Original article

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Ictal SPECT is useful in localizing the epileptogenic zone in infants with cortical dysplasia

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ABSTRACT – *Aims*. To assess the localizing value of ictal SPECT in very young epilepsy surgery candidates when cerebral haemodynamic responses are known to be immature.
Methods. We retrospectively studied 13 infants with intractable focal epilepsy caused by focal cortical dysplasia (FCD). Completeness of resection of the (1) ictal SPECT hyperperfusion zone and (2) cerebral cortex with prominent ictal and interictal abnormalities on intracranial EEG (ECoG or long-term invasive monitoring) and the MRI lesion, when present, were correlated with postoperative seizure outcome.
Results. All five patients with complete resection of the ictal SPECT hyperperfusion zone were seizure-free compared to only one of eight patients with incomplete or no excision of hyperperfusion zones (p=0.00843). Similar results were noted for the MRI/iEEG-defined epileptogenic region; five of six patients with complete removal were seizure-free, whereas only one of seven incompletely resected patients was seizure-free (p=0.02914). All four patients who underwent complete resection of both regions were seizure-free compared to none of the six with incomplete resection (p=0.01179).
Conclusion. Despite age-related differences in cerebral perfusion, ictal SPECT provides useful localization data in infants with FCD. Complete resection of the hyperperfused regions is a strong predictor of favourable outcome. The added information may alleviate the need for invasive EEG evaluations in some patients.

Key words: ictal SPECT, focal cortical dysplasia, epilepsy surgery, infant

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Ictal single-photon emission computed tomography (SPECT) is routinely used for epilepsy surgery planning. Previous studies reveal that ictal SPECT (and ancillary methods, such as SISCOM, ISAS, and STATISCOM) assist in the localization of the epileptogenic zone in patients harbouring focal cortical dysplasia (FCD) and improve surgical outcome (O'Brien *et al.,* 2000; Kaminska, 2003; McNally *et al.,* 2005; Kazemi *et al.,* 2009; Krsek *et al.,* 2013). However, there is no comparable study of ictal SPECT in infants with FCD.

Rare descriptions of ictal SPECT in infants and young children with FCD are provided in case reports or mixed-age cohort studies (Kaminska, 2003; Buchhalter and So, 2004; Gupta *et al.,* 2004; O'Brien *et al.,* 2004). Infantile SPECT studies have occasionally been reported in selective neurological disorders, including West syndrome (Fujii *et al.,* 2013; Haginoya *et al.,* 2001), tuberous sclerosis complex (Koh *et al.,* 2000), Sturge-Weber syndrome (Pinton *et al.,* 1997), hemimegalencephaly (Uematsu *et al.,* 2010), or neonatal seizures (Børch *et al.,* 1998).

Application of SPECT to very young patients raises several important methodological questions. Global cerebral blood flow changes rapidly in normal infants and young children, increasing after birth and peaking by age 5 or 6 years; it then diminishes slowly until it reaches adult levels between ages 15-19 years (Chiron *et al.,* 1996). Furthermore, over the first year of life, regional cerebral blood flow (rCBF) increases more rapidly in occipital rather than frontal cortex, causing an increased antero-posterior gradient (Chiron *et al.,* 1996).

Despite these age-related differences in cerebral perfusion, the ictal SPECT findings in previous case reports or small series of infants are similar to later life, revealing well-defined zones of ictal hyperperfusion and interictal hypo-perfusion (Kaminska, 2003; Buchhalter and So, 2004; Gupta *et al.,* 2004; O'Brien *et al.,* 2004). The aim of our study was to further assess the usefulness of ictal SPECT in a cohort of very young epilepsy surgery candidates with FCD. We analysed ictal SPECT findings in 13 infants with histologically-proven FCD. These subjects were included in the group of 106 children with FCD studied in our two previous publications dealing with the predictive value of SPECT for outcome after epilepsy surgery (Krsek *et al.,* 2013) and the variables influencing the extent of SPECT findings (Kudr *et al.,* 2013).

Methods

Inclusion criteria

Data of all children who underwent excisional epilepsy surgery at Miami Children's Hospital were retrospectively reviewed from a de-identified database in accordance with authorized institutional approval for research on human subjects.

