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Cerebral glucose utilization in pediatric neurological disorders determined by positron emission tomography

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Abstract. We measured local cerebral glucose utilization in 19 patients with Lennox-Gastaut syndrome (LG), partial seizures (PS), atypical and classical phenylketonuria (PKU), Leigh disease, and subacute sclerosing panencephalitis (SSPE), using positron emission tomography (PET). The mean values of regional glucose utilization in interictal scans of LG were significantly reduced in all brain regions when compared with that of PS ($P<0.005$). PET studies of glucose utilization in LG revealed more widespread hypometabolism than in PS. Two siblings with dihydropteridine reductase deficiency, a patient with classical PKU, and a boy with cytochrome c oxidase deficiency showed reduced glucose utilization in the caudate and putamen. A marked decrease in glucose utilization was found in the cortical gray matter of a patient with rapidly progressive SSPE, despite relatively preserved utilization in the caudate and putamen. The PET study of a patient with slowly progressive SSPE revealed patterns and values of glucose utilization similar to those of the control. Thus, PET provided a useful clue toward understanding brain dysfunction in LG, PS, PKU, Leigh disease, and SSPE.

Key words: Positron emission tomography – Epilepsy – Phenylketonuria – Leigh disease – Subacute sclerosing panencephalitis

Recently developed positron emission tomography (PET) using ^{18}F-2-fluorodeoxyglucose (^{18}F-FDG) has enabled us to determine the regional cerebral metabolic rate for glucose (rCMRglu) under noninvasive conditions (Phelps et al. 1979; Reivich et al. 1979). PET studies with ^{18}F-FDG were applied to neurological disorders in order to study the alteration of rCMRglu in these diseases (Kuhl et al. 1982; Engel et al. 1983; Newmark et al. 1983; Bucchsbaum et al. 1984; Cutler et al. 1985). Although extensive studies of cerebral glucose utilization have been performed in adult neurological disorders, these studies have not been extensively applied to childhood neurological disorders. Patients with neurological disorders do not always demonstrate radiological evidence of structural damage on X-ray computed tomographic scans, angiograms, or pneumatoencephalograms. Local glucose utilization, determined by ^{18}F-FDG PET studies, is a more sensitive indicator of altered regional cerebral function than is the accompanying structural abnormality determined by conventional imaging procedures. Thus, the necessity of measuring brain function is now widely recognized.

We undertook the present study to measure local cerebral glucose utilization in pediatric neurological disorders (e.g., Lennox-Gastaut syndrome, partial seizure, hyperphenylalaninemia, Leigh encephalopathy, and subacute sclerosing panencephalitis) in an attempt to reveal the specific alteration of cerebral glucose utilization in these diseases.

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Patients and methods

Patients. Five categories of subjects were studied: six cases with Lennox-Gastaut syndrome (LG), seven cases with partial seizure (PS), two siblings with dihydropteridine reductase deficiency (atypical phenylketonuria), one case of classical phenylketonuria, one case of cytochrome c oxidase deficiency (Leigh disease) and two cases of subacute sclerosing panencephalitis (SSPE). LG and PS were diagnosed on the basis of electroencephalographic (EEG) findings and clincial manifestations. Dihydropteridine reductase deficiency and cytochrome c oxidase deficiency were determined by biochemical studies (Narisawa et al. 1980; Miyabayashi et al. 1985). The diagnosis of SSPE was made by high titer of measles antibody in cerebrospinal fluid (CSF) and serum, typical EEG findings, and clinical symptoms. EEG recordings were performed on all patients in the week before PET studies.

Scanning procedures. ^{18}F-FDG was prepared using a fully automated system (Iwata et al. 1984). All patients were cannulated in the left radial artery 1–2 h prior to the PET studies. Throughout each study all patients were awake with their eyes closed and were placed in subdued light without sedation. The dose of ^{18}F-FDG administered to subjects varied from 2.5 mCi to 6.3 mCi. Serial scans were performed with the ECAT II (EG & G Ortec) at the level of OM + 50 mm. This scanner has a resolution of 17 mm in plane, using shadow shields, medium resolution mode, and medium resolution reconstruction filters. Two additional scans were obtained at OM + 40 mm and OM + 60 mm. Attenuation was corrected on the basis of predetermined transmission scans. Values for glucose utilization were calculated using standard literature values (Phelps et al. 1979). The PET study was carried out within a week

