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Diagnostic imaging of brain tumors in children with *O*-(2-^{18}F-Fluoroethyl)-L-Tyrosine positron emission tomography

Diagnostyczne obrazowanie guzów mózgu u dzieci przy pomocy pozytonowej emisyjnej tomografii z zastosowaniem znakowanej ^{18}F-tyrozyny

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Słowa kluczowe

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Summary

Introduction. Imaging plays a central role in the diagnosis of brain tumors.

Aim. The aim of this study was to evaluate the value of positron emission tomography (PET) imaging based on the use of *O*-(2-^{18}F-Fluoroethyl)-L-Tyrosine (^{18}F-FET) radiotracer in patients with brain tumors.

Material and methods. Thirty four FET-PET scans were performed in 22 patients (median age 10.3 years; range 3.0-17.7 years) with the diagnosis of brain tumor based on previously performed MRI scans. The focal acquisition of radiotracer and the SUV (standard uptake value) dynamics (change of uptake between 10 and 60 min after radiotracer injection) were measured. FET-PET uptake results were referred to histological diagnosis and/or tumor location. Some patients had repeated FET-PET scan in order to evaluate the treatment response.

Results. Increased FET uptake representative for malignant brain tumor was observed in 86% of patients. No FET uptake was observed in three patients. Based on the kinetic analysis of FET uptake we assessed the malignancy degree of suspected tumors finding compliance in 5 of 6 children with confirmed histological diagnosis of gliomas (compliance of 100% in low-grade gliomas, 66.7% in high-grade gliomas). The kinetics of radiotracer uptake was correlated with the clinical course in four children with brain stem tumors without histological confirmation.

Conclusions. These preliminary results indicate that FET-PET is a potentially effective method to identify malignant brain lesions, to monitor the disease course and predict the malignancy degree of lesions with unknown histology, based on kinetic analysis of FET uptake. Further studies are warranted.

Streszczenie

Wstęp. Diagnostyka obrazowa odgrywa zasadniczą rolę w diagnozowaniu nowotworów ośrodkowego układu nerwowego.

Cel pracy. Celem badania była ocena przydatności diagnostycznej badania PET-CT z użyciem znakowanej tyrozyny (^{18}F-FET) u pacjentów z guzami ośrodkowego układu nerwowego (OUN).

Materiał i metody. Wykonano łącznie 34 badania FET-PET u 22 chorych (mediana wieku 10,3 roku; zakres 3,0-17,7 roku) ze stwierdzoną w badaniu MRI obecnością guza w obrębie struktur OUN. Oceniano stopień (ang. *standard uptake value* – SUV) oraz dynamikę wychwytu znakowanej tyrozyny (zmiany SUV pomiędzy 10 a 60 minutą badania) w ogniskach podejrzewanych o charakter rozrostowy. Wyniki zostały odniesione do rozpoznania histopatologicznego i/lub lokalizacji guza. U części chorych powtórne badanie FET-PET służyło do oceny odpowiedzi na leczenie.

Wyniki. Wychwyt znacznika przemawiający za obecnością procesu rozrostowego stwierdzono u 86% chorych. U 3 pacjentów zmiany ogniskowe w obrębie OUN nie wykazywały wychwytu tyrozyny. U dzieci z potwierdzonymi glejakami na podstawie dynamiki wychwytu znacznika oszacowano stopień złośliwości guza, obserwując w 5 przypadkach na 6 zgodność z oceną histologiczną (100% w przypadku LGG, 66,7% w HGG). W guzach pnia mózgu bez weryfikacji histologicznej (4 pacjentów) obserwowana dynamika zmian w badaniu FET-PET korelowała z przebiegiem klinicznym.

Wnioski. Wstępna analiza wyników FET-PET wskazuje na dużą przydatność tego badania w diagnostyce obrazowej guzów OUN, monitorowaniu przebiegu choroby oraz prognozowaniu stopnia złośliwości w przypadku guzów niezweryfikowanych histopatologicznie.

INTRODUCTION

Imaging plays a central role in the diagnosis of brain tumors. Non-invasive, high-resolution techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT) scans are nowadays routinely used in diagnostics of this type of malignancy. MRI has evolved as the most important diagnostic tool for assessing brain neoplasm due to its excellent soft tissue contrast and multiplanar reconstruction capabilities (1). Although morphologic assessment by MRI is precise, it lacks specificity and does not allow for easy determination of tumor activity and metabolism.

