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Ictal and interictal perfusion variations measured by SISCOM analysis in typical childhood absence seizures

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ABSTRACT – Single photon emission computed tomography (SPECT) is currently used in the presurgical evaluation of medically intractable partial epilepsies, but not very often, in generalized epilepsy. In the present study, we used the SISCOM procedure, which represents the fusion of MRI and ictal-interictal difference SPECT images using ^{99m}Tc-ECD, to study cerebral blood flow changes during the ictal and postictal phases of typical childhood absence seizures. The study was performed on four children with typical, difficult to treat absence seizures, aged 10-13 years at the time of scan. The delay between the onset of absence seizures and the injection of ^{99m}Tc-ECD was carefully noted. One scan was performed during the ictal phase and showed diffuse blood flow decreases, while the three other scans performed during the postictal phase, showed generalized blood flow increase. These data are consistent with most previous data reporting generalized changes in functional activity, not limited to the thalamo-cortical circuit in which absence seizures originate, and a decrease in cerebral blood flow during the ictal phase. Our data are concordant with the hypothesis that neuronal activity underlying the occurrence of spike-and-wave discharges does not seem to require an increase in metabolic demand and blood flow rates. [Published with videosequences]

KEY WORDS: cerebral blood flow, SPECT, childhood absence seizures

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Functional imaging and mainly single photon emission computed tomography (SPECT) are currently used in the presurgical evaluation of most medically-intractable types of partial epilepsies. In this respect, its informative value during a seizure reaches 90-100% in temporal lobe epilepsy [1]. However, most probably because of the favorable outcome and the usually positive response to anticonvulsant medication, idiopathic generalized epilepsies have been much less explored by SPECT or other imaging techniques. Currently, there is no real consensus on changes in brain functional activity during the occurrence of spike-and-wave discharges (SWDs).

Previous studies have measured brain metabolism and blood flow in children with typical absence epilepsy and in relevant animal models. However, the measurement of cerebral metabolic rates for glucose performed by positron emission tomography (PET) or by [^{14}C]2-deoxyglucose autoradiography needs at least 30 min and thus, because of the frequency and

short duration of SWDs, represents a mixture of ictal and interictal events. In these mixed conditions, brain metabolism has been shown to be elevated in children with typical absence epilepsy [2, 3], adults with primary generalized absence epilepsy [4, 5] and in the genetic rat model of absence epilepsy, the GAERS (Genetic Absence Epilepsy Rat from Strasbourg) [6]. These increased metabolic rates are rather attributed to interictal inhibition since during absence status epilepticus, brain metabolism is decreased in both humans [5] and GAERS [7]. The measurement of cerebral blood flow can be performed over shorter periods, even continuously. Measurements of cerebral blood flow performed by means of transcranial Doppler sonography in humans [8-12] and GAERS [11], by SPECT [13], the ^{133}Xenon clearance method [14], near-infrared spectrophotometry [15] or fMRI [16] have reported decreases in blood flow during SWDs. Conversely, two studies, one using SPECT and the other one using PET with $H_2{}^{15}O$ reported cerebral blood flow increases during absence seizures, either generalized simply [17] or generalized with further activation in the thalamus [18].

In the present study, we report the measurement of cerebral perfusion performed with SISCOM analysis during ictal and interictal scans in four children with typical difficult to treat absence (failure of first line monotherapy).

Methods

Patients

In the four patients studied, two girls and two boys, the age of onset of absence seizures ranged from two to eight years (median six years). At the time of examination, the patients were aged from 10 to 13 years. All patients had received at least one antiepileptic medication before we performed the scans *(table 1)*. Absence seizures were pycnoleptic, the children were devoid of any episode of generalized tonic-clonic seizures or photosensitivity. Thus, these children were considered as suffering from "pure" absence epilepsy [19], as can be seen on the *video sequences 1 and 2*. Seizure type and EEG patterns were characterized by prolonged video-EEG monitoring. The clinical and radiological examinations performed by MRI were normal in all four cases. The children and their parents were informed about the procedure and gave their signed agreement.

