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Usefulness of HMPAO-SPECT in the diagnosis of nonconvulsive status epilepticus

Sonia Jaraba [a,b,*], Gabriel Reynés-Llompart [c], Jacint Sala-Padró [a], Misericordia Veciana [d], Júlia Miró [a], Jordi Pedro [d], Oriol Puig [e], Jaume Mora [e], Mercè Falip [a]

[a] Neurology Service, Epilepsy Unit, Hospital Universitari de Bellvitge-IDIBELL, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain
[b] Neurology Department, Hospital de Viladecans, Viladecans, Barcelona, Spain
[c] Image Diagnostic Institute (IDI), Nuclear Medicine Department, PET Unit, Hospital de Bellvitge, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain
[d] Neurology Service, Neurophysiology Department, Hospital Universitari de Bellvitge-IDIBELL, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain
[e] Image Diagnostic Institute (IDI), Nuclear Medicine Department, SPECT Unit, Hospital Universitari de Bellvitge, Image Diagnostic Institute, L'Hospitalet de Llobregat, Barcelona, Spain

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ABSTRACT

Background: The diagnosis of nonconvulsive status epilepticus (NCSE) can pose a challenge. Electroencephalogram (EEG) patterns can be difficult to interpret, and the absence of an EEG correlate does not rule out the diagnosis of NCSE. In this setting, neuroimaging tools to help in the diagnosis are crucial. Our aim was to evaluate the role of 99mTc-hexamethyl propyleneamine oxime (HMPAO) single photon emission computed tomography (SPECT) and quantitative HMPAO-SPECT (QtSPECT) in patients with clinical suspicion of NCSE, and to evaluate their value in the final diagnosis of NCSE.
Methods: We recruited consecutive patients admitted in our center with suspicion of NCSE, and selected those who underwent an HMPAO-SPECT. All patients were admitted to the neurology ward and underwent an EEG. We divided the patients into those who were finally with diagnosed NCSE (NCSE-p) and those who were not (non-NCSE) according to the Salzburg Diagnostic EEG criteria. Sensitivity and specificity of the diagnostic tools were calculated. The SPECTs were acquired in a Skylight SPECT (Philips Healthcare, Amsterdam). The injections were done during the clinical episode suspected of being an NCSE. The HMPAO-SPECT was analyzed by two experts and was also quantified. All data were normalized to the SPM SPECT template. We used an external healthy normal database to obtain a Z-score map for each individual versus the normal database. The Z-score maximum (Z_{max}) was extracted from each region of the AAL atlas as was the percentage of voxels with a Z-score higher than 2.5 (N(%)). A logistic regression combining the Z_{max}, N(%), and the effect of patient age was fitted to predict the final NCSE diagnosis. A receiver operator characteristic (ROC) curve and the area under the curve (AUC) were obtained to evaluate the classification performance.
Results: We included 55 patients, 21 of them women (38.9%), with a median age of 62.1 years old (range 25–84). Thirty-six patients were with diagnosed NCSE (62.9%). Initial EEG had a sensitivity of 61.1% and a specificity of 89%. Most of the patients were critically ill with diagnostic difficulties, and it could be one of the main reasons to find low sensitivity of the Salzburg diagnostic EEG criteria. The Z_{max} and N(%) were significantly higher in NCSE-p than in non-NCSE ($p = 0.005$ and $p < 0.001$, respectively). The HMPAO-SPECT qualitative analysis had a sensitivity of 80.5% and specificity of 89.5% while QtSPECT had a sensitivity of 82% and specificity of 81%.
Conclusion: Both 99mTc-HMPAO-SPECT and QtSPECT can be useful in the diagnosis of NCSE.
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1. Introduction

The diagnosis of status epilepticus (SE) can pose a challenge. Nonconvulsive SE (NCSE) is defined as a condition characterized by continuing alteration in behavior and/or mental status from baseline in the absence of major motor signs accompanied by epileptiform activity in the electroencephalogram (EEG), usually accepted for more than 10 min [1].

