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Short Communication

Long-term Positron Emission Tomography Evaluation of Slowly Progressive Gliomas

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Non-invasive positron emission tomography (PET) was performed to identify changes in blood flow and metabolism, specific to early stages of tumour occurrence or recurrence. 2 patients with slowly progressive gliomas from early to late stages of tumour development were analysed by serial PET measurements of circulation and metabolism using ^{15}O-gas and ^{18}F-fluorodeoxyglucose. PET revealed a persistent depression of oxygen metabolism, as indicated by the regional oxygen extraction fraction or metabolic rate of oxygen, in the regions where tumours were later found. Abnormal blood flow and metabolism may precede the morphological changes detected by computed tomography (CT) in patients with gliomas. Copyright © 1996 Published by Elsevier Science Ltd

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INTRODUCTION

EARLY DETECTION and true localisation of tumour lesions, including small infiltrative and disseminated foci, are utmost concerns in the management of gliomas. Recently, positron emission tomography (PET) has been used for the diagnosis of brain tumours, and images of brain tumours, from haemodynamic and metabolic perspectives, have been obtained using various tracers [1–9]. ^{18}F-Fluorodeoxyglucose (FDG)-PET assesses the degree of tumour malignancy and even predicts the length of survival for patients with gliomas, since high-grade gliomas are hypermetabolic compared with low-grade gliomas [1, 4]. In tumour lesions, blood circulation varies widely, but oxygen metabolism appears considerably reduced regardless of malignancy [2, 6]. In the present study, we describe two cases of slowly progressive gliomas which have been monitored by repeated PET studies over an extended period of time, and discuss the clinical usefulness of impaired cerebral circulation and metabolism in the early detection of tumour occurrence and recurrence.

PATIENTS AND METHODS

The subjects eligible for the present study were 2 patients with a slowly progressive glioma which had developed gradually or over a period of approximately 5 years. We performed PET studies using the Headtome III (Shimazu, Kyoto, Japan) [10]. Regional cerebral blood flow (rCBF), cerebral blood volume (rCBV), oxygen extraction fraction (rOEF), and the metabolic rate of oxygen ($rCMRO_2$) were quantitatively measured using $C^{15}O_2$, $^{15}O_2$ and $C^{15}O$ according to the ^{15}O steady-state model [11, 12]. The regional metabolic rate of glucose (rCMRGl) was calculated following an injection of 185 MBq (5 mCi) FDG using the method of Phelps and associates [13]. These circulation and metabolic values were calculated for regions where tumours had developed, and were compared with non-tumorous regions in the ipsi- and contralateral grey matter.

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RESULTS

Patient 1

A 28-year-old female was admitted to the hospital with a 5-month history of persistent headaches. Computed tomography (CT) of the head revealed a poorly defined hypodense area in the right frontal lobe, but no enhancing mass was present (Figure 1a). The headaches gradually dissipated following treatment with only aspirin. Four years and 5 months after the initial diagnosis, the patient again complained of headaches. CT scanning showed a modestly enhancing tumour with calcification and mass effect in the right frontal lobe (Figure 1b). The tumour, including clusters of calcifi-

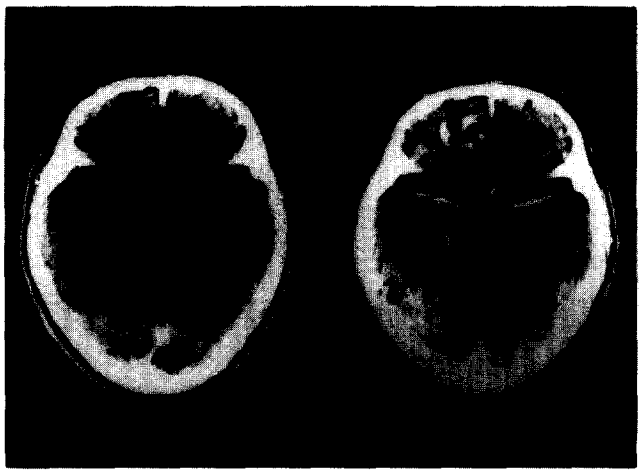

Figure 1. Repeated CT scans from Patient 1. The contrast-enhancing CT scan shows ill-bordered hypodense areas in the right frontal lobe at the time of the first PET examination (left image). Four years and 5 months after the initial diagnosis, a modestly contrast-enhancing mass, with calcification, emerged from the same region (right image).

cation, was widely excised and histologically diagnosed as oligodendroglioma. The patient underwent postoperative radiotherapy and is still alive.

Initial PET images depicted hyperperfused and highly vascular areas in the right mediofrontal lesion where the tumour later developed (first PET study in Table 1). The peak values of rCBF and rCBV were markedly higher than respective values in the left frontal grey matter, contralateral to the tumour site. Oxygen metabolism, indicated by rOEF, was considerably reduced, whereas $rCMRO_2$ was increased in the pretumorous site. The rCMRGl showed a higher value in the lesion than in the contralateral grey matter (Table 1, Figure 2a).

