Imaging of Brain Tumors after Administration of L-(N-13)Glutamate: Concise Communication

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Cyclotron-produced L-(N-13)glutamate was used to visualize malignant intracranial tumors in 12 pediatric patients who had evidence of recurrent disease as documented by computed transaxial tomography (TCT). Imaging was performed using a rectilinear scanner, gamma camera, or a positron-emission tomograph (PET). The results indicate that N-13 is rapidly taken up by a majority of brain tumors following the administration of L-(N-13)glutamate, and that N-13 uptake is correlated with breakdown of the blood-brain barrier as demonstrated by contrast TCT or pertechnetate (Tc-99m) studies. The feasibility of using this agent in conjunction with PET is established.

J Nucl Med 23: 682–687, 1982

Recent advances in the design of gamma-imaging instruments and radiopharmaceuticals have made possible the three-dimensional, quantitative measurement of metabolic and physiological processes within the human brain. Positron-emission tomography (PET) has been used to obtain cross-sectional images of the brain with an in-plane resolution of less than 8 mm, which permits delineation of cerebellar cortex and white matter (*1*). Compounds labeled with positron emitters, such as N-13 ammonia (*2*), F-18 fluorodeoxyglucose (*3*), C-11 carbon monoxide (*4*), and O-15 (*5*) have been used in conjunction with PET in the regional quantification of brain function.

In our recent work with enzymatically synthesized L-(N-13)glutamate, we observed that little N-13 is taken up by the normal brain following intravenous administration of the labeled compound (*6*), but that certain malignant bone tumors showed greatly increased uptake (*7,8*). The possibility of obtaining high-contrast images of intracranial tumors, together with the potential utility of PET with this compound, encouraged us to investigate the use of L-(N-13)glutamate in imaging tumors of the brain. This report describes the patterns of N-13 distribution in a group of patients with a variety of malignant intracranial tumors, and compares the findings with computed transaxial tomography (TCT) and pertechnetate brain scanning.

Received Oct. 26, 1981; revision accepted Mar. 17, 1982.

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MATERIALS AND METHODS

Patient selection. Twelve patients (7 females and 5 males) who ranged in age from 4 to 21 yr were studied with L-(N-13)glutamate. All had evidence of recurrent malignant tumors of the brain as documented by TCT scan; diagnosis was established from histologic specimens obtained earlier during craniotomies. Eleven patients also had contrast TCT studies to assess changes in permeability of the blood-brain barrier. Informed consent was obtained from each patient's parents before the N-13 procedure. All patients were conscious and cooperative during the L-(N-13)glutamate studies, which were performed without sedation. One patient was imaged twice to evaluate the effects of combined radiation and chemotherapy on tumor uptake of N-13. These studies were performed with the approval of the Center's Clinical Investigation Committee and Committee on Radiation. The absorbed radiation doses to the whole body and pancreas (the critical organ) were estimated to be 6.3 and 300 mrad per administered millicurie, re-

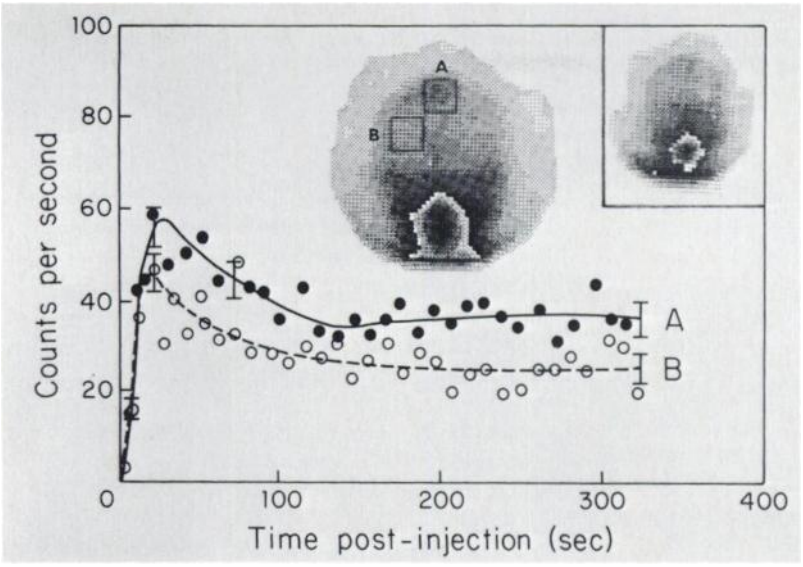

FIG. 1. Time-activity curves of N-13 in patient with meningeal sarcoma, as recorded by gamma camera with high-energy collimator. Bars indicate 1 expected s.d. due to random fluctuations. Regions of interest including tumor (A) and normal tissues (B) are shown. Small inset is normal AP image, showing uptake in salivary glands with minimal visualization of midline vascular structures.

spectively.

