

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/radcr

Case Report

Stroke detection with 3 different PET tracers

Ayca Dundar, MD^{a,*}, Michael S. Bold, MD^a, Busranur Agac, MD^b, Ayse Tuba Kendi, MD^a, Saul N. Friedman, MD, PhD^{a,c}^aDepartment of Radiology, Mayo Clinic, 150 3rd Street SW, Rochester, MN 55905, USA^bDepartment of Neurology, Mayo Clinic, Rochester, MN^cDivision of Nuclear Medicine, Mallinckrodt Institute of Radiology, Washington University School of Medicine, Saint Louis, MO

ARTICLE INFO

Article history:

Received 12 July 2019

Revised 30 August 2019

Accepted 2 September 2019

Available online 1 October 2019

Keywords:

Stroke

PET

68Ga-DOTATATE

11C-Choline

18F-FDG

ABSTRACT

Stroke is a common cause of patient morbidity and mortality, being the fifth leading cause of death in the United States. Positron emission tomography (PET) is a proven tool for oncology patients, and may have utility in patients with stroke. We demonstrate findings of stroke incidentally detected on oncologic PET/CTs using ¹⁸F-FDG, ¹¹C-Choline, and ⁶⁸Ga-DOTATATE radiotracers. Specifically, focal ¹¹C-Choline or ⁶⁸Ga-DOTATATE uptakes localized in areas of MRI confirmed ischemia, and paradoxically increased ¹⁸F-FDG activity was visualized surrounding a region of hemorrhage, in different patients. These cases demonstrate that PET may have utility in evaluating patients with stroke based on flow dynamics, metabolic activity, and receptor expression.

© 2019 The Authors. Published by Elsevier Inc. on behalf of University of Washington.

This is an open access article under the CC BY-NC-ND license.

<http://creativecommons.org/licenses/by-nc-nd/4.0/>

Introduction

Stroke is characterized as a neurologic deficit due to a central nervous system injury by a vascular cause. It is a very common cause of patient morbidity and mortality in the United States with approximately 795,000 people affected yearly, and it is the fifth leading cause of death [1–3]. Ischemic stroke is the most common type, accounting for approximately 87% of strokes. Hemorrhagic stroke is less common but has important distinguishing implications [3]. Because of the differing clinical management of these stroke types, imaging is crucial for diagnosis and follow-up [2]. Due to its ubiquitous nature

with quick and easy access, computed tomography (CT) is the most commonly used imaging modality [4]. However, magnetic resonance imaging (MRI) has superior sensitivity compared to CT and is becoming more common as access increases and scan times become shorter [4].

Positron emission tomography (PET) is not currently used in stroke diagnosis. However, it offers unique opportunities in the evaluation of stroke pathophysiology that may not be detectable on CT and MRI [5]. ¹⁵O-labeled water PET as well as ¹⁸F-fluoromisonidazole (¹⁸F-FMISO) PET has been used to identify the hypoxic penumbra after ischemic stroke via perfusion and oxygen consumption [6,7]. A few studies evaluated stroke detection with ¹⁸F-FDG PET have resulted in conflicting

Declaration of Competing Interest: The authors declare that they have no conflict of interest.

* Corresponding author.

E-mail address: dundar.ayca@mayo.edu (A. Dundar).<https://doi.org/10.1016/j.radcr.2019.09.005>1930-0433/© 2019 The Authors. Published by Elsevier Inc. on behalf of University of Washington. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

data about ^{18}F -FDG uptake in perihematoma and peri-infarct tissues [8,9]. ^{11}C -Choline and ^{68}Ga -DOTATATE PET/CT have not been specifically evaluated in the setting of stroke.

We review 3 oncological cases demonstrating strokes on restaging PET/CT and confirmed with CT and/or MRI. In each case, the patient presented for routine PET/CT follow-up and a stroke was incidentally detected on the study. Ischemic strokes were identified in 2 patients imaged with ^{11}C -Choline or ^{68}Ga -DOTATATE PET/CT (Case 1 and Case 2). A third patient with a hemorrhagic stroke was imaged with ^{18}F -FDG PET/CT (Case 3).

