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Development of Regional Cerebral Blood Flow during Childhood Studied with Iodine-123-IMP SPECT

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ABSTRACT

Regional cerebral blood flow (rCBF) was assessed with single photon emission computed tomograhy (SPECT), ^{123}I-N-isopropyl-iodoamphetamine (^{123}I-IMP), and the Table-Look-Up method in 51 children (27 boys, 24 girls) considered neurologically normal and aged 1 month to 15 years (mean age, 4 years 1 month ; SD 3 years 11 months) divided into seven age groups. The rCBF was measured in cortical regions, the cerebellum, thalamus, and the head of the caudate nucleus. Curves for reference values and standard deviations were defined for each region. The rCBF rapidly increased until 2 years of age, reaching maximum values during the third to fifth periods (2 to 10 years of age) in each region. The rCBFs then decreased, reaching adult levels at 10 to 15 years of age. The rCBF reached maximum values later in the frontal region than in other regions. The rCBF during the early period increased most prominently in the occipital region. These results reflect anatomical development. The rCBF of each region in the last period revealed no substantial differences from values in adult previously reported. We believe that the developmental changes in rCBF values we obtained are reliable and should increase understanding of normal brain development and pediatric neurological diseases. (Jikeikai Med J 2006 ; 53 : 87-92)

Key words : brain, children, ^{123}I-N-isopropyl-iodoamphetamine, regional blood flow, single photon emission computed tomography

INTRODUCTION

Measurements of cerebral blood flow (CBF) with single photon emission computed tomography (SPECT) are useful for gaining an intuitive understanding of clinical conditions. Several studies have qualitatively assessed the development of CBF using ^{123}I-N-isopropyl-iodoamphetamine (^{123}I-IMP) SPECT[1,2]. These studies have revealed that CBF maturation in the brainstem, diencephalon, and cerebellum precedes that in cerebral cortical regions and that CBF development in the frontal lobes occurs more slowly rather than in other cortical regions. However, a qualitative assessment alone based on visual determination cannot detect diffuse alterations in CBF and cannot be used to objectively assess treatment efficacy. Quantitative analysis of CBF development using ^{133}Xe SPECT[3] has shown differences in CBF development among areas of the cerebral cortex and transient hyperperfusion between infancy and adolescence.

A combination of ^{133}Xe and SPECT has been used to obtain normal age-associated CBF values and changes in CBF in children[3]. However, qualitative

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assessment is not sufficiently objective, and CBF measurement with ^{133}Xe is rarely performed because of low spatial resolution and the considerable degree of radiation exposure. Recently ^{123}I-IMP, ^{99m}Tc-hexamethylpropylene amine oxime (^{99m}Tc-HMPAO), and ^{99m}Tc-ethyl cysteinate dimer (^{99m}Tc-ECD) have been used for SPECT more often than has ^{133}Xe. Normal CBF values in children should be obtained with SPECT and these agents. Currently available quantitative methods for determining regional CBF (rCBF) with SPECT involve Matsuda's method[4] with ^{123}I-IMP and the Patlak Plot method with ^{99m}Tc-HMPAO[5] or ^{99m}Tc-ECD[6]. However, because the Patlak Plot method requires an aortic arch, it is difficult to use in small children. Moreover, Matsuda's method requires continuous arterial blood collection and is a highly invasive, tedious technique that is less appropriate for use in children. In this study, we used ^{123}I-IMP and the Table-Look-Up (TLU) method[7], which is considered more convenient than Matsuda's method. To obtain CBF values in each region according to age groups and age-related changes in CBF in childhood, we evaluated rCBF in children using the combination of ^{123}I-IMP SPECT and the TLU method.

