

The importance of PET-CT in the diagnosis of epilepsy

A importância do PET-CT no diagnóstico da epilepsia

DOI:10.34119/bjhrv3n5-276

Recebimento dos originais: 08/09/2020

Aceitação para publicação: 21/10/2020

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ABSTRACT

Introduction: PET-CT (Positron Emission Tomography) is an examination composed of a hybrid set of two exams, where CT can define the anatomy of the region studied and the PET scan defines the cellular metabolism with the aid of FFDG. This examination has been used in the monitoring of several pathologies, including epilepsy, and currently in Brazil, 1.2% of the population are carriers of this disease. Objectives: The aim of this study was to review the importance of PET-CT in the detection of epilepsy and to discuss clinical manifestations, to understand the physical principles and to verify the functioning of the PET-CT scan. Methods: Selection of files through the electronic databases LILACS, PubMed / MEDLINE and SciELO using the following descriptors: PET- CT, epilepsy and FFDG, between the years 2005 to 2017, as well as classic articles. Discussion: Epilepsy is a disease that requires caution for diagnosis, because it is necessary not only to listen to the patient, but also to the relatives of the patient, especially during the seizures.

PET-CT is the most accurate imaging test. During the examination the FFDG marker allows to evaluate the cerebral metabolism, because in normal cerebral cortex the brain presents a high glucose absorption of the marker, however with the pathological brain the marker glucose level is decreased, thus showing the pathology. However the disadvantages of the examination are the high value and the short half-life of the radiopharmaceutical. Conclusion: The PET-CT scan is really effective in the detection of epilepsy, making it a specific method exam.

Keywords: PET-CT, Epilepsy and ¹⁸FFGD.

RESUMO

Introdução: O PET-CT (Positron Emission Tomography) é um exame composto por um conjunto híbrido de dois exames, onde o TC pode definir a anatomia da região estudada e o PET scan define o metabolismo celular com a ajuda do FFDG. Este exame tem sido utilizado na monitorização de várias patologias, incluindo a epilepsia, e actualmente no Brasil, 1,2% da população é portadora desta doença. **Objectivos:** O objectivo deste estudo foi rever a importância da PET-CT na detecção da epilepsia e discutir as manifestações clínicas, compreender os princípios físicos e verificar o funcionamento do exame PET-CT. **Métodos:** Selecção de ficheiros através das bases de dados electrónicas LILACS, PubMed / MEDLINE e SciELO, utilizando os seguintes descritores: PET-CT, epilepsia e FFDG, entre os anos de 2005 a 2017, bem como artigos clássicos. **Discussão:** A epilepsia é uma doença que requer cautela no diagnóstico, porque é necessário não só ouvir o paciente, mas também os familiares do paciente, especialmente durante as convulsões. O PET-CT é o teste de imagem mais preciso. Durante o exame, o marcador FFDG permite avaliar o metabolismo cerebral, porque no córtex cerebral normal o cérebro apresenta uma elevada absorção de glicose do marcador, contudo com o cérebro patológico o nível de glicose do marcador é diminuído, mostrando assim a patologia. Contudo, as desvantagens do exame são o elevado valor e a curta meia-vida do radiofármaco. **Conclusão:** O exame PET-CT é realmente eficaz na detecção da epilepsia, tornando-o num exame de método específico.

Palavras-Chave: PET-CT, Epilepsia e ¹⁸FFGD.

1 INTRODUCTION

Approximately one hundred years after Roentgen's original discovery of X-rays, medicine by image has continued to develop on several fronts, which are bound to be complementary and noncompetitive. Among the new imaging technologies, "molecular imaging, weighted MRI, functional MRI" and "MRspectroscopy"¹ may be included.

"Molecular imaging" techniques contemplate the principles of optical imaging - a future that is increasingly imminent, mainly because of its fundamental non-invasive characteristics (without the use of ionizing radiation); of positron emission tomography (PET). With PET, cerebral chemistry, neurotransmission (pre and post-synaptic neurons), as well as other brain functions can be studied².

Currently, the clinical examination of PET incorporated into the daily routine of many departments of nuclear medicine, allows to obtain: differential diagnosis of dementias, Pick's

disease and dementia with multiple infarctions, and also to distinguish these from depressive states in elderly patients; differential diagnosis between tumor recurrence and post-radiation or post-surgery necrosis; confirmation of brain death, especially in cases of coma due to intoxication with barbiturates¹.

