Age-Related Changes in the Cerebral Distribution of ^{99m}Tc-ECD from Infancy to Adulthood

Ichiei Kuji, Hisashi Sumiya, Yo Niida, Noboru Takizawa, Eiji Ikeda, Shiro Tsuji and Norihisa Tonami

Departments of Nuclear Medicine and Pediatrics, School of Medicine, and Department of Radiological Technology, School of Health Science, Kanazawa University, Kanazawa, Japan

Although cerebral blood flow in infants differs from that in older individuals, the distribution of ^{99m}Tc-ethyl cysteinate dimer (ECD) in infants has not been well studied. This study compared ^{99m}Tc-ECD distribution in infants and children with that in young adults. **Methods:** ^{99m}Tc-ECD SPECT was performed on 37 patients suspected of having epilepsy, ranging in age from 3 mo to 26 y. The patients were divided into two age-matched groups, a drug-free group (n = 19) and a drug-taking group (n = 18), according to their anticonvulsant medication status at the time of examination. ^{99m}Tc-ECD (100–740 MBq) was injected interictally, and SPECT data were acquired using a triple-head gamma camera. Mean whole-brain counts were obtained from 10 sequential SPECT images. Regions of interest were set bilaterally on five areas of the cerebral cortex and on the basal ganglia, thalamus and cerebellum. The brain perfusion index (BPI) was obtained as a ratio of the mean counts in each region of interest to the mean whole-brain counts. The relationship between BPI and age in each region in the drug-free and drug-taking groups was analyzed separately and together using linear regression. The relationship between five patient age groups (<1 y, n = 4; 1–4 y, n = 9; 5–9 y, n = 8; 10–15 y, n = 7; >15 y, n = 9) and BPI in each region was also examined using multiple comparison analyses. **Results:** Significant positive correlations between BPI and age in the frontal cortex and cerebellum were confirmed in the drug-free group. Anticonvulsant drugs did not affect the regression lines of BPI in the frontal cortex and cerebellum. Significant differences in BPI between age groups were seen in the parietal cortex, frontal cortex, occipital cortex, basal ganglia, thalamus and cerebellum in all patients. **Conclusion:** Age-related changes in cerebral ^{99m}Tc-ECD distribution were confirmed and found to be unaffected by the administration of anticonvulsant drugs. ^{99m}Tc-ECD uptake in children and infants is different from cerebral blood flow glucose metabolism as previously reported, especially in the cerebellum.

Key Words: ^{99m}Tc-ethyl cysteinate dimer; brain SPECT; pediatrics; brain maturation; cerebral blood flow

J Nucl Med 1999; 40:1818–1823

Although originally developed as a brain perfusion agent (*1*), ^{99m}Tc-ethyl cysteinate dimer (ECD) was recently found to have a distribution different from that of cerebral blood flow (CBF) in adults (*2*). Regional clearance of ^{99m}Tc-ECD was also reported to be different in the brain regions of healthy volunteers (*3*). ^{99m}Tc-ECD is widely used in ictal and interictal studies of children and infants with epilepsy (*4,5*). Although CBF distribution alters with age, especially in comparisons with infants (*6*), the distribution of ^{99m}Tc-ECD has not been well studied in children and infants. Schiepers et al. (*7*) described the different patterns in children aged 1.3–15.4 y but did not investigate infants less than 1 y old. Because radionuclide studies of healthy children and infants are not ethical, the subjects were patients who were suspected of having epilepsy and had not undergone surgery. The aim of this study was to clarify ^{99m}Tc-ECD distribution in the brains, especially the cerebella, of children and infants compared with that of young adults using a high-resolution triple-head gamma camera.

MATERIALS AND METHODS

Subjects

The subjects were 37 patients (18 males, 19 females; age range 3 mo to 26 y; mean age 9.9 ± 7.9 y) who were suspected of having epilepsy and had not been treated surgically. Table 1 shows their characteristics. Patients who had severe brain disease or abnormal MRI or ^{99m}Tc-ECD SPECT findings, or who had experienced a severe epileptic episode such as status epilepticus that was uncontrollable by medication, were excluded. The epilepsy of all patients, even those less than 1 y old, was considered to be slight. The subjects were divided into two age-matched groups, a drug-free group (n = 19; mean age 8.1 ± 6.9 y) and a drug-taking group (n = 18; mean age 11.7 ± 8.6 y), according to their anticonvulsant medication status at the time of examination. Patients in the drug-free group had taken no anticonvulsant or other drugs during the month before the ^{99m}Tc-ECD-SPECT examination. Adults more than 30 y old were excluded to avoid the effects of ischemic changes.