METHODS

1. *Subjects*

A total of 321 patients were examined with ^{123}I-IMP SPECT using the TLU method at Saitama Children's Medical Center from June 1994 through December 1999. Of these patients, 51 met the following 5 criteria and were included in the study: 1) no abnormal findings on brain magnetic resonance; 2) no abnormal neurological findings except during events; 3) no abnormal findings, including crosswise differences, detected with visual assessment of SPECT; 4) no developmental delays noted on initial or follow-up examinations; and 5) no respiratory or cardiac disease. The 51 patients (27 boys and 24 girls) ranged in age from 1 month to 15 years (mean age, 4 years 1 month; SD, 3 years 11 months) and were divided into seven groups according to age (Table 1). Epilepsy was the most common diagnosis[23]. All studies were performed after informed consent had been obtained from the parents and the child, whenever possible.

2. *Devices and conditions for obtaining data*

A dual-head gamma camera (GCA-90B, Toshiba, Tokyo) was equipped with a slant hole collimator. Data were acquired for 180 degrees and 30 minutes under conditions of a 64-matrix and 1 frame/60 seconds in six-degree steps. Data were processed to generate tomograms with a computer workstation (GMS-550U, Toshiba) with an orbitomeatal line and a 64×64 pixel (4 mm/pixel). A total of 12 16-mm-diameter circular regions of interest (ROI) were drawn manually on the bilateral hemispheres of the cerebellar cortex (at the level of the maximum cerebellar hemisphere), bilateral thalamus, bilateral head of the caudate nucleus, bilateral frontal region, temporal region, and the occipital region (at the level of the

Table 1. Seven periods (age groups) and diagnosis

Period	*n*	Disease (*n*)
1 (1-6 mo)	6	Epilepsy (3), Convulsion (3)
2 (7-12 mo)	9	Epilepsy (7), Acute cerebellar ataxia (1), Acute encephalopathy (1)
3 (1-2 yr)	6	Epilepsy (2), Acute cerebellar ataxia (3), Acute encephalopathy (1)
4 (2-4 yr)	10	Epilepsy (4), Febrile seizure (3), Meningitis (1), Acute cerebellar ataxia (1), Convulsions (1)
5 (4-6 yr)	7	Epilepsy (5), Cerebral palsy (1)*, Involuntary movement (1)
6 (6-10 yr)	8	Epilepsy (2), Acute encephalopathy (4), Alexia (1), Leukemia (1)
7 (10-15 yr)	5	Involutary movement (3), Convulsion (1), Attempted suicide (1)
Total	51	

Patients with acute cerebellar ataxia, acute encephalopathy, or meningitis were examined with SPECT in the convalescent phase, when symptoms had completely resolved.
*This patient was presumed to have cerebral palsy, but we found that he had no abnormal neurological findings after 2 years of follow-up.

maximum thalamus and the head of the caudate nucleus) for early and delayed images, respectively (Fig. 1).

3. Examination protocol

Patients received intravenous (IV) injections of ^{123}I-IMP : 37 MBq for those with a body weight of 10 kg or less, 74 MBq for those weighing 10 kg to 20 kg, and 111 MBq for those weighing more than 20 kg. For patients who could not remain quiet, triclofos sodium, chloral hydrate, or pentobarbital calcium was administered as a sedative. Following the IV injection of ^{123}I-IMP, 30-minute scans were performed at midscan times of 40 minutes (early) and 180 minutes (delayed). Approximately 10 minutes after the IV injection, arterial blood was collected from a site opposite the IV injection. Thereafter, the corrected input function was obtained with complete blood radioisotope counts and the octanol extraction rate to calculate the rCBF using the TLU method[7].

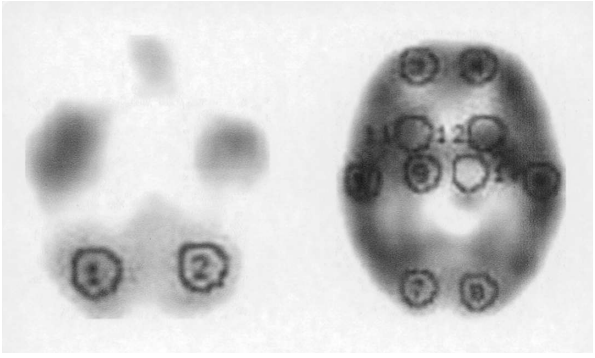

Fig. 1. Layout of 12 ROIs.
Twelve ROIs (16 mm in diameter) were drawn manually on the bilateral cerebellar hemisphere cortices (at level of the maximum cerebellar hemisphere), bilateral thalamus, bilateral head of caudate nucleus, bilateral frontal regions, temporal region, and occipital region (at the level of the maximum thalamus and head of the caudate nucleus).

