

Positron Emission Tomographic Study of Suppression of Gray-Matter Glucose Utilization by Brain Tumors

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Positron emission tomography (PET) scanning with [18F]-2-fluoro-2-deoxy-D-glucose (FDG) was used to study 59 patients with astrocytomas and three patients with other cerebral mass lesions. Suppression of gray-matter glucose utilization ranging from 8% to 64% (mean, 30%) was seen in 92% of cases. Three categories of suppression were apparent, with the greatest degrees of suppression occurring in edematous gray matter adjacent to mass lesions. Lesser degrees of suppression were noted in nonedematous structures (normal attenuation on computed tomographic scan) adjacent to the lesion. Significant suppression was also present in gray matter spatially remote from but functionally linked to the site of the lesion. This approach may become a useful tool for improved understanding of the clinical presentation of certain pathologic entities and for evaluation of disease progression and response to treatment.

It is difficult to evaluate the metabolic status of human brain involved with neoplastic lesions. Approaches to this problem have included experimental studies in animal models and the examination of surgically excised peritumoral tissue [1, 2]. Studies of in vivo metabolism of whole brain or of systemic biochemical correlates of cerebral neoplasms lack neuroanatomic specificity.

The recently developed technique of positron emission tomography (PET) using [18F]-2-fluoro-2-deoxy-D-glucose (FDG) provides a method of evaluating regional cerebral glucose metabolism in vivo. Quantitative images of glucose utilization are based on the autoradiographic method developed by Sokoloff [3] for use with [14C]-2-deoxy-D-glucose. During our study of human cerebral gliomas we have observed focal reductions in FDG accumulation (FDG "suppression") in regions of brain adjacent to and remote from sites of tumor involvement.

Materials and Methods

Fifty-nine patients with astrocytomas (26 with grades I–II and 33 with grades III–IV) and three patients with other cerebral mass lesions were studied. Fifty-nine percent of PET studies were performed before major therapy and 41% were done 2–36 months (mean, 16 months) after surgery, radiation therapy, or chemotherapy. The majority of patients were receiving steroid therapy (60%), anticonvulsant therapy (86%), or both (37%) at the time of the PET study. Images were obtained with the ECAT II scanner (EG&G ORTEC, Oak Ridge, TN) with transverse resolution of 1.7 cm (full

width, half maximum) and plane thickness of 1.8 cm (full width, half maximum). Up to 5 mCi (185 MBq) of FDG was used and quantitation of glucose metabolic rates was done with a modified FDG operational equation [4]. A percentage index of asymmetry was calculated between the affected region and the anatomically comparable contralateral structure. Based on the FDG-PET (ECAT II scanner) study of normal volunteers by Mazziotta et al. [5], which showed a nonsignificant side-to-side mean variation of 2% (5% precision of measurement) throughout the brain, FDG suppression was defined as focal reduction of glucose metabolic rate resulting in regional bilateral asymmetry of 8% or greater. Hypodensity of gray-matter structures was defined as reduction in attenuation on computed tomography (CT) greater than 10 Hounsfield units as compared with the corresponding contralateral structure. Approximate total volumes of tumor and edema were calculated as the product of maximal orthogonal measurements from the CT scan.

Results

Suppression of glucose-utilization in gray-matter structures was seen in 92% of cases. The mean degree of suppression was 30% (SD, 16%; range, 8%–64%). Regression analysis was performed on the degree of suppression against 14 independent variables: gray-matter hypodensity on CT scan; tumor volume; edema volume; tumor-plus-edema volume; tumor grade; tumor glucose utilization; concurrent steroid or anticonvulsant therapy; occurrence of surgery, radiation, or chemotherapy; presence of focal neurologic abnormalities; duration of neurologic findings; and CT contrast enhancement of tumor. The degree of suppression was most strongly correlated with the presence of gray-matter hypodensity, presumably representing edema ($r = 0.66$, $p < 0.0001$); and with the total volume of the lesion (tumor-plus-edema volume) ($r = 0.60$, $p < 0.0001$). Correlations with the other variables were not statistically significant.