When the tumour became visible with CT, the tumour

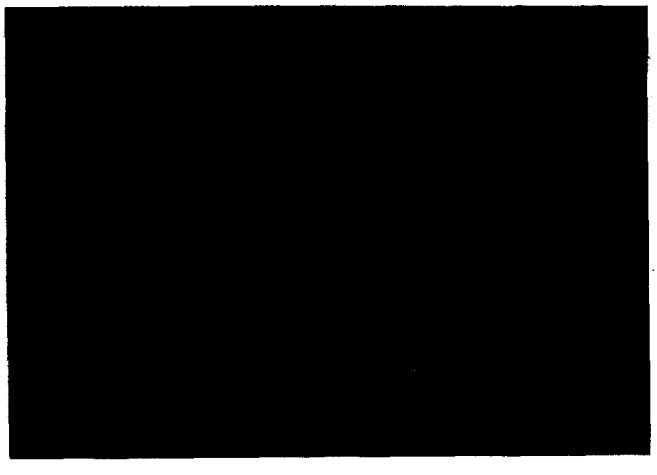

Figure 2. Repeated PET scans from Patient 1. All parameters except for rOEF in the right frontal lobe, particularly in the grey matter, exhibit values exceeding those of other brain tissue (at the time of the initial diagnosis, see top row of images). Four years and 5 months later, the enhancing tumour detected by CT displays a consistently high rCMRGl while oxygen metabolism remains considerably lower (see bottom row of images). CBF, cerebral blood flow; OEF, oxygen extraction fraction; $CMRO_2$, metabolic rate of oxygen; CMRGl, metabolic rate of glucose.

rCMRGl value remained high, whereas the rCMRGl value in the contralateral grey matter was reduced to 60% of the previous value and the rCBF was also reduced (second study). Levels of oxygen metabolism remained low, as indicated by low rOEF and $rCMRO_2$ values (Figure 2b).

Patient 2

The second 27-year-old patient suffered a generalised convulsion. On a CT scan without contrast enhancement, a low-density area was present in the right frontal lobe. The lesion was extensively resected, and histological diagnosis revealed a fibrillary astrocytoma. The patient received postoperative radiation treatments, in conjunction with nimustine (ACNU) chemotherapy. No appreciable tumour recurrence was evident on the CT scans performed at postoperative follow-ups from 1 month to 4 years and 7 months. The patient is still alive.

Six months after the third PET study, the patient suffered from right hemiparesis; CT scans showed an enhancing mass with surrounding low-density in the left frontotemporal region, the opposite hemisphere from the location of the original tumour. Histological examination of the newly developed tumour obtained at the time of second operation indicated an anaplastic astrocytoma.

The preoperative PET scans showed that the original tumour in the right frontal lobe had low values for all parameters measured, a finding indicative of low-grade gliomas (first study in Table 1). All the parameters in the ipsi- and contralateral grey matter to the recurrent left-sided tumour fluctuated with an overall downward tendency. In contrast, in the left frontotemporal region, corresponding to the location of the newly developed tumour, rCBF and rCBV values increased gradually soon after the initial surgery (second study). The rCMRGl levels increased gradually with time and exceeded that of the contralateral mediofrontal grey matter (second to fourth study). A continuous reduction in oxygen metabolism, suggested by rOEF and $rCMRO_2$ values, was evident throughout the studies. The $rCMRO_2$ values fell markedly, resulting in a long-term decrease of rOEF. At the time when mass formation became apparent in CT scans, rOEF and $rCMRO_2$ levels stayed exceedingly low, whereas an incremental change in rCMRGl was noted in the tumour (fourth study).

DISCUSSION

In our study, 2 patients underwent PET scanning prior to initial surgery. Long-term repeated PET studies monitored the development of tumours and provided a haemodynamic and metabolic information at early stages of tumour lesions. Although only subtle changes or seemingly normal anatomical neuro-imaging was evident using CT, the two patients had abnormal circulation and metabolism in the early stages of lesion development.

