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F-Dopa as an Amino Acid Tracer to Detect Brain Tumors

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A 57-yr-old woman suffering from light movement disorder of the left arm and hand was referred for ^{18}F-Dopa PET. The PET study not only proved asymmetrically reduced dopamine uptake in the putamen (influx constant K_i right 0.0064/min, left 0.0086) but also revealed pathologically increased ^{18}F-Dopa accumulation in the right frontal lobe. Further PET examinations demonstrated increased ^{11}C-methionine uptake and low glucose metabolism in this right frontal region. MRI and ^{1}H-MRSI showed a heterogeneous lesion with reduced N-acetyl-aspartate and increased choline and lactate, suggesting a mixed, low-grade glioma. In ^{15}O-water studies, during intentional movements of one hand the respective motor areas were identified, indicating asymmetries due to the mass occupying lesion. The tumor could be removed in open surgery, thus sparing the motor areas; a mild postoperative motor deficit resolved to the presurgical state. Histology confirmed the diagnosis of a grade 2 oligo-astrocytoma. This case impressively demonstrates that ^{18}F-Dopa can be used as an amino acid tracer for brain tumor detection in addition to its established application to assess aromatic acid decarboxylase activity.

Key Words: PET, fluorine-18-Dopa; carbon-11-methionine; fluorodeoxyglucose; oxygen-15-water; brain tumor; Parkinson's disease; magnetic resonance spectroscopy

J Nucl Med 1996; 37:1180–1182

Received Jul. 5, 1995; revision accepted Dec. 13, 1995.

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PET imaging with ^{18}Fluoro-deoxy-phenylalanine (F-Dopa) is an established method to assess dopamine synthesis (aromatic acid decarboxylase activity) in the human brain and therefore is a useful diagnostic procedure in the clinical evaluation of patients with extrapyramidal symptoms, especially hemiparkinson syndrome (review in (*1*)). Since the tracer is a large neutral amino acid, it shows the kinetics of this group of amino acids and is transported and accumulated into brain tumors at a much higher rate than into normal brain tissue (review in (*2*)). The twofold potential of this tracer is demonstrated in a patient suffering from hemiparkinson symptoms, in whom a low-grade glioma was detected in addition to asymmetric F-Dopa turnover in the basal ganglia.

CASE REPORT

A 57-yr-old woman without a familial history of any neurologic disease and without previous neurologic symptoms was referred to the PET center for an F-Dopa study in the evaluation of a light movement disorder and stiffness of the left arm and hand. Physical examination revealed slight hypo-/brady kinesia and rigidity of the left upper extremity pronounced for finger movements, whereas no other focal signs were found. All other routine tests, including blood counts, blood chemistry and sedimentation rate, as well as electrocardiogram, chest radiograph and doppler sonography/ultrasound imaging of cervical and large intracranial arteries were normal. Electroencephalography showed regular alpha-activity without focal abnormalities.

