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Ictal and interictal SPECT findings in childhood absence epilepsy

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The purpose of this study was to investigate the informative value of single photon emission tomography (SPECT) in relation to the pathophysiological functioning of the brain during absence seizures and the origin of ictal discharges in idiopathic generalized epilepsies (IGEs). Six patients with childhood absence epilepsy (CAE) were selected for the study and two consecutive SPECT sessions were performed concomitant with EEG recordings revealing normal results and during hyperventilation (HV) studies where the ictal discharges were induced either alone or accompanied by clinical absence seizures. All six patients had ictal discharges in their EEGs during HV and two of them also had clinical absences. SPECT findings during HV revealed an overall increase in the cerebral blood flow (CBF) with significantly higher values as compared to the baseline data. There was no indication for any focal origin in either the interictal or the ictal SPECT findings. Results of the study were supportive for the concept of subcortical origin for the absence seizures and they were also promising for the diagnostic value of ictal SPECT in epileptic cases with undetermined origin as to whether they were localization-related or generalized.

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Key words: seizure; absence; SPECT; ictal; interictal; hyperventilation.

INTRODUCTION

Among the brain imaging techniques, single photon emission tomography (SPECT) is the currently preferred investigation method to uncover the ictogenic area in pre-surgical evaluation of medically intractable, localization-related epilepsies. When performed ictally, its informative value in that respect is believed to be nearly a 100% in temporal lobe epilepsies[1]. However, probably due to favorable management and outcome of idiopathic epilepsies, brain SPECT does not seem to have a place in either the diagnosis or the follow-up of those patients. A well-known fact for the clinician dealing with epilepsy, on the other hand, is the condition with medically resistant absence epilepsy necessitating inquiry of a possible cortical (frontal?) origin for seizure discharges. Since those cases are almost always cranial MRI-negative and scalp EEG, even during sleep, may not provide support for recognition of primary versus secondary generalization, a searching for other beneficial methods was the rationale behind this study.

As the initial phase of a prospective study, patients with childhood absence epilepsy (CAE), sensitive to hyperventilation (HV), were selected for this study. CAE was chosen to enable optimum availability for detecting seizure activity as well as providing uniformity for the EEG data and experimental conditions. Cerebral blood flow (CBF) changes concomitant with seizure activity in the EEGs were investigated for any possible contributory evidence for the origin of seizure activity and for the pathophysiology of seizure propagation.

MATERIALS AND METHODS

Six patients (aged 7–14 years) with CAE were selected for the study. All patients were otherwise healthy; and all had normal cranial MRIs. Background activity of their previous EEGs were normal; they all had long-lasting 3 Hz bilateral spike-and-wave (SW) activity during HV with interhemispheric synchrony and symmetry as well as clinical absence seizures.

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For SPECT imaging, Tc-99m HMPAO was introduced to each patient at two consecutive sessions, i.e. during the resting state (baseline: B-SPECT) when the EEG was normal and during hyperventilation (HV-SPECT) associated with 3 Hz spike-and-wave discharges alone or with associated clinical seizures. In the B-SPECT phase, each patient was injected with weight-adjusted (within the 7–15 millicurie range) Tc-99m hexamethylene propilantine oxime (HMPAO), (Amersham-UK, prepared according to the manufacturers instructions) and the EEG was continued for at least 5 more minutes to be sure of the non-existence of any pathological discharge immediately following the infusion that might interfere with the results. The HV-SPECT phase after a 5 hour interval was performed at the same settings and the radioisotope was administered immediately following the appearance of seizure discharges on the EEG. The children were thoroughly informed about the procedure and the EEG room was darkened as an IV catheter was inserted into the arm before the recording session to eliminate any possible artefacting effect of the Tc-99m HMPAO injection on the SPECT values. Images were interpreted quantitatively by drawing regions of interest (ROIs) over both hemispheres separating frontal, temporal, parietal, occipital areas and basal ganglia regions. While comparing the SPECT images of baseline (B) and hyperventilation (HV) studies, the interpretation was performed regionally as mentioned above. For quantification, slices were displayed on 128×128 matrices to minimize drawing errors and ROIs were manually positioned by using visual inspection and isocount pixels around the cortex as described in the study by Kabasakal ***et al.***[2] Region selection was based on anatomical structures and regions were defined to approximate cerebral structures demonstrated in an anatomical CT atlas[3]. Avarage counts of ROIs containing at least 100 pixels were obtained from the whole cortex, basal ganglia and cerebellum for each study. All ROIs covered pixel numbers greater than two FWHM (18 mm FWHM). Cerebellar counts were obtained by drawing ROIs over the whole cerebellum in a slice displaying both cerebellar hemispheres. The cerebral-to-cerebellar ratios were calculated for all the slices of both baseline and hyperventilation studies and averaging of these slices was obtained to minimize variances occuring from position changes.