We selected patients who:

– had at least one good-quality ictal SPECT study performed in the first year of life;

– subsequently underwent excisional epilepsy surgery;

– had definite histological evidence of FCD;

– and had known seizure outcome at two years after the (last) surgery.

Two patients (Patients 3 and 9) underwent two ictal SPECT studies and Patient 5 had three ictal SPECT studies in the first year of life. All repeated SPECT studies yielded similar findings and we therefore included only the last SPECT study for purposes of data analysis. SPECT studies were correlated with outcome of the last surgical procedure. Seven patients (Patients 4, 5, 6, 7, 9, 10 and 12) underwent surgery during the first year of life, six patients (Patients 1, 2, 3, 8, 11 and 13) had their surgeries between ages 2-4 years. Three patients (Patients 1, 5 and 13) had repeated surgery; Patient 3 underwent two re-operations.

Ictal SPECT examination

Peri-ictal radioisotope injections were always performed by trained registered radiology technicians during video-EEG monitoring; 99mTc-HMPAO was used in all patients. Doses of the radiotracer were calculated according to the patient's weight (300 μCi/kg). Injections were administered as soon as either clinical or electrographic seizure onset of a habitual seizure was observed. The radiotracer injection was followed by a saline flush. All SPECT studies were considered ictal at the time of examination, however, we were not able to obtain precise data about injection time in five SPECT studies (Patients 1, 3, 5, 10 and 13). In one patient (Patient 12), the injection time was 180 seconds and the length of injected seizure was 340 seconds. The injection times of the remaining studies were between 7 and 40 seconds. All SPECT images were acquired within two hours of the radiotracer injection.

Image acquisition was performed on a three-headed Multispect 3 Siemens' Medical System machine (Hoffman Estate, Illinois, USA) with the parameters: 120-word mode, 360-degree rotations, 40 stops and 120 images, 60 seconds-per-frame imaging, 1.28 magnification factor, fan beam collimation, 7.6-mm FWHM at 10 cm, 31×41 cm FoV, and isometric voxel size of 2.897 mm. Attenuation correction was applied in all studies. A standard series of axial, coronal, and sagittal images were created. Uncooperative or immature patients underwent image acquisition using a paediatric sedation protocol, consisting of

orally-administered chloral hydrate (50-75 mg/kg) or pentobarbital (3-6 mg/kg). Continuous monitoring of the airway and pulse oximetry was performed by a trained registered nurse.

MRI examination

The MRI of all patients was performed on an MR scanner with 1.5T strength field; fluid-attenuated inversion recovery (FLAIR) sequences were obtained routinely for all patients.

Blinded review of SPECT images

Initial visual analysis of peri-ictal scans for localization of a region of the highest increase in the ictal perfusion was performed by a nuclear medicine expert blinded to all patient data. A grey scale of the images was then modified to achieve the best localization of the region with increased perfusion. For the purposes of the study, SPECT images were independently re-evaluated by three reviewers (PK, BM, and AJ) who were aware of the pathological diagnosis, but not the clinical, EEG, MRI data, or postoperative seizure outcomes. Differences between reviewers led to a case being re-reviewed together until a consensus was reached.

In the first step of image analysis, the reviewers were required to localize cortical hyperperfusion zones to 11 anatomically defined regions (frontal central, mesial, convexity, polar, and basal; temporal mesial and lateral; parietal mesial and lateral; and occipital mesial and lateral) or to classify the images as "non-localizing" (*i.e.* SPECT examinations with absent cortical hyperperfusion). The extent of cortical hyperperfusion was then classified as follows:

– well-localized (confined to a region of one gyrus or two contiguous gyri);
– lobar;
– multi-lobar;
– hemispheric;
– and bilateral.

Completeness of hyperperfusion zone removal

In the next phase of the analyses, both SPECT and post-surgical MR images (performed after the last surgery) were presented to the reviewers for correlation of the SPECT findings to the resection cavity. The relationship of the SPECT hyperperfusion zone to the resection was classified as:

– completely resected;
– partially resected;
– and non-resected.