Since implementation of the Salzburg Diagnostic EEG criteria for NCSE diagnosis of EEG can be "definitive NCSE," and in other cases, it is only "possible NCSE" [2,3]. In addition, in some cases, such as, in aphasic SE (ASE), the absence of an EEG correlate does not rule out the

* Corresponding author at: Neurology Department, Hospital Universitari de Bellvitge, Feixa Llarga S/N, 08907 L'Hospitalet de Llobregat, Spain.
E-mail address: soniajaraba@gmail.com (S. Jaraba).

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Table 1
Demographic and clinical characteristics.

	NCSE (n = 36)	Non-NCSE (n = 19)	p-Value
Female	17	5	ns
Age	65.5 (25–84) ± 14.06	55.37 (27–80) ± 17.12	0.034
Etiology	vascular 14 tumor 5 immune 3 toxic 2 neurodegenerative 1 cryptogenic 8 other 3	encephalopathy 3 vascular 2 postcritical 2 neurodegenerative 2 other 10	
Days to SPECT	6.94 ± 7.3	10.26 ± 12.1	ns
mRS at admission	1.28 ± 1.45	1.05 ± 1.47	ns
mRS discharge	2.47 ± 2.24	2.42 ± 2.19	ns
EEG seizures	3	0	ns
EEG PLDs	14	1	0.01
EEG normal	3	3	ns
Deaths	6	2	ns

p-Value is considered nonsignificant (ns) when >0.005. Age, Days to SPECT, mRS at admission, and mRS at discharge are expressed as average ± SD. mRS = modified Rankin Scale, PLDs = Periodic Lateral Discharges.

diagnosis of SE. In these situations, other techniques are needed to confirm or exclude the NCSE diagnosis [4].

It has been previously reported that epileptic activity causes an increase in metabolic demand in the involved cerebral cortex, which is accompanied by temporary hemodynamic changes [5], such as, hypervascular patterns in angiographic studies [6]. Taking this into account, different authors have been able to demonstrate an increase in regional metabolism in patients with NCSE with fluorodeoxyglucose (FDG)-positron emission tomography (PET) (FDG-PET) [4] and a regional hyperperfusion with computerized tomography (CT) [7] or magnetic resonance imaging (MRI) [8]. Regional cerebral blood flow measured by single photon emission computed tomography (SPECT) has been widely used to locate regional hyperperfusion patterns in the epileptic onset zone during an epileptic seizure in patients with drug-resistant epilepsy. Therefore, the same technique and principle could be useful to detect hyperperfusion in patients with NCSE as has already been reported in some cases [9,10] and short series of patients [11,12].

The most sensitive and specific application on 99mTc-hexamethyl propyleneamine oxime (HMPAO)-SPECT in the diagnosis of epilepsy is by subtracting interictal from ictal SPECT with MRI coregistration (SISCOM), using either HMPAO or 99mTc-ethylenecysteine-diethylester (ECD) with concurrent EEG monitoring. The accuracy of