The baseline and hyperventilation ratio

$$(\mathrm{C/Cr\ B\text{-}C/Cr\ HV}) \qquad (1)$$

differences, where C/Cr was cerebral-to-cerebellar, for both hemispheres were calculated. The mean ratios of both hemispheres were expressed as a percentage of increase according to the formula;

$$(\mathrm{C/Cr\ B\text{-}C/Cr\ HV})/(\mathrm{C/Cr\ HV}) \times 100\%. \qquad (2)$$

The calculated ratios were corrected for flow-dependent back diffusion as described by Lassen ***et al.***($\alpha = 1.5$)[4]. The highest value from the hemispheres were accepted as the maximum increase;

$$\text{Corrected C/Cr} = \mathrm{C/Cr}/(1 + \alpha - \mathrm{C/Cr}). \qquad (3)$$

Statistical analyses of the B-SPECT values were compared to the HV-SPECT values by means of a non-parametric Wilcoxon test. A 10-channel Nihon Kohden EEG device and a Siemens Orbiter digitrack, Illinois-micro-delta computer were used for EEG recordings and SPECT evaluations, respectively.

RESULTS

The clinical characteristics of the six patients are summarized in Table 1. The age range was 7–14 years (mean age 9.8) and the male : female ratio was 1 : 1. All patients had several absence seizures daily, and they all were sensitive to hyperventilation. No patient had received any drug up to admission, valproate was prescribed after the study was completed. In the HV-SPECT phase of the study, all patients had 3 Hz spike-and-wave discharges with a mean duration of 9 s (2–14 s) and two of them also had concomitant absence seizures. The mean time of delay for the injection of Tc-99m HMPAO following the onset of discharges was 3 s (0–6 s). No epileptiform discharges were encountered during the B-SPECT sessions.

The HV-SPECT images of all six patients showed a homogeneous, diffuse increase in brain perfusion including the thalamus and no evidence for a regional hyperperfusion. Mean values for B-SPECT versus HV-SPECT were 1.04 ± 0.18 vs. 1.22 ± 0.44 with a statistical significance at $P < 0.005$ (Table 2). When looked of individually these values also revealed significant increases during HV-SPECT images. The increase in perfusion rates was even more striking for the two patients with absence seizures during the HV-SPECT session.

DISCUSSION

Ictal brain-SPECT changes were demonstrated in this study for a group of patients with CAE. CAE was considered as a reliable sample for studying the cerebral blood flow changes during seizure activity in the EEG while questioning the informative value of SPECT as an additional tool to either confirm the EEG findings or to uncover a possible cortical ictogenic area leading to secondary generalization. The latter situation might possibly provide a means for further discussion relating the pathophysiology of bi-hemispheric synchrony.

Table 1: Patients, their demographic features; electrographical and clinical features during EEG recordings for hyperventilation (HV) SPECT.