Case 1

A 76-year-old male with prostate cancer and hypertension presented with rising prostate specific antigen (PSA). A whole body ^{11}C -Choline PET/MRI demonstrated new abnormal focal ^{11}C -Choline uptake within the right basal ganglia (SUV_{max} 2.0

vs 0.2 on the contralateral normal side). Subsequent brain MRI performed 3 days later demonstrated decreased central T1 signal intensity, increased T2 signal, and abnormal enhancement in the right globus pallidus consistent with an acute-to-subacute infarction. The patient was asymptomatic and observed. Imaging findings are presented in Fig. 1.

Case 2

A 14-year-old female with a large right carotid sheath paraganglioma developed early postoperative left hemiparesis and dysphagia. A diagnostic head CT demonstrated thrombosis of the right middle cerebral artery with ischemic changes in the caudate, putamen, and insula. The patient was treated with intra-arterial thrombolysis resulting in partial recanalization of the middle cerebral artery. A restaging ^{68}Ga -DOTATATE PET/CT performed 6 days later revealed abnormally-increased DOTATATE uptake (SUV_{max} 1.6) corresponding to the areas of

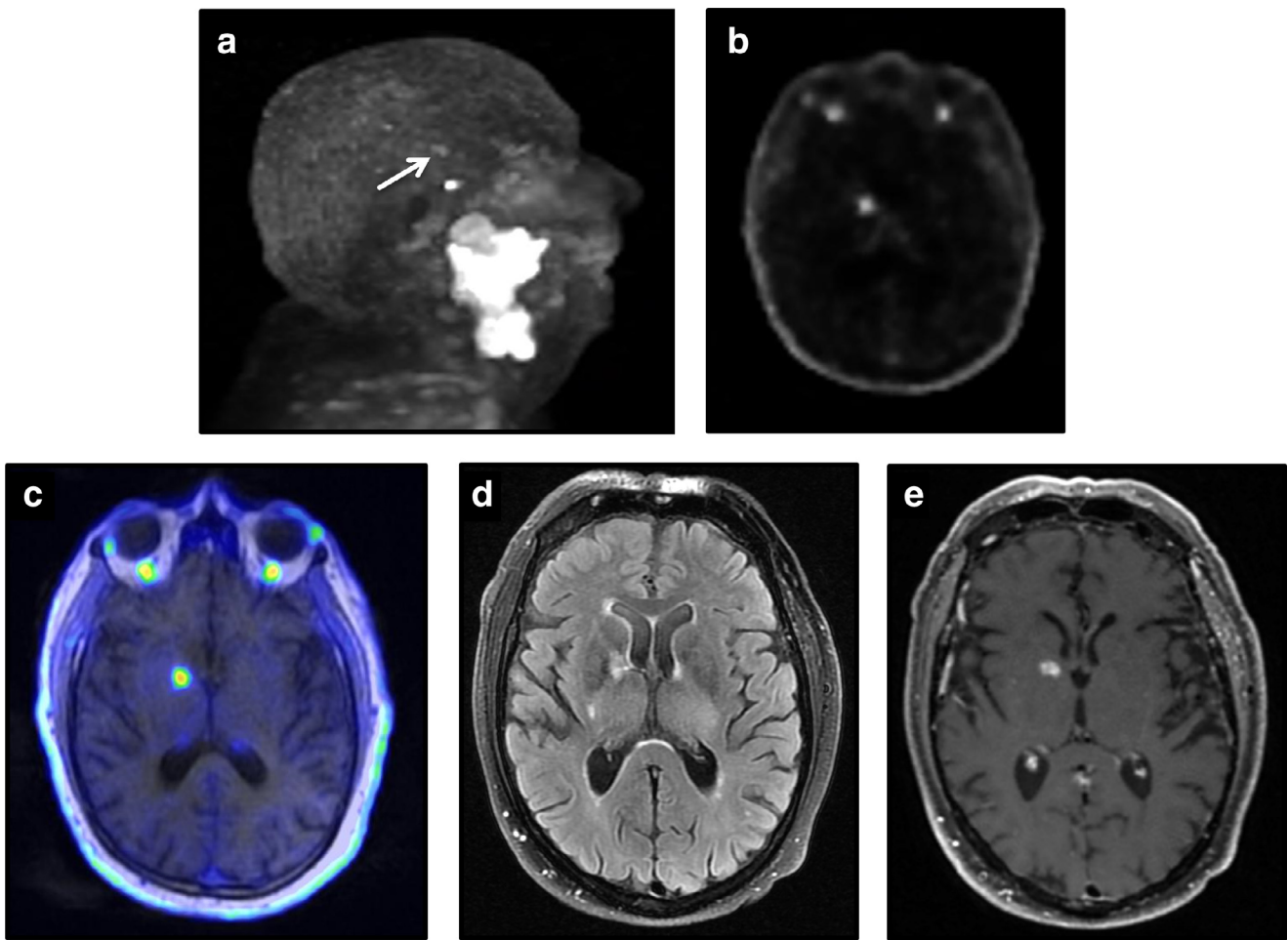


Fig. 1 – A 76-year-old male presented with an acute-to-subacute ischemic stroke in the right basal ganglia on ^{11}C -Choline PET/MRI. (a) Q.Clear MIP image demonstrating faint abnormal choline activity (arrow) superior and adjacent to more intense physiologic pituitary activity. Corresponding axial (b) Q.Clear PET and (c) fused Q.Clear PET/MRI images demonstrating abnormally-increased choline activity localizing to the right basal ganglia. Subsequent diagnostic brain MR (d) FLAIR and (e) postcontrast T1-weighted images demonstrate increased signal and enhancement consistent with a subacute ischemic infarct.