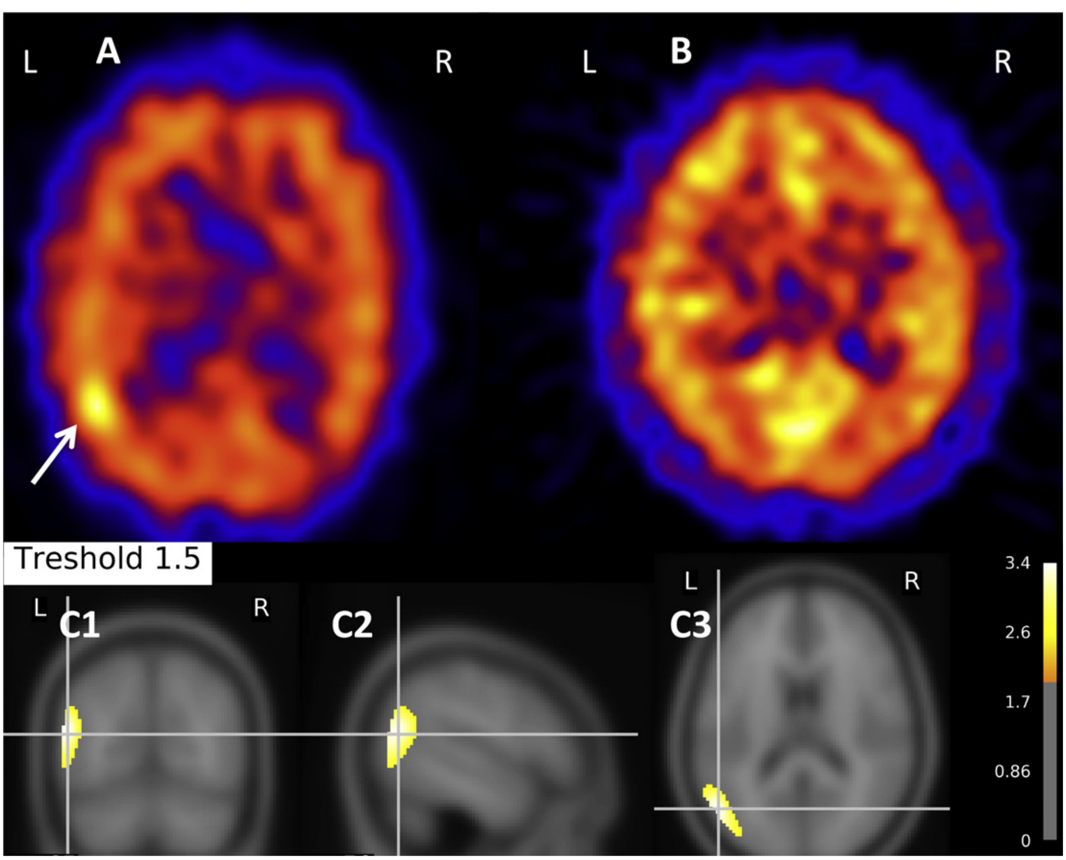

Fig. 1. Aphasic status epilepticus. Both qualitative and quantitative SPECT studies (compared with a normal database). A. Ictal SPECT (axial view) showing left temporal and parietal hyperperfusion. B. Interictal SPECT (axial view) from healthy normal database. C1-C2-C3. Triplanar view of an MRI SPM template with the Z_{max} ($Z > 2$) overlayed, showing the quantitative measurement of cerebral blood flow of the (A) HMPAO SPECT.

SPECT in defining seizure onset zone is further enhanced by the application of statistics using statistical parametric mapping (STATISCOM), or a commercially available statistical software (MIMneuro, MIM Software Inc., Cleveland, Ohio, USA) [13].

Previous studies that used statistical parametric mapping (SPM) showed the benefits of objective SPECT interpretation compared to subjective analysis [13].

When using HMPAO or ECD to detect the seizure onset zone, SISCOM is recommended.

Our aim was to evaluate the role of HMPAO-SPECT, using qualitative and quantitative analysis, in patients with clinical suspicion of NCSE, and to evaluate its value in the final diagnosis of NCSE [14].

2. Material and methods

2.1. Design

We conducted a retrospective, unicentric, observational noninterventional study with patients with NCSE suspicion. We included patients admitted in our center between 2014 and 2018.