Positron emission tomography (PET), a metabolic imaging modality widely used in systemic cancer in general oncology, may be a valuable tool for obtaining additional data and for better treatment of patients with glioma. Molecular imaging with ^{18}F-fluorodeoxyglucose (FDG) PET allows information on tumor metabolism to be gained, identifying zones of highest activity and determining the extension of increased growth activity. PET with FDG may be useful in estimating tumor grade and prognosis of gliomas, but the delineation of the tumor extent is difficult because of high glucose metabolism in the cerebral cortex (2). However, PET with FDG is unreliable at predicting the neoplasmatic nature of a lesion, because of unspecific uptake in inflammation and in relatively benign tumors and high normal brain uptake. Thus, in contrast to MRI, metabolic imaging with PET has gained only a limited role in the diagnostic evaluation of gliomas.

O-(2-^{18}F-Fluoroethyl)-L-Tyrosine (^{18}F-FET) is a new PET tracer that fulfills all requirements for routine clinical application, similar to the widely used ^{18}F-FDG (3). Although this amino acid is not incorporated into proteins, uptake by tumor cells is stereospecific and mediated by amino acid transporters (4). The initial results are promising and indicate that FET-PET is a valuable and applicable tool for the imaging of high-grade glioma (5). Uptake of radiolabeled amino acids is increased in approximately two thirds of low-grade glioma, and a prognostic role for amino acid PET in low-grade glioma has been proposed (6).

AIM

The objective of the study was to evaluate the usefulness of positron emission tomography (PET) using *O*-(2-^{18}F-Fluoroethyl)-L-Tyrosine (^{18}F-FET) in children with brain tumors.

MATERIAL AND METHODS

Patients

Thirty four FET-PET scans were performed in 22 patients (median age 10.3 years; range 3.0-17.7 years) with the diagnosis of brain tumor based on previously performed MRI scans. The focal acquisition of radiotracer and the uptake dynamics (change of uptake between 10 and 60 min after injection) were measured. FET-PET uptake results were referred to histological diagnosis and/or tumor location. Some patients had repeated FET-PET scan in order to evaluate the treatment response.

FET-PET

O-(2-^{18}F-Fluoroethyl)-L-Tyrosine (FET) was synthesized in our laboratory using R&D Synchrom module (Raytest) in the two-step method. Synthesis of ^{18}F-FET was accomplished in about 50 min with an overall radiochemical yield of 20%. Radiochemical purity was controlled by HPLC analysis.

The patient was fasted for at least six hours before scanning PET/CT to keep the same imagining conditions. Imaging was performed on whole-body high-resolution PET/CT scanners: Biograph 6 and Biograph mCT 128. Since FET accumulates in tumor tissue and normal brain tissue within 10-15 minutes after injection and remains relatively stable thereafter PET images were acquired at two time points: 10 and 60 minutes after intravenous injection of 350 ± 20 MBq FET.

^{18}F-FET uptake in the tissue was expressed as standardized uptake value (SUV) by dividing the radioactivity (Bq/mL) in the tissue by the radioactivity injected per body weight.

Diagnosis of brain tumors

Diagnostics of brain tumors in children included MRI, FET-PET, and tumor biopsy, if surgical intervention was possible. The results of histology, wherever possible, was regarded as a gold standard in analysis.

In the analysis of the discriminative value of ^{18}F-FET-PET imaging parameters in patients with newly diagnosed cerebral lesions suspicious for brain tumors, kinetics of ^{18}F-FET-PET was evaluated (7, 8). High-grade gliomas (HGG) are characterized by an

early peak of the time-activity curve at 10-15 minutes after tracer injection, followed by a decrease of ^{18}F-FET uptake. In contrast, slightly and steadily increasing time activity curves frequently suggest low-grade gliomas (LGG).

RESULTS

In 13 patients brain malignancy was biopsy-confirmed with histopathology examination, while in 8 children microscopic verification was not possible (4 brain stem tumors, 1 disseminated brain tumor, 1 opthic pathway glioma, 2 others) (tab. 1).

Increased FET uptake representative for malignant brain tumor was observed in 86% of patients. No FET uptake was observed in three patients. Basing on the kinetic analysis of FET uptake we assessed the malignancy degree of suspected tumors finding compliance in 5 of 6 children with confirmed histological diagnosis of gliomas (compliance of 100% in low-grade gliomas, 66.7% in high-grade gliomas). The kinetics of tracer uptake was correlated with the clinical course of four children with brain stem tumors without histological confirmation.

DISCUSSION

This is the first study in Poland with the use of FET-PET in diagnostics of brain tumors. Our study is unique as it was carried out in pediatric group. Our results suggest that the combined use of MRI and FET-PET is superior to that of MRI alone for the non-invasive distinction of tumor tissue and peritumoral brain tissue in children with brain tumors. Results of FET-PET imaging well corresponded with biopsy verification.

A meta-analysis of thirteen studies including 462 mainly adult patients, showed that FET-PET demonstrated excellent performance for diagnosing primary brain

Table 1. Patient characteristics and FET-PET results.

