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SPECT in periodic lateralized epileptiform discharges (PLEDs): a form of partial status epilepticus?

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Periodic lateralized epileptiform discharges (PLEDs) are a well defined electroencephalographic entity but whether PLEDs represent an ictal condition or not remains debated. Much work has been done using electroencephalography (EEG) but new approaches using cerebral perfusion imaging may give more information about this question. We aimed to evaluate if PLEDs were associated with high regional cerebral blood flow (rCBF).

We studied 18 patients with PLEDs and different pathologies, and performed brain single-photon-emission computed tomography (SPECT) during and, for three cases, after the disappearance of PLEDs. Qualitative variations and locations of rCBF were compared with PLEDs. Association with seizures and type of seizures were also assessed.

SPECT showed high rCBF in 18/18 patients (100%). The location of PLEDs and high rCBF matched in 17/18 cases (94%). In the three cases where SPECT was performed after PLEDs disappeared, the high rCBF had cleared (100%). Eighteen cases (100%) presented seizures before recording of PLEDs, mainly motor (partial motor or generalized tonic–clonic).

Where there was a decreased rCBF (related to a lesion) there was little relationship to PLEDs and all patients with decreased rCBF had an adjacent increased rCBF. These results confirm preliminary case reports. Hyperperfusion adds further to the argument that PLEDs may be related to a form of partial status epilepticus.

Key words: periodic lateralized epileptiform discharges (PLEDs); status epilepticus; SPECT; regional cerebral blood flow (rCBF).

INTRODUCTION

Periodic lateralized epileptiform discharges (PLEDs) were first described by Chatrian *et al.* in 1964[1]. They consist of spikes or sharp wave complexes occurring in a periodic or pseudo-periodic fashion, every 0.3–4 seconds, on EEG recordings. Their variable EEG appearance, their temporal evolution, their associated underlying pathology and their relationship to seizures has been extensively studied[2–9]. One question remains to be settled; whether they represent an ictal condition or not. In addition to clinical and EEG data, functional neuroimaging may add further information about pathophysiological mechanisms.

Functional neuroimaging is widely used to determine the epileptic focus in surgical evaluation of pharmacoresistant seizures. Ictal blood flow studies during video-EEG monitoring show increased regional cerebral blood flow (rCBF) in more than 90% of cases[10–13]. Preliminary case reports showed an increased rCBF or metabolism in three patients with PLEDs[15–17]. The purpose of this study was to evaluate the CBF pattern using brain single-photon-emission computed tomography (SPECT) in 18 patients with PLEDs.

METHOD

Eighteen patients (46–95 years old) were studied retrospectively between 1994 and 1998. They were included when PLEDs occurred for at least 20 minutes recording on a standard 16-channel EEG. Patients were referred after various types of seizures or to exclude nonconvulsive status epilepticus.

Brain SPECT was performed for clinical evaluation of perfusion abnormalities. Images were acquired 30 minutes after intravenous injection of 925 MBq

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(25 mCi) of ^{99m}Tc hexamethyl-propylenamine oxime (HMPAO) or 740 MBq (20 mCi) of ethylcysteinate dimer (ECD), with EEG monitoring to ensure that PLEDs were continuing during and after the injection. HMPAO-SPECT was performed during 1994–95. In 1995, ECD was introduced in the Division of Nuclear Medicine as the standard imaging procedure for brain perfusion evaluation of all patients with epileptic seizures or PLEDs. SPECT examinations were performed using a dual-head Picker PRISM-2000 gamma camera or a three-head Toshiba GCA 9300/11G gamma camera with fan-beam collimators, introduced in 1996 (ictal SPECT). The protocol was respectively a 180° or 120° rotation in step-by-step mode, with a 6° step and a 60 second acquisition per step. Reconstruction was done using filtered back-projection and we obtained, for all patients, transaxial, coronal and sagittal slices.

Table 1: Localisation of PLEDs on EEG, and of ictal and basal SPECT in 18 cases.

Patient	PLEDs	Ictal SPECT		Basal SPECT
		hyper rCBF	hypo rCBF	
1	L FT	L FT		
2	L/R PTO	R/L PTO		
3	R FP	R FP	R PO	
4	L PTO	L TO		
5	L FT	R P		
6	L PTO	L PTO		
7	L PT	L T	LO	
8	R FPT	R F		
9	R PTO	R PT	R O	
10	R FP	R F	R FP	
11	R PTO	R TO		
12	R FPT	R FT	R P	
13	R PO	R PO		Normalization
14	R PTO	R PTO		
15	L PTO	L PTO	L O	Normalization
16	L PT	L PT		
17	L FT	L T	L F	Normalization
18	L PTO	L PT		

L = left, R = right, F = frontal, P = parietal, T = temporal, O = occipital, rCBF = regional cerebral blood flow.