Table 1. Clinical and PET features of study population in Lennox-Gastaut syndrome (LG) and partial seizure (PS)

Patient number	Sex	Age (y)	Diagnosis	Mean[a] cortex CMRglu	% of[b] change at focus	Medication[c]
1	F	17	LG	5.3	−27	VPA, DPH, NZP
2	F	15	LG	8.2	−21	VPA, DPH, NZP, CBZ
3	F	14	LG	7.8	−11	VPA, ETX, CZP, PM, DX
4	M	13	LG	7.7	−39	VPA, DPH, CZP
5	M	12	LG	4.7	N	VPA, CBZ, CZP
6	M	10	LG	7.0	−21	NZP
7	M	10	PS	6.7	N	CBZ, CZP, NZP, DX
8	F	10	PS	11.0	−14	CBZ, PM, NZP
9	M	15	PS	10.5	−18	PB, CBZ, DX
10	F	12	PS	11.2	−17	PB, DPH
11	F	9	PS	12.2	N	CBZ, NZP
12	F	14	PS	10.4	N	CBZ
13	F	12	PS	7.2	−13	DPH, CBZ

[a] Mean cortex CMRglu was expressed as mg/100 g brain tissue per min in the cortical areas

[b] % change at focus was defined at the percentage decrease of rCMRglu at focus in contrast to that of contralateral region. N = normal patterns of glucose utilization

[c] Abbreviations as follows: VPA, valproic acid; DPH, diphenylhydantoin; NZP, nitrazepam; CBZ, carbamazepine; ETX, ethosuximide; CZP, clonazepam; PM, primidone; DX, acetazolamide; PB, phenobarbital

following CT or magnetic resonance imaging (MRI). PET studies were also performed on five normal controls aged 29 to 39 years. None of the controls had evidence of any neurological dysfunction.

MRI was carried out on a Bruker BMT-1000J machine (a 0.14 tesla magnet). We obtained 32 echoes with a Curpurcell Meiboom-Gill pulse sequence using a repetition time of 3000 ms and an echo time of 12 ms. Total summation images (T2 enhanced images) were used for evaluation. CT was performed on a GE 8800 scanner or a new generation Philips unit.

Results

Comparative study of Lennox-Gastaut (LG) syndrome and partial seizure (PS)

Table 1 lists clinical and PET features of the study population in LG syndrome (six cases) and PS (seven cases). As shown in Table 1 and Fig. 1, the mean values of cerebral glucose utilization in the interictal scans of LG were reduced in all brain regions when compared with PS. The difference in local cerebral glucose utilization between the two groups was statistically significant. The reduced (30%–35%) cerebral glucose utilization separated the patients with LG from those with PS ($P<0.005$). One case showed generalized hypometabolism without local abnormalities (patient 5). Most of the LG cases revealed more widespread hypometabolism than PS (Fig. 2), in most cases these hypometabolic areas were associated with epileptic foci determined by EEG. A few LG patients showed focal hypometabolism which mismatched with focal findings on EEG. Three PS patients had normal cerebral glucose metabolic patterns.

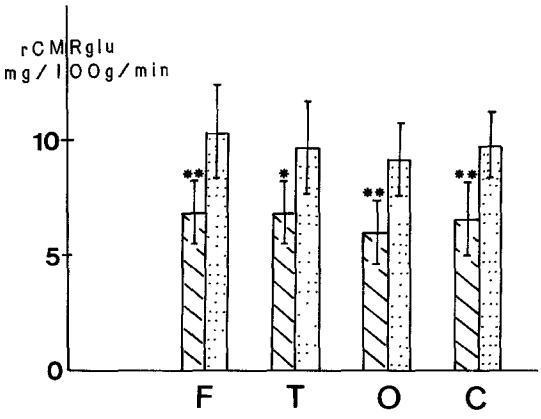

Fig. 1. Regional cerebral metabolic rate for glucose (rCMRglu) in Lennox-Gastaut syndrome (LG) and partial seizures (PS). The rCMRglu is expressed as mg of glucose/100 g brain tissue per min in the regions of *F* (frontal cortex), *T* (temporal corext), *O* (occipital cortex), and *C* (caudate and putamen). One and two asterisks indicate the following degree of significance between PS and LG: $*P<0.025$, $**P<0.005$. Error bars represent once standard deviation. ▨ = LG; □ = PS

