# Peptide T and Glucose Metabolism in AIDS Dementia Complex

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AIDS dementia complex (ADC) is the most common presenting neurologic manifestation of human immunodeficiency virus (HIV)-1 infection. We report FDG-PET studies in a 39 yr-old man who had ADC and completed a 12-wk treatment protocol with 1.2 mg/day of intranasal peptide T, one before and one after 12 wk of treatment with peptide T. Peptide T is an octapeptide under investigation for treatment of ADC patients. Values of rCMRglc were converted to Z scores using the mean and standard deviation of values of rCMRglc in three HIV-seronegative matched controls, each of which was studied twice, at the beginning and end of a 12-wk interval. Thirty-five of 60 regions assayed showed Z scores with absolute values ≥3 (considered abnormal) in the baseline study. Regions with high absolute values of Z scores were located in subcortical areas and in the limbic system, and to a lesser degree in the frontal, temporal and parietal lobes. Thirty-four of these 35 regions showed remission (decrease in the absolute values of Z scores) after treatment. Only one region showed no improvement in the second study. Three regions with absolute values of Z scores <3 in the baseline study manifested Z scores with magnitudes ≥3 in the second study. These preliminary observations suggest that functional neuroimaging techniques provide a useful tool in the evaluation of the response to treatment in ADC patients.

**Key Words:** AIDS dementia; peptide T; glucose metabolism; brain imaging

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The most common presenting neurologic manifestation of human immunodeficiency virus (HIV)-1 infection is AIDS dementia complex (ADC). The major clinical features of ADC include lack of attention, mental slowing, reduced motor performance and incoordination (*1*). The pathology of ADC is described as a subacute subcortical encephalomyelitis, with compromise of the white matter and basal ganglia but with relative sparing of the cortex (*2,3*). The etiopathogenic mechanisms involved in the evolution of HIV infection in the brain are not yet clear. Several lines of evidence suggest that gp120, the HIV envelope protein, may produce the neurological impairment and dementia seen in AIDS patients (*4–6*). Peptide T, a threonine-rich octapeptide with an amino acid sequence similar to that of vasoactive intestinal peptide, blocks the binding of radiolabeled gp120 to the cell surface antigen CD4 (*7*). Treatment with peptide T has been shown to improve the neuropsychological performance in severely impaired ADC patients (*8,9*).

Regional cerebral metabolic rates for glucose (rCMRglc) can be measured using [$^{18}$F]fluorodeoxyglucose (FDG) and PET. The FDG-PET method (*10,11*) has provided useful insights into dementing disorders, such as Alzheimer's disease, Huntington's disease and multi-infarct dementia (*12–14*). In addition, patients with ADC have been examined previously using PET and FDG. Rottenberg et al. (*15*) reported relatively high rCMRglc in the basal ganglia at early stages of the disease as compared with controls. In addition, lower rCMRglc in the temporal cortex was reported (*16*), as was a higher value of an index of asymmetry in the prefrontal area in asymptomatic HIV-1 positive subjects (*17*) as compared with values in age-matched control subjects. Treatment with zidovudine reversed baseline focal abnormalities (where normalized rCMRglc was either unusually high or low) in two of four patients, and increased global glucose metabolism in the other two patients tested (*18*). We report here the results of FDG-PET studies on one patient who completed a 12-wk treatment protocol with peptide T.

## CASE REPORT

A 39-yr-old homosexual man diagnosed in 1988 with HIV infection was enrolled in a 1992 clinical trial of the efficacy of peptide T in the treatment of AIDS. The clinical trial was conducted at Sibley Hospital in Washington, D.C. At the time of admission into the clinical trial, the patient presented with clinical signs of ADC, which were confirmed by neuropsychological evaluation (Trailmaking, Repeat Battery, Grooved Pegboard and Stroop Color Test). Concurrent with ADC, the patient had a history of atypical tuberculosis of the gut, cytomegalovirus retinitis in the right eye, intermittent pancreatitis and alcoholism, although he denied having ingested alcohol for at least 2 mo before the first PET scan. The subject was intolerant to zidovudine, and at the time of enrollment into the study, his medications included rifampin, trimethoprim and sulfamethoxazole, acyclovir, ciprofloxacin, clofazimine, ethambutol, folic acid and multivitamin supplements. He self-administered 1.2 mg/day (in three divided doses) of intranasal peptide T for 12 wk. A MRI brain scan was obtained to verify the absence of abnormal brain morphology and to enhance accuracy of placement of regions of interest (ROIs) in the PET analysis. Approximately 8 wk after enrollment into the trial, the subject was hospitalized for sepsis, but peptide T treatment was not suspended. He received two PET studies, 12 wk apart, one before starting (8/28/92) and another after completing (12/4/92) the peptide T treatment. The patient died of complications of AIDS in July 1993.