2.2. Patients

We reviewed all patients who underwent HMPAO-SPECT as part of their diagnostic workup in our center. Among them, we recruited consecutively the ones with clinical suspicion of NCSE. All patients were admitted to the neurology ward and underwent a complete workup including an EEG. Like Leitinger et al., we classified patients as NCSE and non-NCSE following a consensus decision between different raters inferred from all clinical and paraclinical data, including EEG readings, laboratory data, therapeutic response, follow-up, and final outcome. For all patients and recordings, two authors evaluated these data independently, blinded to HMPAO-SPECT results. When consensus was not achieved in the diagnosis, a third author evaluated the patients [3]. We divided the patients into those who were diagnosed with NCSE (NCSE-p) and those who were not (non-NCSE). We excluded patients with suboptimal EEG recordings and patients with NCSE because of hypoxic–anoxic etiology, when consensus was not achieved between experts, as well as those on whom EEG and HMPAO-SPECT were not performed simultaneously, understood as tracer injection during the EEG recording or less than 4 h following the EEG recording. The study was approved by the Ethical Committee of the Hospital Universitari de Bellvitge with PR177/16. All patients or their relatives signed an informed consent form in accordance with the Helsinki declaration. The confidential information of the patients was handled in accordance with Spanish regulations.

2.3. SPECT data acquisition and processing

The SPECT scans were all performed within 120 min from the administration of 740 Mbq (20 mCi) of 99mTc-HMPAO (Amersham International, Arlington Heights, IL). The patients were scanned in a Philips Skylight two-head gammacamera equipped with an LEGP collimator. The acquisition protocol was a 180° rotation in step-by-step mode. Reconstruction was done using filtered back-projection, and transaxial, coronal, and sagittal slices were obtained. Interictal SPECT was realized whenever possible. The images were presented in a digital support so the intensity could be adjusted, and they were fused with a diagnostic CT or MRI when either of these were available for improved anatomical localization. The injections were done during the clinical episode suspected of being an SE, while patients were monitored with video-EEG. To do the quantified SPECT (QtSPECT), all data were normalized to the SPM SPECT template, which is a software package for analysis and processing of neuroimaging data sequences. We used an external healthy normal database [15] to obtain a Z-score map for each individual's ictal SPECT scan versus that normal database. The reason why we