Relation of SPECT findings to MRI and EEG localization

Finally, completeness of the SPECT hyperperfusion zone removal was correlated with the MRI and intracranial EEG findings (ECoG or long-term invasive monitoring). Completeness of resection was always determined at the time of surgery by an epilepsy team that included neurologists, neuroradiologists, and neurosurgeons. We defined complete resection as the entire removal of the MRI abnormality (if present) and the cortical region exhibiting prominent ictal and interictal iEEG abnormalities (Jayakar *et al.*, 1994; Krsek *et al.*, 2009; Paolicchi *et al.*, 2000). As SPECT findings were never considered when the MRI and iEEG were assessed, both zones (MRI and iEEG) were analysed as independent variables.

Following the comparison of completeness of the SPECT hyperperfusion zone and the MRI/iEEG-defined epileptogenic region with the anatomical limits of the excavation cavity, we identified four outcomes:

– The SPECT hyperperfusion zone and MRI/iEEG-defined epileptogenic region were both completely removed;
– only the SPECT hyperperfusion zone was removed;
– only the MRI/iEEG-defined epileptogenic zone was removed;
– and neither region was removed completely.

Surgical outcome

We routinely assess surgical outcomes two years after the (last) surgery. Outcomes were determined via outpatient visits and telephone contact, and classified according to Engel's classification scheme:

– (I) completely seizure-free, auras only or only atypical early postoperative seizures;
– (II) $\geq$90% seizure reduction or nocturnal seizures only;
– (III) $\geq$50% seizure reduction;
– (IV) <50% seizure reduction. For the purposes of statistical evaluation, we classified patients as either seizure-free (Engel class I) or non-seizure free (Engel class II, III, IV).

Correlation of results and statistical analysis

Completeness of removal of the SPECT hyperperfusion zone and MRI/iEEG epileptogenic region and histological findings were related to post-surgical seizure outcomes. We used the Pearson's chi-square test or (when possible) the Fisher exact test with two-tailed *p* value for accepting or rejecting the null hypothesis of independency of the above-mentioned nominal variables. All statistical calculations were performed using Statistica® software.

Results

Characteristics of patients, SPECT findings, surgery, and postsurgical outcome (*table 1*)

Thirteen ictal SPECT studies from 13 patients met all inclusion criteria. Mean age at SPECT examination was six months (range: one month and three weeks to 11 months and three weeks). Hyperperfusion zones were always present. One SPECT study was considered well localized, four were lobar, and eight were multilobar. The injected seizure was evaluated as partial in nine patients, and three SPECT examinations were performed during secondary generalized seizures, and one during spasms. Data concerning length of injected seizures and injection time were available only in a proportion of studies.

MRI changes typical of FCD were apparent in 12 patients. One patient with normal MRI was diagnosed histopathologically.

Mean age at last surgery was 17 months (range: 2-58 months). Ten patients underwent one-stage excisional procedures guided by pre-excision electrocorticography; long-term invasive monitoring utilizing implanted subdural electrodes was performed in three subjects (Patients 3, 5, and 13).

There were four subjects with FCD type I and nine with FCD type II according to the ILAE classification (Blümcke *et al*., 2011).

Six patients were seizure-free (Engel class I) following the last surgery and seven patients were non-seizure-free (two patients with Engel class III and five patients with Engel class IV).

Completeness of removal of SPECT hyperperfusion zone and its relation to surgical outcome (*table 1*)

All five patients with complete resection of the SPECT hyperperfusion zone were seizure-free compared to only one of seven patients with incomplete removal (one patient with Engel class III and five with Engel class IV; p=0.00843). One patient with an unresected hyperperfusion zone had Engel class III outcome.

Completeness of removal of MRI/iEEG-defined epileptogenic region and its relation to surgical outcome (*table 2*)

For patients with complete removal of MRI/iEEG-defined epileptogenic regions, five patients were seizure-free and one was not seizure-free (Engel class IV). For patients with an incomplete resection, only one patient was seizure-free, whereas six patients were not seizure-free (two with Engel class III and four with Engel class IV; p=0.02914).

Combined impact of SPECT findings and MRI/iEEG localizations on surgical outcome (*table 2*)

All four patients with complete removal of the epileptogenic region, defined both by SPECT and MRI/iEEG, were seizure-free. When both regions were incompletely removed, no patient was seizure-free; two patients had Engel class III outcome and four had Engel class IV outcome (p=0.01179). One patient with only removal of the SPECT hyperperfusion zone was seizure-free. For patients with only MRI/iEEG-defined epileptogenic regions, one was seizure-free and one was not seizure-free (Engel class IV outcome).