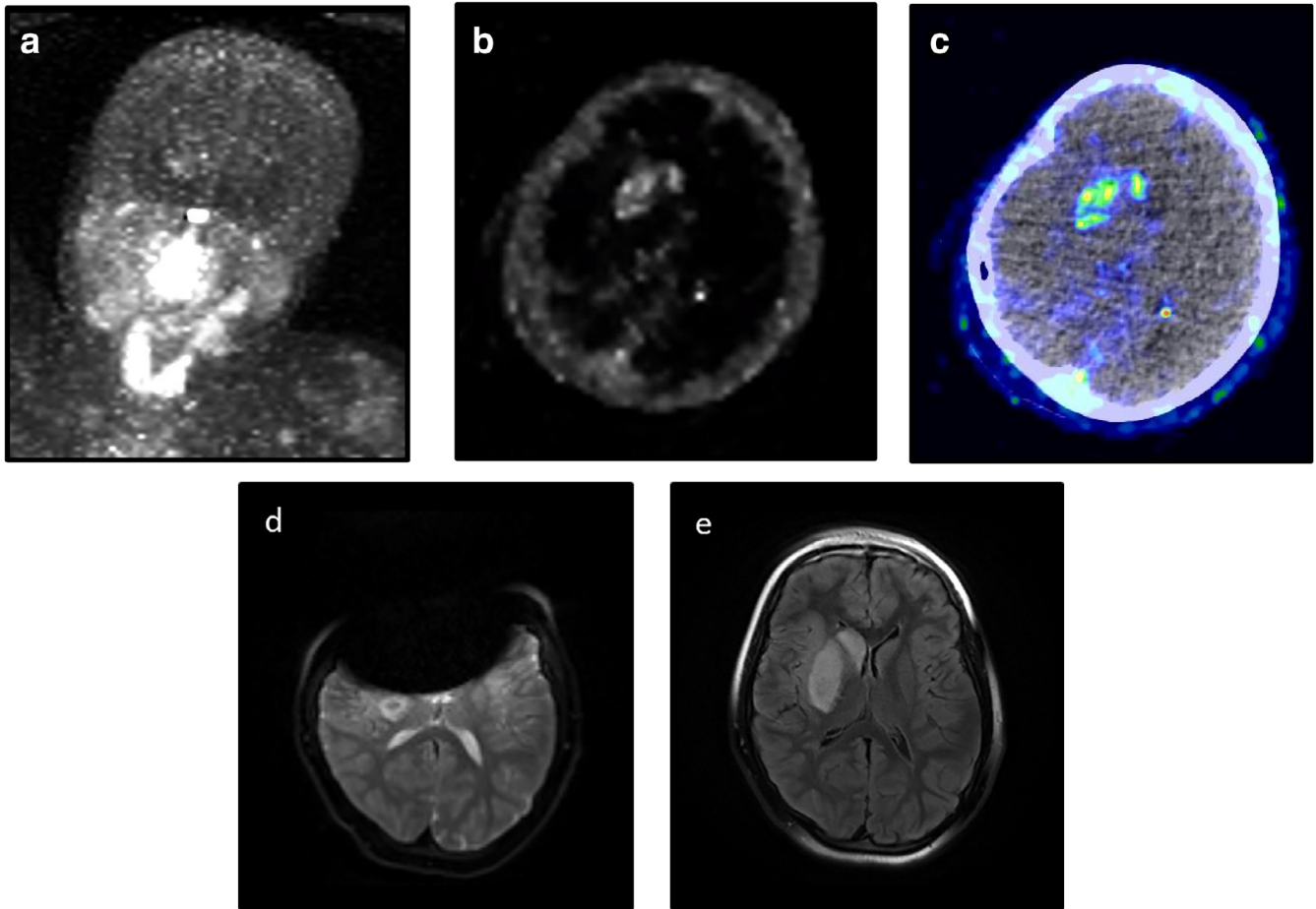


Fig. 2 – A 14-year-old female with a large carotid body paraganglioma presented with an early postoperative ischemic stroke in the right middle cerebral artery territory. Subsequent restaging ^{68}Ga -DOTATATE PET/CT demonstrates mildly-increased activity in the right caudate on the (a) Q.Clear MIP image, (b) Q.Clear PET axial image, and (c) fused Q.Clear PET/CT axial images. Follow-up brain MRI demonstrated (d) restriction diffusion in this region (orthodontic hardware susceptibility artifacts are present) as well as increased T2 signal on (e) FLAIR.

subacute ischemia seen on the preintervention CT and a later MRI. Imaging findings are presented in [Fig. 2](#).

Case 3

An asymptomatic 64-year-old male with lymphoma presented for a restaging ^{18}F -FDG PET/CT after 6 cycles of hyper-CVAD chemotherapy. His past medical history included hypertension, hypercholesterolemia, diabetes mellitus type 2, and a remote hemorrhagic stroke in the right basal ganglia. On the PET/CT, a large right hemispheric intraparenchymal hemorrhage with ventricular extension was detected on the CT images. The PET images demonstrated intense ^{18}F -FDG uptake (SUV_{max} 15.5) in the adjacent right hemispheric cerebral parenchyma surrounding the hemorrhage. The patient was observed and treated by medical management without surgical intervention. Follow-up anatomic imaging remained stable. Imaging findings are presented in [Fig. 3](#).

Discussion

Our cases suggest that regions of acute/subacute ischemic stroke demonstrate increased ^{11}C -Choline and ^{68}Ga -DOTATATE uptake, and regions adjacent to hemorrhagic stroke demonstrate increased ^{18}F -FDG uptake.

^{11}C -Choline PET is FDA approved for metastatic prostate cancer, but also has an emerging application for parathyroid adenoma assessment. The mechanism of choline uptake is not fully understood, however, choline kinase is upregulated in tumor cells [10]. Choline kinase activity is noted to increase under hypoxic conditions in prostate cancer cells [10,11]. Delaunay et al observed increased ^{18}F -Choline uptake in acute ischemic stroke in a prostate cancer patient [12]. They suggested the concept of choline precursors promoting repair in neurologic diseases, and increased choline uptake during inflammatory and repair process in acute ischemic stroke may relate to this [12]. Scremin et al demonstrated increased extracellular choline concentration in ischemia, which may support the role of choline or choline precursors in ischemia