Data Acquisition and Analysis

^{99m}Tc-ECD (100–740 MBq) was injected in a dark, quiet room when the subjects were awake and free of seizures. In younger children and infants, venous access was prepared in advance and the injections were performed when the patients were quiet and calm, with oral Trichloryl (triclofos sodium; Nippon Glaxo, Tokyo, Japan) administered for sedation, if necessary, more than 5 min after the injection. From 15 to 45 min after ^{99m}Tc-ECD injection, SPECT data for 90 projections were acquired for 20 min using a triple-head gamma camera (GCA9300A/HG; Toshiba, Tokyo, Japan) with high-resolution fanbeam collimators (128 × 128

Received Nov. 11, 1998; revision accepted Apr. 19, 1999.
For correspondence or reprints contact: Ichiei Kuji, MD, 10 River Rd., Apt. 4P, Roosevelt Island, NY 10044.

TABLE 1
Patient Characteristics

Patient no.	Age (y)	Sex	Seizure	EEG	Medication	Diagnosis
1	0.2	F	CPS	N	CBZ	Partial epilepsy
2	0.2	F	CPS	N	—	Partial epilepsy
3	0.6	M	CPS	N	—	Febrile convulsion
4	0.9	M	CPS	N	VPA	Febrile convulsion
5	1.3	M	CPS	N	—	Afebrile convulsion
6	1.5	F	GMS	N	—	Febrile convulsion
7	2.7	M	CPS	L-T spikes	—	Partial epilepsy
8	3.1	M	GTS	N	CBZ + ZSM	Partial epilepsy
9	3.7	F	GMS	N	VPA	West's syndrome
10	3.7	F	CPS	B-F spikes	CBZ	Partial epilepsy
11	3.7	M	CPS	L-O spikes	—	Febrile convulsion
12	4.2	F	CPS	L-FTPO spike & waves	—	Epilepsy
13	4.2	M	GTC	L-O spike & waves	—	Epilepsy
14	5.3	F	CPS	R-TO spike & waves	—	Febrile convulsion
15	6.2	F	CPS	L-F spikes	—	Partial epilepsy
16	6.3	F	CPS	R-FT spike & waves	VPA	Epilepsy
17	6.4	M	CPS	N	—	Epilepsy
18	7.5	F	CPS	N	CBZ	L-temporal lobe epilepsy
19	7.5	M	CPS	R-TP spike & waves	CBZ	Temporal lobe epilepsy
20	7.9	M	CPS	R-F spikes	VPA	Epilepsy
21	9.0	M	CPS	N	—	Idiopathic hypoglycemia
22	10.1	M	CPS	B-P spikes	—	Epilepsy
23	10.2	F	CPS	L-O lazy	CBZ	L-temporal lobe epilepsy
24	10.5	F	—	N	—	Prolonged QT interval syndrome
25	12.1	M	CPS	N	—	Epilepsy
26	12.4	M	CPS	R-T spikes	VPA	Epilepsy
27	12.7	M	CPS	R-FT spikes	—	Epilepsy
28	14.9	M	CPS	B-FT spikes	CBZ	Epilepsy
29	18.0	F	CPS	R-T spike & waves	—	Partial epilepsy
30	18.6	M	CPS	R-F spike & waves	CBZ	Epilepsy
31	19.9	F	GTS	N	VPA	Epilepsy
32	20.1	F	GTS	N	—	Epilepsy
33	21.0	F	CPS	L-FT spikes	CBZ	Epilepsy
34	23.4	F	GTS	N	PHT + VPA	Epilepsy
35	24.6	M	CPS	N	—	Convulsion
36	25.1	F	SPS	B-T spikes	CBZ	Epilepsy
37	25.9	F	GTS	B-FT spike & waves	VPA	Epilepsy