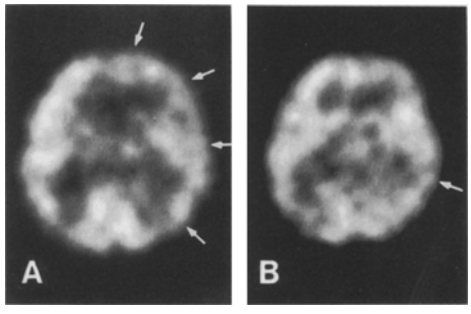

Fig. 2A, B. Typical PET images of Lennox-Gastaut syndrome **A** and partial seizure **B**. The *arrows* on PET images indicate areas of regional hypometabolism in the brain. **A** Patient 6. **B** Patient 10

Hyperphenylalaninemia

Two siblings with dihydropteridine reductase deficiency (atypical phenylketonuria) demonstrated reduced glucose utilization in bilateral areas of caudate and putamen in which calcifications could be detected by X-ray CT. In an 8-year-old girl with classical phenylketonuria, local glucose utilization was similarly depressed in caudate and putamen, regardless of an adequate level of serum phenylalanine (13.2 mg/dl) or absence of caudate atrophy. This finding means that the visual appearance of PET images from phenylketonuria patients can be distinguished from those of controls.

Leigh disease

In an 11-year-old boy with cytochrome c oxidase deficiency we found regional hypometabolism in the area near the bilateral caudate, as shown in Fig. 4. The focal abnormalities were greater than predicted from T2 weighted MRI. X-ray CT could not delineate any significant abnormalities at the time of the PET study. Serial CT scans showed typical