Since 1996, three patients were evaluated, using the same procedure (using ECD as a marker, and a three-head Toshiba GCA 9300/11 gamma camera), when PLEDs had completely resolved as confirmed by their disappearance on the EEG (basal SPECT). No other paroxysmal activity was recorded. SPECT analysis was performed by two experienced nuclear medicine physicians (JPP, GWG) who determined the location of decreased or increased rCBF, without knowledge of the EEG data, in the frontal (F), parietal (P), temporal (T), occipital lobe (O) or a combination of different lobes. Changes were analysed by comparing abnormalities with all other regions of the brain. Abnormalities had to be present in at least on two adjacent slices to be significant. The distinction between increase or decrease was made by comparison with brain cortical areas in regions not adjacent to the suspected lesion (i.e. the parietal cortex was compared to the frontal cortex in other slices) and a comparison of the lesion with subcortical grey matter (i.e. thalamus and caudate) was also performed. Then the location of the PLEDs, defined by the region of maximum amplitude of the EEG anomalies, was correlated to the rCBF findings. Total concordance of EEG and SPECT data was found when different brain areas (F, P, T, O, or combination) matched perfectly together (e.g. patient 1, PLEDs in F and T, and rCBF in F and T; see table 2). Partial concordance was found when location of PLEDs matched only some of the areas with altered rCBF (e.g. patient 11, PLEDs in P, T and O and rCBF in T and O; see table 2). The type and occurrence of seizures, neurological findings, and results of structural neuroimaging methods (CT-scan, MRI) or autopsy in one case, were also assessed.

RESULTS

Ictal SPECT showed a focal increase of rCBF in 18 patients (100%). Its location was parieto-temporal (PT) in three patients (9, 16, 18), parieto-occipital (PO) in one (13), parieto-temporo-occipital (PTO) in four (2, 6, 14, 15), fronto-parietal (FP) in two (3, 10), frontal (F) in two (8, 10), temporal (T) in two (7, 17), or parietal (P) in one (5).

In 17 patients (94%) the location of the increased rCBF corresponded to the location of the PLEDs: nine cases showed total concordance (1, 2, 3, 6, 10, 13, 14, 15, 16) defined as two or three lobes with increased rCBF in SPECT corresponding to the location of the PLEDs in the same topography; eight showed partial concordance (4, 7, 8, 9, 11, 12, 17, 18) defined as two and three lobes respectively with increased rCBF or two lobes with PLEDs and three lobes with rCBF increase in SPECT. Increased rCBF was found contralateral to the PLEDs in one patient (5) with a left hippocampal tumour, ipsilateral to the PLEDs.

Seven patients (39%) showed a decreased rCBF corresponding to a stroke (ischemic in 3, 9, 17, or haemorrhagic in 12, 15), a tumour in patient 10, or an unidentifiable lesion on CT scan (7). In these seven patients, the decreased rCBF was posterior to the PLEDs in patients 3, 7, 15; in the caudal part of the PLEDs area in patients 9, 12; in the same region in patients 10 and 17. All these patients with a decreased rCBF had an adjacent increased rCBF in SPECT (see above).

Basal SPECT showed disappearance of focal increase rCBF compared to the ictal SPECT in the three cases imaged twice (13, 15, 17). These findings are summarized in Table 1. The example of patient 15 is shown in Fig. 1.

Table 2: Clinical data and results of structural neuroimaging methods or autopsy in 18 cases.

Patient	Age	Seizure type	Clinical findings	CT/*IRM*/autopsy*	Remarks
1	95	Partial complex, II generalized	Aphasia, R hemiparesis	Atrophy	
2	66	Partial motor	Coma	Leucoencephalopathy	Hepatic cirrhosis (alcoholic)
3	69	Generalized, tonic–clonic	L hemiparesis	R T stroke (old)	Chronic alcoholism
4	91	Generalized, tonic–clonic	Coma, R hemiparesis	Atrophy	Dementia
5	60	Partial complex, II generalized	Aphasia	*Left hippocampal tumor*	
6	91	Partial motor	Aphasia	Atrophy, leucoencephalopathy	Dementia
7	90	Partial motor	Confusional state	Atrophy, leucoencephalopathy	
8	50	Partial complex, II generalized	Confusional state	R TPO tumor	Chronic alcoholism
9	75	Partial complex	L hemianopia	R P stroke	
10	53	Partial motor, II generalized	L hemiparesis	*R FP tumor*	
11	53	Partial motor, partial complex	Normal	Normal	Hepatic cirrhosis (post hepatitis)
12	51	Partial sensitive	L hemiparesis, hemihypesthesia	*L P hemorrhage*	Chronic alcoholism
13	62	Partial complex	L hemiparesis, hemianopia	R subcortical PO stroke (old)	
14	81	Motor status	L hemiparesis	R sylvian stroke*	Hepatic cirrhosis (alcoholic)
15	73	Generalized, tonic–clonic	R hemiparesis and hemianopia	L occipital hemorrhage	Chronic alcoholism
16	67	Generalized, tonic–clonic	Aphasia	L subdural hematoma	Chronic alcoholism
17	46	Partial motor	Aphasia, R hemiparesis	*L F stroke (old), L capsulothalamic hemorrhage (old)*	
18	53	Generalized, tonic–clonic	R hemianopia	Moderate atrophy	Hepatic cirrhosis (alcoholic)

R = right, L = left, II generalized = secondary generalized, F = frontal, P = parietal, T = Temporal, O = occipital.