Preparation of L-(N-13)glutamate. This agent was synthesized in high specific activity (300 mCi per micromole) from cyclotron-produced N-13 ammonia and alpha-ketoglutaric acid, using enzymatic procedures described elsewhere (*6*). For injection purposes the enzyme was immobilized on CNBr-activated Sepharose, isotonicity was adjusted, and the solution filtered through 0.22 μm Millex. Approximately 150 μCi/kg were administered intravenously in a 2–6 ml volume.

Imaging of N-13 distribution. Static imaging of the head of all subjects was begun between 3 and 7 min after the administration of L-(N-13)glutamate; where possible, two views were obtained, usually anteroposterior and left lateral, with P-A or right lateral views if this helped to keep clear of interfering activity in the salivary glands (*6*). Eight patients were studied with a high-energy gamma (HEG) rectilinear scanner (*9*). Three patients (Cases 9–11) were imaged by gamma camera (*10*) with a parallel-hole tungsten collimator, computerized (PDP-11/70) for dynamic data display and analysis. One patient (Case 12) was studied using a PC-4200 PET, which is capable of simultaneously acquiring 23 transverse sections in a body region 35 cm square (*11*).

Other radionuclide imaging procedures. Nine patients underwent sodium pertechnetate (Tc-99m) brain scanning within 2 wk of the glutamate examination, using either a large-field-of-view gamma camera in magnification mode with a general-purpose low-energy collimator, or a portable gamma camera with a high-resolution collimator.

Image display and analysis. L-(N-13)glutamate scan data were corrected for physical decay and stored digitally by a PDP 11/70 computer, with display by electrostatic printer-plotter in dot-density format. The PC-4200 PET data were rearranged by computer to produce thin coronal or sagittal sections of the brain. Pertechnetate scans were displayed in standard microdot format. In five cases where digital data were available for both L-(N-13)glutamate and pertechnetate lateral images ratios between tumor (max) and adjacent normal brain were calculated. Tumor uptakes of N-13 and Tc-99m were qualitatively rated as follows: (−) = normal pattern, (+) = abnormal in region of known disease, but tumor not clearly delineated, (++) = clear delineation of tumor from surrounding normal structures, (+++) = very high tumor contrast. The normal distribution of N-13 in the head was previously determined from anteroposterior and left lateral HEG images of normal volunteers (*6*). Specifically, N-13 concentrated in the salivary glands and in the scalp and its muscles: blood levels of N-13 were low at the time of scanning.

RESULTS

L-(N-13)glutamate brain findings were positive in 9 out of 12 patients, compared with 7 out of 9 by pertechnetate scan. The majority of the positive glutamate studies showed clear delineation of the tumor from surrounding normal structures. In the nine cases where both L-(N-13)glutamate and pertechnetate scans were performed, similar results were obtained in 7. The qualitative and quantitative comparisons of the uptake of the two agents, along with the results of contrast TCT, are summarized in Table 1. Although these data show no consistent relationship between a tumor's N-13 uptake and its histologic picture, we observed that the tumors concentrating N-13 most avidly (Cases 5, 7, and 12) tended to be derived from primitive neuroectodermal elements.

The dynamic uptake of L-(N-13)glutamate by meningeal sarcoma (Case 11) and by a region of normal tissue (including brain and overlying normal scalp and

TABLE 1. COMPARISON OF L-(N-13)GLUTAMATE, PERTECHNETATE (Tc-99m) AND TCT FINDINGS IN PATIENTS WITH MALIGNANT INTRACRANIAL TUMORS