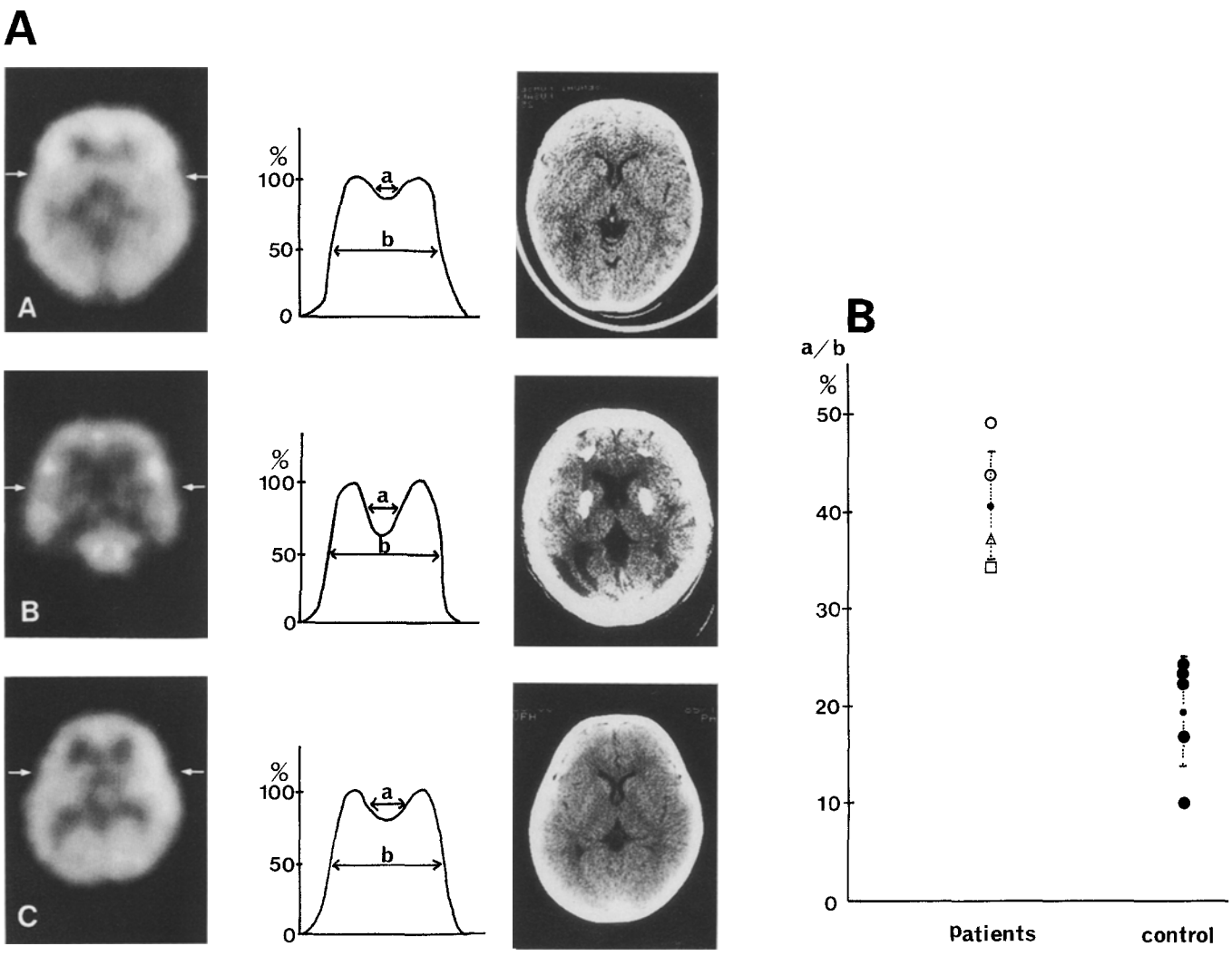

Fig. 3A, B. The PET study in hyperphenylalaninemia. **A** Measurement of caudate metabolic rate indices in control (*A*), dihydropteridine reductase deficiency (*B*), and classical PKU (*C*). **B** Values of caudate metabolic rate index in hyperphenylalaninemia (○; dihydropteridine reductase deficiency, □; classical PKU) and Leigh disease (△), compared with those of control normal volunteers (●)

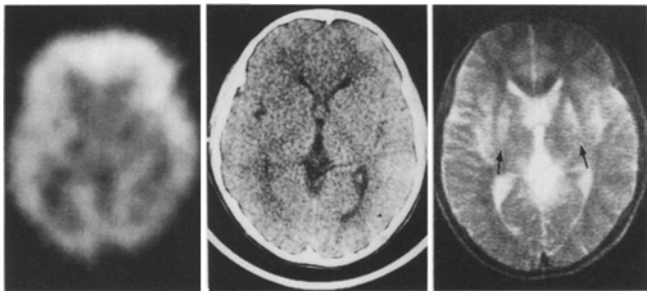

Fig. 4. The PET image, X-ray CT, and MRI in one case of Leigh disease. The *arrows* in T2 weighted MRI indicate the area of focal abnormalities in basal ganglia

bilateral radiolucency of the basal ganglia in the late stages. The value of glucose utilization in the patient was 5.7–7.7 mg/100 g brain tissue per min.

SSPE

As shown in Fig. 5, glucose utilization was markedly lowered in the cortex of rapidly progressive SSPE without ap-

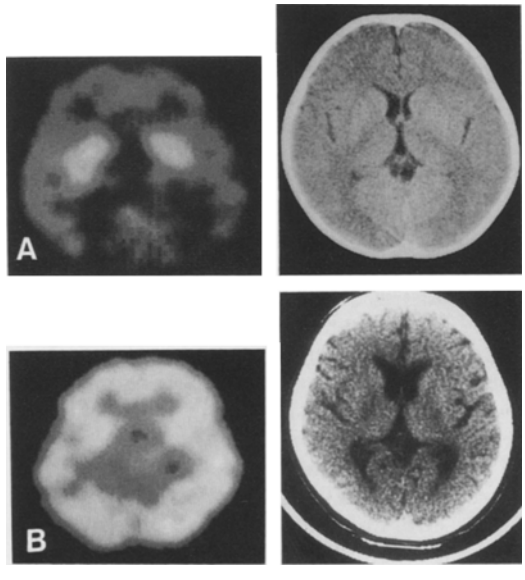

Fig. 5. The images of PET and X-ray CT in SSPE with different clinical courses. **A** Rapidly developing SSPE. **B** Slowly developing SSPE

parent shrinkage of cortical tissues. However, glucose utilization was preserved in caudate nuclei and putamen. The values of glucose utilization in the cortex and striatum were calculated to be 4.1 ± 0.4 mg/100 g per min and 7.3 ± 0.7 mg/100 g per min, respectively. An FDG-PET study in slowly developing SSPE with long term remission revealed patterns and values (10.3 mg/100 g per min) of glucose utilization similar to those of the controls in spite of progressive cortical atrophy and ventricular dilatation demonstrated by X-ray CT.