Urine specimens and a breathalyzer test were collected prior to each study to test for the presence of illicit drugs and/or alcohol, respectively. The subject was allowed free access to cigarettes up to 6 hr before the PET study. No evidence of illicit drug use was found during the study.

The subject fasted for 4–6 hr before each FDG injection and during the radiotracer uptake and scanning periods. For 30 min before FDG injection, and extending throughout the radiotracer uptake period and PET scanning, he was given a Continuous

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Performance Task and wore earphones that presented constant white noise. The purpose of these procedures was to maintain a constant level of activation across sessions and to minimize potential effects of noises in the room. Fifteen simultaneous slices were acquired for 20 min beginning at 40 min after the FDG injection, using a PET tomograph with a resolution of ~6.5 mm FWHM.

The rCMRglc values were calculated using standard rate constants, a lumped constant of 0.42 and an operational equation (*19*). The resultant images were transferred to a computer and analyzed using a modified version of the IMAGE 1.55 program (*20*). Two independent raters measured rCMRglc in 60 ROIs which comprised a set of brain regions that were identified on the coregistered MRI scan. The global cerebral metabolic rate for glucose (CMRglc) was estimated by calculating the area-weighted average of all the values of rCMRglc.

The rCMRglc values were transformed to Z scores using the means and standard deviations of corresponding rCMRglc values from three age-matched homosexual HIV-seronegative males (40.5 ± 3.6 yr of age) who also participated in similar paired assays of FDG-PET scans 12 wk apart as follows:

$$\left(Z_{ROI_i} = \frac{(ROI_i - \bar{X}_{ROI_c})}{SD_{ROI_c}}\right),$$

where $ROI_i$ was the value of rCMRglc measured in the patient; $\bar{X}_{ROI_c}$ and $SD_{ROI_c}$ were the mean rCMRglc value and standard deviation, respectively, for the corresponding ROI in the control group. Z scores with absolute values ≥3 were considered abnormal.

## RESULTS

Baseline global CMRglc in the ADC subject (12.43 ± 3.00 mg/100 g/min) was 36% higher than mean global CMRglc in the control group (9.15 ± 1.45 mg/100 g/min). A 33% decrease in global CMRglc was observed between the first and second PET scans of the patient (8.33 ± 1.66 mg/100 g/min) (Fig. 1), whereas only a 7% decrease was observed in the second PET scan in the control group (8.55 ± 1.40 mg/100 g/min) (Fig. 2).

The rCMRglc values in the baseline study were higher than in the control group, with the exception of the left and right amygdala (46% and 18% lower, respectively), the right dorsal inferior frontal gyrus (2% lower) and the left precentral gyrus (18% lower). Changes in rCMRglc were heterogeneous. They ranged from an increase of 42% in the left amygdala (the only region that showed an increase in rCMRglc after treatment) to a decrease of 45% in the right putamen, which showed values of rCMRglc almost twice as high as the control group in the pretreatment study.

Analysis of the normalized data in the ADC subject revealed that 35 of 60 ROIs had Z scores with absolute values ≥3 in the baseline study (Table 1). Consistent with previous reports (*3,15*), abnormalities were located in subcortical structures (caudate nucleus, putamen, thalamus, pons), where rCMRglc was higher than in the control group (Figs. 1, 2). Abnormalities were also present in the limbic system, consistent with hippocampal cytotoxic effects of gp120 (*4–6,21–24*), and to a lesser degree in the temporal (*16*), frontal (*25*) and parietal lobes. Abnormalities in the subcortical structures, and the limbic and temporal cortices accounted for 66% of all regions showing Z scores ≥3.