Case	Age/ Sex	Histological diagnosis	Glu scan	TcO_4^- Scan	Tumor-to-normal ratio Glu	Tumor-to-normal ratio TcO_4^-	TCT findings*
1	21/M	Embryonal pineal carcinoma	++	++	2.2	2.8	Extensive tumor blush, posterior third ventricle
2	7/M	CNS dysgerminoma	+	NP			Calcific density R. temporal region
3	9/F	Pineoblastoma	++	++	2.8	2.7	Large area of contrast enhancement involving both thalami.
4	13/M	Poorly differentiated glial tumor	−	NP			Small posterior contrast-enhancing lesion
5	7/F	Primitive neuroepithelial tumor	+-+++ ++	7.1	2.3		Diffuse low-density area, L. frontal lobe
6	14/F	Medulloblastoma	++	+	2.4	1.8	Posterior-fossa mass extending into L. thalamus
		Medulloblastoma†	+	+			Decrease in size of thalamic lesion
7	10/M	Primary cerebral neuroblastoma, desmoplastic variety	+-+++ ++	3.2	2.9		Large lobulated mass involving both frontal lobes
8	16/F	Grade III astrocytoma	−	−			No definite mass, but small area of increased density at site of craniotomy
9	5/F	Medulloblastoma	−	++			Areas of contrast enhancement near left sylvian fissure and great longit. fissure
10	8/M	Medulloblastoma	+	−			Enhancing mass just behind fourth ventricle
11	4/F	Meningeal sarcoma	++	++			Density in R. superficial parietal lobe
12	10/F	Primary cerebral neuroblastoma, desmoplastic variety	+- NP ++				Area of increased density, R. frontal lobe, with surrounding edema

* Patient 8 had no contrast study. All the remaining patients had evidence of contrast enhancement in the tumor region.
† Second study performed after therapy with neuraxis RT and vincristine. NP = not performed.

skeletal muscle and associated vessels) is shown in Fig. 1. Both regions show maximum counting rate at approximately 25 sec after administration due to the initial passage of blood-borne radioactivity through the brain, followed by a clearance phase, with the radioactivity in the tumor region remaining at a higher level than in normal tissue after 2 min postinjection.

Figure 2a shows the distribution of N-13 in the head of a 9-yr-old girl with pineoblastoma (Case 3). This image, obtained 5 min after administration of L-(N-13)glutamate, shows an area of increased uptake in the posterior temporal region; in the anterior view it was seen to occupy the midbrain, extending slightly to the left of midline. Pertechnetate scanning showed an area of increased uptake with diffuse borders in the same location (Fig. 2b). TCT demonstrated enlargement of a contrast-enhancing, third-ventricular mass, which involved both thalami and extended anteriorly into the region of the interventricular foramen (Monro).

Figure 3a is an L-(N-13)glutamate scan of a 7-yr-old girl (Case 5) with desmoplastic neuroblastoma in the left frontal lobe, recurrent following resection from the right frontal lobe. Both L-(N-13)glutamate and pertechnetate scans (Fg. 3b) show a well-defined, intense accumulation of tracer in the left frontotemporal region. A common-carotid arteriogram showed the lesion to be highly vascular. TCT scan showed a poorly outlined, low-density area in the left frontal lobe; upon injection of contrast, a lobulated area of enhancement was noted in the left lobe lesion.

Figure 4a (Case 6) shows L-(N-13)glutamate uptake in a medulloblastoma that originated midline in the posterior fossa and extended into the brain stem and thalamus on the left side, with compression and shift of the third ventricle to the right. By TCT the tumor density increased only slightly upon contrast injection. Pertechnetate scanning (Fig. 4b) showed a faint area of increased uptake in the temporoparietal region. The patient, a 14-yr-old girl, was subsequently treated with neuraxis radiation (4200 rad, plus 1500 rad to the pos-

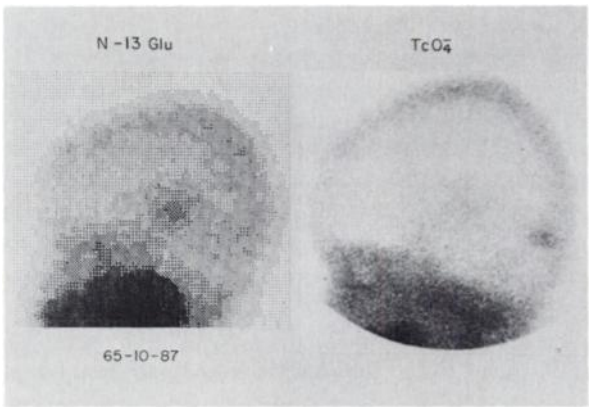

FIG. 2. (a) Left lateral digital N-13 image of patient with pineoblastoma (Case 3). (b) Pertechnetate image.