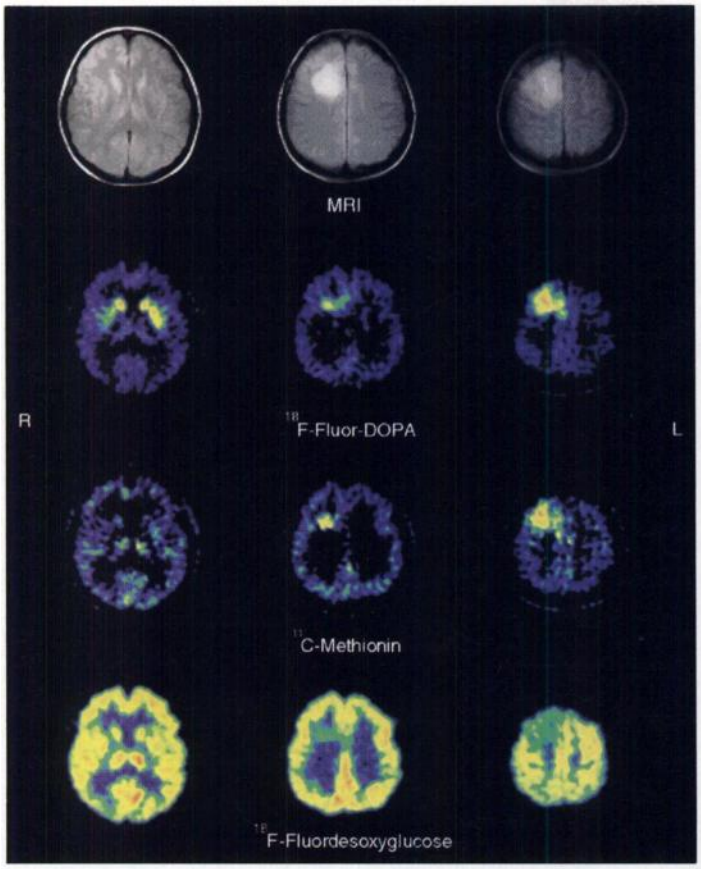

FIGURE 1. Coregistered transaxial brain slices through the basal ganglia, the centrum semiovale and below vertex in the patient with hemiparkinsonism on the left and a right frontal oligo-astrocytoma grade 2. The tumor is clearly seen on magnetic resonance tomography (proton density MRT). With ^{18}F-Dopa PET, the asymmetric reduction of dopamine uptake in the right putamen and the increased ^{18}F-Dopa accumulation in the tumor is demonstrated. With ^{11}C-methionine PET, only the increased amino acid uptake in the tumor is shown. Glucose metabolism, measured by FDG-PET, is moderately diffusely reduced and the tumor is hypometabolic compared to the corresponding contralateral region.

