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Subcortical SISCOM hyperperfusion: Should we pay more attention to it?

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ABSTRACT

Purpose: Demonstrating cerebral blood flow changes during seizures, ictal-interictal single photon emission computed tomography (SPECT) with co-registration to MRI (SISCOM) reflects brain activation and its pathways of spread. To investigate subcortical ictal hyperperfusion patterns during focal seizures, we retrospectively reviewed SISCOM analysis of patients who became seizure-free after cortical resection. Our aim was to evaluate the relationship between epileptogenic zones and subcortical hyperperfusion.
Method: 67 patients were identified as having SISCOM evaluation and having remained seizure-free for at least one year after surgical resection. SISCOM analysis was blindly reviewed for localization of basal ganglia (BG), thalamic (TN) and cerebellar (CH) hyperperfusion based on three different thresholds. Subcortical activation and epilepsy characteristics were then compared between patients. For a given region of interest and threshold, the sensitivity, specificity and positive and negative predictive value for correct lateralization of the epilepsy side was calculated.
Results: Depending on the threshold used, BG hyperperfusion was found in 37.3–73.9% of patients, TN hyperperfusion in 31.3–68.1% and CH hyperperfusion in 13.5–29%. For a threshold of 1.5, the best predictive positive value for correct lateralization of the epilepsy side was obtained with BG/CH coactivation (89%). For a threshold of 2.0 and 2.5, it was obtained with BG/TN coactivation (88%) and BG activation (82%), respectively.
Conclusion: Subcortical SISCOM hyperperfusion could offer additional clues in terms of lateralization.

1. Introduction

Ictal-interictal single photon emission computed tomography (SPECT) with co-registration to MRI (SISCOM) has proven its value in localizing epileptogenic zones [1–7]. This non-invasive tool remains crucial in challenging cases such as extra-temporal and/or non-lesional epilepsies [8]. Cerebral blood flow changes demonstrated during seizures reflect brain activation and its pathways of spread [9,10]. Its usefulness to establish sites for intracranial implantation and improve surgical outcome is now widely recognized [11,12].

Although focal epilepsy is considered a cortical disease, the subcortical regions such as the basal ganglia, thalamus and cerebellum are important pathways for seizure propagation and regulation [13–18]. Unfortunately, scalp EEG cannot correctly reflect the involvement of deep structures. On the contrary, subcortical SPECT hyperperfusion has been linked to specific semiology such as dystonic posturing [19–21] and tonic-clonic generalization [22]. The activation of subcortical structures during seizures may not be random and could potentially be correlated to the epileptogenic zone. Nevertheless, few studies have focused specifically on SPECT subcortical activation during focal seizures and none has studied SISCOM and thalamic, basal ganglia and cerebellum hyperperfusion concomitantly [23,24].

To investigate subcortical ictal hyperperfusion patterns, we retrospectively reviewed the SISCOM analysis of patients who became seizure-free after cortical resection. Our aim was to evaluate the relationship between epileptogenic zones and subcortical hyperperfusion.

2. Patients and methods

2.1. Patients

The study was approved by the Cleveland Clinic institutional review

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board. We retrospectively screened all consecutive patients who underwent surgical resection from January 2007 to September 2015 at the Cleveland Clinic Epilepsy Center. Among these 1279 patients, we screened 313 patients over 15 years old who underwent presurgical SISCOM evaluation and had preoperative and postoperative brain MRI. Patients with a previous history of epilepsy surgery were ineligible. We included the 67 patients who became seizure-free postoperatively with a minimum of one year of follow-up (Engel 1 – last follow-up was used as the outcome endpoint). In all patients, resective surgery strategy and extent of resection were determined consensually during a daily patient management conference based on clinical information and presurgical assessment. This included video-EEG monitoring, invasive evaluation if needed, high-resolution brain MRI, brain [18 F]-fluorodeoxyglucose positron emission tomography (FDG-PET), SPECT, magnetoencephalography (MEG), and neuropsychological assessment.

2.2. SPECT evaluation

Ictal injections were performed in the Cleveland Clinic epilepsy-monitoring unit during inpatient non-invasive video-EEG evaluation by epilepsy-trained nurses who sat by the patient's bedside. Tracer (99mTc-ECD – ethyl-cysteinate dimer; or 99mTcHMPAO – hexa-methyl-propylene-amine-oxime) was injected into a forearm vein immediately after noting seizure onset. SPECT images were acquired on a Siemens (Erlangen, Germany) Symbia dual-head camera (SPECT: 30 s per stop for 60 stops, 128 × 128 matrix, zoom 1.23, iterative reconstruction with CT attenuation correction, six iterations, eight subsets; CT: 30 mAs, 5 mm slice) within 2 h after radiopharmaceutical injection. Interictal SPECT studies were accomplished after a minimum of 24 h without seizures. Injection and flush time were calculated afterwards during video-EEG review. Injection time was defined as the time point at which the radio-pharmaceutical-containing syringe plunger had been completely depressed. Thus, injection time was based on video-EEG recording analysis. If patients received more than one ictal-SPECT study, the ictal-SPECT with the earliest injection was chosen.

