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Subtraction ictal single-photon emission computed tomography (SPECT) co-registered to MRI (SISCOM) in presurgical diagnostics of epilepsy

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SUMMARY

Success of surgically treated epilepsy depends on the accuracy of epileptogenic zone localization. Single-photon emission computed tomography (SPECT) using SISCOM (subtraction ictal SPECT co-registered to MRI) protocol is the only imaging method that allows identification of ictal onset zone by injection and fixation of a special radioactive tracer in the area of increased cerebral blood flow. The review outlines the key stages of SPECT using SISCOM protocol, generalizes and analyzes data for related opportunities and disadvantages as well as its prospects for use in preoperative examination of patients with epilepsy. It was demonstrated that the technique showed high sensitivity (mean 70–75%) to localize epileptogenic zone in patients with pharmacoresistant epilepsy in case if brain structural changes were not detected by magnetic resonance imaging (MRI). However, the organizational features of the procedure in combination with its specific limitations for epilepsy patients do not allow it to be considered as a routine diagnostic method.

KEYWORDS

Single-photon emission computed tomography, SPECT, SISCOM, epilepsy, epilepsy surgery, epileptogenic zone.

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The authors declare no conflict of interest regarding this publication.

Authors' contribution

Ishmuratov E.V. – publications search and analysis, text writing;
Zuev A.A. – text editing, final approval of the manuscript

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Однофотонная эмиссионная компьютерная томография с протоколом SISCOM в предхирургической диагностике эпилепсии

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РЕЗЮМЕ

Успешность хирургического лечения эпилепсии зависит от точности локализации эпилептогенной зоны. Однофотонная эмиссионная компьютерная томография (ОФЭКТ) с применением протокола SISCOM (англ. subtraction ictal SPECT co-registered to MRI) является единственным методом визуализации, который позволяет идентифицировать зону иктального начала путем введения и фиксации специального радиоактивного трейсера в области усиления мозгового кровотока. В обзоре представлены ключевые этапы проведения ОФЭКТ с применением протокола SISCOM, обобщены и проанализированы данные о возможностях и недостатках данного метода, а также о перспективах его применения в предоперационном обследовании пациентов с эпилепсией. Показано, что методика имеет высокую чувствительность (в среднем 70–75%) в локализации эпилептогенной зоны у пациентов с фармакорезистентной эпилепсией, когда структурные изменения головного мозга не выявляются при магнитно-резонансной томографии. Однако организационные особенности проведения процедуры в сочетании с ее специфическими ограничениями в отношении больных эпилепсией не позволяют рассматривать ее как рутинный диагностический метод.

КЛЮЧЕВЫЕ СЛОВА

Однофотонная эмиссионная компьютерная томография, ОФЭКТ, SISCOM, эпилепсия, хирургия эпилепсии, эпилептогенная зона.

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INTRODUCTION / ВВЕДЕНИЕ

Currently, epilepsy is defined as a brain disease that meets at least one of three criteria proposed by the International League Against Epilepsy (ILAE) [1]:

– two or more unprovoked (or reflex) epileptic seizures with more than 24 hour-long interval;

– a single unprovoked (or reflex) seizure with a high relapse probability (60% or more);

– epileptic syndrome diagnosed.

It is known that about 1/3 of patients are resistant to drug therapy [2]. In case of developing drug resistance, surgery represents one of the effective treatment approaches. The success of surgical treatment depends on the accurately identified epileptogenic focus, which excision may eliminate seizures [3]. According to the concept by H.O. Lüders et al., the epileptogenic zone encompasses several zones (irritative, ictal onset, functional deficit, epileptogenic anatomical lesion and symptomatogenic sites) [4].

The major methods in presurgical epilepsy diagnostics are presented by magnetic resonance imaging (MRI) according to the epileptological protocol and continuous electroencephalographic (EEG) video monitoring with seizures recording [5–7]. Brain MRI can identify diverse anatomical epileptogenic compartments such as hippocampal sclerosis, tumors, and brain developmental abnormalities. Continuous video-EEG monitoring solves an issue of searching for zones of irritation, seizure onset of and the symptomatogenic zone.