Patient 1 had demonstrable circulatory and metabolic hyperfunction in the right frontal lobe at the time of the first PET study. The vascular response to tumour infiltration in gliomas varies with the degree of infiltration and cell type [14, 15]. Morphometric measurements have shown that the vessel density decreases in some cases of slightly infiltrated cortex, but increases in some cases of markedly and completely infiltrated cortex. These infiltrative tumour cells initially utilise pre-existing vessels and capillaries that are radially penetrated from the meninges and then induce neo-vascularisation [15]. Also, it is likely that cortical neurons and glial cells are

Table 1. Blood flow and metabolism determined by repeated PET studies

PET parameters	PET study in Patient 1		PET study in Patient 2				
	1st	2nd		1st	2nd	3rd	4th
rCBF (ml/100ml/min)			rCBF (ml/100ml/min)				
Tumour	92.9 (16.9)	42.3 (20.4)*†	Recurred tumour	11.9 (2.4)	18.5 (3.0)*	22.6 (4.0)*	22.7 (4.1)*‡
Ipsifrontal	71.5 (17.7)	29.9 (6.5)*	Ipsifrontal	38.9 (6.6)	39.3 (6.7)	32.9 (8.7)*	24.4 (3.9)*
Contrafrontal	48.9 (9.2)	35.9 (10.1)*	Contramediofrontal	38.5 (6.8)	30.5 (8.5)*	25.5 (8.0)*	38.5 (10.3)
rCBV (ml/100ml)			rCBV (ml/100ml)				
Tumour	4.80 (1.29)	4.53 (2.04)	Recurred tumour	1.34 (0.75)	1.94 (0.84)*	1.85 (1.05)*	1.34 (0.94)
Ipsifrontal	3.97 (0.96)	2.21 (1.43)*	Ipsifrontal	4.82 (1.69)	5.48 (1.59)	4.21 (1.27)	3.27 (1.17)*
Contrafrontal	3.57 (1.40)	2.69 (1.68)*	Contramediofrontal	4.52 (1.74)	4.02 (1.59)	3.31 (1.55)*	3.60 (1.85)*
rOEF			rOEF				
Tumour	0.32 (0.06)	0.26 (0.09)*	Recurred tumour	0.38 (0.06)†	0.35 (0.06)*†	0.35 (0.05)*	0.16 (0.06)*
Ipsifrontal	0.40 (0.08)	0.38 (0.15)	Ipsifrontal	0.47 (0.03)	0.39 (0.07)*	0.39 (0.05)*	0.29 (0.04)*
Contrafrontal	0.49 (0.04)	0.47 (0.07)	Contramediofrontal	0.39 (0.03)	0.36 (0.06)*	0.43 (0.08)*	0.25 (0.04)*
$rCMRO_2$ (ml/100ml/min)			$rCMRO_2$ (ml/100ml/min)				
Tumour	4.83 (0.92)‡	1.47 (0.42)*‡	Recurred tumour	0.85 (0.16)	1.26 (0.31)*	1.58 (0.42)*	0.70 (0.23)*
Ipsifrontal	4.68 (0.97)	1.46 (0.36)*	Ipsifrontal	3.48 (0.56)	2.92 (0.83)*	2.57 (0.73)*	1.42 (0.24)*
Contrafrontal	4.04 (0.94)	2.31 (0.63)*	Contramediofrontal	2.87 (0.63)	2.03 (0.58)*	2.07 (0.53)*	1.88 (0.46)*
rCMRGl (mg/100ml/min)			rCMRGl (mg/100ml/min)				
Tumour	6.91 (0.42)‡	6.75 (0.81)	Recurred tumour	ND	2.12 (0.87)	2.74 (0.81)*	2.93 (0.56)*‡
Ipsifrontal	6.95 (0.71)	3.77 (0.85)*	Ipsifrontal	ND	5.12 (1.19)	4.51 (0.91)*	2.75 (0.31)*
Contrafrontal	6.65 (0.54)	4.01 (0.69)*	Contramediofrontal	ND	3.18 (0.96)	3.66 (0.55)*	2.60 (0.49)*

Numbers represent mean (S.D., $n = 75$) values obtained from regions of 75 pixels (3 cm^2) in size. ND: not determined because no FDG-PET study. "Ipsi" and "contra" specify a side to the original tumour in Patient 1 or to the recurred tumour in Patient 2. Patient 1 underwent PET studies at the time of initial diagnosis (1st) and 4 years and 5 months after (2nd, at the time of tumour development); Patient 2 underwent PET studies pre-operatively (1st), 3 months after (2nd, postoperative), 4 years 7 months after (3rd), and 5 years 1 month after (4th, at the time of apparent tumour recurrence and prior to re-operation).

*Statistically significant from 1st PET study (FDG-PET studies of Patient 2 from 2nd study) by Student's t-test at the level of $P = 0.01$. All parameters in tumours show significance difference from ipsi- and contralateral grey matter, except that tumour parameters are different only from ipsifrontal (†) or only from contralateral grey matter (‡).

stimulated by or reactive to the infiltrative tumour cells. Hypermetabolism may actually represent an accelerated response of the defence mechanism.

PET studies of Patients 1 and 2 revealed a persistent depression of oxygen metabolism. Since changes in $rCMRO_2$ and rCBF correlated well with each other, the rOEF was a good indicator of oxygen metabolism in the lesions. The rOEF values remained persistently low in both patients throughout the studies. Thus, initial reduction in oxygen metabolism may be a sign of early stages of glioma development.

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