Quantification of cerebral perfusion rates by SISCOM Data Acquisition

SPECT imaging studies were performed with a low-energy, high-resolution, double-head camera (Helix, Elscint) using 150-300 MBq of ^{99m}Tc-ECD (Neurolite, Du Pont). The camera was operated in the « stop and shoot » mode, with acquisitions at 3° intervals and a total acquisition time of 30 min (120 projections, 64^2 matrix). The total number of counts was 3 million. Slices were reconstructed by filtered back-projection using a Metz filter (FWMH of 8 mm). The venous catheter was inserted into the arm and connected to the ECD syringe before the onset of the recording session. The interictal studies were performed after a 24-h seizure-free period. Video-EEG recording was used prior to and during isotope injection. For ictal studies, patients underwent continuous video-EEG monitoring and the isotope was injected immediately after the clinical onset of a seizure *(video sequence 3)*. The EEG recording was continued for at least five more minutes in order to make sure that no SWD would interfere with the period of fixation of ECD and hence the final results. Slices were acquired 30 min after the injection of ECD. The MR studies used for SISCOM were obtained with a 3D inversion recovery gradient echo sequence, using a 25.6-cm field of view and a 128^3 matrix. SISCOM images were obtained on a Hewlett-Packard C360 workstation using the 3D medical image analysis software MEDIMAX (http://www-ipb.u-strasbg.fr/ipb/gitim). The procedure consisted of three steps:

1) *SPECT-MRI registration*. The ictal and interictal SPECT images were successively registered on the MRI using a

Table 1. Patients' clinical and EEG features.

Patient	Sex	Age at seizure onset (years)	Age at scan (years)	Absence seizure type	EEG pattern	Drugs at time of interictal scan	Drugs at time of ictal scan
1	Female	6	10	Simple	Bilateral, synchronous, symmetrical SWDs, 3Hz	VPA	VPA
2	Male	6	10	Complex	Bilateral, synchronous, symmetrical SWDs, 3Hz	ESM, VPA	ESM, VPA
3	Female	8	12	Complex	Bilateral, synchronous, symmetrical SWDs, 3-3.5 Hz	ESM, LTG	ESM, VPA
4	Male	2	13	Simple	Bilateral, SWDs and polySWDs, irregular, sometimes asymmetrical, 3Hz	VPA, LTG	VPA, LTG

Abbreviations: VPA: valproate; ESM: ethosuximide; LTG: lamotrigine.

fully automated, data-driven registration algorithm. This algorithm relies on a robust voxel similarity-based method that enables accurate, rigid registration of dissimilar multimodal 3D images [20].

2) *Ictal-interictal difference*. Despite the use of exactly the same dose of radioactivity during the ictal and interictal study, the two studies were normalized (according to the total activity of the brain) before subtraction. Since the variations in blood flow were of low amplitude, normalization was also based on the assumption that the total quantity of blood present in the brain was identical during the ictal, postictal and interictal phases. In any case, the intra-individual variation of the total activity of the brain was superior to 5 %. To obtain the SPECT difference, firstly, interictal SPECT images were subtracted from ictal SPECT images and secondly, each voxel value of this subtracted image was divided by the mean voxel value of the interictal SPECT. The result was represented as a percentage of cerebral perfusion variation relative to the interictal SPECT. In other studies, the subtraction was performed by dividing regional values by the value of region with the highest level of radioactivity, or by the value of a reference structure, such as the cerebellum for example. The technique used in the present study was chosen because it appears to be the one which introduces the fewest potential errors. In any case, the method chosen would only influence the absolute value of the difference, but not the significance of the data.

3) *Fusion of MRI and different SPECT images (SISCOM)*. In this study positive or negative perfusion variations of 10 % or more that were statistically significant ($p < 0.05$) were retained in order to create the SISCOM images. The 10 % cut-off level was chosen since the maximal rate of change in cerebral perfusion was about 25 %, except in a few structures in patient 4. Thus, we used the double of the root square value of this maximal variation as the significant cut-off level for perfusion changes.