Relation of histological type of FCD to surgical outcome (*table 2*)

Five of six seizure-free patients had FCD type II, but there was no statistically significant difference in outcome between FCD types I and II using the Fisher exact test.

Discussion

Ictal SPECT (and derived methods) has been repeatedly confirmed to be a highly effective localizing tool for planning epilepsy surgery in patients with FCD (O'Brien *et al*., 2000; Kaminska, 2003; McNally *et al*., 2005; Kazemi *et al*., 2009; Krsek *et al*., 2013), but there is no similar data in infants. The absence of data in this age range is particularly unfortunate as FCD is a major cause of pharmaco-resistant focal epilepsy in very early life. Although our cohort is small, it represents the largest known series of infants with FCD undergoing ictal SPECT before undergoing excisional epilepsy surgery. Limitations of our study include the absence of subtraction of ictal and interictal SPECT findings and co-registration to MRI (SISCOM technique), however, our previous study, conducted on a larger population of paediatric FCD patients, showed comparable results of SISCOM to simple visual evaluation of SPECT findings (Krsek *et al*., 2013).

All five patients with complete removal of the SPECT hyperperfusion zone became seizure-free, whereas seven of eight patients with incomplete or non-resected SPECT hyperperfusion zone experienced an unfavourable outcome. These results support previous reports of ictal SPECT in older populations (O'Brien *et al*., 1998; O'Brien *et al*., 2000; Kaminska, 2003; Gupta *et al*., 2004; Krsek *et al*., 2013) and confirm that ictal SPECT hyperperfusion is also a reliable predictor of favourable post-surgical outcome in very young candidates.

We obtained similarly favourable outcomes using MRI and iEEG parameters to measure completeness; five of six patients with complete resection based on these

Table 1. Details about patients, presurgical evaluation, surgical details, and postsurgical outcome.

Patient	Sex	Age at SPECT (months, days)	Type of injected seizure	SPECT hyperperfusion zone localization	MRI - FCD localization	Age at surgery (months, days)	Resection site (after the last surgery)	Invasive monitoring	Completeness of removal of SPECT hyperperfusion zone	Completeness of removal of MRI/EEG-defined epileptogenic region	Histological type of FCD	Seizure outcome at two years (Engel scale)
1	F	1 m., 23 d.	PS	L PO	L PO + R C	17 m., 6 d.	L TPO*	No	Incomplete	Incomplete	I	IV
2	F	11 m., 22 d.	PS	L FCT	L CP	12 m., 9 d.	L HEMI	No	Complete	Complete	II	I
3	M	3 m., 14 d.	PS	R FCP	R FTP	15 m., 8 d.	R HEMI*	Yes	Complete	Complete	II	I
4	M	5 m., 2 d.	PS	L FC	L FT	5 m., 24 d.	L FT	No	Incomplete	Incomplete	II	IV
5	F	8 m., 24 d.	SGS	R FC	R F	9 m., 4 d.	R FTP*	Yes	Incomplete	Complete	II	IV
6	M	4 m., 4 d.	PS	R FCP	R F	9 m., 14 d.	R F	No	Incomplete	Incomplete	I	IV
7	M	11 m., 3 d.	PS	L FCTP	L F	11 m., 9 d.	L F	No	Incomplete	Incomplete	II	IV
8	F	8 m., 6 d.	PS	R O	R TO	19 m., 0 d.	R TO	No	Complete	Incomplete	I	I
9	M	1 m., 13 d.	PS	R FCP	R FCP	2 m., 13 d.	R FP	No	Complete	Complete	II	I
10	M	1 m., 26 d.	PS	R TO	R TPO	2 m., 19 d.	R TPO	No	Complete	Complete	II	I
11	M	8 m., 1 d.	Spasms	R O	L T	55 m., 1 d.	L TPO	No	Not resected	Incomplete	I	III
12	F	2 m., 14 d.	SGS	R FTO	R TO	2 m., 21 d.	R TPO	No	Incomplete	Incomplete	II	III
13	M	9 m., 0 d.	SGS	R FC	Normal	58 m., 13 d.	R FP*	Yes	Incomplete	Complete	II	I

PS: partial seizures; SGS: secondary generalized seizures. R: right; L: left; F: frontal; C: central, P: parietal; O: occipital; T: temporal; *Repeat surgery.