EEG = electroencephalogram; CPS = complex partial seizure; N = within normal limits; CBZ = carbamazepine; VPA = sodium valproate; GMS = generalized myoclonic seizure; T = temporal lobe; GTS = generalized tonic seizure; ZSM = zonisamide; B = bilateral; F = frontal lobe; O = occipital lobe; P = parietal lobe; PHT = phenytoin; SPS = simple partial seizure.
Medication was indicated as anticonvulsant drugs at SPECT examination.

matrix) in continuous rotation through 120° in four steps of 5 min for each detector, alternating clockwise and counterclockwise. SPECT data were corrected with a triple-energy window scatter method. A Butterworth filter with a cutoff of 0.17 cycle/cm and an order of eight was used along with a ramp filter for reconstruction. The spatial resolution was 7.4 mm full width at half maximum. Mean whole-brain counts were obtained from 10 sequential SPECT images above the lower base of the basal ganglia. On five areas of the cerebral cortex and on the basal ganglia, thalamus and cerebellum, regions of interest were carefully placed bilaterally according to reference MR or CT images (Fig. 1). A brain perfusion index (BPI), or ratio of the mean counts of each region of interest to the mean whole-brain counts, was obtained. Regions for which electroencephalography (EEG) showed abnormal spiking were excluded. The BPIs of a two-sided region were averaged when both sides showed normal EEG findings.

Linear Regression Analysis

The BPI in each region in the drug-free and drug-taking groups was analyzed separately and together using linear regression with a least squares method. Regression lines were compared statistically. Two regression lines were considered identical if an unpaired t test showed no significant difference between them in either trends or residuals. $P < 0.05$ was considered significant.

Age-Grouping Analysis

All subjects were divided into five groups by age: group <1, less than 1 y old (n = 4); group 1–4, from 1 to 4 y old (n = 9); group 5–9, from 5 to 9 y old (n = 8); group 10–15, from 10 to 15 y old (n = 7); and group >15, from 16 to 26 y old (n = 9). Differences among the age groups were considered significant at the $P < 0.05$ level using analysis of variance and Bonferroni adjustment for multiple comparisons.

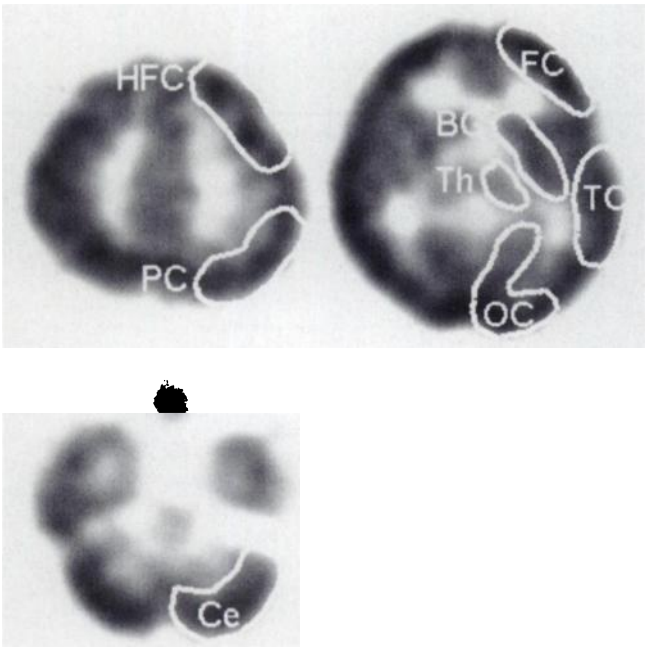

FIGURE 1. Setting of regions of interest on SPECT images. BG = basal ganglia; Ce = cerebellum; FC = frontal cortex; HFC = high frontal cortex; OC = occipital cortex; PC = parietal cortex; TC = temporal cortex; Th = thalamus.

RESULTS

Figure 2 shows the relationship between age and BPI in all regions in the drug-free and drug-taking groups. All regression lines were well fitted to the regression lines, with small SDs of residuals from the lines. Significant positive correlations were observed in the frontal cortex and cerebellum in the drug-free group and in the thalamus and cerebellum in the drug-taking group. Significant positive correlations were shown in the frontal cortex, thalamus and cerebellum for all subjects. Two regression lines between BPI and age in all regions in both groups were statistically identical.