Results

SPECT images cannot be quantified and the visual analysis of interictal and ictal SPECT images was not very informative. Therefore, in the present study, we used the SISCOM procedure, which visualizes the difference between the ictal and interictal scans and affords good anatomical definition of the areas of interest. The absence seizures recorded in the present study, as in most others, were quite short, except in patient 1. It is generally considered that about 15 s are necessary for ECD to reach the brain after being injected i.v. and for the first passage of ECD through the blood-brain-barrier (BBB) to occur. About 80 % of the tracer is then fixed by the brain during the first passage lasting 1-2 s and further fixation of 20 % of the tracer will occur over the following 45 s [21, 22]. Thus, given the delay between the onset of the seizure and the time of ECD injection (2-5 s), plus the delay between the injection and 80 % fixation of ECD during the first passage through the BBB which lasts 1-2 s, the data obtained in the present study represent ictal events in patient 1 and postictal events in patients 2-4.

In patient 1, the seizure induced by hyperventilation lasted for 38 s and the injection of ECD, which was performed over 3 s, started 3 s after the onset of the seizure *(video sequence 3)*. In this case, the major proportion of ECD fixation occurred during the ictal phase and perfusion rates were significantly reduced by 9-21 % compared to control levels in most brain regions, except in the thalamus where the decrease was less than 5 % and hence not significant *(figure 1)*.

In patient 2, the seizure induced by hyperventilation lasted for 20 s and the injection of ECD, which was performed over 5 s, started 4 s after the onset of the seizure. In this case, the seizure was brief and the fixation of ECD occurred mostly during the postictal phase. Perfusion rates were significantly increased by 8-35% compared to control levels in all brain regions *(figure 2)*.

In patient 3, the seizure induced by hyperventilation lasted for 11 s and the injection of ECD, which was performed over 2 s, started 3 s after the onset of the seizure. In this case, the seizure was also too brief to allow the fixation of ECD during the ictal phase and the data represent postictal values. Perfusion rates were significantly increased by 10-28 % compared to control levels in most brain areas, mainly the frontal and parietal cortices, median cingulate gyrus, thalamus and cerebellum.

In patient 4, the seizure induced by hyperventilation lasted for 16 s and the injection of ECD, which was performed over 2 s, started 2 s after the onset of the seizure. In this case, the seizure was also brief and the fixation of ECD occurred mostly during the postictal phase. Perfusion rates were significantly increased by 7-41 % compared to control levels in all regions. The largest increases in perfusion rates (32-41 %) occurred in frontal cortex and anterior cingulate gyrus.

Discussion

The present study represents the first report of blood flow changes entirely recorded during an absence seizure. This measurement was made possible by the exceptionally long duration of the absence seizure (38 s as can be seen in video sequence 3), which is a very rare event. All data prior to this report always measured blood flow during mixed ictal and interictal states. Our data show that cerebral perfusion is diffusely reduced throughout the brain during the occurrence of a typical absence seizure, while it is increased during the postictal phase.

Typical absence seizures are characterized by the spontaneous occurrence of SWDs that usually occur in quiet