In 32% of cases, suppression was seen on FDG-PET scan in peritumoral regions corresponding to hypodense gray-matter structures seen on CT scan. The mean degree of suppression in this group was 43% (SD, 15%; range, 14%–64%). Ninety percent of these cases showed suppression equal to or greater than 30%. Figure 1 shows the CT scan and the PET scan on such a patient, who proved at surgery to have edematous cerebral cortex overlying a thin (<1 cm) rim of grade III astrocytoma, which bordered the large temporal lobe cyst seen on the CT scan. The patient's major symptoms were recent personality change with left-hemisphere

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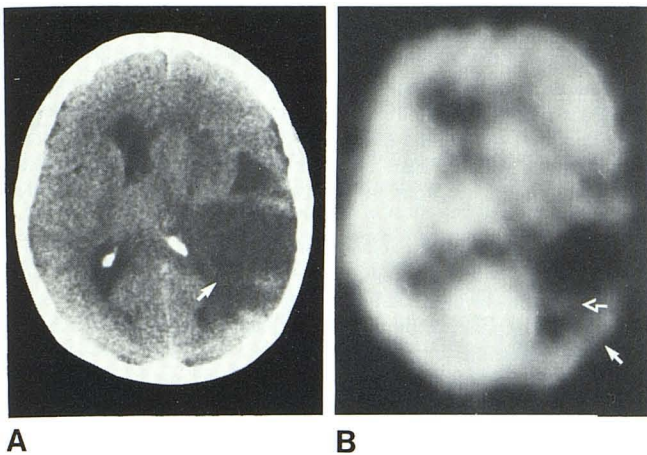


Fig. 1.—A, CT scan in patient with thin rim of grade III astrocytoma around cystic mass in left temporal lobe (*arrow*). Mass effect and surrounding reduced attenuation in adjacent white matter and cortex. B, FDG-PET scan shows 60% suppression of glucose utilization in low-attenuation cortex adjacent to mass lesion (*closed arrow*). Activity from thin rim of astrocytoma tissue (*open arrow*).

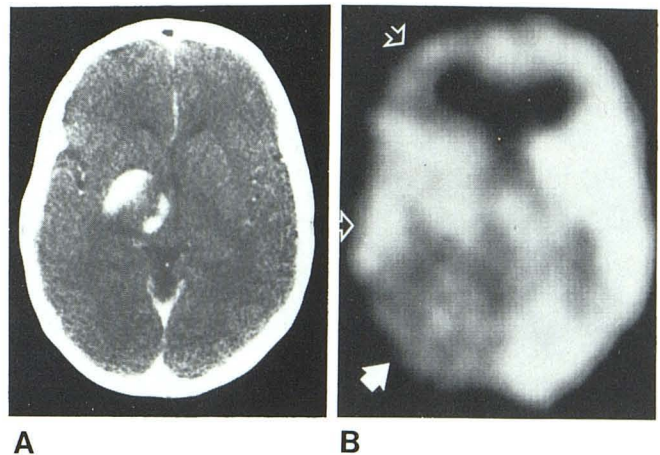


Fig. 3.—A, CT scan in patient with calcified nonenhancing mass lesion involving right thalamus, basal ganglia, and posterior limb of internal capsule. No cortical hypodensity. B, FDG-PET scan shows 37% suppression of glucose utilization in right parietooccipital cortex (*closed arrow*). Lesser degrees of suppression remotely in frontal, insular, and temporal cortex (*open arrows*).

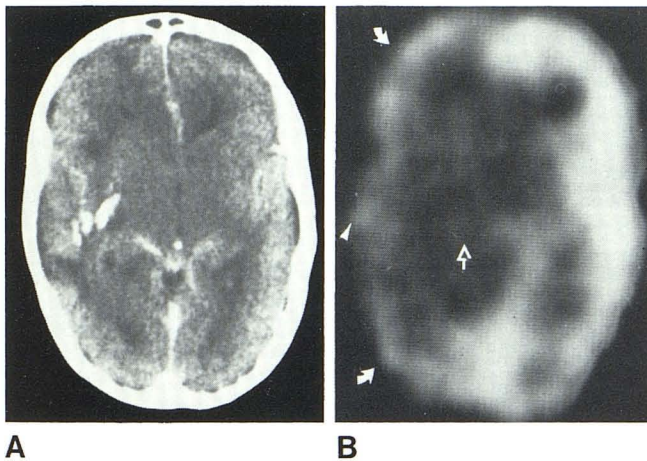


Fig. 2.—A, CT scan in patient with calcified grade II astrocytoma in deep white matter of right temporal lobe. Slight reduction in white-matter attenuation in right frontal and parietal regions. Cortex adjacent to lesion has predominantly normal attenuation. B, FDG-PET scan. Suppression of glucose utilization to 36% in normal-attenuation cortex adjacent to calcified white-matter lesion (*arrowhead*). Significant suppression also in right thalamus adjacent to lesion (*open arrow*) and remotely in right frontal and parietal cortex (*curved arrows*).

seizures and mild right hemiparesis. Reduction of FDG accumulation by 60% relative to the comparable contralateral cortex is seen on the PET scan in the region corresponding to low-attenuation cortex on the CT scan.