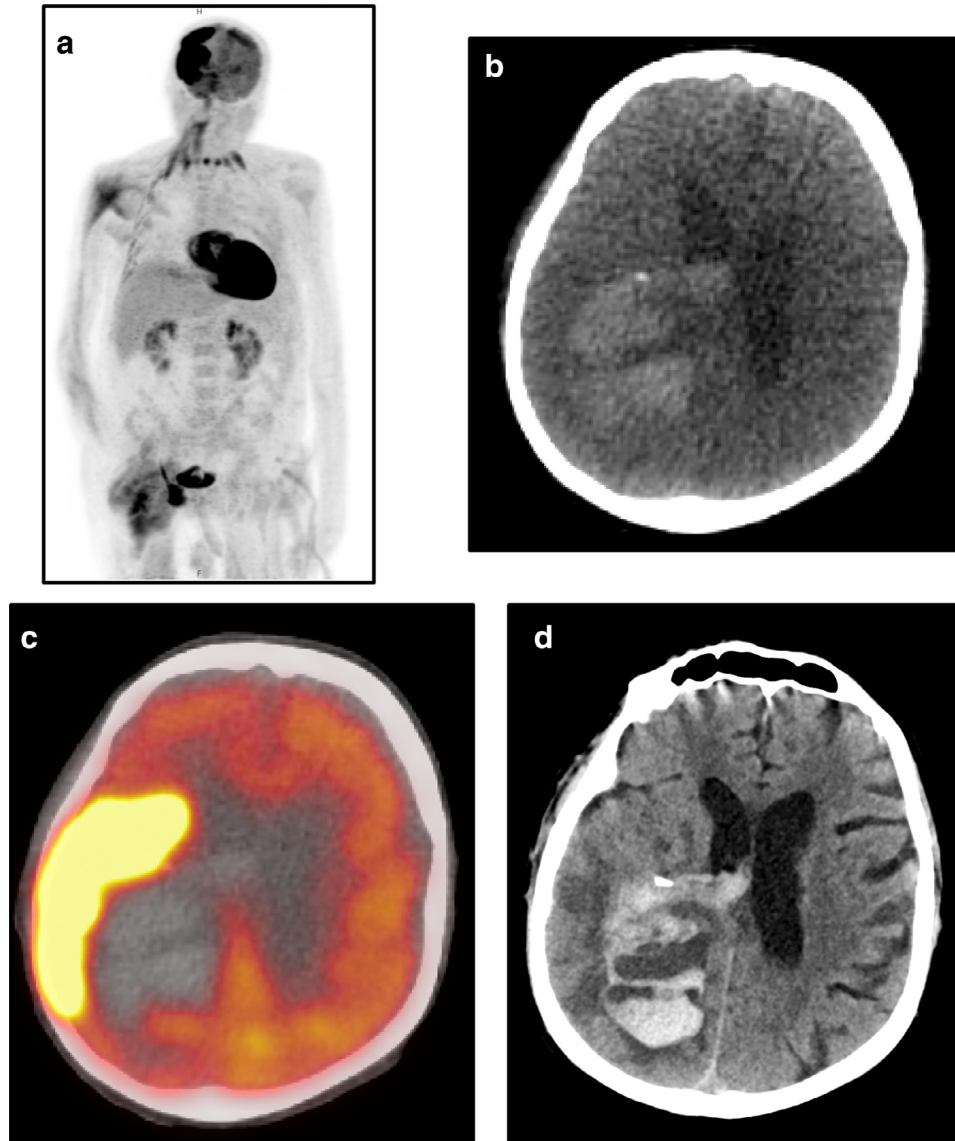


Fig. 3 – A 64-year-old asymptomatic male presented with acute hemorrhagic stroke on a restaging oncologic ^{18}F -FDG PET/CT. Marked increase right cerebral FDG activity is visualized on the (a) MIP image. (b) Corresponding unenhanced low-dose fusion CT axial image of the head demonstrates a right hemispheric parenchymal hemorrhage with extension into the right lateral ventricle. (c) The corresponding fused PET/CT axial image demonstrates marked FDG activity (SUV_{max} 15.5) in the cerebral parenchyma surrounding the hemorrhage. (d) Short-term follow-up diagnostic head CT demonstrates a stable intraparenchymal hemorrhage.

repair [13]. These mechanisms may explain the uptake we observed in the basal ganglia stroke.