Neurological diseases are a type of pathology that affect the central and peripheral nervous system, involving disorders at various levels of the brain. Some of the diseases that affect the CNS are, for example: Parkinson's Disease, Multiple Sclerosis and Epilepsy³. Being that Epilepsy is a neurological problem characterized by the presence of convulsive crises, in which the individual can lose consciousness or not.

Neurological diseases is a pathology that reaches 700 million people in the world, making this type of disease represent a third of all non-communicable diseases. In the case of epilepsy in Brazil, there is a prevalence of about 1,2% of the population, which represents almost 2 million carriers⁴.

The state-of-the-art equipment presents a CT scan coupled to PET scan, a hybrid set called PET-CT, thus joining two well-established imaging modalities in a single exam⁵, being able to define cell metabolism through PET scan and delimit the anatomy with CT. As a result, there is an economic and specific method that improves the diagnosis and provides the appropriate choice of treatment.

In clinical practice, the use of multimodality imaging methods is already a reality, especially in the field of nuclear medicine, and virtually all PET devices actually represent integrated PET-CT systems. The interpretation of PET without fusion with other imaging modalities, with better anatomical definition, such as CT and / or magnetic resonance imaging (MRI), presents low specificity and a decreased positive predictive value⁶.

PET-CT has an enormous and effective importance in the diagnosis of neurological diseases because it shows that the knowledge and level of information that this examination possesses are of great value for all, since in addition to saving time during the diagnostic attempt, it already shows precisely where the pathology is. The general objective of this review is: to identify the importance of PET-CT in the detection of epilepsy; and the specific ones are: to address the clinical manifestations of epilepsy, to understand the physical principles of PET-CT and to verify how the equipment works and how PET-CT is performed.

2 METHODS

The selection of articles was performed by electronic search in three databases: LILACS (Latin American and Caribbean Literature in Health Sciences), PubMed / MEDLINE (Medical Literature Analysis and Retrieval System Online) and SciELO (Scientific Electronic Library Online) with the following descriptors: PET-CT, epilepsy and ^{18}F FDG. Articles published between the years 2005 to 2016, available online, preferably in English or Portuguese language, were considered eligible articles that were related to the theme of this review, as well as classic articles. Greater emphasis was placed on the more recent articles, with outstanding technical innovations based on scientific evidence. It is highlighted as exclusion criteria were articles presented in other languages, besides those that approach other neurological disorders, except epilepsy.

3 LITERATURE REVIEW

The Literature Review has three topics, thus subdivided into: Epilepsy, PET-CT and Interface between PET-CT and Epilepsy, which address the topic of PET-CT.

3.1 EPILEPSY

Epilepsy is a syndrome, that is, a set of signs and symptoms that characterize a certain condition and indicate that, for some reason, a group of brain cells behaves in a hyperexcitable way⁷.

Epilepsy may produce clinical manifestations, is partial epileptic seizures (if electrical signals are disorganized in only one of the cerebral hemispheres), or total (if this disorganization occurs in both hemispheres). In the vast majority of cases, seizures disappear spontaneously, but the tendency is for them to recur from time to time⁸.

Epilepsy is not considered a disease, but a group of disorders that have in common an increased predisposition to epileptic seizures. Its definition involves: 1: history of at least two seizures; 2: permanent change in the brain that increases the likelihood of new seizures; 3: associated conditions, such as ictal and interictal cognitive deficits, social stigma, restrictions, exclusion and psychological consequences for the patient and his family⁸.

To characterize epilepsy, it is indispensable to have spontaneous recurrence of seizures with interval of at least 24 hours between them. A single episode is not indicative of the syndrome. Listening to the patient's story and reporting the people who witnessed the crisis also helps to determine the diagnosis. In addition, it is necessary to make sure that there is no precipitating factor of the crisis, whether it is toxic or caused by some other disease⁷.

The basis of the effective treatment of epilepsy is due to the clarification made to the patient and family member with the objective of avoiding misconceptions and myths about the pathology, always affirming that it is possible to control the seizures in the majority of cases in which the patient follows the therapeutic scheme prescribed. For ease of adhesion, the simplification of the drug regimen can be simplified, and always alert to the importance of taking the medicines at the right times, obtaining a good adhesion².