4. Statistical analysis

The Mann-Whitney U-test was used to compare data among age groups and regions. In addition, the average CBF in each region is expressed as quintic approximated curves.

Results

For CBF values in each region, bilateral average values were used (Table 2), as well as the average values of the 6 ROIs in the cerebral cortex and those of all 12 ROIs. Fig. 2 to 7 show the quintic approximated curves of the average values with standard deviations in each region. In all regions, CBF values rapidly increased during the first to third periods (1 month to 2 years of age), reached maximum average

Table 2. rCBF (Mean±SD)

Period	1	2	3	4	5	6	7
Age	1-6 mo	7-12 mo	1-2 yr	2-4 yr	4-6 yr	6-10 yr	10-15 yr
Frontal*	23.9±3.9[c]	35.4±4.4	43.9±8.0	46.7±7.8	47.6±7.8	47.7±10.3	42.8±9.6
Temporal*	30.4±3.2	40.4±6.3	51.4±9.5	55.6±10.0	54.7±7.0	53.4±6.8	46.4±10.9
Occipital*	29.9±3.6[a]	42.3±7.0[a]	47.3±5.4	51.4±11.0	51.7±5.2	50.6±8.7	37.5±13.9
Cerebellum*	27.1±2.6	33.2±6.8[c,d]	38.7±4.3[c]	40.6±6.9[b,e]	41.0±6.3[b]	45.9±5.3[c]	39.1±8.2
Thalamus*	27.4±4.6	36.4±5.6	44.7±7.0	46.0±7.4[c]	45.8±8.1	47.1±8.8[c]	37.2±8.2
Caudate nucleus*	26.8±4.9	36.2±5.9	46.1±7.5	46.9±8.4	46.2±7.3[c]	45.8±5.2[b]	41.4±10.5
m6ROIs	28.1±3.6	39.4±3.6	47.5±3.8	51.2±4.4	51.4±3.6	50.6±2.8	42.2±4.5
m12ROIs	27.6±2.4	37.3±3.4	45.4±4.2	47.9±5.1	47.9±4.8	48.4±3.0	40.7±3.5

mean value (ml/100 g/min)±SD
*bilateral average value each region
[a] significantly different from frontal region in each period ($P<0.05$)
[b] significantly different from temporal region in each period ($P<0.01$)
[c] significantly different from temporal region in each period ($P<0.05$)
[d] significantly different from occipital region in each period ($P<0.01$)
[e] significantly different from occipital region in each period ($P<0.05$)
m6ROI=mean cerebral blood flow of 6 ROIs of cerebral cortical regions
m12ROI=mean of 12 all ROIs

values during the third to fifth periods (2 to 10 years of age), and then decreased from the peak in the seventh period (10 to 15 years of age). The average values were highest during the fourth period in the temporal region and the head of the caudate nucleus, during the fifth period in the occipital region, and during the sixth period in the frontal region, the cerebellar region, and the thalamus. In the frontal and temporal regions, significant differences in rCBF were observed between the first and second periods and between the second and fourth periods. In the occipital region, significant differences in rCBF were observed between the first and second periods and between the sixth and seventh periods. The increase in CBF from the first period to the second period was greatest in the occipital region. In all periods blood flow tended to be higher in the temporal region than in other regions (Table 2). Fig. 2 to 7 show CBF values with standard deviations in each region and the corresponding approximated curves. The approximated