Patients	Age, gender, dominant hand	Epileptic syndrome	Features on EEG during HV	Absence+/−
1-A.G.	14, F, right hand	CAE	3 Hz Spike and wave	−
2-Ç.Ç.	13, F, right hand	CAE	3 Hz Spike and wave	−
3-Z.G.	12, F, right hand	CAE	3 Hz Spike and wave	+
4-A.U.	6, M, right hand	CAE	3 Hz Spike and wave	−
5-F.H.	10, M, right hand	CAE	3 Hz Spike and wave	−
6-Y.Y.	7, M, right hand	CAE	3 Hz Spike and wave	+

CAE, childhood absence epilepsy.
Absence +/− shows the presence of absence seizures associated with the 3 Hz spike-and-wave discharge.

Table 2: Mean values and ratios of baseline and HV SPECT regionally.

Patients		Frontal		Temporal		Occipital		Basal ganglia		Thalamus		Parietal	
		R	L	R	L	R	L	R	L	R	L	R	L
A.G.	Baseline	0.909	0.869	0.883	0.882	0.891	0.887	0.878	0.877	0.96	0.88	0.88	0.864
	HV	0.962	0.91	0.913	0.895	0.917	0.933	1.049	1.045	0.992	0.978	0.913	0.896
	Ratio %	5.51	4.51	3.29	1.45	2.84	4.93	16.30	16.08	3.23	10.02	3.61	3.57
Ç.Ç.	Baseline	1.065	1.098	0.983	1.015	0.998	1.043	1.229	1.222	1.101	1.081	1.037	1.057
	HV	0.981	1.021	1.027	1.052	1.054	1.087	1.166	1.168	1.152	1.203	1.06	1.026
	Ratio %	−8.56	−7.54	4.28	3.52	5.31	4.05	−5.40	−4.62	4.43	10.14	2.17	−3.02
Z.G.	Baseline	1.31	1.336	1.358	1.362	1.399	1.429	1.459	1.444	1.335	1.408	1.351	1.411
	HV	1.915	1.963	2.02	2.091	2.085	2.129	2.096	2.159	2.031	2.021	2.048	2.113
	Ratio %	31.59	31.94	32.77	34.86	32.90	32.88	30.39	33.12	34.27	30.33	34.03	33.22
A.U.	Baseline	0.901	0.941	0.838	0.811	0.827	0.844	0.859	0.859	0.892	0.833	0.86	0.853
	HV	1.203	1.209	1.103	1.09	1.154	1.14	1.251	1.212	1.191	1.159	1.134	1.086
	Ratio %	25.10	22.17	24.03	25.60	28.34	25.96	31.33	29.13	25.10	28.13	24.16	21.45
F.H.	Baseline	0.906	0.951	0.865	0.9	0.898	0.902	1.001	1.046	0.953	0.977	0.94	0.873
	HV	0.961	0.985	0.909	0.925	1.038	1.03	1.043	1.074	1.036	1.046	0.993	0.951
	Ratio %	5.72	3.45	4.84	2.70	13.49	12.43	4.03	2.61	8.01	6.60	5.34	8.20
Y.Y.	Baseline	0.91	0.9	0.84	0.81	0.86	0.89	0.96	0.96	0.9	0.86	0.86	0.89
	HV	1.06	1.12	1.01	1.06	1.07	1.11	1.12	1.22	1.19	1.19	1.03	1.1
	Ratio %	14.15	19.64	16.83	23.58	19.63	19.82	14.29	21.31	24.37	27.73	16.50	19.09
Average of ratios		12.25	12.36	14.34	15.29	17.08	16.68	15.16	16.27	16.57	18.82	14.30	13.75
	SD	14.59	14.63	12.27	14.47	12.15	11.61	14.44	14.82	13.01	10.96	12.91	13.29

R, right; L, left; Baseline, Baseline SPECT; HV, hyperventilation SPECT; SD, standard deviations of values.