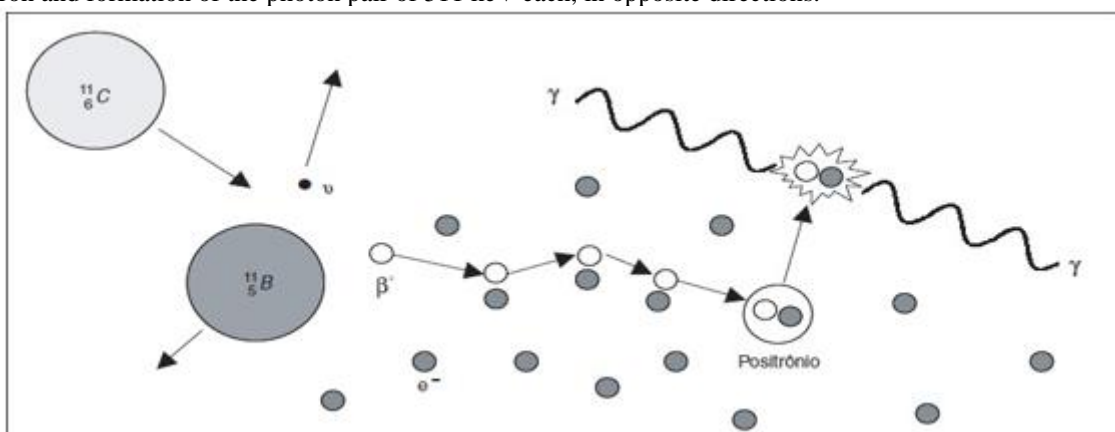
3.2 PET-CT

3.2.1 Physical Principles

The scheme that records the distribution of a positron-emitting radiopharmaceutical into a specific cut of the body is termed as PET; better known as positron emission tomography. During its realization the decay of the parent radionuclide to the son nuclide occurs, causing immediate emission of a positron (β^+) and a neutrino (ν)⁹.

The chemical behavior of the compound is not altered in reactions involving electrons from the outermost orbits of the atom, occurring between an organic compound and radioactive isotopes. Similarly, the chemical state of an atom does not affect its nuclear radioactive patterns. These concepts are part of the principles for the development of radiopharmaceuticals in nuclear medicine¹⁰. Figure 1 illustrates the decay map of ($^{11}\text{C}_6$) to ($^{11}\text{B}_5$), the path to the elimination of positron with one electron from the medium and the subsequent formation of the photon pair of 511 keV each, in opposite directions. This inversion allows them to detect the images externally, allowing the information to be used for the reconstruction of the tomographies⁹.

Figure 1: Positron emission tomography (PET): decay scheme of $^{11}\text{C}_6$ to $^{11}\text{B}_5$ and annihilation of positron with electron and formation of the photon pair of 511 keV each, in opposite directions.



* Positronium is the system formed by the positron and the electron before annihilation, which results in the production of the pair of photons.

SOURCE: ROBILOTTA, 2006.

In 1951 Gordon L. Brownell, William H. Sweet, Frank R. Wrenn and associates idealized the proposition to detect brain tumors through the use of emitters of positrons in the organism. However, it was observed that only the conceptions of the studies by Brownell were able to produce a visible path of radiopharmaceutical sharing, through the observation of the pair of photons resulting from the dematerialization of the positron with two crystals of sodium iodide activated with thallium [NaI Tl)], arranged on opposite sides of the patient's head and linked to a tracking system. Michel M. Ter-Pogossian and William E. Powers assimilated the use of ^{15}O (Oxygen-15) in internal parts of malignant neoplasias⁹.

He concluded that the medicine uses the positron-emitting radionuclides that are produced by cyclotrons⁹. Table 1 presents radionuclides with some of their physical characteristics, these being the most applied. Radionuclides ^{11}C and ^{15}O are part of a constituent of elements of living organisms, a circumstance that makes them due to the labeling of biomolecules. But since their physical half-lives are ephemeral, similar to ^{13}N , they should only be used if the accelerator for their production is in the accommodation of the diagnostic center.