Table 2. Relation between seizure outcome, completeness of removal of SPECT hyperperfusion zone and MRI/EEG-defined epileptogenic region, and histopathology.

	Outcome	
	Non-seizure-free	**Seizure-free**
Completeness of removal of SPECT hyperperfusion zone (*p*=0.00843)*		
Complete (*n*=5)	0	5
Incomplete (*n*=7)	6	1
Non-resected (*n*=1)	1	0
Completeness of removal MRI/EEG-defined epileptogenic region (*p*=0.02914)**		
Complete (*n*=6)	1	5
Incomplete (*n*=7)	6	1
SPECT vs MRI/iEEG (*p*=0.01179)*		
Resection of both regions complete (*n*=4)	0	4
Only SPECT hyperperfusion removed (*n*=1)	0	1
Only MRI/iEEG-defined epileptogenic region removed (*n*=2)	1	1
Removal of both regions incomplete (*n*=6)	6	0
Histological type of FCD (*p*=0.55944) **		
FCD type I (*n*=4)	3	1
FCD type II (*n*=9)	4	5

*Pearson's chi-square test.
**Fisher exact test with two-tailed *p* value.

criteria were rendered seizure-free. We reported similar results in our series of all paediatric FCD patients operated on in the Miami Children's Hospital; 83% of patients undergoing complete resections, based on combined MRI/iEEG criteria, achieved favourable postsurgical seizure outcomes (Krsek *et al.,* 2009).

These findings suggest that complete resection of the epileptogenic region defined by either ictal SPECT or MRI/iEEG are strong predictors of favourable postsurgical outcome, whereas incomplete resection of both regions is associated with uniformly poor seizure outcomes. These findings therefore extend the value of the ictal SPECT to infants with FCD and do not support a lower age cut-off for ictal SPECT in surgical candidates. Scalp EEG findings in infants are often non-localized or non-lateralized (Duchowny, 1987). Although similar findings might also be hypothesized for ictal SPECT, all infants in our study exhibited localized hyperperfusion. Similarly, seizure semiology in infancy differs markedly from that in older children. Seizures in early life are more frequent and have a more limited repertoire of ictal manifestations, including features indicating localized onset (such as auras) which are often absent or unidentifiable (Acharya *et al*., 1997). For example, Patient 11 underwent SPECT examination during clinical spasms, and hyperperfusion was localized to the occipital lobe. Although we cannot assess whether the hyperperfusion zone correctly localized the epileptogenic zone in this patient as the hyperperfusion zone was not resected, this result is concordant with previous studies of patients with spasms and West syndrome, providing evidence of localizing neurophysiological abnormalities in the posterior quadrants (Haginoya *et al*., 2001; Fujii *et al.,* 2013).

In summary, we found that despite age-related differences in cerebral perfusion (*i.e.* increasing global cerebral blood flow in young children, with an increasing antero-posterior gradient in the first year of life) (Chiron *et al*., 1996, 1992) and more extensive epileptogenic zones in infants, ictal SPECT provides localized findings concordant with the epileptogenic zone. Several of our subjects with anterior quadrant epileptogenic foci revealed robust hyperperfusion in the appropriate region. Although ictal SPECT is not a mandatory diagnostic test in most epilepsy surgery protocols, it is nonetheless an important adjunctive procedure for planning surgery in very young surgical candidates. Ictal SPECT may reduce the necessity for long-term intracranial EEG recordings and potentially provide information leading to more restricted resections. Despite the methodological challenges associated with the ictal SPECT in infants (such as the need for sedation), we believe that its utility argues strongly in favour of its use in selected patients. □

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TEST YOURSELF

(1) Is the global and regional cerebral blood flow different between adults and children?

(2) What was the proportion of localized ictal SPECT findings in our study?

(3) Could ictal SPECT localize seizure onset in "generalized" seizure types, typical for infants?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".