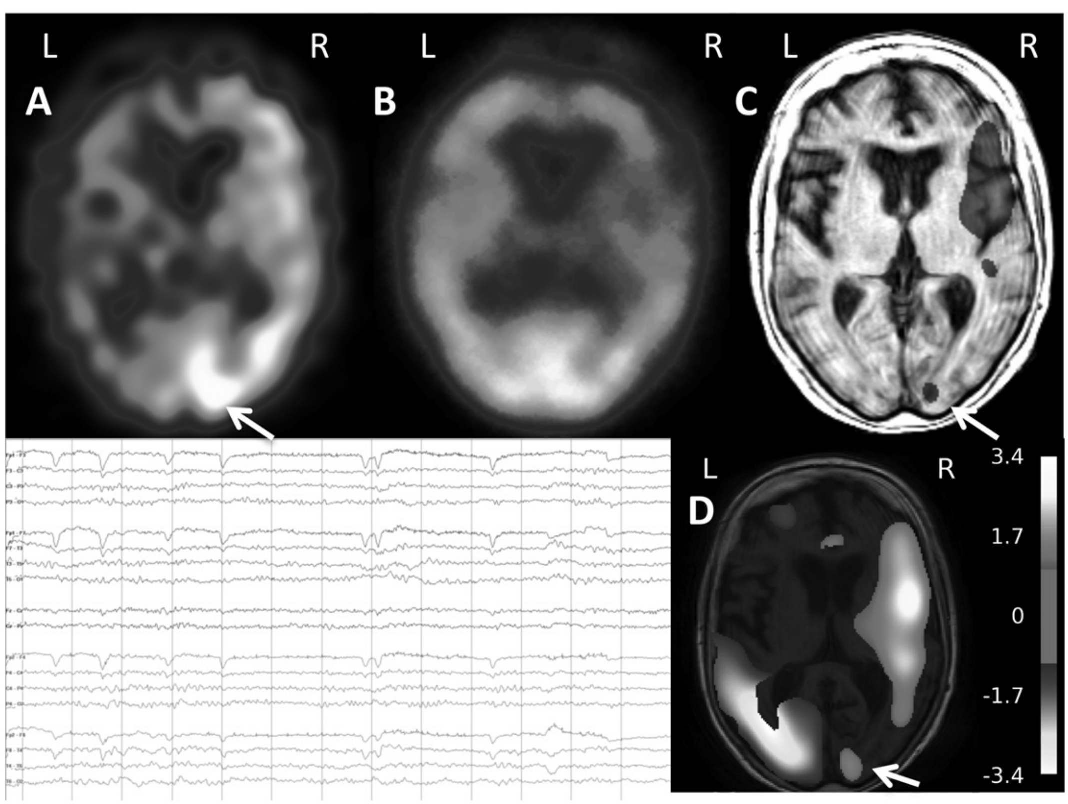

Fig. 2. Right occipital status epilepticus. Both qualitative and quantitative SPECT (compared with an interictal study) tracer injected with EEG control. A. Ictal SPECT (axial view) showing right hemispheric hyperperfusion, maximum in occipital area. B. Interictal SPECT (axial view) with normal perfusion C. SISCOM (axial view) showing hyperperfusion in occipital lobe and temporal-insular region. D. Z_{max} of cerebral blood flow SPECT showing hyperperfusion in the same areas. EEG. Bipolar montage, showing irregular delta waves in right occipital area.

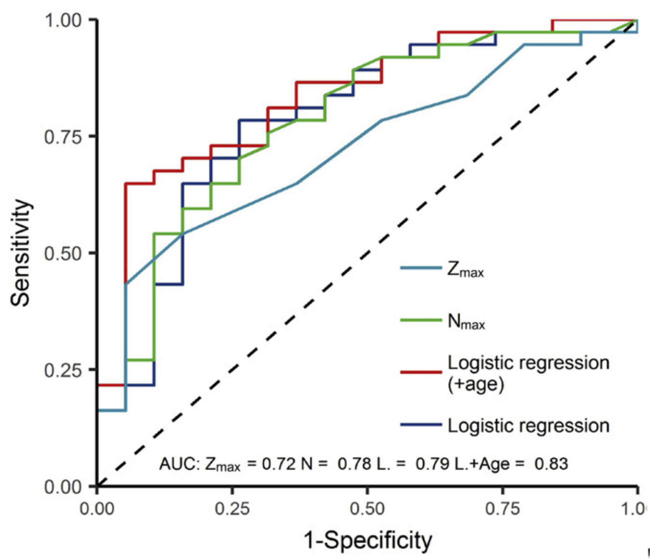

Fig. 3. ROC curve to evaluate the optimal cutoff of quantitative SPECT study. Prediction ROC curves for each individual factor and the resulting combined logistic regression.

used the normal database is that we need to obtain a result as fast as possible, which could help us to diagnose and treat our patients appropriately, and we could not wait for an interictal SPECT. The Z-score maximum (Z_{max}) was extracted from each region using the Automated Anatomical Labeling (AAL) atlas, as well as the percentage of voxels with a Z-score higher than 2.5 (N(%)). The main reason for using a Z-score higher than 2 is because when a single study is compared to a normal database instead of its own interictal study noisier results are expected. Only the voxels inside a mask of the brain (excluding the sublobar areas) were considered, and all clusters of fewer than 100 pixels were also excluded. From the resulting map the maximum value (Z_{max}), the number of significant voxels with Z-score > 2.5 (N) and the anatomical region with the maximum value were recorded. The latter was obtained using the AAL, which is software and a digital human brain atlas with a labeled volume. Labels indicate macroscopic brain structures.

In any event, we tried to obtain an interictal SPECT in order to validate our results by means of a SISCOM image, perfromed using the SPM12 software for the MRI and SPECT coregistration and our inhouse software (python 3.6) for the subtraction of the ictal and interictal images.