^{68}Ga -DOTATATE PET is primarily used for neuroendocrine tumor assessment and works by binding to somatostatin receptors (SSTRs), with specifically high affinity for SSTR type 2 (SSTR₂). The mechanism for ^{68}Ga -DOTATATE uptake in ischemia is not known; however, Vallee et al suggested that uptake may be within receptors on macrophages from the inflammatory response in addition to possible neuronal receptor activation under ischemic conditions [14]. Moreover, several studies detected SSTR₂ expression in human macrophages [15,16]; however, Tarkin et al demonstrated high levels of SSTR₂ expression specifically in activated

proinflammatory M1 macrophages [15–17]. They demonstrated marked ^{68}Ga -DOTATATE activity in the coronary arteries of the patients with atherosclerotic plaques, correlating with macrophage activity [17,18]. Strong correlation of carotid SSTR₂ mRNA level with in vivo ^{68}Ga -DOTATATE PET imaging findings has also been demonstrated [17]. Specifically, ^{68}Ga -DOTATATE correctly differentiated culprit carotid arteries from nonculprit carotid arteries in patients with transient ischemic attack or stroke [17].

^{18}F -FDG uptake has more commonly been evaluated in the setting of ischemic stroke than hemorrhagic stroke [19]. However, a few studies have looked at ^{18}F -FDG uptake in hemorrhagic stroke. Zazulia et al found increased ^{18}F -FDG uptake in

perihematomal regions in the acute period (2–4 days) of intracerebral hemorrhage in 6 out of 13 patients [9]. However, they did not find any difference in the uptake during the sub-acute period (5–8 days) compared to baseline. Lin et al demonstrated that ^{18}F -FDG uptake decreases in perihematomal tissues within 5 days after intracerebral hemorrhage in cat models [9]. Neither of these studies evaluated the chronic phase of stroke. The markedly increased ^{18}F -FDG-uptake in the perihematomal regions of our patient suggests a more acute process, however, an MRI was not available for confirmation.

Although not illustrated in our cases, some investigators have proposed the use of ^{18}F -FDG in evaluation of viable brain tissue in the setting of ischemic stroke [19–21]. Several studies on animals demonstrated a reduced ^{18}F -FDG uptake in the presumed ischemic core regions and, while results are less consistent, transient increase has also been observed in the peri-ischemic “penumbra” region [19]. Characterization of the penumbra size helps guide clinical management in the decision to attempt revascularization. Proposed explanations of the underlying pathophysiology include activation of GLUTs, activation of hexokinase, and neuroinflammation [19].

Dedicated use of PET in the setting of stroke has several limitations that impede dedicated use, including access to radiopharmaceuticals, long uptake times, and lack of standardized protocols. However, this does not diminish the importance of identifying and understanding key characteristics that may be visualized in incidentally observed strokes. As new tracers are approved and become more commonly used in clinical practice, we must continue to identify key characteristics of ubiquitous pathology, including stroke.

Conclusion

Despite the primary role of PET in oncology, incidental strokes are not infrequently detected. Our cases demonstrate abnormally-increased uptake in both ischemic and hemorrhagic strokes using 3 different radiotracers. More work is required to understand the mechanism behind these phenomena; however, we have presented prominent theories for underlying mechanisms, and familiarity with the spectrum of stroke appearances on PET is vital for optimal patient care.