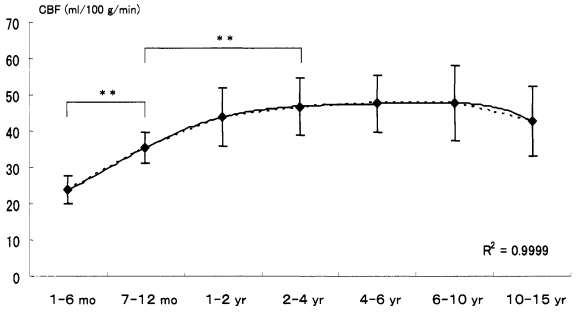

Fig. 2. Quintic approximated curves of the average values of rCBF with SD in the frontal region
$^{**}P<0.01$

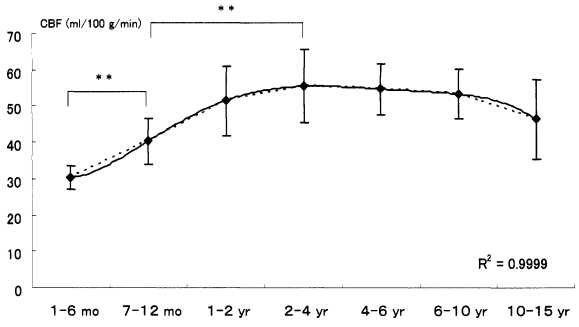

Fig. 3. Quintic approximated curves of the average values of rCBF with SD in the temporal region
$^{**}P<0.01$

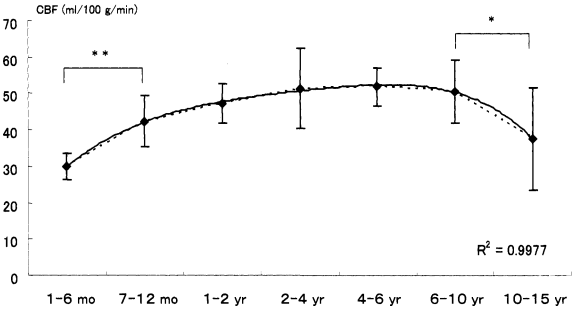

Fig. 4. Quintic approximated curves of the average values of rCBF with SD in the occipital region
$^{*}P<0.05$, $^{**}P<0.01$

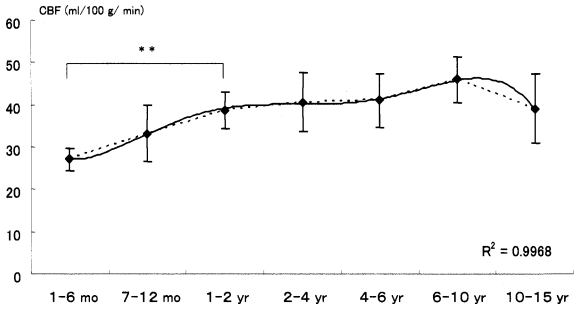

Fig. 5. Quintic approximated curves of the average values of rCBF with SD in the cerebellum
$^{**}P<0.01$

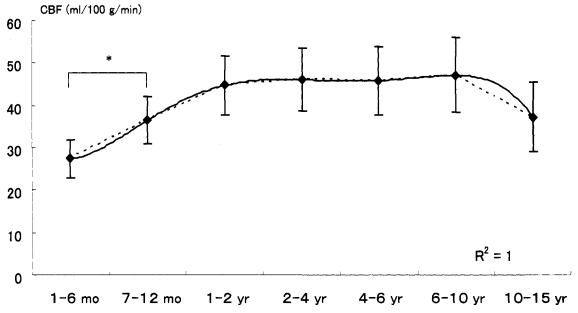

Fig. 6. Quintic approximated curves of the average values of rCBF with SD in the thalamus
$^{*}P<0.05$

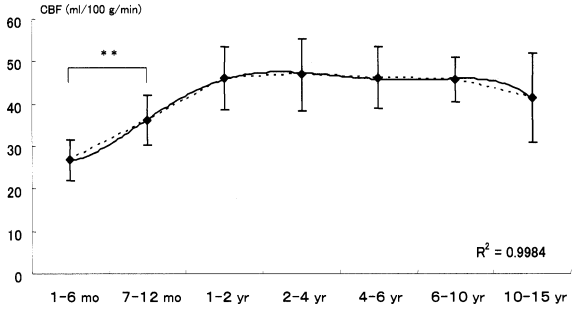

Fig. 7. Quintic approximated curves of the average values of rCBF with SD in the head of the caudate nucleus
$^{**}P<0.01$

curves had extremely high correlation coefficients, and similar tendencies were observed (Table 2).