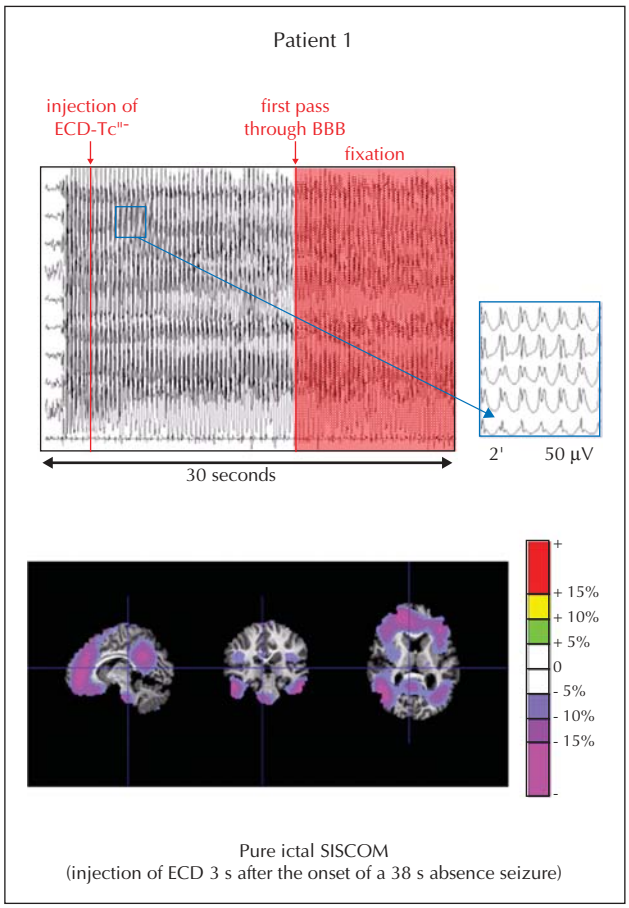

Figure 1. *EEG recording performed during the injection and fixation of ^{99m}Tc-ECD in patient 1 experiencing a 38 s absence seizure, with the injection of ECD starting 3 s after the beginning of the seizure and lasting 3 s. The estimated time of the first passage of ECD through the BBB is indicated by a red line, and the subsequent fixation period is shown on a red background. The period of highest fixation of ECD clearly occurs during the occurrence of SWDs. The electrodes were placed according to a referential montage with a Wilson reference (upper panel). In this patient, the cerebral blood flow measured ictally demonstrated a generalized decrease on the SISCOM images shown in the lateral, frontal and horizontal plane. This decrease was mostly seen in the frontal, parietal, temporal and occipital cortices, the cingulate gyrus and cerebellum (lower panel).*

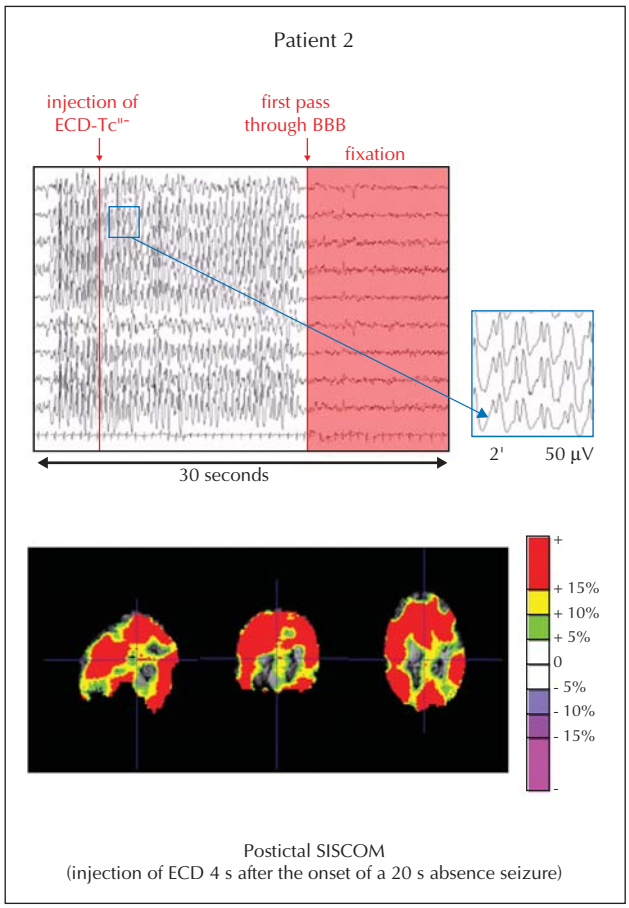

Figure 2. *EEG recording performed during the injection and fixation of ^{99m}Tc-ECD in patient 2 experiencing a 20 s absence seizure, with the injection of ECD starting 4 s after the beginning of the seizure and lasting 2 s. The estimated time of the first passage of ECD through the BBB is indicated by a red line, and the subsequent fixation period is shown on a red background. The period of highest fixation of ECD clearly occurs at the end of the occurrence of SWDs. The electrodes were placed according to a referential montage with a Wilson reference (upper pannel). In this patient, the cerebral blood flow measured postictally demonstrated a generalized increase on the SISCOM images shown in the lateral, frontal and horizontal planes. This decrease was mostly seen in the frontal, parietal, temporal and occipital cortices, the cingulate gyrus, thalamus and cerebellum (lower panel).*