Significant differences were shown in the parietal cortex, frontal cortex, basal ganglia, thalamus and cerebellum in all subjects (Fig. 3). Significant changes were shown in more regions with the age-grouping analysis than with the linear regression analyses.

Figure 4 shows representative SPECT images from patients of various ages in the drug-free group. The contrast between ^{99m}Tc-ECD uptake in the cerebellum and that in the cerebrum decreased with age.

DISCUSSION

This study revealed age-related changes in ^{99m}Tc-ECD distribution in the brain from infancy to young adulthood. Significant correlations between distribution and patient age were seen in the frontal cortex and cerebellum in the drug-free group and in the frontal cortex, thalamus and cerebellum in all subjects. The regression lines for all regions were identical to those in the drug-taking groups. Significant changes were seen in the frontal cortex, parietal cortex, occipital cortex, basal ganglia, thalamus and cerebellum.

We speculated that significant changes were detected in more regions with the age-grouping analysis than with the linear regression analyses because the relationship between BPIs and age is not simply linear.

Because the reference for BPI, the cerebrum, is large and unaffected by regional changes, this index is stable. Only global changes in cerebral perfusion change BPI. BPI is a mean and thus does not always indicate the true perfusion; however, BPI is less affected by measurement errors and more sensitive to distributional changes in the cerebrum than are absolute CBF measurements. Because mean CBF gradually decreased in patients more than 10 y old, an increase in BPI in the cerebellum may occur without any particular change in ^{99m}Tc-ECD uptake in individuals of this age. Mozley et al. (*8*) stated that most changes in the ratio of cerebral-to-cerebellar ^{99m}Tc-hexamethyl propyleneamine oxime (HMPAO) uptake with age occurred during young adulthood and that the distribution appeared to remain relatively stable throughout middle age, suggesting that changes in BPI found using ^{99m}Tc-ECD may be subtle after the age of 30 y.

The possibility exists that changes in BPI were caused by the severity of the underlying disease, the administration of anticonvulsant drugs and the conditions for tracer injection. Although epilepsy that begins by the time patients are 1 y old is generally considered to be severe, our patients who were less than 1 y old included those with febrile convulsions, and the remaining patients with epilepsy had no severe clinical features. The age-related smooth change in BPI was considered to be independent of the severity of epilepsy.

Some anticonvulsant drugs may change CBF; however, this study showed such drugs to have no significant effect on BPI. Anticonvulsant drugs were shown to have only a slight effect on BPI in patients, like ours, with epilepsy. Although the sedation of younger children may have affected CBF, the changes in ^{99m}Tc-ECD distribution were almost negligible because the children were sedated more than 15 min after injection.

BPI changes in the parietal, frontal and occipital cortices in infancy were similar to those previously reported (*8*); however, the low BPI in the cerebellum in comparison with that in the cerebrum was a ^{99m}Tc-ECD–specific phenomenon.

Accumulation of ^{99m}Tc-ECD in the brain depends on intracellular and membranous nonspecific esterases (*9*). Therefore, ^{99m}Tc-ECD distribution is not identical to CBF distribution. The accumulation of ^{99m}Tc-ECD may be modified by esterase activity and brain metabolism. Changes in ^{99m}Tc-ECD distribution agreed with those reported for