No	Histological diagnosis	Tumor location	Age (years)	SUV_{60} or SUV_{10}/SUV_{60}	PET conclusion/the uptake dynamics
1	Xanthoastrocytoma	brain stem	4.7	2.3	neoplasmatic tumor
2	Pilocytic astrocytoma	frontal lobe	5.3	1.9/2.2	LGG
3	Low-grade glioma	quadrigeminal body	5.6	1.8/2.6	LGG
4	Anaplastic oligoastrocytoma	IVth ventricle	11.6	2.5/2.9	LGG
5	Glioblastoma	parietal lobe	17.7	1st PET: 4.5/2.9 2nd PET: 6.5/5.0 3rd PET: 7.9/5.1	HGG
6	Glioblastoma	temporal lobe	17.7	1st PET: 4.6/3.0 2nd PET: no uptake	HGG after treatment response
7	PNET	brain stem	3	1st PET: no uptake 2nd PET: no uptake 3rd PET: no uptake	not evaluable
8	–	brain stem	3.6	4.9	neoplasmatic tumor
9	–	brain stem	5	1st PET: 3.29/3.07 2nd PET: 1.4/2.1	uptake like in HGG uptake like in LGG (after treatment response)
10	–	brain stem	7.4	2.3/2.2	uptake like in HGG
11	–	brain stem	9.4	1st PET: 2.2/2.5 2nd PET: 6.2/5.2	uptake like in LGG like in HGG (progression)
12	–	disseminated in supratentorial area	3.6	1st PET: 4.0/3.6 2nd PET: 3.6/2.7	uptake like in HGG uptake like in HGG
13	–	optic pathway	4.7	1st PET: 1.8 2nd PET: 1.8 3rd PET: 2.5/1.8	neoplasmatic tumor neoplasmatic tumor uptake like in HGG
14	Anaplastic ependymoma	supratentorial	3.7	1st PET: 1.5 2nd PET: 1.9	probable neoplasmatic tumor neoplasmatic tumor
15	Retinoblastoma	suprasellar	8.3	2.4	tumor uptake not to estimation because of high uptake of the background
16	Ganglioglioma	cerebellum	12.1	1st PET: 2.4 2nd PET: 1.4/2.1	neoplasmatic tumor uptake like in LGG
17	Medulloblastoma	cerebellum	13.3	3.3/4.1	uptake like in LGG
18	Malignant tumor following radiotherapy	right hemisphere	14.5	3.9/4.4	uptake like in LGG
19	Pineoblastoma	frontal lobes	15.9	2.5/1.8	uptake like in HGG
20	Germinoma	suprasellar	16.2	3.4/2.8	uptake like in HGG
21	- [1]	frontal lobe	11.1	no uptake	not evaluable
22	- [2]	pineal body	13.5	no uptake	not evaluable

PNET – primitive neuroectodermal tumor, LGG – low-grade glioma, HGG – high-grade glioma, [1]- – probable DNT (dysembryoplastic neuroepithelial tumor) based on MRI imaging, [2]- – probable cyst of the pineal body, based on MRI imaging

tumors (9). This meta-analysis indicated also that the best diagnostic value for differentiating primary brain tumors from nontumoral lesions had a mean tumor-to-background ratio (TBR) threshold of at least 1.6 and a maximum TBR of at least 2.1.

In the retrospective study by Jansen et al., the authors evaluated the diagnostic value of kinetic FET-PET in 127 patients with newly diagnosed MRI-suspected LGG prior to histopathological assessment (7). They found in the patients with MRI-suspected LGG that kinetic analysis of FET uptake enabled the detection HGG with high accuracy (sensitivity 95%, specificity 72%, positive predictive value 74%, and negative predictive value 95%).

FET exhibits no uptake in inflammatory cells and in inflammatory lymph nodes, promising a higher specificity for the detection of tumor cells (3). It should be noted, that the specificity of FET-PET for neoplastic lesions may be affected by possible tracer uptake in the area of benign processes (for example, cerebral hematoma, ischemia, and inflammatory processes) (8, 10, 11).

The tracer administration and process of imaging was safe for all patients. This is confirmed by large experience published already. No side effects have been reported to date with the use of these tracers after several thousand studies have been performed worldwide (8).

These results indicate that FET-PET is a potentially effective method to identify malignant brain lesions, and to monitor the disease course. Based on kinetic analysis of FET uptake, this imaging can predict the malignancy degree of lesions with unknown histology.

CONCLUSIONS

In conclusion, compared with morphological MRI, FET-PET adds valuable information to the data acquired in cases of newly diagnosed cerebral lesions suspicious for brain tumors in children. However, a histological biopsy-based evaluation of suspicious brain lesions remains necessary in most circumstances.

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