IV. 4 Cerebral Glucose Utilization in Pediatric Neurological Disorders
Determined by Positron Emission Tomography

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1. Introduction

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 disease (Kuhl et al. 1982; Engel et al. 1983; Newmark et al. 1983; Buchsbaum 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 neurologic disorders. Patients with neurological disorders do not always demonstrate radiological evidence of structural damage on X-ray computed tomographic scans, angiograms, or pneumatocerebralograms. 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.

2. Patients and Methods

Patients

Five categories of subjects were studied: 6 cases with Lennox-Gastaut syndrome (L-G), 7 cases with partial seizure (PS), 2 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). L-G and PS were diagnosed on the basis of electroencephalographic (EEG) findings
and clinical 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 determined by high titer of measles antibody in CSF and serum, typical EEG findings, and clinical symptoms.

Positron emission tomographic studies with $^{18}$F-FDG

$^{18}$F-FDG was prepared using a fully automated synthesis system (Iwata et al. 1984). The dose of $^{18}$F-FDG administered to subjects varied from 2.5 to 6.3 mCi per subject. The FDG method for determining rCMRglu in humans (Phelps et al. 1979) is similar to the $^{14}$C-deoxyglucose autoradiographic method (Sokoloff et al. 1977). Throughout each study all patients were awake with eye closed and were placed in subdued light without sedation. An operational mathematical equation allowed calculation of rCMRglu with the predetermined lumped constant value (0.42). The PET studies were also performed on 5 normal controls aged 29 to 39 years. None of the controls had any evidence of any neurological dysfunction.

3. Results

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

Table 1 lists clinical and PET features of the study population in Lennox-Gastaut syndrome (6 cases) and partial seizure (7 cases). As shown in Figure 1 and Table 1, the mean value of rCMRglu in the interictal scans of L-G were reduced in all brain regions compared with that of PS. The difference in rCMRglu between the two groups was statistically significant. On average, a moderately reduced (30-35%) cerebral glucose utilization separated the patients with L-G from those with PS (p<0.005). One case showed a generalized hypometabolism without local abnormalities (patient number 6). PET studies of cerebral glucose utilization revealed more widespread hypometabolism in L-G than in PS (Figure 2). These hypometabolic foci were sometimes associated with epileptic foci determined by EEG. However, a few patients showed focal hypometabolism which mismatched with focal findings on EEG. In contrast, patients with PS have limited focal hypometabolism which almost coincided with the EEG focal findings.

Hyperphenylalaninemia

Two siblings with dihydropteridine reductase deficiency (atypical phenylketonuria) demonstrated reduced glucose utilization in bilateral areas of caudate-putamen in which calcifications could be detected by X ray CT (Figure 3). 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. The average value of CMRglu was comparable to that of patients with PS. This finding means that the visual appearance of PET images from patients with phenylketonuria 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 and putamen as shown in Figure 4. The focal abnormalities were greater than predicted from T2 weighted NMR images. The value of glucose utilization in the patient was 5.7-7.7 mg/100 g brain tissue/min.

SSPE

As shown in Figure 5A, the rCMRglu was markedly lowered in the cortex without apparent shrinkage of cortical tissues in rapidly progressive SSPE. On the other hand, glucose utilization was preserved in caudate nuclei and putamen in contrast to the cortex. The rCMRglu in the cortex and striatum was calculated to be 4.1±0.4 mg/100g/min and 7.3±0.7 mg/100g/min, respectively (Figure 6). A FDG-PET study in slowly developing SSPE, with long term remission, revealed patterns and values of rCMRglu similar to those of the control in spite of progressive cortical atrophy and ventricular dilatation demonstrated by X-ray CT (Figure 5B).