In 34% of cases, suppression was seen in peritumoral gray matter corresponding to regions of normal attenuation on CT scan. The mean degree of suppression in this group was 24% (SD, 10%; range, 10%–47%). Seventy-five percent of these cases showed suppression of less than 30%. The scans shown in figure 2 represent a case of extensive FDG suppression—to 36%—in normal-attenuation cortex and thalamus adjacent to a surgically proven grade II astrocytoma. Significant suppression is also seen in normal-attenuation ipsilateral frontal cortex, remote from the lesion. The patient's preoperative symptoms were an 11 year history of right-

hemisphere seizures, recent personality change, and minimal left upper extremity weakness. Microscopic examination of the cortex adjacent to the tumor in the temporal lobectomy specimen revealed no edema or tumor invasion.

In 26% of cases, regions of FDG suppression corresponded to gray-matter structures with normal attenuation that were spatially remote from the mass lesion and edema demonstrated by the CT scan. The mean degree of suppression in these cases was 18% (SD, 8%; range, 8%–37%). In two cases, mass lesions of the thalamus produced suppression of 27% and 37%, respectively, in ipsilateral cortex corresponding to radiating thalamic projections and internal capsule white-matter tracts. Figure 3 illustrates one of these cases, in which the CT scan shows a calcified nonenhancing lesion involving the thalamus, basal ganglia, and internal capsule. This is associated with a 37% suppression of glucose utilization in the ipsilateral parietooccipital cortex. Cortical attenuation is normal. Lesser degrees of suppression are seen in the frontal, insular, and temporal cortical regions. A 12% reduction of glucose utilization was also seen in the contralateral cerebellar hemisphere in this patient (not shown). The patient had mild left hemiparesis and a visual field defect. Conversely, FDG suppression in thalamic activity by 18% and 21%, respectively, was seen with ipsilateral frontal cortical surgical lesions in two cases.

Of 21 cases in which adequate PET scans of the posterior fossa (complete, with symmetric plane orientation) were obtained, 12 demonstrated 8%–34% FDG suppression (mean, 16%; SD, 4%) of the entire cerebellar hemisphere contralateral to a supratentorial mass lesion. Appearance and attenuation of the cerebellum was normal and symmetric on CT scan. Clinically demonstrable involvement of the cortico-ponto-olivo-cerebello-thalamo-cortical circuitry was a consistent finding in these patients. An example of cerebellar suppression (to 34%) is shown in figure 4. This patient was hemiplegic as a result of a surgically proven mass lesion of delayed radiation necrosis involving the right-hemisphere motor cortex and deep white matter.

Twenty-four percent of cases in this study showed simultaneous adjacent and remote FDG suppression or separate regions of remote suppression (e.g., the thalamic lesion with ipsilateral cerebral cortical and contralateral cerebellar suppression shown in fig. 3).

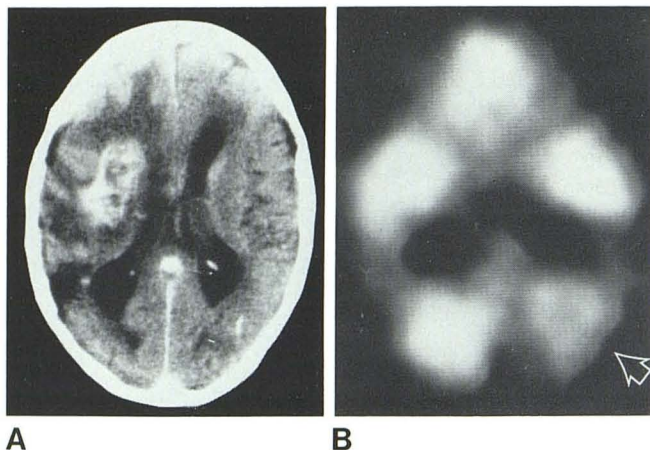


Fig. 4.—A, CT scan in patient with irregularly enhancing mass lesion of delayed radiation necrosis in right hemisphere, surrounded by extensive white-matter and cortical edema. B, FDG-PET scan of anatomically symmetric posterior fossa in same patient shows 34% suppression of glucose utilization in left cerebellar hemisphere (arrow). Images at level of supratentorial lesion showed suppression to 48% in adjacent edematous cortex (not shown).