Thirty-four of the 35 regions with absolute values of its Z scores that were ≥3 in the baseline study showed absolute values of Z scores <3 after treatment. The remaining region showed a reduction in magnitude and reversal of the sign of the Z score. Three regions with absolute values of Z scores <3 in the baseline study manifested Z scores that were ≥3 in the second study.

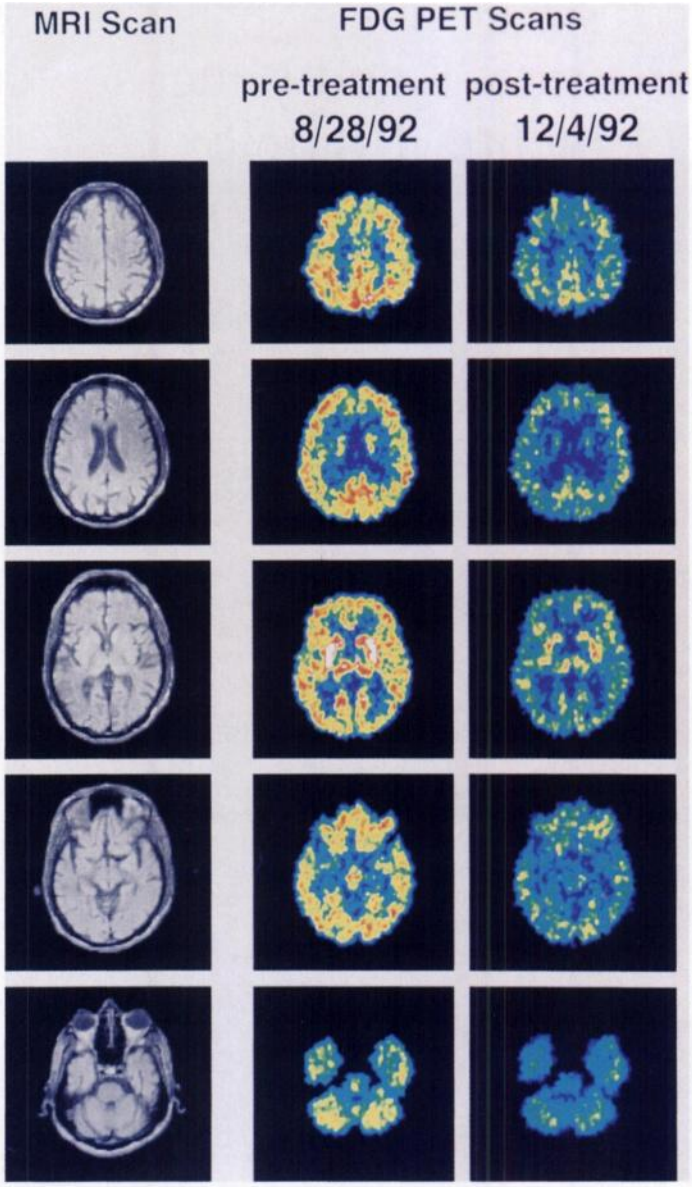


**FIGURE 1.** MRI and color-coded transforms of FDG-PET scans at five different levels of the brain of the ADC patient showing the baseline study and the study after a 12-wk treatment protocol with 1.2 mg/kg of intranasal peptide T.

## DISCUSSION

PET studies can provide helpful information about the neuroanatomical basis of the HIV infection, as well as staging and progression of the disease. The FDG method is a sensitive technique that can discriminate functional abnormalities undetectable by MRI scanning (*26*) and can be used to monitor the response to treatment (*18*), thereby optimizing the use of antiviral therapies.

The results of this report revealed a need for more research to elucidate the metabolic pattern characteristic of the progression of ADC, thus clarifying the interpretation of results from therapeutic trials. In this report, both cortical and subcortical structures showed a decrease in rCMRglc in a single patient re-tested 4 mo later (*15*). In the study by Brunetti et al. (*18*), two of four patients presented focal abnormalities in the baseline study. One of two patients showed reversal of the focal