Visual diagnosis was performed independently by two experts in nuclear medicine blinded to all other clinical information; when their diagnosis was not concordant, a third expert was required. The SPECTs were considered positive for SE when there was at least one area of focal uptake compared to the adjacent or contralateral areas of the brain. The QtSPECT was analyzed by a physicist. The two final diagnoses were compared.

Electroencephalogram was done during the SPECT injection whenever possible. Short video-EEG monitoring was performed in all patients with a 32-channel Deltamed at patient bedside. All scalp EEG recordings were placed according to the standard international 10–20 system for at least 30 min with standard procedure (eyes closed, impedances b5 kΩ, band-pass = 0.5–70 Hz, notch filter ON, sampling rate = 256 Hz, longitudinal bipolar montage). Activation maneuvers were performed according to a standard procedure and tailored to the patient level of awareness (auditory, tactile stimuli, and pain level). The EEG findings were described according to the glossary of the International Federation of Clinical Neurophysiology [16], the American Clinical Neurophysiology Society Standardized Critical Care EEG Terminology (SCCET) [17], and the Salzburg Consensus Criteria for NCSE [2]. All EEG recordings were made and evaluated by neurophysiologists and neurologists specialized in epilepsy.

Continuous video-EEG or prolonged video-EEG were done, whenever was possible.

2.4. Statistics

Descriptive and frequency statistical data were obtained, and comparisons were performed with the software SPSS Statistics (version 22.0, IBM, Armonk, NY, USA). Categorical variables were analyzed using a one-tailed chi-square analysis (with Yates correction when warranted); quantitative data were analyzed using Student *t*-test or Mann–Whitney *U* test and analysis of variance (ANOVA), and Kruskal–Wallis test was used for nonparametrical analysis. All tests were two-tailed; p-values < 0.05 were considered significant.

A logistic regression combining the Z_{max}, N(%), and the effect of patient age was fitted to predict SE diagnosis. A receiver operator characteristic (ROC) curve and its area under the curve (AUC) were obtained to evaluate the classification performance; the Youden index optimal cutoff was used to find a diagnostic threshold.

3. Results

We included 55 patients, 22 of them women (40%), with a median age of 62.0 years old (range 25–84). Final diagnosis was NCSE in 36 patients (65.5%). See Table 1 for further demographic and clinical characteristics.

Electroencephalograms were considered definitive for diagnosis of NCSE, in accordance with Salzburg criteria, in 4/55 patients (7.2%) and possible in 20/55 (36.6%). Twenty-four patients obtained NCSE diagnosis with EEG,with correct diagnosis in 22 and incorrect in 2. The sensitivity of first EEG using Salzburg Criteria was 22/36 (61.1%) while the specificity was 17/19 (89%).

Visual SPECT was considered positive in 31/55 patients. Among them, 29 were with diagnosed NCSE after complete evaluation (80.5%). In the non-NCSE group, SPECT was negative in 17/19 (89.5%). These two positive SPECTs were considered false positive, corresponding to a patient with a tumor and another with stroke-like migraine attacks after radiation therapy (SMART) syndrome. Of 24 negative SPECT, 7 patients were diagnosed as NSCE. Sensitivity was 80.5%, and specificity was 89.5%. See Fig. 1 and Fig. 2.

In all patients, QtSPECT was also done using a normal database. The Z_{max} and N(%) were significantly higher in NCSE-p than in non-NCSE ($p = 0.005$ and $p < 0.001$, respectively). Results from the logistic regression presented an AUC of 0.79, with and optimal cutoff values of $Z_{max} = 2.85$ and N(%) = 4.85. See Fig. 3. Comparing the NCSE-p and non-NCSE groups, a statistical trend was found for age, with the patients from the NCSE-p older than those from the non-NCSE group ($p = 0.06$). Sensitivity and specificity using the Youden index optimal cutoff value were 0.82 and 0.81, respectively. The number of significant voxels N and the Z_{max} were highly correlated ($r = 0.89$); thus, only the latter was included in the logistic model as it was the one with the lower p-value ($p = 0.08$, using a *t*-test). The anatomical region was statistically significant ($p = 0.01$, using a Fisher exact test) as was the patient age ($p = 0.01$, using a *t*-test).