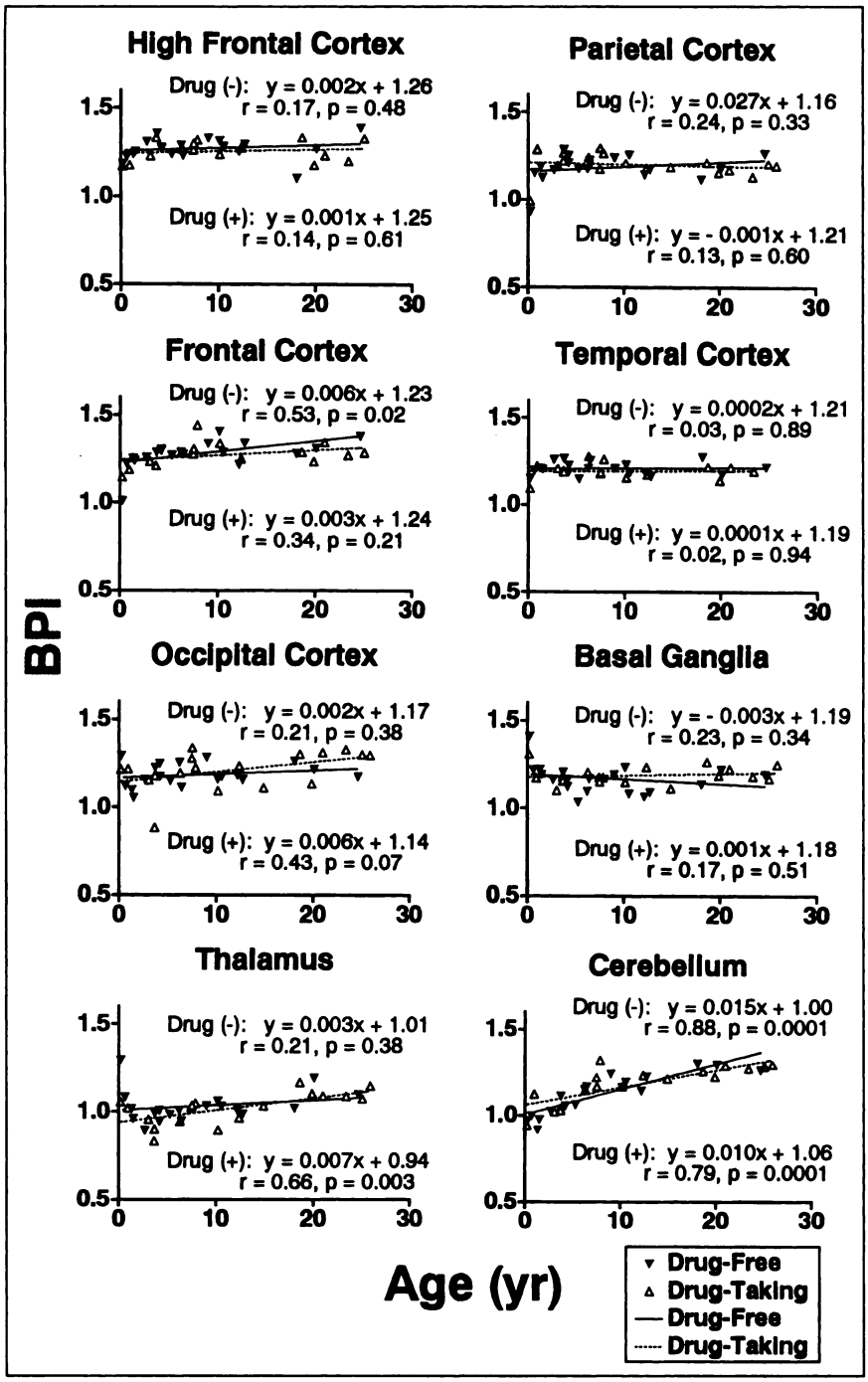

FIGURE 2. Age-related changes in brain perfusion indices (BPIs) in all regions. BPIs in basal ganglia and all cortices except frontal did not correlate with age, whereas BPIs in frontal cortex, thalamus and cerebellum correlated significantly. BPI in cerebellum correlated strongly with age, although regression line in drug-free group was statistically identical to that in drug-taking group.

healthy volunteers aged 1.3–15.4 y (*7*). Changes in ^{99m}Tc-ECD uptake in the basal ganglia and thalamus were like those of CBF examined using ^{133}Xe (*10*). The data showed that CBF in the basal ganglia and thalamus increased with age in individuals more than 1 y old, whereas the CBF in the cerebrum was relatively constant.

