ, provided the investigation is performed with video-EEG, the tracer is administered as early as possible during the seizure, and ictal – interictal subtraction images are analysed in combination with video-EEG and other clinical data. Given the good anatomical correlation with intracranial EEG, its ability to investigate the whole brain and to show both the onset (EZ) and the propagation of the discharge, ictal SPECT is an excellent tool to help the surgeon determine the optimal site of implantation for intracranial recording. Ictal SPECT provides a major complementary tool to optimize intracranial EEG, which remains the only method able to determine the relationship between the EZ and the lesion and that between the onset of the discharge and its propagation. These findings justify the development of ictal SPECT in routine practice in the non-invasive presurgical work-up of pharmacoresistant epilepsy in children. Since it shows the whole of the area of the brain which is involved in the epileptic discharge, including subcortical and subtentorial regions, ictal SPECT should also contribute to the establishment of the semiology of seizures in young children and to our understanding of the pathophysiology of propagation pathways in patients in this age range.
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References


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