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Introduction

Age-related brain shrinkage in the living human was quantitatively reported using X-ray computed tomography.[9,22] Further studies clearly demonstrated that brain atrophy starts as early as 5th decade of age[6,17] and significant gender difference was reported.[6] Age-related changes in regional cerebral blood flow and metabolism were evaluated by several authors using ^{133}Xe technique[14,15] and positron emission tomography (PET).[5,16] However, because of limited resolution of PET, observed values were inevitably affected by regional heterogenious mixture of brain tissues[4,7,10] and correction of brain atrophy was proposed.[3,8] However, it is not known whether PET-measured blood flow and metabolism linealy relates to brain atrophy or not. Its relations was little known especially for patients with ischemic symptoms. The present work was done to clarify the problems comparing between brain atrophy assessed with X-ray CT and CBF and oxygen metabolic rate in the normal aged and parients recovered from a reversible ischaemic attacks (RIA),[13] which includes transient ischaemic attacks and reversible ischaemic neurological diseases.

Subjects and Methods

Thirteen normal volunteers, 6 males and 7 females, and 11 patients, 6 males and 4 females, who previously experienced reversible ischemic attack(RIA) admitted to the study. Age range was 50-85 y. o. for the normal and 58-78 y. o. for the RIAs. All the patients manifested recent transient ischemic symptom and recovered completely within three weeks. Any focal abnormality suggestive of minor infarction in CT scans excluded the case from the study. Summary of clinical parameters is shown in Table 1.

X-ray tomography: Conventional unenhanced computerized tomography(CT) was performed on the planes pararell to the orbito-meatal line (OM line). Slice thickness was 10 mm, resolutions depended on the CT systems of each referring hospital.

Positron tomography: Positron emission tomography was performed pararell to OM lines using ECAT II, Ortec, USA with 17 mm of axial resolution. Patients' head was carefully positioned using layser lights to keep scan slices match to that of X-ray CT. Head movements were monitored using video camera and manually corrected if neccessary. Cyclotron produced 150-labelled CO_2 and O_2 was continuously introduced subject's face mask and steady-state brain activity was measured with PET. With attenuation correction using previously measured transmission data and blood volume correction measured ^{11}C-labelled CO [11,12], regional cerebral blood volume (CBV%), blood flow (CBF ml/100g/min), oxygen extraction fraction (OEF) and oxygen metabolic rate ($CMRO_2$ ml/100g/min) were calculated.[5] In three normal subjects only CBF data was used for the analysis as blood volume scans were not obtained.

Quantitation of brain atrophy: Three sequential CT images of OM + 40, 50, 60 mm were used for the volume measurement. Cranial volume, brain volme and CSF volume were measured by area counting of the CT films taken by multiformat cameras. Images were degitized using video camera and desk-top computer DG10SP (Data General) into 256*256*8 bits for an image. Contour of the brain and CSF cavities were delineated following the pixels which had the threshold intensity value that is the maximum intensity difference among neighboring pixels. The brain was separated into right and left hemispheres by the vertical center line set manually at the time of digitizing. The ratio of the brain area to cranial area was temred as the cerebro-cranial index (CCI) as previously reported.[22] Average CCI for each hemisphere of three planes was used for the analysis.

PET data analysis: 12 ROIs set on the gray matter of OM + 50 mm PET images were selected. ROIs of 3*7 pixels, 1.7 sq cm were taken from frontopolar, frontolateral, temporal, temporooccipital, occipital, and putamens of each hemisphere. Mean hemispheric gray matter value was obtained by averaging of hemispheric gray matter value was obtained by averaging of total six ROIs of each side. Statistical differences were tested using the regression analysis with F-test and Student's T-test.

Informed consent was obtained from normal volunteers, patients after detailed explanation of the procedures. Clinical protocol was approved by the Clinical Committee, Tohoku University Hospital.

Results

Age-related decline of brain atrophy and CBF in normals and RIAs are shown in Fig 1. CCI decreased linealy as progression of ages ($p<0.001$). Although CBF tends to decrease in older age group, the changes is not significant. Brain atrophy effects on CBF and the rate of oxygen metabolism

are analysed in Fig. 2. CBF decreased as the progression of brain shrinkage (CBF=0.917*CCI - 45.6, $p < 0.005$). CCI and other parameters are compared between normals and RIAs in Table 1. There found no difference in any parameters between groups. Then both groups were combined and analysed to evaluate CCI effects on flow and metabolism. As the average CCI of whole subjects was 0.911 + 0.036, the subjects were divided into two groups with the value as a border, i. e. higher and lower CCI groups. The significant differences were found between the groups in age and CBF ($p < 0.001$ and $p < 0.01$ respectively). Oxygen metabolic rate was similar in two groups. The difference between hemispheres was analysed taking intermemispheric ratio in CBF (Fig. 3). Although maximal interhemispheric difference is small, it correlated with hemispheric changes in CBF ($p < 0.05$).