Changes in ^{99m}Tc-ECD uptake in the cerebellum were different from those reported for CBF. BPI in the cerebellum was markedly lower in younger patients, whereas the ratio of CBF in the cerebellum to that in the cerebral cortices was relatively constant at all ages (*10*). Changes in cerebellar BPI were also different from changes in glucose metabolism revealed by ^{18}F-fluorodeoxyglucose PET (*6*). Therefore, the decrease in cerebellar ^{99m}Tc-ECD did not depend on glucose metabolism. On the other hand, cerebellar uptake of ^{99m}Tc-HMPAO, another ^{99m}Tc-labeled brain perfusion tracer, compared with mean uptake in the cerebral cortices was significantly low in the 2 mo–1 y and 1–2 y age groups, whereas the mean ratios ranged from 1.0 to 1.1 in subjects more than 2 mo old (*11*). These ratios are equal to about

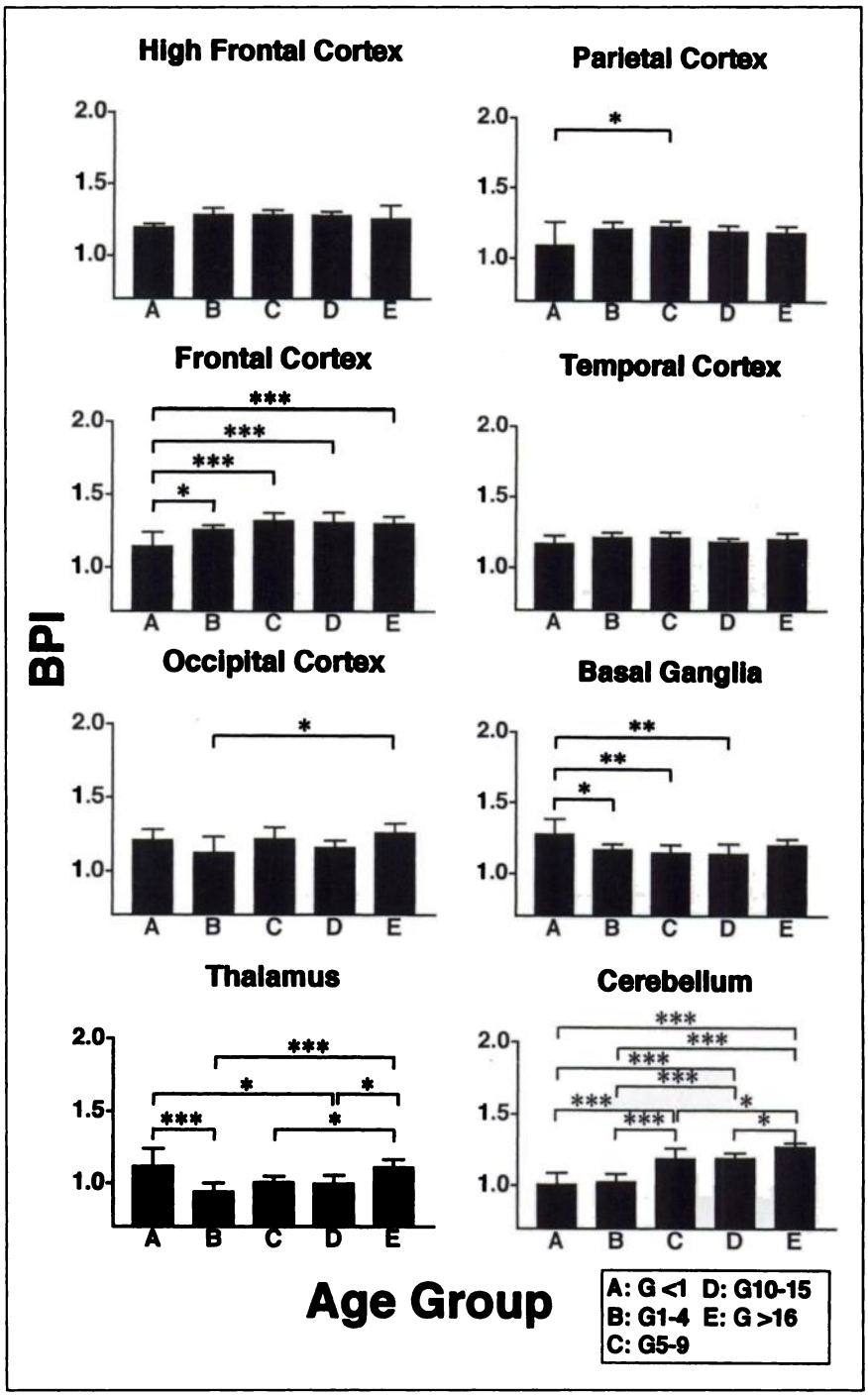

FIGURE 3. Brain perfusion index (BPI) as revealed by ^{99m}Tc-ECD in each region and among age groups. Significant age-related changes in BPIs were seen in more regions than were shown with linear regression analyses (Fig. 2). Significant differences between age groups were indicated by asterisks. *$P < 0.05$, **$P < 0.01$ and ***$P < 0.001$. G <1 = patients less than 1 y old; G1–4 = patients 1–4 y old; G5–9 = patients 5–9 y old; G10–15 = patients 10–15 y old; G >15 = patients 16–26 y old.