Table 1: Main emitters of positrons and their characteristics.

Radionuclídeo	T _{1/2} (min)	E _β , max (MeV)	Maximum reach in water (mm)
Carbon-11 ^{11}C	20.4	0.959	5.0
Nitrogen-13 ^{13}N	9.96	1.197	5.4
Oxygen-15 ^{15}O	2.07	1.738	8.2
Fluorine-18 ^{18}F	109.8	0.650	2.4
Gallium-68 ^{68}Ga	68	1.899	9.4
Rubidium-82 ^{82}Rb	1.3	3.350	15.6

SOURCE: ROBILOTTA, 2006.

By means of two types of equipment they cover positron emission images with the systems applied and supported by scintillation cameras. During the use of the electronic collimation, it is promoted registration of the coincidence events, occurring to the detection by means of the pairs of photons in variant positions. Attention is paid to the short time interval where coincidence is applied, predefined by the manufacturer to create the phenomenon¹¹.

The responses obtained to be used in the formation of the tomographic image are absorbed by the two scan photons that are in full coincidence. If the two localized photons arise from the same disintegration of positron, without relating to the medium, we can define it as true coincidence, and the point of annihilation superimposed on the response trait. Photons that originate from the same disintegration, but one of them relates to the medium, we understand that the point of annihilation will no longer be superimposed on the trace of response we will call it a scattered event. However, if both photons start from distinct disintegrations, the detected pair will present an incorrect response line, providing the random event¹¹.

3.2.2 Equipment

The anatomical (CT) and functional (PET) information transcribed in a single image compose the PET-CT system, the same translates the functionality of CT and PET into the unified physical system, promoting the patients to perform both examinations. The results of the images, TC and PET, are conceived in the same spatial follow-up the need for a junction alignment between the two systems¹².

The interrelationship of CT and PET images has innovated the development of imaging of nuclear medicine. Mainly some technical advantages have boosted this advance: fast repair, slowing of photon attenuation noise in PET, amplified resolution in anatomical images; promoting specific identification of the tumor using as base higher concentration of the radiopharmaceutical; support information in the final diagnosis in relation to the precise size of the tumor and detection of lesions not only in PET, caused by the lower concentration of radiopharmaceutical in the analyzed sites¹¹.

PET adequates a metabolic agent that serves as a contrast and clarifies the distinction of malignant tissues from the benign, early detection of tumors not yet visible on CT¹⁰. The basis for the construction of a PET-CT system is the effectiveness of a combined system in the same gantry, which enables the device to develop a more compact and proximal image in relation to the two systems involved.

The engineering disparity provider is not in the PET-CT junction complex within the same gantry, but in the patient's position relative to the distinct systems.

The resolution for improper movement of the patient was to couple the PHS (Patient Handling System) between the two detector rings as shown in the figure below. Figure 2 shows how the PET-CT equipment is¹⁰.

Figure 2: PET-CT equipment.



LEGEND: (a) PET-CT system marketed. (b) Positional mode in the part of the gantry. (c) Construction model of the PET-CT system.

SOURCE: WERNICK; AARSVOLD, 2004.

Accurate acquisition of the image is gained by the decrease in the vertical position of the PHS, in the act of displacement to the inner part of the gantry. When introducing a carbon fiber composite board, it supports the patient's weight and fits the sliding carpet, driven by the traction of a motor. In view of the minimum displacement, it is necessary to adjust this value at the moment of conception of the images so that there is no deviation from the anatomical pattern¹⁰. Table 2 shows the characteristics of the PHS for the acquisition of PET- CT images.

Table 2: PHS and PET-CT system physical characteristics.

Patient support (PHS)		Gantry	
Width	42cm	Height	202cm
Length	379cm	Width	239cm
Weight	726kg	Depth	156cm
Maximum patient weight	204kg		
Horizontal reach PET-CT	190cm	Diameter of the ring where the patient enters	70cm
Horizontal movement	264cm		
Vertical movement	53-101cm	Gantry weight	2402kg

SOURCE: TOWNSEND; BEYER; BLODGETT, 2003.