4. Discussion

There have been some reports on the regional cerebral function in childhood neurological disorders (Schwartz et al. 1983; Gur et al. 1982; Doyle et al. 1983; Volpe et al. 1983; Volpe et al. 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/100g/min during the first year of life. The rCMRglu increased to 3.5-6.1 mg/100g/min during the second year. Between 3 and 7 years of age, mean rCMRglu reached 8.8-11.2 mg/100g/min in contrast to 3.4-6.0 mg/100g/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 rCMRglu in children between 3 and 7 years of age is comparable to that in partial seizure (PS) as determined by our PET studies. This indicates that brain regions other than focal hypometabolic areas might not be damaged in patients with PS. The value of rCMRglu in Lennox-Gastaut syndrome (L-G) was significantly reduced compared to the value in PS. Extensively reduced cerebral glucose utilization in L-G may reflect the severe brain damage and underlying pathophysiology of this disease as shown by comparing the results from our PET studies with the reported control values.

To quantify alterations in glucose metabolism in the area of 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)×100 (Figure 7). The index increased with a decline in caudate glucose utilization. In Huntington's disease the caudate metabolic rate index was 42.1±8.8% in contrast to 16.7±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 8). The indices in the patients (n=4) and normal control volunteers (n=5) were 40.7±5.5 and 19.4±5.2, respectively. These data indicate that the basal ganglia may be hypometabolic in patients with phenylketonuria or Leigh disease.

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

The positron emission tomographic methods using $^{18}$F-FDG was used to demonstrate specific alterations of local glucose utilization for L-G, 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.

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

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Diagnosis</th>
<th>Mean(^1) cortex CMRglu</th>
<th>% of(^2) change at focus</th>
<th>Medication(^3)</th>
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<tr>
<td>1</td>
<td>F</td>
<td>17</td>
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<td>-13</td>
<td>DPH, CBZ</td>
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\(^1\) Mean cortex CMRglu was expressed as miligram/100 gram brain tissue/min in the cortical area.

\(^2\) % of change at focus was defined as the percentage decrease of rCMRglu at focus in contrast to that of contralateral region. N = no significant change.

\(^3\) Abbreviations as follows: VPA, Valproic acid; DPH, Diphenylhydantoin; NZP, Nitrazepam; CBZA, Carbamazepine; ETX, Ethosuximide; CZP, Clonazepam; PM, Primidone; DX, Acetazolamide; PB, Phenobarbital.
Fig. 1. 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.

Fig. 2. Regional cerebral metabolic rate for glucose (rCMRglu) in Lennox-Gastaut syndrome (L-G) and partial seizures (PS). The rCMRglu is expressed as mg of glucose / 100 gram brain tissue / minute in the regions of F (frontal cortex), T (temporal cortex), O (occipital cortex), and C (caudate and putamen). One and two asterisks indicate the following degree of significance between PS and L-G: *P<0.025, **P<0.005. Error bars represent one standard deviation.
Fig. 3. The PET images and X-ray CT in two siblings with dihydropteridine reductase deficiency (A₁ and A₂) and one case of classical PKU (B). C: normal control volunteer.

Fig. 4. The PET image, X-ray CT, and NMR-CT in one case with Leigh's disease. The arrows in the T₂ weighted NMR image indicate the area of focal abnormalities in this disease.
Fig. 5. The images of PET, X-ray CT, and NMR-CT in SSPE with different clinical courses. A: Rapidly developing SSPE. B: Slowly developing SSPE.

Fig. 6. Regional cerebral metabolic rate for glucose (rCMRglu) in two patients with SSPE (A: shaded columns, B: dotted columns) and the 7 age-matched controls (open columns). The control values of rCMRglu was obtained from each region of age-matched PS (without mental retardation).
Fig. 7. Measurement of caudate metabolic rate indices in normal subject and subject with hyperphenylalaninemia. a = central separation of caudate activity; b = bilateral separation of cortical activity. Caudate metabolic rate index is defined as the ratio, a/b×100(%).

Fig. 8. Values of caudate metabolic rate index in subjects with hyperphenylalaninemia (○), dihydropteridine reductase deficiency, □, classical PKU) and Leigh's disease (△), compared with those of control normal volunteers (●).