An option of using surgical treatment may be considered in case the data obtained from the two abovementioned diagnostic tools are sufficient and do not contradict each other [8, 9]. Otherwise, require to be further examined. One of the techniques that may be used to solve this issue is provided by a subtraction ictal single-photon emission computed tomography (SPECT) co-registered to MRI (SISCOM).

SPECT AS A METHOD FOR PRESURGICAL EPILEPSY DIAGNOSTICS / ОФЭКТ КАК МЕТОД ПРЕДХИРУРГИЧЕСКОЙ ДИАГНОСТИКИ ЭПИЛЕПСИИ

SPECT allows for a nuclear visualization to assess altered blood perfusion in brain tissue. For this, intravenously administered radioactive tracer is used that becomes accumulated and sustained in small vessels for several hours [10]. If an epileptic seizure occurs in the initiation zone, hyperperfusion and increased radionuclide agent accumulation are noted in the brain tissue.

Among diverse radiopharmaceuticals, gamma emitters are most commonly used. Tracing agents that can be used to identify a zone of seizure onset should meet certain characteristics: lipophilicity, and small molecular size to quickly enter intact blood-brain barrier [11–13]. Technetium 99 (^{99m}Tc) preparations such as ^{99m}Tc-HMPAO (Ceretec® – GE Healthcare Ltd. (United Kingdom), Theoxym® – Diamed LLC (Russia)) or ^{99m}Tc-ECD (Neurolite® – Lantheus Medical Imaging (USA)). Drugs penetrate into brain cells owing to intrinsic lipophilic property to be further transformed into hydrophilic compounds [14].

A gamma tomograph is used to record a gamma emitter-signal accumulated within the hyperperfusion zone. Next, SISCOM allows to process ictal and interictal images and overlap with brain MRI images.

SPECT USING SISCOM PROTOCOL / ОФЭКТ С ПРИМЕНЕНИЕМ ПРОТОКОЛА SISCOM

Indications for the procedure / Показания к проведению

The major indication for the SPECT in patients with epilepsy is based on a need to localize epileptogenic focus not detected before clearly with other diagnostic tools.

Usually, SPECT is applied to patients with MRI-negative epilepsy or those having conflicting data from previous examinations. In some cases of MRI-negative epilepsy, SPECT may have a navigation function when MRI data may be re-analyzed after identifying putative site of ictal seizure onset that allows to detect an epileptogenic substrate so that a patient is no longer considered MRI-negative [12, 15–18].

The technique is useful for proper positioning invasive electrodes (subdural or deep) for installation and can reduce their quantity while developing an epileptogenic zone hypothesis also being used to clarify an epileptogenic zone in post-surgery patients in case a first operation failed to eliminate seizures [16].

Contraindications for the procedure / Противопоказания к проведению

The following SPECT contraindications may be specified [10, 14]:

– pregnancy and breastfeeding (breastfeeding is interrupted for 24 hours if SPECT is indicated for a nursing mother);

– patient interaction with medical personnel is failed or profoundly complicated (including diverse conditions such as concurrent ongoing mental disorders, prominently declined cognitive functions, prolonged post-seizure psychosis and episodes of disorientation interfering with medical examination);

– short-term seizures (it is necessary to estimate the minimum length of a seizure suitable for SPECT, based on timeframe required for radioactive tracer agent to be administered and transported to the brain tissue comprising about 10 sec);

– benzodiazepines-uncontrolled frequent seizures due to complicating conduction of one of the examination stages (no seizures should be observed at least 2 hours before interictal SPECT).