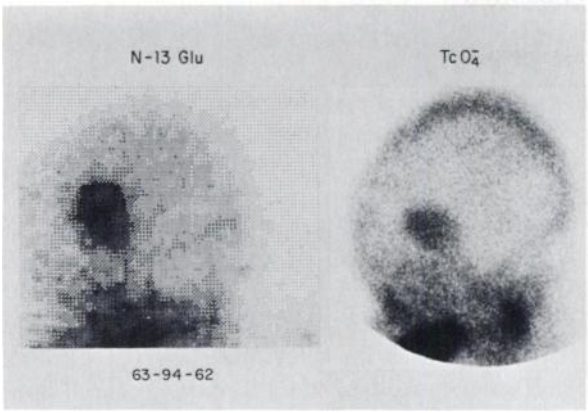

FIG. 3. (a) Left lateral N-13 image of patient with cerebral neuroblastoma (Case 5), showing intense uptake in frontal lobe. (b) Pertechnetate image.

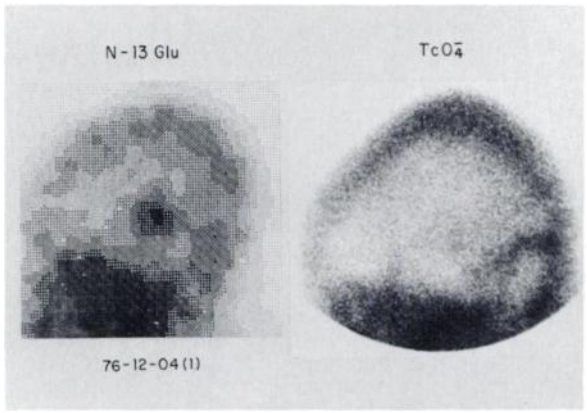

FIG. 4. (a) Pretherapy N-13 image of patient with medulloblastoma (Case 6). (b) Pertechnetate image does not distinctly demonstrate lesion, which was only slightly contrast-enhancing on TCT.

terior fossa) and vincristine. Following radiation therapy, she experienced a reduction in vomiting, and a second TCT scan showed a significant decrease in the size of the lesion in the thalamic area. Follow-up glutamate and pertechnetate scans (Fig. 5) also showed appreciable reduction in tumor uptake.

Figure 6a shows the distribution of L-(N-13)glutamate in the head of a 4-yr-old girl with medulloblastoma (Case 9). There is no evidence of increased N-13 uptake in the brain, but pertechnetate concentrated in the left temporal region, appearing to lie superficial and adjacent to the calvarium and extending upwards and posteriorly (Fig. 6b). TCT revealed areas of contrast enhancement near the left Sylvian fissure and longitudinal cerebral fissure.

Figure 7 shows reconstructed transaxial, longitudinal, and sagittal sections through the head of an 11-yr-old girl with primary cerebral neuroblastoma of the desmoplastic variety (Case 12). These PET images show a region of abnormal N-13 uptake in the frontoparietal region of the right cerebral hemisphere. This may be compared with TCT, which shows a rounded area of increased density in the right frontal lobe with evidence of contrast enhancement (Fig. 8).

DISCUSSION

These imaging studies indicate that N-13 is rapidly concentrated in malignant brain tumors after intravenous administration of L-(N-13)glutamate. The dynamic data of Case 11 suggest that the concentration of N-13 in the tumor reached its plateau at about 3 min. In normal volunteers (*6*) the blood concentration is still falling at that time. It appears that glutamate does not readily cross the intact blood-brain barrier, as demonstrated by Oldendorf in rats (*12*) and confirmed by these studies, and that a disruption of the blood-brain barrier is necessary for tumor visualization with L- (N-13)glutamate. All nine patients who had positive L-(N-13)glutamate scans showed evidence of blood-brain barrier breakdown, as demonstrated by increased uptake of pertechnetate or by contrast enhancement of the TCT image. However, in two patients who showed no evidence of N-13 uptake (Cases 4 and 9), there was demonstrable disruption of the blood-brain barrier, suggesting that other factors are necessary for N-13 localization in tumor tissue. It is

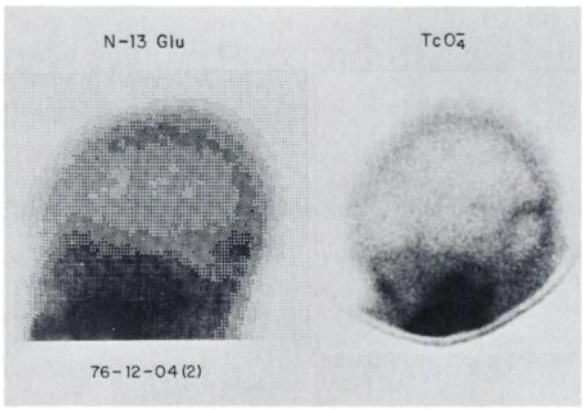

FIG. 5. Posttherapy N-13 and Tc-99m images, Case 6. Tumor is not demonstrated in N-13 image (compare with Fig. 4a).