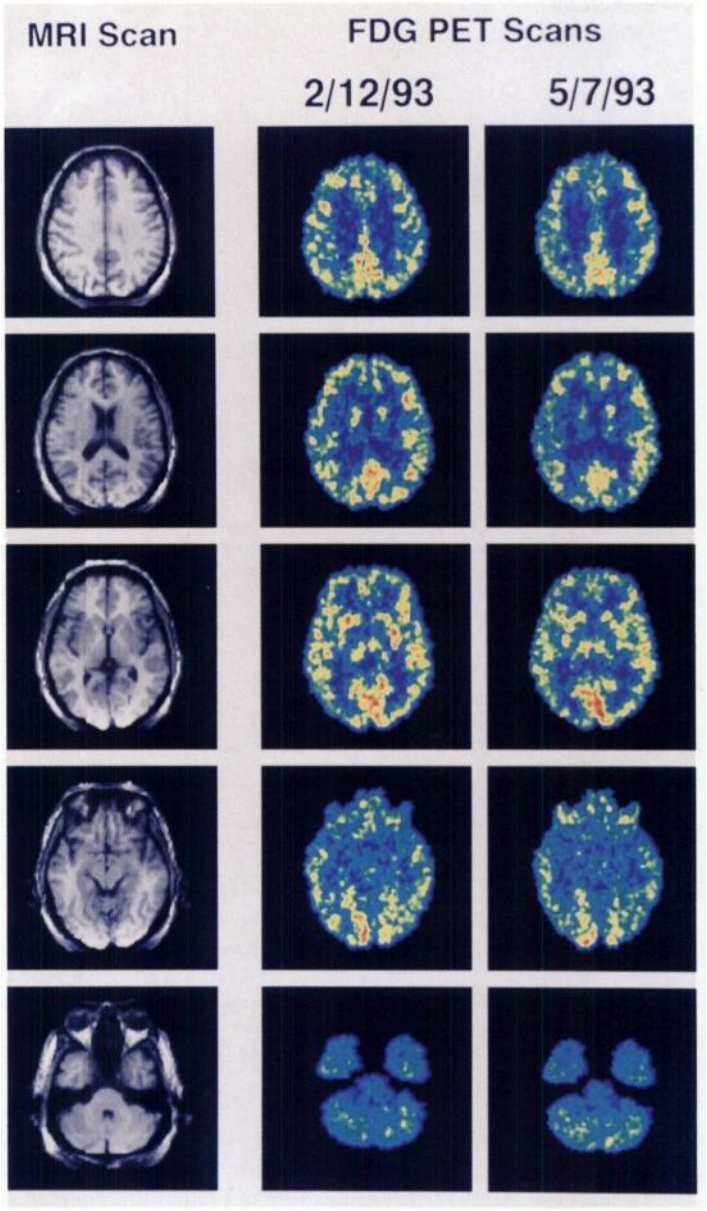


**FIGURE 2.** MRI and color-coded transforms of FDG-PET scans at five different levels of the brain of a representative control subject who participated in paired FDG-PET scans 12 wk apart.

abnormalities and a 35.1% increase in cortical CMRglc after treatment with zidovudine. The other patient also showed reversal of the focal abnormalities but cortical CMRglc decreased by 25.1% after treatment with zidovudine. The authors concluded that the remission of the focal abnormalities was consistent with the clinical improvement observed in the patient. The patient in the present report showed changes that resembled the results obtained in the latter patient treated with zidovudine, except that his baseline study showed CMRglc values that were 36% higher instead of 5% higher than the values in controls reported by Brunetti et al. (*18*).

Our results suggest that FDG-PET poses great potential in the assessment, follow-up and evaluation of treatment response in ADC patients and will be a useful tool in the characterization of the neurologic manifestations of the AIDS epidemic. Further studies to determine whether the focal abnormalities are related to neurologic impairment, by testing the hypothesis that the number and/or degree of abnormalities are correlated to scores on neurologic tests and/or to progression of the disease, are warranted.