Procedure methodology / Методика проведения

SPECT is a multi-stage examination technique that requires a cooperation between multidisciplinary medical specialists (neurologist-epileptologist, nursing staff, neuroradiologist), each of whom should clearly understand own role during procedure and be able to act with the others quickly and in harmony. Several stages of examination procedure may be distinguished:

(1) preparation stage;
(2) ictal SPECT;
(3) interictal SPECT;
(4) SISCOM;
(5) evaluation of the data obtained.

Below are the main features of the SPECT stages.

Preparation stage

Patient preparation stage is conducted according to the European Association of Nuclear Medicine (EANM) SPECT guidelines. Before proceeding to examination procedure [14]:

– avoid smoking, taking stimulants (such as caffeinated drinks), alcohol, and any medications that may affect cerebral blood flow;

– it is recommended that examination procedure is carried out in a quiet, dimly lit room;

– patient takes a comfortable (preferably lying) position;

– patient's eyes should be open, avoid moving, speaking or reading;

– intravenous catheter is installed;

– EEG is available to record seizure onset pattern.

However, these recommendations cannot be fully implemented in patients with epilepsy. In some cases, only sleep seizure recording is possible, when the eyes are closed, or a certain seizure provocation is required (e.g., by hyperventilation) and a resting state before radiopharmaceutical agent is administered cannot always be ensured. Preparation stage also includes planning for partial or complete withdrawal of antiepileptic therapy to increase probability for seizure development.

Ictal SPECT

Ictal SPECT implies rapid radiopharmaceutical agent administration after seizure onset. In connection with

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this, patient undergoes continuous video-EEG monitoring. Sometimes, it is recommended to store ready-to-use syringes in epilepsy monitoring unit to ensure that radiopharmaceutical agent might be administered as quick as possible [8, 12, 14]. Once a neurologist-epileptologist clinically or based on EEG-verified data realizes that a seizure develops, a nursing staff should be informed that a radiopharmaceutical agent should be administered. Currently, an automated radioactive tracer-injector is available, that should be connected to a patient in advance, and tracer injection is started from control panel or remotely [19, 20].

The timing of radionuclide gamma-emitter administration is critical to examination procedure [18]. Generally, early injection without providing a specific time limit is noted. In addition, it is also observed that a gamma-emitter should be administered within 15–45 sec after seizure onset [10, 15]. The injection time while using an automated radioactive tracer-injector comprises less than 5 sec that may optimize examination procedure and ensure higher SPECT accuracy [19, 20].

After tracer administration and patient stabilization, it is necessary to record emitted radiation signal using a gamma tomograph. To avoid repeated seizures during scanning procedure, short-acting benzodiazepines may be used, but not earlier than 5 min after tracer administration [14]. Images may be obtained even several hours after paroxysm end. To obtain best image quality, it is recommended to delay imaging by 30–60 min for ^{99m}Tc-ECD tracer and 30–90 min for ^{99m}Tc-HMPAO. Avoid excessive delay in scanning; due to radioactive decay, it is recommended to perform procedure within 4 hours after tracer administration [14, 21].

Interictal SPECT

Due to half-life, interictal SPECT is carried out not earlier than 24 hours after radiopharmaceutical agent administration during ictal period. Preparation stage corresponds to that described for ictal SPECT protocol. It is also recommended to conduct continuous video-EEG monitoring at least 2 hours before radiopharmaceutical agent administration and 15 min afterwards to exclude a potential for emergence of epileptic seizures shortly before and during radiopharmaceutical administration [10, 14].

After tracer administration, visualization is also carried out using gamma tomograph. A time interval between radiopharmaceutical administration and scanning should be similar to that described in ictal SPECT protocol [14].

SISCOM protocol

In 1976, SPECT began to be applied together with intravenously administered ^{99m}Tc (^{99m}Tc-HMPAO, ^{99m}Tc-ECD)-labeled preparations to measure cerebral perfusion and seek for an epileptogenic zone, but in most cases only the ictal phase was assessed [22]. Since 1986, a comparative analysis (subtraction) of SPECT data in ictal and interictal periods began to be carried out. Interictal SPECT images are subtracted from ictal SPECT images. The difference between the two examinations is considered to be the presumptive seizure onset zone [16].