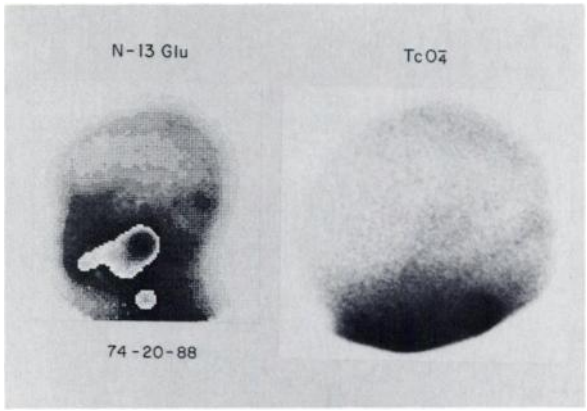

FIG. 6. (a) N-13 image of patient with medulloblastoma (Case 9). (b) Tc-99m image shows lesions in left temporal region, not seen in N-13 image.

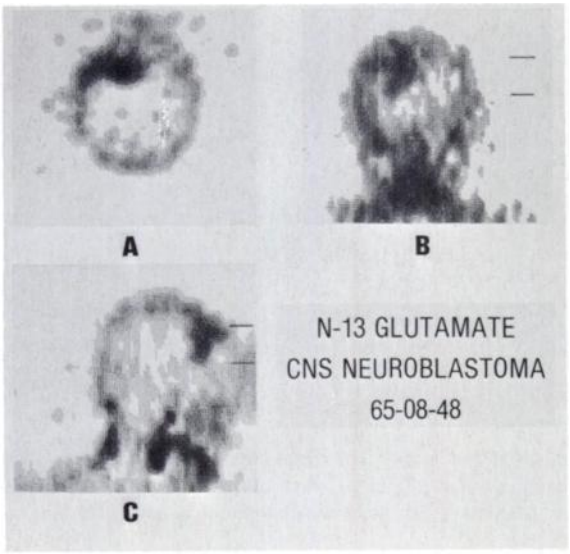

FIG. 7. (a) Transverse-section image of N-13 in primary cerebral neuroblastoma in right frontal lobe (Case 12). (b) Thin coronal section through tumor obtained by rearranging data from 23 transverse sections. (c) Thin sagittal section.

possible that increased uptake of L-(N-13)glutamate is also a reflection of accelerated tumor-cell metabolism.

The reduction in tumor uptake after effective chemotherapy observed in Case 6 may reflect reduced cellular viability. Clinical imaging and histologic studies in osteogenic sarcoma have shown that the degree of reduction in uptake of L-(N-13)glutamate is closely correlated with the degree of tumor necrosis or residual viability following chemotherapy (*13*). The successful use of L-(N-13)glutamate with PET (Case 12) indicates that this quantitative technique may be useful in evaluating the effects of antitumor therapy, especially when performed in conjunction with TCT.

In conclusion, we have shown that malignant brain tumors can be visualized after intravenous administration of L-(N-13)glutamate, and that a disruption of the blood-brain barrier appears necessary for N-13 localization to occur. It was not our intent to determine the efficacy of L-(N-13)glutamate brain scanning relative to other imaging modalities; indeed, this agent would have only limited clinical application in the detection of brain tumors, due to its restricted availability and to the elegant sensitivity of TCT. However, L-(N-13)glutamate and other labeled amino acids are of potential value in the quantitative in vivo evaluation of brain-tumor function as reflected by amino acid transport and metabolism, and hence may play a role in the development of therapeutic modalities for malignant brain tumors.

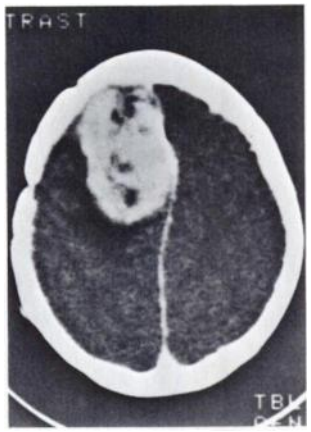

FIG. 8. TCT image of same patient as in Fig. 7.

ACKNOWLEDGMENTS

This work has been supported by USDOE Contract No. EE-77-S-02-4268-A002 and NCI Grant No. CA-18153-05. This paper was presented in part at the 27th Annual Meeting of the Society of Nuclear Medicine, Detroit, Michigan, June 24-27, 1980.

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