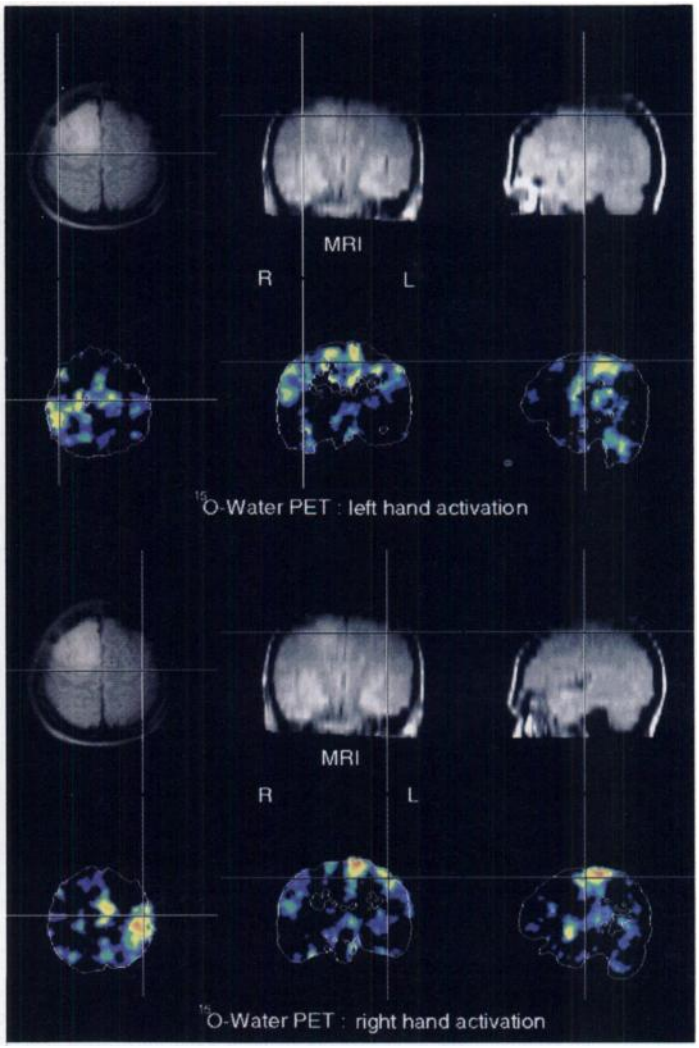

FIGURE 2. Transaxial and reconstructed frontal and sagittal MRI slices matched to the differential images subtracting rest from activated perfusion PET studies. Left hand movement shows bilateral activation of supplementary motor area and less increase in primary center, which is slightly shifted posteriorly, than movement of right hand, by which strong activation of the primary and the left supplementary areas is obtained.

PET studies were performed using a tomograph that covered the whole brain within 47 slices at a spatial resolution of 6 mm transaxial and 5 mm axial (*3*). For the first examination aimed at the assessment of presynaptic dopaminergic nerve terminals in the basal ganglia 370 MBq (= 10 mCi) ^{18}F-Dopa (specific activity 20–40 MBq/μmole) were injected intravenously after a light breakfast, 4 hr fasting and 100 mg carbidopa premedication. A dynamic series of 21 frames was acquired over 90 min after tracer injection and specific ^{18}F-dopamine accumulation into striatal tissue (influx constant K_i) was calculated from all slices containing basal ganglia. In the images obtained 15 min after tracer injection, dopamine concentration in the right basal ganglia, especially the putamen, was significantly decreased (Fig. 1). The influx constant (K_i) for dopamine accumulation was reduced to 0.0064/min in the right and to 0.0086/min in the left putamen (values in normal controls were above 0.012/min) and not significantly affected in the caudate (right: 0.0113; left: 0.0135/min). Additionally, a focus with intense activity of the tracer was found in the right frontal lobe extending from the prefrontal cortex far into the white matter and close to the midline but clearly separated from the basal ganglia and the corpus callosum (Fig. 1). CT and MRI performed for further diagnostic clarification revealed a heterogeneous lesion suggestive of a mixed, low-grade glioma without remarkable edema (Fig. 1).

This diagnosis was supported by an increased concentration of choline and lactate and a reduced concentration of N-acetyl-aspartate in the area of the tumor as shown by proton magnetic resonance spectroscopic imaging (^{1}H-MRSI at 1.5 T). To further evaluate the biologic activity of the lesion and its effect on the precentral motor region, additional PET studies were performed. After i.v. injection of 740 MBq (20 mCi) ^{11}C-methyl-methionine, intense tracer uptake was found in a region identical to that in the F-Dopa images, but bilateral low uptake and no differences were observed in the basal ganglia (Fig. 1). After injection of 370 MBq (10 mCi) ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG), the area with increased amino acid uptake was represented as a hypometabolic region when compared to the corresponding contralateral area (Fig. 1). Glucose metabolism was comparatively low in all other brain regions, including the caudate and putamen (CMR_{glc} global 26.4, caudate 32.7 and 33.0, putamen 37.0 and 36.0 μmole/100 g/min, normal range: global 36.4 $\pm$ 4.50, putamen 39.6 $\pm$ 6.9, caudate 38.8 $\pm$ 5.7 μmole/100 g/min).

In perfusion studies performed with repeated injections of 10 mCi ^{15}O-water at rest and during unilateral hand movements (two sequences of: rest, right hand activation, left hand activation, were summed up and differences between activated and resting states were calculated) hyper- and hypoperfused areas were found in the lesion. The primary motor center detected by movement of the left hand was slightly shifted posteriorly and less activated than the contralateral motor center activated by movement of the right hand (Fig. 2). While right hand movement activated the supplementary

motor area on the left, a bilateral activation of the supplementary motor areas was seen with left hand movement (Fig. 2). This indicates an effect of the tumor located in close vicinity but also the increased effort necessary for voluntary movements in asymmetric extrapyramidal disorders. The patient underwent surgery with the precaution to spare the areas activated during the motor task, and a $3 \times 4 \times 4$ cm^3 tumor was removed. After surgery, the patient suffered a moderate accentuation of the motoric impairment of the left arm and hand, which recovered within 2 wk to the preoperative state. Histological examination classified the tumor as an oligoastrocytoma grade 2.