Seizures occurred in our 18 cases (100%): mainly with motor manifestations in 15 cases (motor status epilepticus, repetitive partial motor seizures, generalized tonic–clonic seizures), partial sensory in one case (5.5%), and partial complex in two cases (11%). During EEG recordings, 14 patients (77.5%) presented with a focal deficit, two patients (11%) with a confusional state, two patients (11%) with a coma and one patient (5.5%) with a normal bedside neurological examination. Relevant medical information were hepatic cirrhosis in four cases (22%), chronic alcoholism in five cases (28%), dementia in two cases (11%), and previous stroke in three cases (17%). Six patients were above 74 years old (33%).

Seizure type, main clinical findings, neuroimaging (CT/or MRI), and other relevant medical information are summarized in Table 2.

DISCUSSION

In the present retrospective study, we qualitatively examined rCBF using SPECT in 18 patients with PLEDs (ictal SPECT) and with a second examination in three patients after PLEDs cleared (basal SPECT).

We demonstrated increased rCBF in ictal SPECT in all 18 patients (100%). In 17 patients (94%) a concordance of the location of both PLEDs and rCBF was found. Topographically, PLEDs are found scattered throughout the involved hemisphere with some predominance in the temporal, parietal and occipital regions, both in the literature[1,6] and our patients. We defined their topography by the maximum amplitude of electrical activity. Since these are rather diffuse electrical activities, involving broad regions—as opposed to the sharper focus seen in surgical epilepsy imaging—we feel the topographical matching of both PLEDs and increased rCBF is very satisfactory.

Recently, in addition to an ictal hyperperfusion region, an ictal hypoperfusion region and combined ictal hyperperfusion–hypoperfusion regions have been described using substracted SPECT[18]. Nevertheless, our findings are in agreement with the increased rCBF and metabolism of ictal regions seen in the evaluation of focal intractable seizures[10–14], in epilepsia partialis continua[19] and confirm the findings of previously published preliminary case reports[15–17]. In these case reports, patients demonstrated increased rCBF or metabolism corresponding with the area of maximal amplitude of PLEDs in the EEG.

Further, an increase of cerebral blood volume may occur due to abnormal vasodilatation that may be the result of a decreased oxygen extraction fraction. After an ischaemic infarction reflow hyperaemia may occur due to spontaneous thrombolysis. This phenomenon was called luxury perfusion and reflects an uncoupling of rCBF and metabolism[20].

Since in our study, patients with different diseases were studied, increased rCBF could be explained by a metabolic alteration of cells in structurally preserved tissue due to different aetiologies, e.g. ischaemia, the toxic effect of metabolites near a lesion, or overexcitation by neurotransmitters. In contrast to PET examination allowing quantification of cerebral blood flow, image interpretation of brain perfusion studies using ECD and HMPAO are always done visually without