1.2–1.3 as our BPI and are higher than those of ^{99m}Tc-ECD. Thus, the differences in age-related changes among tracers seem to depend on how the tracers accumulate, leading to speculation that this change in ^{99m}Tc-ECD distribution depends on the specific characteristics of ^{99m}Tc-ECD accumulation.

Inoue et al. (*12*) reported that, in *Cynomolgus* monkeys, the metabolic rate of ^{99m}Tc-ECD in cerebellar gray matter was lower than that in the cerebral cortex. We thought that the ^{99m}Tc-ECD accumulation was modified by the esterase activity in the cerebellum. To our knowledge, however, no histologic evidence of low concentrations of esterases in the human cerebellum has been reported.

Because many studies on epilepsy in children and infants have used ^{99m}Tc-ECD SPECT, one should remember that ^{99m}Tc-ECD distribution in children and infants is different from that in adults. ^{99m}Tc-ECD uptake in the cerebellum is used as a reference for the measurement of absolute CBF in adults (*13*). However, ^{99m}Tc-ECD uptake in the cerebellum is lower in children and infants than in adults because of

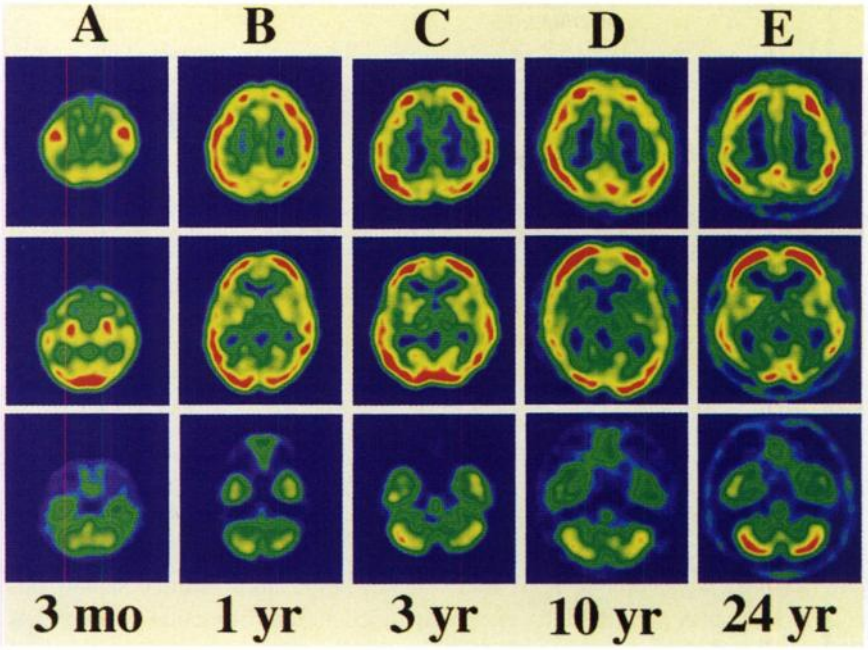

FIGURE 4. Representative ^{99m}Tc-ECD SPECT images of age groups displayed on color scale adjusted to each mean count in cerebrum. Note age-related differences in activity between cerebellum and cerebrum. At 3 mo, activity was low in cerebral cortex and very low in cerebellum compared with that in basal ganglia. A = 3-mo images; B = 1-y images; C = 3-y images; D = 10-y images; E = 24-y images.

^{99m}Tc-ECD–specific factors, making the cerebellum unsuitable as a quantitative reference for measuring CBF in this age group.