2.3. Image co-registration and subtraction

Ictal and interictal SPECT studies were coregistered using an automatic registration algorithm based on maximal mutual information and the interictal image was subtracted from the ictal after normalization for global brain counts. The subtracted image was smoothed using a three-dimensional (3D)–Gaussian smoothing kernel (full width at half maximum = 12 mm) after normalization. This information was transformed into z-scores using the mean and standard deviation of the differences in all brain voxels. The mean activation map was then used for co-registration to establish the preoperative MRI for anatomic localization. Three different Z-score thresholds were used for analysis (1.5, 2.0, 2.5).

2.4. SISCOM interpretation

A trained authorized user of radioactive materials (GW) analyzed SISCOM results to define brain activation during focal seizures and generate hypotheses about the localization of the epileptogenic zone. Then, subcortical localization was retrospectively assessed by consensus after SISCOM images has been reviewed by two independent trained neurologists (JA, SW) initially blinded to clinical data. Subcortical structures were divided into three regions of interest (ROIs): basal ganglia (BG, including caudate nucleus (CN) and lenticular nucleus (LN)), thalamus (TN) and cerebellar hemisphere (CH). Subcortical activation was defined as an increased ictal uptake compared to interictal uptake. Activation was divided into bilateral symmetric, asymmetric left or right and no activation for the different ROIs and z-scores. In the event of bilateral asymmetric subcortical activation, the side of maximal activation was defined as left or right.

2.5. Clinical data

Demographic, clinical and presurgical evaluation data as well as post-op MRI and pathology were obtained for all patients after blinded retrospective SISCOM interpretation. All scalp video-EEG of ictal-SPECT recorded seizures were reviewed and evaluated by two independent trained epileptologists (JA, SW). Ictal semiology during injected seizure was categorized according to the International League Against Epilepsy (ILAE) classification [25] with a particular focus on motor signs. The main clinical feature during the seizure was considered as the most relevant for the study. Seizure-freedom after a minimum of one year of follow-up was used to establish the seizure lateralization based on the surgery side as well as the ictal onset zone based on the resected region. Resected regions were assessed on surgical and post-MRI reports. Seizure lateralization and localization of cortical resection were compared to subcortical SPECT activation. We hypothesized that BG and TN hyperperfusion should be ipsilateral to the seizure focus and contralateral for the CH (cerebellar diaschisis). When SISCOM activation was asymmetric, the side of the maximal activation was defined as ipsilateral or contralateral to seizure onset. By definition, the site of resection should encompass the true epileptogenic zone in patients who remained seizure-free following epilepsy surgery, thus validating the lateralization of their epilepsy. Therefore for a given ROI, the sensitivity (Sen), specificity (Spe), positive predictive value (PPV) and negative predictive value (NPV) for correct lateralization of the epilepsy side was defined as follows: true positive (TP), if there was an ipsilateral activation to the seizure focus (ipsilateral hyperperfusion and bilateral hyperperfusion); false positive (FP), if there was a contralateral activation to the seizure focus (contralateral hyperperfusion and bilateral hyperperfusion); true negative (TN), if there was no contralateral activation to the seizure focus (ipsilateral hyperperfusion and absence of hyperperfusion); and false negative (FN), if there was no ipsilateral activation to the seizure focus (contralateral hyperperfusion and absence of hyperperfusion). Thus, each SISCOM comprised two categories depending on the side of hyperperfusion or its absence. Sensitivity, specificity, PPV and NPV (Sen = TP/(TP + FN), Spe = TN/(FP + TN), PPV = TP/(TP + FP) and NPV = TN/(FN + TN)) were calculated for each ROI and each Z-score. Initially, hyperperfusion was investigated in detail for each subcortical region independently. Subsequently, we focused specifically on subcortical structure co-activation (BG and TN, BG and CH, TN and CH) and calculated Sen, Spe, PPV and NPV with the same methodology.

2.6. Statistical analysis

Statistical analysis was performed with IBM® SPSS® statistics 23 software. To study the relationship between subcortical ictal-SPECT hyperperfusion (dependent variable) and explanatory variables, we used the two-tailed Student *t*-test with *post-hoc* Bonferroni correction for multiple analysis if needed for numeric data, and the Khi2 test or Fisher's exact test if $N < 5$ for categorical data with respect to age, handedness, duration of epilepsy, injection time, duration of seizures, surgical resection, pathology and motor signs.

3. Results

3.1. Patients' characteristics

67 seizure-free patients (42 males) were included in the study and 80.6% of them were right-handed. The mean age at epilepsy onset was 18.5 +/− 14.5 y. The mean duration of epilepsy was 17.4 +/− 13.5y. At time of injection, the mean age of patients was 36.2 +/− 14.3y.

3.2. Epilepsy characteristics

Final lateralization of the epileptogenic zone was right in 55.2% of