3.3 PET-CT INTERFACE AND EPILEPSY

With the technological advance, new techniques have been improved to assist in the diagnosis of pathologies of neurodegenerative character. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) are techniques that work with principle in the acquisition of images in vivo with neurochemical character, allowing the identification and knowledge of the pathophysiological aspects of neurodegenerative diseases. They are noninvasive and efficient techniques, which quantitatively measure biological processes of great importance

in the brain. This technique seeks the development of probes that are labeled by a positron-emitting isotope for PET¹³. Initially, the patient is adequately trained to eliminate artifacts and errors in image interpretation. The patient should avoid performing exhaustive physical exercises in the 24 hours prior to the examination and exercise the required fasting time of at least four hours preceding it. For restless patients, it is necessary to apply a muscle relaxant or sedative, because it is of utmost importance the immobility at the time of the examination so that no errors occur. A dose of a marker substance is injected intravenously (the radiopharmaceutical ¹⁸FFDG) which takes about 45 minutes to be absorbed by the body. In the meantime, the patient should be kept in rest for 30 to 60 minutes and after this time, refer to the equipment where the test will be performed¹⁴.

The biomarkers or radiotracers of PET-CT are used to evaluate the functional activity of proteins, cells and pathological processes. The detection of radiation transmitted by radiopharmaceuticals allows the early diagnosis of many diseases. In addition, it is a high sensitivity technique, where it is possible to obtain biological results and information with levels of biomarkers concentrations in nano or picomolar¹⁴.

In the diagnosis of epilepsy, PET-CT is the most assertive for the pathology. Because generalized epilepsies affect a large part of the brain, it is often difficult to isolate the epileptic focus from other affected areas secondarily. However, in the case of partial epilepsies and other types of crisis that originate from a specific focus, ¹⁸FFDG PET may be useful in identifying the primary site^{13,15}.

Generally ¹⁸FFDG PET shows that during a crisis metabolism and cerebral blood flow are significantly increased and, in the interictal period, both metabolism and cerebral blood flow are decreased. In the case of generalized seizures, focal areas of interictal hypometabolism are not observed in ¹⁸FFDG PET. For partial seizures, however, ¹⁸FFDG PET usually shows focal areas of increased metabolic activity in the ictal period and decreased in the interictal period¹⁶.

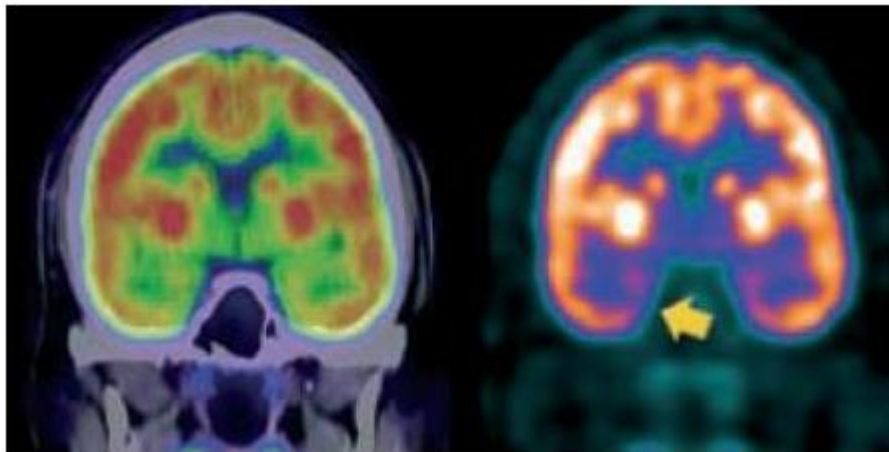
4 DISCUSSION

An epilepsy is a pathology that is a menstruation and a family for the same, by an interview (anamnesis), to aid in the detection, mainly in the convulsive crises. Among the tests that the patient develops for the identification of this disease are: physical examinations, laboratory tests, imaging tests, such as Magnetic Resonance (MRI) or Computed Tomography (CT). However, for diagnosis, but accurate health, is PET-CT, because the same, with the use of ¹⁸FFGD, identifies even more precisely the pathology⁷.

PET-CT is an exam that is being widely used for the diagnosis of epilepsy. The use of ^{18}F FDG-labeled fluordesoxyglucose allowed the rapid and safe evaluation of the cerebral metabolism of patients with epilepsy without PET-CT. The functional images with hypometabolism generated in this case are evidences of a dysfunctional neural network, resulting from loss of synapses and abnormal electrical activity¹⁷.