A limitation of this study is that the subjects were not healthy volunteers but patients suspected of having epilepsy. These subjects were chosen because, for ethical reasons, healthy children may not volunteer. Interictal ^{99m}Tc-ECD distribution, if not normal, may show only subtle changes because patients with severe disease such as those with abnormal MRI findings and regions with abnormal EEG findings were excluded. The results from the drug-free group seemed to approximate those from healthy volunteers. Significant age-related changes in ^{99m}Tc-ECD uptake in the frontal cortex and cerebellum are difficult to attribute to epilepsy alone. In this study of patients without severe disease, the changes found were considered to be those associated with regular maturation and not with epilepsy. The results showed that general changes may be found not only in epilepsy patients but also in healthy volunteers.

CONCLUSION

^{99m}Tc-ECD distribution in the brains of children and infants was different from that of young adults, and the administration of anticonvulsant drugs did not affect age-related changes in distribution. Age-related patterns of ^{99m}Tc-ECD uptake in the cerebellum differed from those found for CBF using PET and measures of glucose metabolism and HMPAO uptake. Therefore, the cerebellum is not suitable as a quantitative reference for measuring CBF using ^{99m}Tc-ECD in children and infants. The low uptake of ^{99m}Tc-ECD in infants and children was derived from the ^{99m}Tc-ECD–specific mechanism of tracer accumulation.

ACKNOWLEDGMENTS

The authors thank Masato Yamada, Junichi Nishida, Minoru Tobisaka and Junsei Horii for technical support and John S. Gelblum for assistance in preparing the manuscript.

REFERENCES

1. Leveille J, Demonceau G, De Roo M, et al. Characterization of technetium-99m-L,L-ECD for brain perfusion imaging: part 2. Biodistribution and brain imaging in humans. *J Nucl Med.* 1989;30:1902–1910.
2. Koyama M, Kawashima R, Ito H, et al. SPECT imaging of normal subjects with technetium-99m-HMPAO and technetium-99m-ECD. *J Nucl Med.* 1997;38:587–592.
3. Ichise M, Golan H, Ballinger JR, Vines D, Blackman A, Moldofsky H. Regional differences in technetium-99m-ECD clearance on brain SPECT in healthy subjects. *J Nucl Med.* 1997;38:1253–1260.
4. Grunwald F, Menzel C, Pavics L, et al. Ictal and interictal brain SPECT imaging in epilepsy using technetium-99m-ECD. *J Nucl Med.* 1994;35:1896–1901.
5. Menzel C, Steidele S, Grunwald F, et al. Evaluation of technetium-99m-ECD in childhood epilepsy. *J Nucl Med.* 1996;37:1106–1112.
6. Chugani HT, Phelps ME, Mazziotta JC. Positron emission tomography study of human brain functional development. *Ann Neurol.* 1987;22:487–497.
7. Schiepers C, Verbruggen A, Casser P, De Roo M. Normal brain perfusion pattern of technetium-99m-ethylcysteinate dimer in children. *J Nucl Med.* 1997;38:1115–1120.
8. Mozley PD, Sadek AM, Alavi A, et al. Effects of aging on the cerebral distribution of technetium-99m hexamethylpropylene amine oxime in healthy humans. *Eur J Nucl Med.* 1997;24:754–761.
9. Jacquier-Sarlin MR, Polla BS, Slosman DO. Cellular basis of ECD brain retention. *J Nucl Med.* 1996;37:1694–1697.
10. Chiron C, Raynaud C, Mazière B, et al. Changes in regional cerebral blood flow during brain maturation in children and adolescents. *J Nucl Med.* 1992;33:696–703.
11. Denays R, Ham H, Tondeur M, Piepsz A, Noel P. Detection of bilateral and symmetrical anomalies in technetium-99m-HMPAO brain SPECT studies. *J Nucl Med.* 1992;33:485–490.
12. Inoue Y, Momose T, Ohtake T, et al. Metabolism of technetium-99m-L,L-ethyl cysteinate dimer in rat and *Cynomolgus* monkey tissue. *J Nucl Med.* 1997;38:1731–1737.
13. Tsuchida T, Yonekura Y, Nishizawa S, et al. Nonlinearity correction of brain perfusion SPECT based on permeability-surface area product model. *J Nucl Med.* 1996;37:1237–1241.