REFERENCES

- [1] Kochanek KD, Murphy SL, Xu J, Arias E. Mortality in the United States, 2013. NCHS Data Brief 178 2014:1–8 <https://www.cdc.gov/nchs/products/citations.htm>.
- [2] Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44(7):2064–89.
- [3] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation* 2016;133(4):e38–360.
- [4] Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. *Lancet* 2007;369(9558):293–8.
- [5] Read SJ, Hirano T, Abbott DF, Sachinidis JJ, Tochon-Danguy HJ, Chan JG, et al. Identifying hypoxic tissue after acute ischemic stroke using PET and ^{18}F -fluoromisonidazole. *Neurology* 1998;51(6):1617–21.
- [6] Baron JC. Mapping the ischaemic penumbra with PET: implications for acute stroke treatment. *Cerebrovasc Dis* 1999;9(4):193–201.
- [7] Baron JC. Perfusion thresholds in human cerebral ischemia: historical perspective and therapeutic implications. *Cerebrovasc Dis* 2001;11 Suppl 1:2–8.
- [8] Lin X, Tang Y, Sun B, Hou Z, Meng H, Li Z, et al. Cerebral glucose metabolism: influence on perihematomal edema formation after intracerebral hemorrhage in cat models. *Acta Radiol* 2010;51(5):549–54.
- [9] Zazulia AR, Videen TO, Powers WJ. Transient focal increase in perihematomal glucose metabolism after acute human intracerebral hemorrhage. *Stroke* 2009;40(5):1638–43.
- [10] Castellucci P, Fuccio C, Rubello D, Schiavina R, Santi I, Nanni C, et al. Is there a role for ^{11}C -choline PET/CT in the early detection of metastatic disease in surgically treated prostate cancer patients with a mild PSA increase <1.5 ng/ml? *Eur J Nucl Med Mol Imaging* 2011;38(1):55–63.
- [11] Glunde K, Shah T, Winnard PT Jr, Raman V, Takagi T, Vesuna F, et al. Hypoxia regulates choline kinase expression through hypoxia-inducible factor-1 alpha signaling in a human prostate cancer model. *Cancer Res* 2008;68(1):172–80.
- [12] Delaunay K, Le Jeune F, Garin E, Devillers A, Palard-Novello X. ^{18}F -choline uptake in acute ischemic stroke. *Clin Nucl Med* 2017;42(2):e121–2.
- [13] Scremin OU, Jenden DJ. Focal ischemia enhances choline output and decreases acetylcholine output from rat cerebral cortex. *Stroke* 1989;20(1):92–5.
- [14] Vallée É, Paquet N, Buteau JP, Turcotte É. ^{68}Ga -DOTATATE uptake in ischemic stroke. *Clin Nucl Med* 2018;43(1):46–7.
- [15] Armani C, Catalani E, Balbarini A, Bagnoli P, Cervia D. Expression, pharmacology, and functional role of somatostatin receptor subtypes 1 and 2 in human macrophages. *J Leukoc Biol* 2007;81(3):845–55.
- [16] Dalm VA, van Hagen PM, van Koetsveld PM, Achilefu S, Houtsmuller AB, Pols DH, et al. Expression of somatostatin, cortistatin, and somatostatin receptors in human monocytes, macrophages, and dendritic cells. *Am J Physiol Endocrinol Metab* 2003;285(2):E344–53.
- [17] Tarkin JM, Joshi FR, Evans NR, Chowdhury MM, Figg NL, Shah AV, et al. Detection of atherosclerotic inflammation by ^{68}Ga -DOTATATE PET compared to ^{18}F FDG PET imaging. *J Am Coll Cardiol* 2017;69(14):1774–91.
- [18] Rominger A, Saam T, Vogl E, Übleis C, la Fougère C, Förster S, et al. In vivo imaging of macrophage activity in the coronary arteries using ^{68}Ga -DOTATATE PET/CT: correlation with coronary calcium burden and risk factors. *J Nucl Med* 2010;51(2):193–7.
- [19] Bunevicius A, Yuan H, Lin W. The potential roles of ^{18}F -FDG-PET in management of acute stroke patients. *Biomed Res Int* 2013;2013:634598.
- [20] Sobrado M, Delgado M, Fernández-Valle E, García-García L, Torres M, Sánchez-Prieto J, et al. Longitudinal studies of ischemic penumbra by using ^{18}F -FDG PET and MRI techniques in permanent and transient focal cerebral ischemia in rats. *Neuroimage* 2011;57(1):45–54.
- [21] Walberer M, Backes H, Rueger MA, Neumaier B, Endepols H, Hoehn M, et al. Potential of early ^{18}F -2-fluoro-2-deoxy-D-glucose positron emission tomography for identifying hypoperfusion and predicting fate of tissue in a rat embolic stroke model. *Stroke* 2012;43(1):193–8.