wakefulness or drowsiness. Numerous findings support the proposal by Jasper and Kershman [23] that the thalamo-cortical system is involved in the generation of SDWs that appear on a normal background of cortical activity. Thalamic neurons have the unique ability to shift between the oscillatory and tonic firing mode. The alertness state is characterized by a desynchronized EEG caused by the tonic firing of thalamo-cortical neurons. During the transition from wakefulness to drowsiness or sleep, the firing pattern of the thalamo-cortical neurons shifts to an oscillatory, rhythmic, synchronized mode of electrical activity, which underlies the shift from a desynchronized to a synchronized state of the EEG [24-26]. Whether SWDs originate in the thalamus or the cortex is still a matter of debate. A recent study in a rat model of absence epilepsy, the WAG/Rij rat, argues for a focal cortical dysfunction that drives widespread cortico-thalamic networks during spontaneous absences [27]. However, although SWDs occur only in the cortex and thalamus, and cannot be recorded from limbic areas, as shown in various animal models [for review see 28], changes in cerebral functional activity recorded up to now, in children with absence epilepsy and relevant animal models, have no anatomical substrate and are usually

diffusely distributed in all brain areas, whether or not they express SWDs [2-6, 13, 14, 16, 17]. The results of the present study confirm the lack of distinct anatomical substrate for functional activity changes during or after absence seizures. Indeed, we recorded bilateral and widespread blood flow changes, i.e. diffuse decreases during the ictal phase and generalized increases during the postictal state.

The present results are in agreement with numerous previous studies reporting a decrease during absence seizures in blood flow velocities measured in the middle cerebral artery of children with typical absence epilepsy by transcranial Doppler ultrasonography [8-12], SPECT [14] or the ^{133}xenon clearance technique [16]. Our data are also in very good accordance with a recent study using fMRI showing that seizure-related BOLD- (blood oxygen level-dependent) changes, time-locked to the occurrence of SWD, induced profound negative changes in all brain areas with the exception of the thalamus [16]. Likewise, a decrease in cortical blood flow was measured by the Laserflow Doppler technique in GAERS during each episode of SWD [11]. Conversely, our results are in disagreement with two other studies. The first study used SPECT and found diffuse increases in cerebral blood flow during absence seizures [14]. The second study was the only one that used $H_2{}^{15}O$ PET to measure blood flow in absence seizures [18]. In both studies, the authors do not mention if they took into account the delay between the injection and the time of fixation of the tracer. As can be seen in the present study, this is critical, and if one does not take into account this delay, it is most likely that the fixation of the tracer would occur after the end of the seizure unless the seizure is very long, which is not the usual case. Thus, the increases recorded by the authors of those studies may be due to the fact that the fixation of the tracer could have occurred during the postictal period. Moreover, in the first study [14], as stated above, the visual analysis of interictal and ictal SPECT images is usually not very informative and the use of SPECT procedures alone does not allow a good anatomical definition of the areas of interest. This is the difference with the SISCOM procedure, which visualizes the differences between the ictal and interictal scans and superimposes these images onto the MRI scan of the individual and onto the human brain atlas.

In the PET study using $H_2{}^{15}O$ to measure blood flow in absence seizures, Prevett *et al*. [18] found a mean global increase in blood flow during absence seizures. In addition, they recorded a focal activation in the thalamus during absences, which was attributed to the key role played by this structure in the pathogenesis of absence seizures. Likewise, in their recent fMRI study, Salek-Haddadi [16] reported a 3 % increase in the thalamus against a background of generalized decreased activity. Likewise, in the present study, in patient 1, cerebral perfusion was reduced all over the brain, but the thalamus was not affected. SWDs represent an abnormal response pattern of cortical neurons to afferent thalamo-cortical volleys that are normally involved in the generation of spindles. SWDs are characterized by a short period of increased cortical excitation corresponding to the spike on the EEG, which is followed by a longer-lasting period of cortical inhibition corresponding to the wave component [29-31]. Although inhibition is generally assumed to be an energy consuming process [2, 32], hypometabolism could occur at the efferent projection sites of the inhibited neurons [33]. More recently, it was reported that the hemodynamic changes evoked by neuronal activity are not always related to the spike rate in a given region; they depend on the afferent input function linked to presynaptic input and postsynaptic processing, but are independent of the efferent function, i.e. the spike rate in the same region [for review see 34]. Thus, the present data confirm reduced energy demand and hence blood flow during the expression of SWDs, and suggest higher energy demand and hence greater blood flow during the postictal and interictal states.