There exists few reported SPECT studies during absence seizures. A generalized reduction in blood flow of cortical areas and a similar reduction, less in the frontal cortex as compared to parietal regions, were noted in two case reports, both of which were performed on two individual patients with absence seizures and absence status, respectively, during adulthood[5,6]. Results of the former study were interpreted in favor of the centrencephalic hypothesis for the origin of absence discharges, the latter was found to be indicative of lobar disparities in neuronal firing patterns. Dissimilarities within the patient samples and applied methodological differences posed a difficulty when comparing our results to those of the studies mentioned above, as the present study revealed consistent results suggesting an overall increase in CBF for each of the six similar cases, especially for the two with seizures. In Positron Emission Tomography (PET) studies, HV-induced 3 Hz spike-and-wave discharges and/or absence seizures were reported to be associated with considerable increases in cerebral glucose metabolism (CGM) in various clinical[7,8] and experimental settings[9]. In another FDG-PET study on the other hand, increases in brain metabolism were encountered during HV induced absence discharges in contrast to absence status associated with decreased metabolic rates[10]. Although there exists few observations as to dissimilar conditions on absence stati, results are rather suggestive of a diffuse decrease in both CBF and CGM. Since the discussion about the pathophysiology of absences is yet incomplete and data are controversial, remote considerations may be worthwhile at least, to a limited extent.

As is well-known from the literature, ictal-SPECT in temporal lobe epilepsies reveals two common patterns; one of which is a global unilateral temporal hyperperfusion with relative decreased perfusion in other cortical areas of the ipsilateral temporal lobe and the contralateral hemisphere[1, 11], the other being hyperperfusion localized to the mesial structures, usually associated with decreased lateral cortical perfusion or relative neocortical temporal hypoperfusion[11]. A switch-over phenomenon is addressed for the interictal studies as well as late post-ictal changes where the large areas of hypoperfusion may affect the epileptogenic area, a fact that necessitates obtaining the ictal injections within the first minute after the electrographic and clinical onset of temporal lobe epilepsy[12]. Although, there is almost always a lesion as hippocampal sclerosis underlying the mesial temporal lobe epilepsy (MTLE), the above-mentioned, well-documented SPECT changes may be extrapolated in regards to the present discussion. Initial ictal changes in absence seizures may likely be of hyperperfusion representing a cortical demand for increased metabolism which later may compensatorily switch-over to reduced demand during absence status where the spike-and-wave activity becomes intermingled with slow waves in the EEG. An argument derived from evidence of failure of brain glucogen resynthesis after prolonged seizures[13, 14] is in favor of this concept, while active inhibitory processes are also indicated to be responsible for the metabolic exhaustion[15].

Patients in the present study were chosen among those without any treatment to avoid a possible factor that might complicate the results; however, a methodological deficiency that still exists is the effect of pure hyperventilation on the SPECT itself. Due to the natural behaviour of this particular type of epilepsy, i.e. ready induction of seizure activity during HV, a self-control session of HV was not possible for our patients. A control group of either age-matched healthy children or rather, a group with absence seizures unresponsive to HV might be complementary in interpreting the results and might yield challenging data. In two studies with H2(15)O and PET on healthy volunteers, significant decreases in global CBF with no regional change in the former and with an absolute increase in motor and pre-motor cortices in hypocapnic state during HV in the latter were reported[16, 17]. Naturally, whether these data might possess any value of reference for possible HV-SPECT changes in our children is debatable. In a methodologically similar study, but again on CGM, providing HV as an intra-individual control condition induced a 2.5–3.5-fold diffuse ictal increase in global CGMGlc, yet normal patterns for local cerebral metabolic rate were detected[7]. The authors interpreted the high values as reflective of the nonexistance of post-ictal depression in absence seizures when compared to other studies presenting averaged values relating to other generalized and partial seizures associated with post-ictal hypometabolism; and they claimed that these values might represent an increase in both excitatory and inhibitory synaptic activity during petit mal absences[7].

Results of our study seem to be indicative of an overall increase in CBF, possibly to meet the increased metabolic demand for glucose utilization during absence seizures. Absence of local perfusion changes may further support the reliability of clinico-EEG'ic considerations for diagnosing these epilepsies as generalized and may provide a challenge for future studies aimed at recognition of mimicking conditions of focal cortical origin.

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