Discussion

The present work confirmed the previous observations that brain atrophy advanced with progression of age.[9,22] The correlation was nearly linear with a constant of -0.0025 and Y-intercept of 1.08($p < 0.001$). Mean gray matter blood flow and oxygen metabolic rate were relatively preserved upto 80 years of age. However, the variations of CBF and $CMRO_2$ between individuals were large. When the correlations of CBF and $CMRO_2$ with CCI were analysed, significant relationships between the formers and the latter were observed.

Age related decline of cerebral blood flow was already reported using ^{133}Xe studies[14,15,20] and ^{15}O positron emission tomography.[5,16] However, a more precise quantitation reported that age changes in CBF in humans are subtle compared to oxygen metabolism.[21] CBF measurement using the Oxygen-15 steady-state inhalation method was reported labile to the errors in the procedure and tissue heterogenuity because of non-linear relations of blood flow and brain radioactivity.[4,10] The Errors in CMRO2, however are relatively smaller than CBF because of cancellation effects of OEF against CBF fluctuations.[4] One of reasons for variation in CMRO2 and its vague correlation to age in our study may be older age of the subjects compared to other studies. Close correlation of brain atrophy assessed with CT and gray matter measured with ^{133}Xe has been reported.[18,20] However our report may be the first that revealed closer correlation among CBF, CMRO2 and CCI by measuring the all parameters in the same tranvers sections. Another observation of ours is that CBF correlated more closely with brain atrophy than age. Cerebral blood flow in normal subjects with normocapnea is determined on the balance of arterial input and tissue energy demands. The condition of carotid arteries in our subjects is normal except two cases who had severe carotid stenosis. Threrfore blood supply in most cases seemed adequate to the tissue demands which suggested by normal OEF level. Then the changes in CBF must be derived from decreases in tissue demands. The reasons for desreased demands are explaned by either decreased cellular density or decreased cellular metabolism. It is well documented that numbers of neurons

decreases in course of aging.[1,2] Around 0.8% of neurons are reported to diminish.[2] Its criticism is that neurons does not disappears so fast but they shrink with age.[19] Our report does not answer the problem, however it suggests that brain shrinkage as a result from either neuronal loss or its shrinkage is one of the main factor for changes blood flow and metabolism measured with PET.

Hemispheric asymmetry in the brain atrophy is not rare even in normal subjects. Brain scans performed strictly pararell to the transaxial plane, some asymmetry still exist. Though the asymmetry is not large in our study, significant correlation between the asymmetry in brain atrophy and hemispheric blood flow was observed.

It has been proposed that PET data should be corrected for brain tissue were determined.[3,8] There were no significant changes with age in the corrected values. However, what more important in PET brain study is to measure how many functioning neurons exist in the brain as a whole. Therefore the comparisons between age groups or normals and dementia need to be assessed using regional data not corrected for tissue atrophy.

References

1) Brody H., J. Comp. Neurol. 102 (1955) 511.
2) Brody H., Interdiscipl. Topics Geront. 7 (1970) 9. (8% annual decrement in neurons. A 60-year span of adulthood would then result in a loss of 50% of cortical neurons).
3) Chawluk J. B., Alavi A., Dann R., Hurtig H. I., Bais S. et al., J. Nucl. Med. 24 (1987) 431.
4) Correia J. A., Alpert N. M., Buxton R. B., Ackerman R. H., J. Cereb. Blood Flow Metabol. 5 (1985) 591.
5) Frackowiak R. S. J., Lenzi G. L., Jones T., Heather F. D., J. Comput. Assist Tomog. 4 (1980) 727.
6) Hatazawa J., Ito M., Yamaura H., Matsuzawa T., J. Amer. Geriat. Soc. 30 (1982) 235.
7) Herscovtch P. and Raichle M. E., J. Cereb. Blood Flow Metabol. 3 (1983) 407.
8) Herscovitch P., Auchus A. P., Gado M., Chi D., Raichle M. E., J. Cereb. Blood Flow Metabol. 6 (1986) 120.
9) Ito M., Hatazawa Y., Matsuzawa T., Brit. J. Radiol. 54 (1981) 384.
10) Lammertsma A. L., Jones T., Frackowiak R. S. J., Lenzi G. L., J. Comput. Assist Tomog. 5 (1981) 544.
11) Lammertsmma A. A., Jones T., J. Cereb. Blood Flow Metabol. 3 (1983) 416.
12) Lammertsmma A. A., Baron J. C., Jones T., J. Cereb. Blood Flow Metabol. 3 (1987) 372.
13) Loeb C., Neurol. (Paris) 141 (1985) 694.
14) Meyer J. S., Ishihara N., Deshmukh V. D. et al., Stroke 9 (1978) 195.