The data from this study, as those of many other, may be affected by the fact that the children were receiving an antiepileptic medication at the time of both the interictal and ictal scans *(table 1)*. It is well know that antiepileptic therapy affects blood flow and metabolism [35, 36]. However, in the present study, the treatment of our patients was similar at the time of ictal and interictal scans, except for patient 1 who was receiving a slightly higher dose of valproate at the time of the interictal scan (750 mg/kg *versus* 500 mg/kg for patient 1). Only patient 3 had her interictal lamotrigine treatment replaced by valproate at the time of the ictal scan. Thus, even though the antiepileptic drugs affect brain metabolism and flow, it is most likely that the significance of the present data, which have been recorded in most patients under the same type of medication, is unaffected by the treatment.

In the present study, hyperventilation was used to initiate the seizures and to avoid the occurrence of a complex absence seizure. Hyperventilation decreases arterial $PaCO_2$, which in turn decreases cerebral blood flow which is known to be very sensitive to $PaCO_2$ changes [37]. To avoid the introduction of a potential error linked to an indirect effect due to a hyperventilation-induced $PaCO_2$ decrease, the children studied here were subjected to an episode of hyperventilation, similar in duration, during both the ictal and interictal scans, which should have lowered the level of $PaCO_2$ to the same degree during both scans. Thus, the decrease in perfusion recorded in patient 1, in which the major part of the ECD fixation occurred during the seizure, should not be influenced by the $PaCO_2$ changes induced by hyperventilation, otherwise no increase in perfusion rates could be detected in the three other patients recorded mostly during the postictal phase. Another argument in favor of the direct link between perfusion rates, as measured here and ictal or postictal events, rather than subtle differences in $PaCO_2$

Legends of video sequences

Video sequence 1
Absence with automatisms - this is a typical example of a prolonged absence episode recorded in patient 1.
Video sequence 2
Standing absence - this is a typical example of a prolonged absence episode recorded in patient 1 while standing.
Video sequence 3
Ictal SPECT displays the recording of the prolonged absence episode induced by hyperventilation and during which the ictal SPECT measurement was performed in patient 1. The catheter through which the injection of ^{99m}Tc-ECD was administered was inserted in the right arm, and it is obvious from the recording that fixation of the tracer took place mostly during the ictal period.
Video sequence 4
Interictal SPECT displays a typical example of a hyperventilation episode which does not lead to an absence episode. The injection of ^{99m}Tc-ECD was performed at the end of the hyperventilation phase. The patient keeps her eyes open.
A Codec driver for video reading is included in the CD.

that could have occurred between the two scans performed in each patient, comes from our study on GAERS. In these rats, the injection of haloperidol and ethosuccimide decreased $PaCO_2$ but the former drug decreased cerebral metabolic rates while the latter did not, which demonstrated that changes in $PaCO_2$, were not the critical factor in haloperidol-induced metabolic decreases that were rather reflecting the absence status epilepticus induced by the drug [7]. Moreover, there is quite a consensus in the literature about a decrease in blood flow induced by absence seizures, whether or not they were initiated by hyperventilation [8-12].

Conclusion

In conclusion, the present study validates most previous reports on the relationship between cerebral blood flow decreases and the occurrence of absence seizures. The use of SISCOM allowed us to confirm the diffuse nature of the cerebral blood flow changes, thus generalizing to the whole brain the previous data that were most often recorded by transcranial Doppler ultrasonography in the middle cerebral artery. The generalized nature of SWD-induced cerebral blood flow changes recorded in the present study also confirms that the reactivity of all brain vessels from the middle cerebral artery to small capillaries is similar during absence seizures in the human brain. □

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