DISCUSSION

Decreased dopamine uptake, especially in the putamen, is suggestive of a primary degeneration of dopaminergic nigrostriatal neurons typical for idiopathic Parkinson's disease (*4*). The additional detection of a frontal glioma, however, raises the question, if the extrapyramidal syndrome could be secondary to the frontal lesion. In the prefrontal cortex origins, one of the main afferent pathways to the basal ganglia containing fibers predominantly terminating in the caudate (*5*), while the putamen receives topographic projections from the primary motor cortex, premotor areas and the somatosensory cortex, forming the anatomical basis of two different functional basal ganglia-thalamo-cortical circuits, an association and a motor loop (*6*). Since the asymmetric reduction of dopamine activity in this patient is most prominent in the putamen (where glucose metabolism is bilaterally depressed in relation to the global metabolic reduction) and shows the profile of more severe reduction in the posterior section typical for idiopathic Parkinson's disease (*7*), it must be concluded that two independent disorders are present in this patient: degenerative Parkinson's disease with asymmetric distribution clinically manifested on the left side and a low-grade frontal glioma not yet causing focal neurological deficits. Both pathologies were detected by the F-Dopa PET study.

Clinical evaluation of brain tumors by nuclear medicine—which in all instances must be based on modalities for imaging morphology as x-ray CT and MRI—usually requires two tracers, one for grading of neoplastic activity (which is related to prognosis), the other for detection of tumorous tissue in contrast to normal brain. FDG is the clinically established marker of biological activity: glucose uptake and turnover is significantly different between low-grade and high-grade gliomas (*8–10*). This is apparently due to an increase of FDG turnover by hexokinase reaction (*11*) and probably also to higher cellular density (*12*). Even in gliomas classified histologically as belonging to the same grade, differences in survival were significantly correlated to differences in metabolic activity of the tumor relative to contralateral brain (*13–15*). On the other hand, amino acids, such as ^{11}C-methionine and ^{18}F-tyrosine, are incorporated not only in high-grade gliomas but exhibit intense uptake also in most low-grade gliomas with comparably low glucose turnover. Therefore, the amino acid tracers are mainly utilized to detect brain tumors and recurrences and to distinguish tumorous from normal brain tissue (*16–20*). When applied together, the two tracers yield a reliable assessment of a tumor's proliferative activity and extension. Especially when gliomas are located in the vicinity of or within a functional center, activation studies during performance of pertinent tasks may help in planning therapeutic interventions to spare important functional centers.

F-Dopa PET is still the only method to demonstrate the basic disturbance in Parkinson's disease (*21,22*). The examination images semiquantitatively presynaptic dopaminergic terminals and is of diagnostic value in early and unilaterally predominant disease (*23,24*). Semiquantitative analysis of dopamine concentration also enables monitoring the course of the disease and assessing the progression of neuronal degeneration (*25*). As shown in our patient, in addition to its established application as a selective marker of aromatic acid decarboxylation, F-Dopa can also be used as a more general amino acid tracer, since the unmetabolized form is transported actively into tumor tissue. As demonstrated earlier with ^{18}F-2-fluoro-L-tyrosine (*19*), the accumulation of large neutral amino acids in gliomas is mainly due to an activated transport process, whereas potential changes in protein synthesis are apparently less important for the measured tracer accumulation. Thus, F-Dopa may have potential as a tumor tracer, even though it is probably not incorporated into proteins. Due to the longer half-life and better detectability of the label, F-Dopa may even have an advantage over ^{11}C-methyl-methionine for imaging brain tumors.

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