Discussion

The significance of FDG suppression is not entirely clear. A discussion of the factors most likely to be responsible for suppression will illustrate the complexity of the phenomenon. Peritumoral suppression appears to be produced primarily by local physical, physiologic, and metabolic changes. Remote suppression is probably mediated primarily by transneuronal mechanisms.

A consistent finding in this study was the association of more profound degrees of suppression of glucose metabolism with areas of peritumoral cortical edema demonstrable on CT scan. This finding apparently is not attributable solely to physical expansion of tissue volume by edema fluid (which would result in volume averaging or volume "dilution" of metabolically active tissue). A study of excised peritumoral edema tissue in man demonstrated a 20% mean increase in white-matter volume (78% maximum) and only an 8% mean increase in gray-matter volume (45% maximum) [2]. The occurrence in the present study of FDG suppression to 64% in edematous cortex, to 47% in cortex without edema demonstrable on CT, and to 37% in temporal cortex without demonstrable edema at pathology suggests that the mechanism of peritumoral suppression on PET scan is complex and caused by more than tissue volume expansion alone.

Previous studies of human and animal peritumoral cerebral edema tissue have demonstrated changes in local blood flow, breakdown in the blood-brain barrier (BBB) at the tumor-brain interface [1], lactate accumulation with pH reduction, and electrolyte abnormalities. Peritumoral blood flow has been shown to be reduced with advanced degrees of peritumoral edema in man [6] and around large tumors in animals [1]. The association of larger tumor-plus-edema volumes with greater degrees of suppression in the present study suggests that suppression in peritumoral edema may be related to reduced FDG delivery to tissue in areas of local ischemia caused by compressive mass effect [7] or edematous tissue volume expansion [8]. However, reduced blood flow may not be a sufficient explanation for all cases of peritumoral FDG suppression in light of recent demonstrations by PET in man of normal to increased blood flow adjacent to cerebral tumor [9, 10] and autoradiographic studies of rat brain showing both reduced and elevated blood flow adjacent to implanted glioma tumor masses

[1]. Simultaneous studies of cerebral blood flow and glucose metabolism are needed to clarify this point.

Breakdown of the BBB would not be expected to result in FDG suppression, according to the Sokoloff model, since intracellular hexokinase appears to be the rate-limiting step for FDG accumulation even under conditions of intact BBB [3]. However, the postulated independence of BBB status and FDG or 2-deoxyglucose metabolism in the peritumoral region has not yet been clearly established.

A consistent finding in excised human peritumoral cerebral tissue, correlated with the degree of edema, is a reduction in pH associated with elevated tissue lactate concentration [2]. Lactate accumulation appears to be caused by tissue hypoxemia resulting in a shift to anaerobic glycolysis for energy metabolism. One author suggests that the equilibrium point for energy metabolism, and therefore for anaerobic glucose utilization, is shifted to a lower level than normal in edematous, functionally compromised tissue [2]. PET studies of oxygen in man have shown both reduced oxygen delivery and reduced utilization relative to blood flow in peritumoral regions [9, 10]. Simultaneous studies of in vivo oxygen and glucose metabolism are needed to elucidate the role of energy metabolism in peritumoral suppression. Brain may also be capable of utilizing noncarbohydrate substrates such as fats and amino acids for energy metabolism.

Peritumoral electrolyte changes in excised human tissue include elevation of Na⁺ and reduction of K⁺ concentrations in gray matter [2, 11]. An in vitro study of cultured human astroglia [12] and the observation that hexose sugar uptake in mammalian excitable tissue appears to be a function of both Na⁺ and K⁺ extracellular concentrations suggest that electrolyte abnormalities may produce significant changes in FDG and glucose transport in edematous peritumoral tissue. It is likely that similar local mechanisms produce suppression in normal-attenuation gray matter adjacent to tumor. In addition, local transneuronal mechanisms may contribute to suppression through involvement of adjacent white-matter tracts by tumor.