Discussion

The need to measure local glucose utilization in patients with neurological dysfunction is widely recognized. However, there have been few reports on the regional cerebral function in childhood neurological disorders and normal controls (Schwartz et al. 1983; Gur et al. 1982; Doyle et al. 1983; Volpe et al. 1983, 1985). Chugani et al. (1986) reported the regional cerebral metabolic rates for glucose during brain development. In the latter report, mean rCMRglu varied between 3 and 4.6 mg/100 g per min during the first year of life. The rCMRglu increased to 3.5–6.1 mg/100 g per min during the second year. Between 3 and 7 years of age, mean rCMRglu reached 8.8–11.2 mg/100 g per min in contrast to 3.4–6.0 mg/100 g per min in adults. These data indicate that the value for age matched controls is needed to reveal the alteration of rCMRglu in disease.

The reported value of glucose utilization in children between 3 and 7 years of age is comparable to that in the PS patients as determined by our PET studies. This would indicate that brain regions other than focal hypometabolic areas might not be damaged in PS patients. There are three previous studies using PET in LG reported in the literature (Gur et al. 1982; Chugani et al. 1987; Theodore et al. 1987). Our findings demonstrated that the LG patients had widespread focal abnormalities and/or diffuse hypometabolism in the brain. These data are essentially in agreement with the others. Since pediatric neurological patients usually suffer from epilepsy, many of those patients are taking anticonvulsant medications. It is possible that the anticonvulsants would contribute partially to the values and patterns of local cerebral glucose utilization in these patients (Theodore et al. 1986). We could not compare the absolute values of the patients with those of normal control children. In this paper, the values for selected contralateral regions in PS were used as control values because these age matched patients were taking similar anticonvulsants (Table 1). The values of glucose utilization in LG were significantly reduced when compared to the values in PS. Extensively reduced cerebral glucose utilization in LG might reflect the severe brain dysfunction and pathophysiology of this disease.

To quantify alterations in glucose metabolism in the area of the caudate and putamen, a caudate metabolic rate index was used by Kuhl et al. (1982). This index (%) was defined as the ratio: intercaudate activity separation (a)/ bilateral diameter of the brain activity profile (b) $\times$ 100 (Figure 3A). The index increased with a decline in caudate glucose utilization. In Huntington's disease, the caudate metabolic rate index was $42.1\% \pm 8.8\%$ in contrast to $16.7\% \pm 2.6\%$ in age matched normal control subjects (Kuhl et al. 1982). In our PET studies, the caudate metabolic rate index was significantly elevated not only in patients with hyperphenylalaninemia but also in those with Leigh disease (Figure 3B). The indices in the patients ($n=4$) and normal control volunteers ($n=5$) were $40.7\% \pm 5.5\%$ and $19.4\% \pm 5.2\%$, respectively. These data indicate that the basal ganglia may be hypometabolic in patients with phenylketonuria or Leigh disease.

Leigh disease (subacute necrotizing encephalomyelopathy) is a neurodegenerative disorder primarily affecting infants and children. Clinical presentation may vary in each patient and biomedical abnormalities are inconsistent. The diagnosis of Leigh disease is based mainly on its characteristic pathological findings. A proper diagnosis is sometimes difficult to establish during life. Brain CT has been used to identify bilateral and symmetrical radiolucencies in basal ganglia, thalamus, brain stem, and cerebellum (Hall and Gardner-Medwin 1978). Few abnormalities were documented on X-ray CT in the early stage of our patient, however, the PET study demonstrated widespread hypometabolism in the basal ganglia at this stage. The present study underscores the potential utilities of PET and MRI in the early diagnosis of Leigh disease.

Cerebral glucose utilization in SSPE varied quite widely with the clinical course of the disease. The determination of rCMRglu in SSPE may thus enable us to differentiate a rapidly developing SSPE from a slowly developing one and to provide clinical information of prognostic significance in the early stage of the disease (Yanai et al. 1987).

The positron emission tomographic method using ^{18}F-FDG was used to demonstrate specific alterations of local glucose utilization in LG, PS, phenylketonuria, Leigh disease, and SSPE. This method is indispensable for understanding the underlying pathophysiology of neurological disorders and appears to have great potential for aiding the management of pediatric neurological disorders.

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