**TABLE 1**
Z Scores* of rCMRglc in One Patient before and after Treatment with Peptide T

| | Pre-Peptide T | | Post-Peptide T | |
|---|---|---|---|---|
| | Left | Right | Left | Right |
| Dorso prefrontal lobe | | | | |
| Superior frontal gyrus | 1.07 | 2.50 | −2.36 | −1.19 |
| Middle frontal gyrus | 2.00 | 2.60 | −1.73 | −3.26§ |
| Inferior frontal gyrus | 5.63† | −0.62 | 0.18 | −4.17§ |
| Ventro prefrontal lobe | | | | |
| Superior frontal gyrus | 3.54† | 14.39† | −0.24 | 0.53 |
| Middle frontal gyrus | 2.09 | 2.71 | −2.85 | −0.76 |
| Inferior frontal gyrus | 4.08† | 3.40† | 0.44 | 0.71 |
| Parietal lobe | | | | |
| Superior parietal gyrus (dorsal) | 1.96 | 3.23† | 1.31 | 0.63 |
| Superior parietal gyrus (ventral) | 1.02 | 9.83† | −1.00 | −4.76‡ |
| Inferior parietal gyrus | 5.47† | 9.05† | 1.06 | −0.32 |
| Paracentral gyrus | 2.27 | 3.23† | 0.27 | −0.05 |
| Precuneus | 2.71 | 1.27 | 0.70 | −2.05 |
| Temporal lobe | | | | |
| Superior temporal gyrus | 4.24† | 2.67 | −1.46 | −2.35 |
| Middle temporal gyrus | 2.25 | 1.72 | 0.45 | 0.06 |
| Inferior temporal gyrus | 8.94† | 3.83† | 0.79 | 1.22 |
| Insula | 3.53† | 7.85† | −0.43 | 1.30 |
| Occipital lobe | | | | |
| Calcarine cortex | 0.81 | 0.16 | −0.84 | −0.64 |
| Lateral occipital gyrus | 4.94† | 1.78 | 0.89 | 0.10 |
| Cuneus | 5.02† | 1.40 | −2.72 | −7.52§ |
| Limbic system | | | | |
| Anterior cingulate gyrus | 5.88† | 3.42† | −2.33 | 0.57 |
| Posterior cingulate gyrus | 5.52† | 5.65† | 0.26 | 1.03 |
| Amygdala | −2.68 | −2.37 | −1.23 | −1.75 |
| Hippocampus | 4.95† | 18.29† | 1.29 | 0.03 |
| Gyrus rectus | 8.67† | 8.40† | 0.41 | 0.96 |
| Orbitofrontal cortex | 7.48† | 6.17† | 1.87 | 0.48 |
| Subcortical regions | | | | |
| Caudate nucleus | 3.34† | 5.66† | 0.69 | 1.17 |
| Putamen | 11.80† | 7.30† | 2.40 | 2.93 |
| Thalamus | 4.75† | 2.46 | 0.03 | 0.77 |
| Cerebellar cortex | 3.34† | 6.13† | −0.22 | −0.74 |
| | Midline | | Midline | |
| Pons | 14.59† | | −0.08 | |
| Cerebellar vermis | 2.62 | | −0.38 | |

*Z scores were calculated using the means and standard deviations of the corresponding rCMRglc values of the three HIV-seronegative control subjects.

†Absolute values of Z scores ≥3 were considered abnormal.

‡Region that showed reduction in magnitude and reversal of the sign of the Z score.

§Regions that manifested absolute values of Z scores ≥3 only in the second assay.