15) Naritomi H., Meyer J. S., Sakai F., Yamaguchi F., Shaw T., Arch. Neurol. 36 (1979) 410.
16) Pantano P., Baron J. C., Lebrun-Grandie P. et al., Stroke 15 (1984) 635.
17) Takeda S. and Matsuzawa T., J. Am. Geriatr. Soc. 32 (1984) 520.
18) Takeda T., Matsuzawa T., Matsui H., Jap. J. Geriat. 25 (1988) 19.
19) Terry R. D., DeTeresa R., Hansen L. A., Ann. Neurol. 21 (1987) 530.
20) Yamaguchi T., Hatazawa J., Kubota K. et al., J. Am. Geriatr. Soc. 31 (1983) 412.
21) Yamaguchi T., Kanno I., Uemura K., Shishido F., Inugami A. et al., Stroke 17 (1986) 1220.
22) Yamaura H., Ito M., Kubota K. and Matsuzawa T., J. Gerontol. 35 (1980) 492.

Table 1. Physiological data of subjects.
Values for mean and s. d. are shown.

	Normals	RIAs	Total
Number	13	11	24
Sex(F/M)	7/6	4/7	11/13
Age(years)	65 ± 10	66 ± 5	66 ± 8
Blood Pressure (mean, mmHg)	10 ± 11	100 ± 9	100 ± 12
Arterial O2 content	0.18 ± 0.01	0.18 ± 0.01	0.18 ± 0.01
Pa CO2	40.6 ± 2.2	40.2 ± 1.7	40.4 ± 2.0

Table 2. Craniocerebral index (CCI) and measured PET parameters using 150 inhalation technique in Normals and RIAs. Mean(top) and s. d(bottom) for gray matter of each hemisphere are shown.

	AGE	CCI	CBV	CBF	CMRO2	OEF	CBF/CBV
Normals	66	0.906	4.0	38	3.2	0.46	10.0
	11	0.044	1.0	10	1.1	0.07	2.6
RIAs	67	0.917	4.2	38	3.1	0.45	9.6
	5	0.022	0.9	8	0.9	0.08	2.7
Total	66	0.911	4.1	38	3.1	0.46	9.8
	9	0.036	0.9	9	1.0	0.07	2.7

Table 3. Mean CBV(%), CBF(ml/100g/min), CMRO2(ml/100g/min), OEF in the gray matter of studied cases. Values from each hemisphere are divided into two groups according to CCI with the border CCI value of its average, 0.911.

	AGE	CCI	CBV	CBF	CMRO2	OEF	CBF/CBV
Lower	72[a]	0.880	3.9	34[b]	3.0	0.47	9.6
CCI	7	0.029	0.7	7	1.0	0.07	2.6
Higher	62[a]	0.935	4.2	41[b]	3.2	0.45	9.9
CCI	7	0.018	1.0	10	0.9	0.08	2.7

a: $p < 0.001$, b: $p < 0.01$

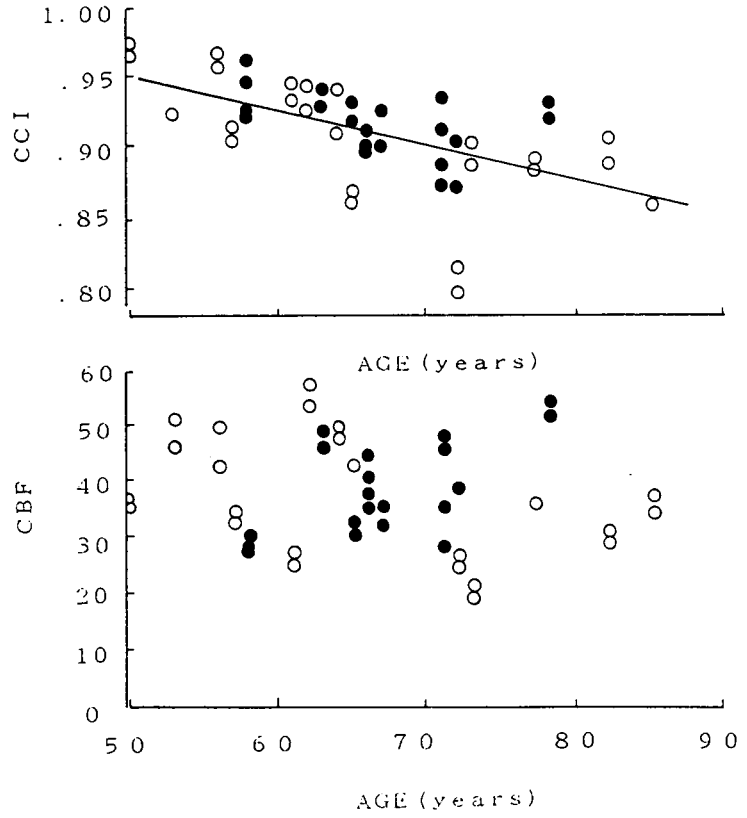
1.00
.95
.90
.85
.80
CCI
AGE (years)
60
50
40
30
20
10
0
CBF
50
60
70
80
90
AGE (years)

Fig. 1.