In 1998, T.J. O'Brien et al. [23] combined resulting subtraction data with high-resolution brain MRI (performed under anesthesia). The technique overlapping images obtained after subtraction for interictal and ictal SPECT and MRI data was called "subtraction ictal SPECT co-registered to MRI" (SISCOM). It was shown that SISCOM enhances sensitivity for identifying epileptogenic zone by 43.1%. This examination procedure was introduced intro clinical practice for imaging of MRI-negative epileptogenic zones and in other doubtful cases [16, 22, 23].

Data evaluation

After data processing, the desired hyperperfusion pattern in epileptogenic zone is obtained on brain MRI images [10, 24].

Hyperperfusion of the ipsilateral basal ganglia, thalamus, motor cortex, or contralateral hyperperfusion of the cerebellum are additionally assessed [24].

Sometimes, a SPECT radioactive tracer cannot be administered quickly during an ongoing seizure and instead it is injected postictally. A phenomenon of postictal hypoperfusion exists describing that cerebral blood flow in epileptogenic focus drops sharply for several minutes after seizure end. Moreover, the level of postictal vs. interictal hypoperfusion is lower by 30–92%. This phenomenon may also be visualized using SISCOM. Postictal hypoperfusion focus is usually more common [25].

Methodology effectiveness / Эффективность методики

In this regard, the most recent meta-analysis was published in 2016 that summarizes 11 studies conducted between January 1995 and June 2015 assessing 320 patients with epilepsy [26]. A total of 142 patients were MRI-negative and using SISCOM allowed to determine the epileptogenic zone in 119 of them (83.8%). The positive predictive value for this diagnostic assay in post-surgery seizure-free patients (Engel I) was 56% (95% confidence interval 49–64).

T.J. O'Brien et al. showed that SISCOM allowed to visualize epileptogenic zones in 45 of 51 (88.2%) examined patients with focal epilepsy [23], whereas previously used SPECT alone identified 39.2% (20 out of 51 patients) ($p<0.001$). A series of studies estimated SPECT sensitivity and specificity to be 64.8–86% and 40.7–75%, respectively [12, 24, 27–29].

T.J. Von Oertzen et al. reported the data on 175 patients providing insufficient information about epileptogenic zone localization, who were examined using SISCOM regarding installation of intracerebral electrodes [30]. SISCOM data were fully consistent with the epileptogenic zone in 82% of cases, reaching specificity of 75% in the presence of multiple epileptogenic substrates.

The major characteristics for SISCOM predictive value obtained in a series of studies are shown in **Table 1**.

The reported postsurgery outcomes were usually assessed by using commonly accepted Engel scale, where Engel I – seizure-free, Engel II – rare seizures, Engel III – marked improvement, Engel IV – lack of effectiveness [33]. In some studies, Engel I and II outcomes were combined together into a set of positive effects. Summarized data on the effectiveness of surgical treatment in patients with epilepsy,

Table 1. Major parameters of predictive value for subtraction ictal single-photon emission computed tomography co-registered to magnetic resonance imaging (SISCOM)

Таблица 1. Основные показатели прогностической ценности однофотонной эмиссионной компьютерной томографии с применением протокола SISCOM

Authors / Авторы	Year / Год	Sensitivity, % / Чувствительность, %	Specificity, % / Специфичность, %	PPV, %	NPV, %
M.V. Spanaki et al. [27]	1999	86,0	75,0	–	–
A. Desai et al. [28]	2013	87,0	–	–	–
T. Chen et al. [26]	2016	–	–	56,0	–
G. Aungaroon et al. [29]	2018	64,8	40,7	–	–
K. Kaur et al. [31]	2021	83,3–85,7	50,0	90,0–90,9	25,0–33,3
M. Prener et al. [32]	2023	76,0–83,3	65,0–73,0	70,0–75,0	20,0–50,0

Note. *PPV – positive predictive value; NPV – negative predictive value.*

Примечание. *PPV (англ. positive predictive value) – положительная прогностическая ценность; NPV (англ. negative predictive value) – отрицательная прогностическая ценность.*

which resection zone corresponds to hyperperfusion zone based on SISCOM data are presented in **Table 2**.