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## REFERENCES

1. Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. *Ann Neurol* 1986;19:517–524.
2. Navia BA, Cho ES, Petito CK, Price RW. The AIDS dementia complex. I. Neuropathology. *Ann Neurol* 1986;19:525–535.
3. Price RW, Brew B, Sidtis J. The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. *Science* 1988;239:586–592.
4. Hill JM, Ruff MR, Pert CB. AIDS as a neuropeptide disorder: Peptide T, VIP and the HIV receptor. *Psychopharmacol Bull* 1988;24:315–319.
5. Buzy JM, Brenneman DE, Siegal FP, Ruff MR, Pert CB. Cerebrospinal fluid from cognitively impaired patient with acquired immunodeficiency syndrome shows gp120-like neuronal killing in vitro. *Am J Med* 1989;87:361–362.
6. Pert CB, Smith CC, Ruff RM, Hill JM. AIDS and its dementia as a neuropeptide disorder: role of VIP receptor blockade by human immunodeficiency virus (HIV) envelope. *Ann Neurol* 1988;23:S71–S73.
7. Ruff MR, Martin BM, Ginns EI, Farrar WL, Pert CB. CD4 receptor binding peptides that block HIV infectivity cause human monocyte chemotaxis: relationship to vasoactive intestinal polypeptide. *FEBS Lett* 1987;211:17–22.
8. Bridge PT, Heseltine PNR, Parker ES, et al. Improvement in AIDS patients on peptide T. *Lancet* 1989;226–227.
9. Bridge PT, Heseltine PNR, Parker ES, et al. Results of extended peptide T administration in AIDS and ARC patients. *Psychopharmacol Bull* 1991;27:237–245.
10. Reivich M, Kuhl D, Wolf A, et al. The [$^{18}$F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res* 1979;44:127–137.
11. Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE. Tomographic measurement of local cerebral glucose metabolic rate in humans with [$^{18}$F]2-fluoro-2-deoxy-D-glucose. Validation of method. *Ann Neurol* 1979;6:371–388.
12. Horwitz B, Grady CL, Schlageter NL, Duara R, Rapoport SI. Intercorrelations of regional cerebral glucose metabolic rates in Alzheimer's disease. *Brain Res* 1987;407:294–306.
13. Kuhl DE, Metter EJ, Riege WH, Markham CH. Patterns of cerebral glucose utilization in Parkinson's disease and Huntington's disease. *Ann Neurol* 1984;15:S119–S125.
14. Kuhl DE, Metter EJ, Riege WH. Patterns of cerebral glucose utilization in depression, multiple infarct dementia and Alzheimer's disease. *Res Publ Assoc Res Nerv Ment Dis* 1985;63:211–226.
15. Rottenberg DA, Moeller JR, Strother SC, et al. The metabolic pathology of the AIDS dementia complex. *Ann Neurol* 1987;22:700–706.
16. van Gorp WG, Mandelkern MA, Gee M, Hinkin CH, et al. Cerebral metabolic dysfunction in AIDS: findings in a sample with and without dementia. *J Neuropsychiatry Clin Neurosci* 1992;4:280–287.
17. Pascal S, Resnick L, Barker WW, et al. Metabolic assymetries in asymptomatic HIV-1 seropositive subjects: relationship to disease onset and MRI findings. *J Nucl Med* 1991;32:1725–1729.
18. Brunetti A, Berg G, Di Chiro G, et al. Reversal of brain metabolic abnormalities following treatment of AIDS dementia complex with 3'-azido-2',3'-dideoxythymidine (AZT, zidovudine): a PET-FDG study. *J Nucl Med* 1989;30:581–590.
19. Huang SC, Phelps ME, Hoffman EJ, Sideris K, Selin CJ, Kuhl DE. Noninvasive determination of local cerebral metabolic rate of glucose in man. *Am J Physiol* 1980;238:E69–E82.
20. Rasband WS. *Image: image processing and analysis*. Rockville: National Institutes of Health, Research Services Branch; 1990.
21. Brenneman DE, Westbrook GL, Fitzgerald SP, et al. Neuronal cell killing by the envelope protein of HIV and its prevention by vasoactive intestinal peptide. *Nature* 1988;335:639–642.
22. Kimes AS, London ED, Szabo G, Raymon L, Tabakoff B. Reduction of cerebral glucose utilization by the HIV envelope glycoprotein gp120. *Exp Neurol* 1991;112:224–228.
23. Pert CB, Hill JM, Ruff RM, et al. Octapeptides deduced from the neuropeptide receptor-like pattern of antigen T4 in brain potently inhibit human immunodeficiency virus receptor binding and T-cell infectivity. *Proc Natl Acad Sci USA* 1986;83:9254–9258.
24. Pulliam L, West D, Haigwood N, Swanson RA. HIV-1 envelope protein gp120 alters astrocytes in human brain cultures. *AIDS Res Hum Retroviruses* 1993;5:439–444.
25. Ketzler S, Weis S, Haug H, Budka H. Loss of neurons in the frontal cortex in AIDS brains. *Acta Neuropathol* 1990;80:92–94.
26. Kuhl DE, Markham CH, Metter EJ, Riege WH, Phelps ME, Mazziotta JC. Local cerebral glucose utilization in symptomatic and presymptomatic Huntington's disease. *Res Publ Assoc Res Nerv Ment Dis* 1985;63:199–210.


# 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

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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.