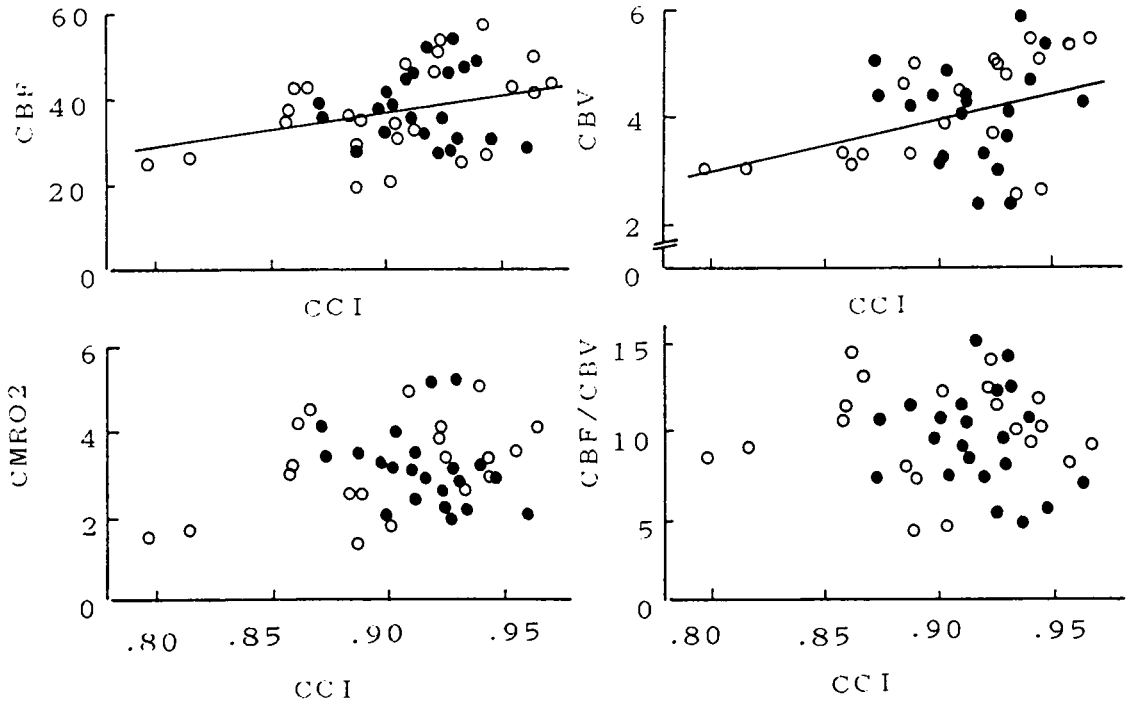
60
40
20
0
CBF
CCI
6
4
2
0
CBV
CCI
6
4
2
0
CMRO2
.80
.85
.90
.95
CCI
15
10
5
0
CBF/CBV
.80
.85
.90
.95
CCI

Fig. 2.

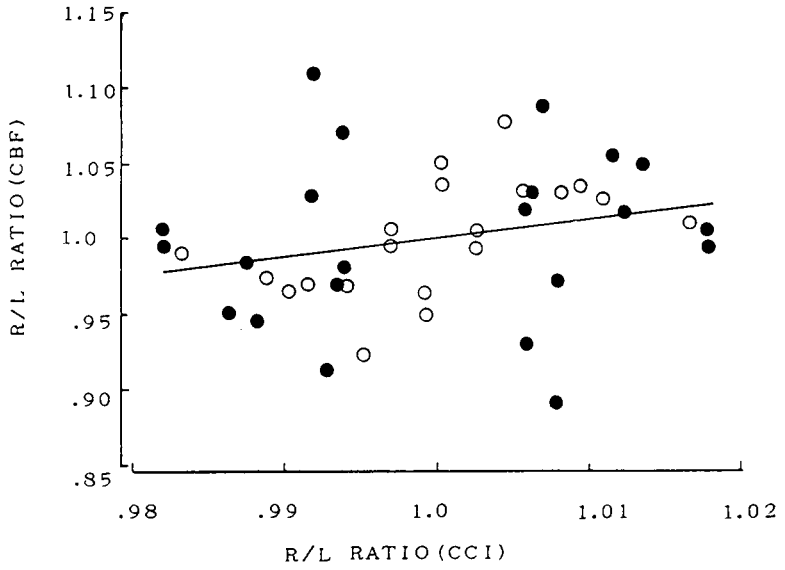

Fig. 3.