Non PET-CT glucose metabolism follows the perfusion pattern, resulting in hypermetabolism in the ictal study and in interictal hypometabolism. It is clear that because of the average half-life of fluoride-18, there are limits to a PET-CT scan during an inpatient waiting for a seizure event. However, interictal studies with PET-CT are feasible and are disclosed as the main images of SPECTAVANES for the crisis to detect the focus of epilepsy, as shown in figure 3¹⁸.

Figure 3: Interictal PET-CT brain with ^{18}F FDG shows mild hypometabolism in the mesial portion of the right temporal lobe.

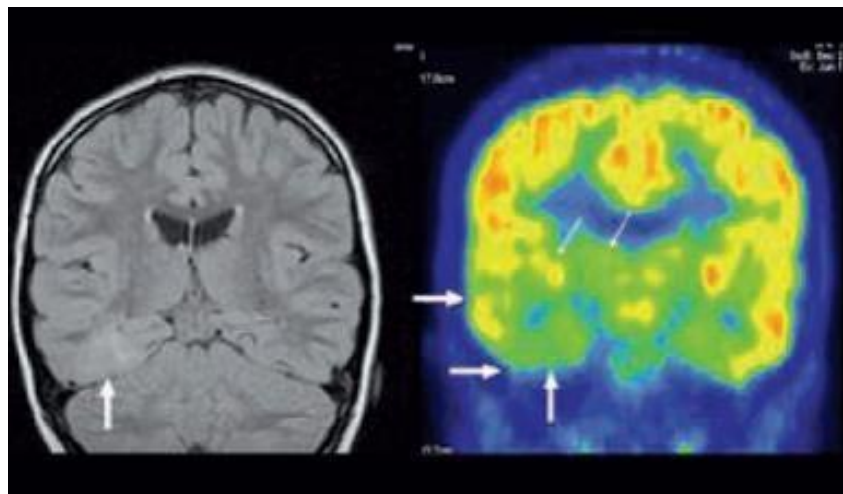


SOURCE: CORDEIRO, 2007.

The cerebral cortex and normal base nuclei have, as a characteristic, a high absorption of marked glucose, a symmetric character throughout the brain. The cerebellum, on the other hand, usually shows a lower absorption, which can be further reduced in patients who use antiepileptic drugs. The white matter and brainstem generally have a low glucose metabolism and high absorption in this local area is always pathological¹⁹.

Glucose dysfunction in the cerebral cortex has a lower than average consumption, and this fact about the usefulness of PET is based. The epileptic focus will be similar to a cortical hippocaptant area, with an area equal to or greater than the MR or CT with the visible lesion, as shown in figure 4¹⁹.

Figure 4: Left RM in FLAIR sequence and the right PET scan image evidencing lesion by epilepsy.



SOURCE: SCHÜTZE, 2013.

One of the major disadvantages of the PET-CT examination is cost, since the value varies from R\$ 3,500 to R\$ 4,000.00, varying, however, by the area of study. In addition to the marker, used during the ^{18}F FDG examination, which has a very short half-life of only 2 hours. For the manufacture of ^{18}F FDG it is necessary that near the place of accomplishment of the examination has a Nuclear Technology Development Center, because the transport of the same has to be done quickly and effectively, so that there is no loss of the half-life⁵.

5 CONCLUSION

The PET-CT scan is an effective technique for the detection of neurological problems, such as epilepsy. The same is of great precision, being part of the differential diagnosis of the pathology approached, however due to the existing limitations that involve this technology, the examination is not accessible to all. In epilepsy the main clinical manifestations of the disease are: seizures, cerebral detachment (fainting) or complex partial crisis. In the detection of epilepsy, it is important that it is done early, so that the patient has an improvement in the quality of life.

The PET-CT examination has the combination of anatomy and physiology in the same image of the organ that will be studied. The physical principles of PET-CT are injection of the radiopharmaceutical, which captures the radiation emitted by the marker, ^{18}F FDG, where in the encephalon the marker signal is of hypocaptation, thus demonstrating the presence of epilepsy and being in the brain without epilepsy the marker signal is hypercaption.

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