Discussion

Iida et al.[8] have determined average CBF values in healthy adults (mean age, 41 years; SD, 6 years 4 months) using the ^{123}I-IMP-TLU method: 43.4±2.0 ml/100 g/min in the cerebral cortical gray matter and 40.7±3.1 ml/100 g/min in the cerebellum with an average of 37.4±6.8 ml/100 g/min in cortical gray matter, white matter, the cerebellum, and deep gray matter. The mean CBF values were obtained in the cerebellum, 6 ROIs in cerebral cortical regions, and the average of all 12 ROIs in the seventh period (10 to 15 years of age) were similar to those in adults reported by Iida et al.[8] In addition, changes in rCBF from the first period to the seventh period (1 month to 15 years of age) were similar to those reported by Chiron et al.[3] using ^{133}Xe and SPECT. Chugani et al.[9] investigated brain development in children using positron emission tomography and found that alterations in glucose metabolism in the brain may reflect brain development. Because age-related changes in glucose metabolism in children's brains are similar to changes in CBF[3], our results are likely relevant to brain development.

The rCBF in the frontal region was lower than that in other regions of the cortex during all periods except for the seventh period (10 to 15 years of age). The maximum rCBF of the frontal region was observed in a later period than were those of other regions. From an anatomic point of view, expansion of dendritic fields and an increase in capillary density in the frontal lobe are observed from around 8 months[10,11]. Myelination of association areas is considered to be complete around 10 years of age, with some additional completion for up to more than 20 years of age[12], indicating that the frontal lobe may develop over a longer period than do the temporal and occipital lobes. These results may agree with anatomical development. The increase in rCBF from the first period to the second period (1 to 12 months of age) was greater in the occipital region than in the temporal region. Myelination is completed earlier in the optic radiation than in the auditory radiation[12]. The rapid increase in rCBF in the occipital region during the initial period suggests the rapid development of visual function. The similarity of blood flow values in the cerebellum during the seventh period (10-15 years of age) to those in adults suggests that the development of the cerebellum may reach the adult level during the seventh period (10 to 15 years of age). Moreover, blood flow values in the cerebellum significantly increased throughout the third period (1 to 2 years of age), suggesting that this incraese is associated with the completion of myelination in the cerebellum in 10 months[13]. On the other hand, the "late increase" in rCBF in the cerebellum from the fifth period to the sixth period was not observed in other regions. This "late increase" phenomenon suggests that blood flow changes in the cerebellum may not be explained by myelination alone. The changes may be associated with the development of exercise abilities and elaborative skills during the fifth period to the sixth period (4 to 10 years of age). The development of rCBF in the thalamus and the head of caudate nucleus was similar to that in cortical regions.

Few studies have determined quantitative normal values for CBF in children, probably because of difficulties in the selection of patients and techniques. No studies have previously been performed with the TLU method. Strictly speaking, the patients we studied were not healthy subjects, and the number of patients may be insufficient. However, comparison of previously reported normal values of CBF in adults with those in each region during the seventh period (10 to 15 years of age) in this study revealed no substantial differences in any region or in the average values. Therefore, we conclude that the values we measured in this study may be appropriate as reference values. The autoradiographic method[14], a more convenient version of the TLU method, is used mainly to measure CBF with ^{123}I-IMP. Values measured with the TLU method (x) correlate strongly with those measured with the autoradiographic method (y) ($y=1.07\ x-3.21$ [$r=0.97$, $p<0.001$])[8]. Therefore, we conclude that the results of this study may be applicable to clinical and research using the above formula.

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