Our observation of significant FDG suppression in brain remote from tumor and its surrounding edema suggests that transneuronal interactions are important mechanisms for suppression. The cellular pharmacology and physiology of such interactions, even across several orders of synapses remote from the lesion site, have been reviewed [13]. Not only glucose metabolism but also oxygen metabolism, protein and neurotransmitter synthesis, and other cellular metabolic parameters including neuronal viability may be affected by these transneuronal interactions. The distribution of remote suppression seen in our cases is consistent with known anatomy and physiology as well as with recent pathologic, autoradiographic, and in vivo PET observations.

In the present study a functional metabolic link between thalamus and cortex was suggested by the two cases that showed suppression in parietooccipital cortex associated with ipsilateral thalamic mass lesions and by two patients who had suppression of thalamic activity associated with ipsilateral frontal cortical surgical defects. Reduction of FDG accumulation by 15% in temporal cortex associated with ipsilateral basal ganglia infarcts and by 44% in thalamus associated with ipsilateral frontoparietal stroke have been shown by PET scan in man [14]. Microscopic destructive lesions of thalamus in rat have recently been demonstrated in association with induced cortical seizure foci, and depression of 2-deoxyglucose utilization in ipsilateral basal ganglia, thalamus, and brainstem has been demonstrated in monkeys with cortical destructive lesions [15]. In three of our cases thalamic tumors were also associated with contralateral cerebellar suppression of 8%, 12%, and 13%, respectively, and one patient showed simultaneous suppression of ipsilateral parietooccipital cortex as well (fig. 3). These findings

suggest that malfunction of any component of the cortico-thalamo-cerebellar circuitry may result in alterations in metabolism of any or all of the other elements of the circuit.

The 12 cases of suppressed glucose metabolism in cerebellum are interesting because of their clinical significance. The functional metabolic relation between the cerebral cortex and cerebellum has recently been explored in autoradiographic techniques using [14C]-2-deoxyglucose [15, 16]. Unilateral arm and hand movements in experimental animals produced increased glucose metabolism in the ipsilateral cerebellum and contralateral cerebral cortex. Baron et al. [17] and Lenzi et al. [18] have recently shown by PET scanning that cerebellar oxygen metabolism is decreased transiently in patients with hemiparesis due to acute infarctions in the contralateral hemisphere ("crossed cerebellar diaschisis"). In all 12 of our cases in which glucose metabolism in the contralateral cerebellum was significantly suppressed, there was tumor or edema involving principally the frontal lobe in areas known to be neuronally connected to the cerebellum (i.e., the motor cortex, the anterior corona radiata, and the thalamus). All but one of these patients had varying degrees of hemiparesis. The single exception had paraparesis secondary to drop metastases in the spinal cord. In the nine cases without significant suppression of cerebellar metabolism, the primary lesion did not involve the motor cortex. However, in three cases in which edema extended into the corona radiata a subtle lack of coordination of the contralateral upper extremity was noted.

This clear association of clinical findings with remote cerebellar suppression contrasts with the complex relations that seem to exist between local peritumoral suppression, neurologic deficits, and electroencephalographic (EEG) findings. The presence or degree of peritumoral suppression in our study was not an accurate predictor of the severity of the neurologic deficit or the likelihood of seizure activity. Peritumoral suppression was seen in patients with and without focal slowing on EEG, and the relation of spike foci to suppression was unclear.

Also in contrast to the larger series of cases, in which little correlation was seen between the presence or degree of suppression and the degree of malignancy, the subgroup of patients with cerebellar suppression showed a positive correlation with the presence of higher grade gliomas and the attendant prominent edema. This agrees with the original observations by von Monakow [19] and those of Riese [20] specifically related to tumor, which emphasized rapid growth as an essential element for diaschisis.

In conclusion, PET with FDG is useful for demonstrating metabolic abnormalities of the brain adjacent to tumor and for studying secondary functional disturbances of regions remote from the primary lesion. This technique may become a tool for improved understanding of the clinical presentation of certain pathologic entities and for evaluation of disease progression and response to treatment. In addition, when correlated with studies of cerebral blood flow and oxygen metabolism, it may help to elucidate the metabolic neuroanatomy and neurophysiology of the brain.

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