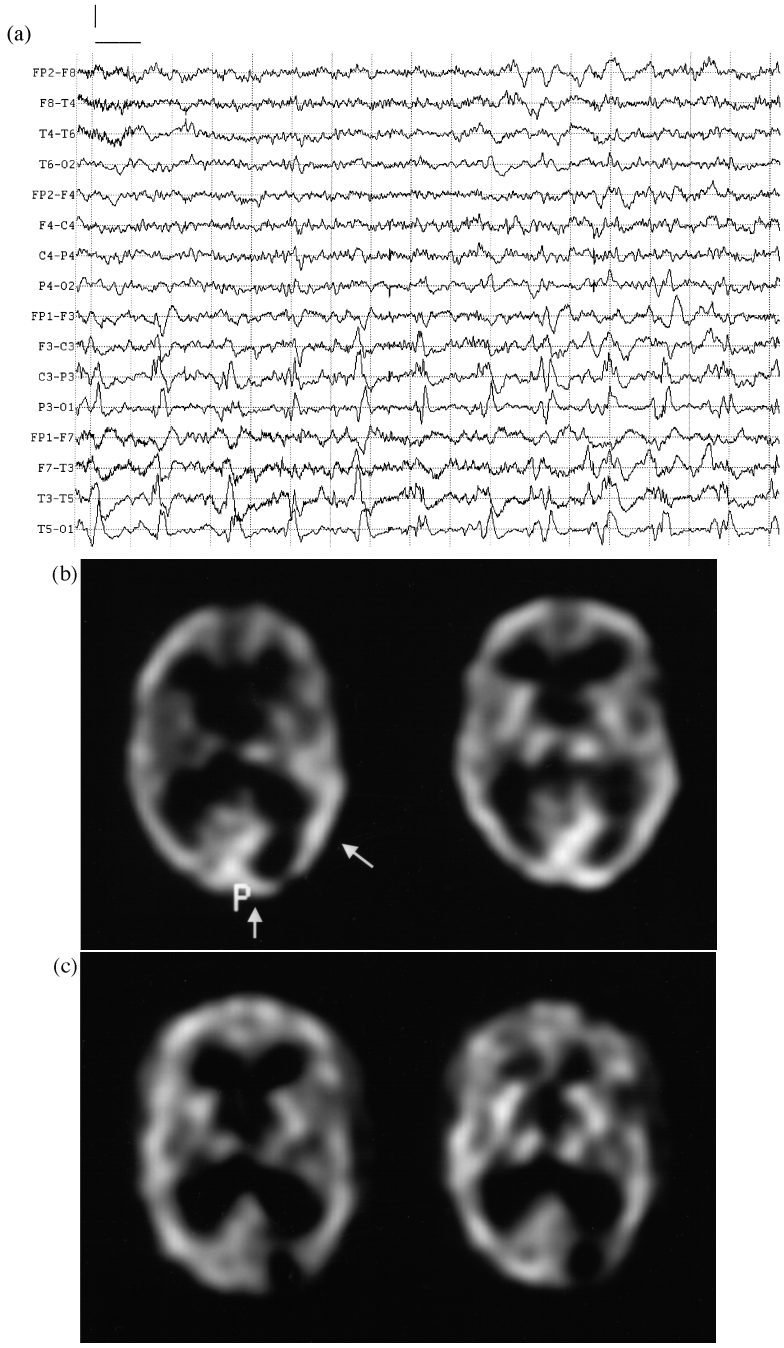

Fig. 1: Example of patient 15. EEG with PLEDs of maximum of amplitude over the left parieto–temporo–occipital regions; scale-bar $= 100\ \mu$V per second (a). SPECT during PLEDs showing hyperperfusion in the parieto–temporo–occipital regions of the left hemisphere (arrow), surrounding an hypoperfused region in the left occipital lobe (b). SPECT after normalization of EEG showing the disappearance of hyperperfusion (c).

the possibility to quantify rCBF. In this study, identification of hyperperfused areas was performed in comparison with normal brain regions defined by the two experienced readers within the same imaging study.

Decreased rCBF probably represents the centre of the brain lesion in stroke or tumour, where perfusion is the most compromized. Since HMPAO and ECD are flow markers, there is lack of uptake in damaged brain areas showing decreased blood flow. Further, if brain cells are extensively damaged and can no longer take up the radiopharmaceutical, SPECT imaging using these tracers will show decreased uptake (even if rCBF might be preserved).

In the three cases with basal SPECT, increased rCBF resolved when the PLEDs cleared. This may indicate that this abnormal enhanced metabolic activity or

metabolic derangement of cells with a concomitant increase of rCBF ends with the disappearance of PLEDs.

Both the increased rCBF during PLEDs in 18 cases and the normalization of rCBF in the three basal SPECT cases give more evidence for a dynamic process underlying PLEDs in the brain. We feel that PLEDs are a metabolic sign of partial nerve cell damage in neurons with the ability to recover. Therefore, PLEDs, as an analogy to the epileptic discharges of neurons with metabolic derangements, may indeed represent a special form of partial status epilepticus, defined by an increase of neuronal activity visualized by an increase of rCBF.

Some authors suggest a possible additional role of metabolic abnormalities in the pathogenesis of PLEDs[8] and that PLEDs may represent a benign form of nonconvulsive status epilepticus, particularly in the elderly[4]. We cannot address the influence of metabolic alterations and old age in a brain area as an underlying mechanism for the development of PLEDs with such a small series of various pathologies. It remains unclear if these factors (hepatic cirrhosis, chronic alcoholism, old age, dementia) are needed as a predisposition for PLEDs, and if so, how this influence could be investigated.

CONCLUSION

We confirm previous case reports. Our results suggest that hyperperfusion is always present in patients with PLEDs. Prospective studies with quantification of rCBF using positron emission tomography (PET) may help to better identify areas with altered metabolic activity and help better delineate between areas with increased metabolic activity and areas of irreversibly damaged brain tissue. Further imaging of individual patients at different time points are necessary to highlight the dynamics of brain alteration in patients with PLEDs.

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