In four patients who recovered from NCSE, an interictal study and an MRI were done. In all 4 cases, SISCOM showed hyperperfusion on the same areas as QtSPECT. See Fig. 2.

Table 2
Sensitivity and specificity of techniques used to diagnose NCSE.

	Sensitivity	Specificity
EEG	61.1%	89%
SSPECTCOM	80.5%	89.5%
QtSPECTCOM	82%	81%

See Table 2 to compare sensitivity and specificity of each technique used to read the SPECT results.

4. Discussion

In our study, EEG sensitivity using Salzburg criteria was low, probably because of a patient selection bias. Patients included in the study were not all patients in SE—just the ones in whom an HMPAO SPECT was done—so they were patients with whom we experienced diagnostic difficulties. Most of them were critically ill patients; in only 3 of them (8.3%), the EEG was completely normal while in most of them (20/36) a slow (<2.5 Hz) rhythmic pattern was observed. Similar findings were obtained by Struck et al., also in a critically ill population [18].

To date, there is little information about the utility of neuroimaging techniques as a diagnostic tool for SE. Most of the published studies are case series [4,7,8,12,18–21], and no direct comparison of EEG and neuroimaging studies accuracy was carried out in most of them. Nevertheless, in the ones in which neuroimaging studies were done while EEG showed clear ictal activity [7,8,20], a sensitivity rate higher than 70% was always noted. On the other hand, little information exists about its specificity. Neuroimaging techniques are not routinely performed in patients with critical neurologic illness for other reasons, limiting the ability to generate a relevant set of control subjects. The study of Struck et al. [18] obtained a specificity of 100% for FDG-PET in 18 critical patients.

Our study found that HMPAO-SPECT, visually analyzed or quantified done with QtSPECT, had high sensitivity and specificity in our selected population of critically ill patients. Visual analysis of SPECT was as sensitive as QtSPECT, but probably more specific. There are several possible explanations for these findings: quantitative analysis is nowadays not as good as visual expert analysis, and the selected $Z_{max} > 2$ can affect results. The study of Newey et al. [22] suggests that $Z_{max} > 1.5$ was more sensitive than and as specific as $Z_{max} > 2$ in localizing ictal onset zone in a single seizure. These findings were not replicated in the study of De Coster et al., 2018, [23] in which $Z_{max} > 2$ or more than 1.5 showed the same sensitivity but with a higher interobserver agreement compared to when using a $Z_{max} > 2$. Appropriate Z_{max} in patients with NCSE remains unknown in all likelihood, and more studies on this topic are recommended.

The Z_{max} and N(%) were significantly higher in the NCSE-p than in non-NCSE group, confirming the hypothesis that perfusion techniques can differentiate patients with NCSE from those with non-NCSE.

Our study shows that HMPAO-SPECT, both visually analyzed and done by quantitative analysis, has high sensitivity and specificity in the diagnosis of NCSE.

This is the first study, to our knowledge, using this methodology: comparing with a normal database, in patients with NCSE. Further studies are needed to confirm and validate our results. It would also be desirable to employ the same technique using different Z-score values in order to increase sensitivity and, in particular, specificity.

The low number of patients included is a limitation of the present study. This may have affected the diagnostic value of cerebral perfusion SPECT imaging. We used a normal database in all patients to analyze ictal HMPAO-SPECT and an interictal SPECT when available, which was not often. Larger prospective studies with ictal and interictal individual studies with HMPAO-SPECT are needed to confirm our initial findings.

5. Conclusions

Regional cerebral blood flow measured with SPECT is useful in the diagnosis of NCSE. Both qualitative and quantitative methods are highly sensitive and specific. Their results are comparable nowadays in patients with NCSE.

Declaration of competing interest

All the authors declare that they do not have any conflicts of interest. They confirm that they have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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