Comparing SISCOM with other approaches for presurgery diagnostics reported by A. Desai et al. with 45 adult patients underwent invasive video-EEG monitoring to confirm seizure onset zone, showed greater sensitivity compared with 18F-fluorodeoxyglucose positron emission computed tomography (^{18F}FDG PET-CT) reaching 87% and 56%, respectively [28].

In contrast to ^{18F}FDG PET-CT more preferably used for temporal lobe epilepsy, SPECT demonstrates better data with extratemporally localized epileptogenic zone [36].

In the pediatric patients, this assay also demonstrates sufficient agreement between the data obtained and epileptogenic zone [37]. Among 54 postsurgery children with a drug-resistant structural epilepsy, brain MRI revealed an epileptogenic substrate in 21 of 54 cases (39%), a hyperperfusion zone was detected by SISCOM in 36 of 54 observations (67%), whereas hypometabolism zone – in 31 of 54 cases (57%) while using ^{18F}FDG PET-CT.

Previous studies comparing the diagnostic effectiveness for SISCOM and magnetoencephalography (MEG) showed conflicting data and were limited by small sample sizes [38–40]. One recent study found insignificantly better data for SPECT than for MEG in terms of good postoperative outcome [31].

According to EANM and O'Brien T.J., the following essential reasons for incorrect SPECT data have been identified [14, 23]:

– unexpected brain activation;

Table 2. The effectiveness of surgical treatment in patients with pharmacoresistant structural epilepsy, whose resection zone coincided with the results of subtraction ictal single-photon emission computed tomography co-registered to magnetic resonance imaging (SISCOM)

Таблица 2. Эффективность хирургического лечения пациентов с фармакорезистентной структурной эпилепсией, зона резекции у которых совпадала с результатами однофотонной эмиссионной компьютерной томографии с применением протокола SISCOM

Authors / Авторы	Year / Год	Engel I outcomes / total post-surgery patients, n // Исходы класса Engel I / общее число прооперированных, n	Engel I outcomes, % / Исходы класса Engel I, %
T.J. O'Brien et al. [23]	1998	10/16	62,5
T.J. Von Oertzen et al. [30]*	2011	22/26	84,6
E.B. Cho et al. [34]	2015	25/39	65,8
T. Chen et al. [26]	2016	100/176	56,1
T. Foiadelli et al. [35]	2019	16/24	66,7
K. Kaur et al. [31]	2021	31/42	73,8
M. Prener et al. [32]	2023	25/56	44,0

Note. ** Engel I–II outcomes were assessed in the study.*

Примечание. ** В исследовании оценивали исходы классов Engel I–II.*

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– artifacts obtained at various examination stages (patient movements during scanning on a gamma tomograph, incorrect data processing);

– taking medications affecting cerebral circulation;

– late radiopharmaceutical administration (more than 45 s from seizure onset).

CONCLUSION / ЗАКЛЮЧЕНИЕ

Subtraction ictal SPECT coregistered to MRI (SISCOM) shows a sufficiently high sensitivity (mean about 70–75%), moderate specificity (40–75%) and positive predictive value (56%) for patients with drug-resistant focal structural epilepsy able to identify ictal onset zone and may be used for presurgery diagnostics.

It cannot be argued that SISCOM is the only option able to replace other non-invasive and invasive assays. In contrast, SISCOM may be rather used in conjunction with them. The technique is also applied to predict an extent of invasive diagnostic procedure (stereo-EEG, subdural electrode installation). Despite SISCOM diagnostic value, a series of limitations for patients with epilepsy as well as related labor intensity do not allow using it in wider clinical practice and create an obstacle due to its inaccessibility.

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