Dynamic SPECT with Iodine-123 IMP in Meningiomas

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Dynamic studies of single photon emission computed tomography (SPECT) were performed with intravenous administration of N-isopropyl-p-[^{123}I]iodoamphetamine ([^{123}I]IMP) in 12 patients with meningiomas. Their vascularities were also assessed by angiography. Regions of interest (ROIs) were placed over the lesion and the contralateral presumed normal area, the symmetrical one if possible. Time-activity curves (TACs) were then constructed and the counting-rate ratio for the lesion to the contralateral presumed normal area (L/N ratio) was calculated in the first image of the dynamic SPECT. TACs were classified into three types: type I, an initial high uptake and rapid washout type, type II, an initial high uptake and slow washout one, and type III, an initial low uptake one. L/N ratios of angioblastic meningiomas were over 300%, while those of many fibroblastic ones were under 100%, at most 105%. We compared L/N ratios with angiographic vascularities and histologic types and conclude that dynamic SPECT with [^{123}I]IMP is the examination of choice for evaluating the vascularity of lesions.

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N-isopropyl-p-[^{123}I]iodoamphetamine ([^{123}I]IMP), a lipophilic tracer, is distributed in correlation to regional cerebral blood flow (rCBF). It crosses the blood-brain barrier easily and is extracted almost completely during a single passage through cerebral circulation in normal brain tissue. Brain uptake of [^{123}I]IMP is thought to be a result of an affinity for high capacity, relatively nonspecific binding sites for amines (*1,2*). However, in brain tumors, even in meningiomas, there is no [^{123}I]IMP uptake in the lesions in the static single photon emission computed tomography (SPECT) because they were reported to have low extraction efficiencies and no binding sites for [^{123}I]IMP in their tissues (*3–5*). The purpose of our present study is to investigate the usefulness of the dynamic SPECT with [^{123}I]IMP in evaluating regional blood flow of meningiomas and kinetic behavior of [^{123}I]IMP in them.

MATERIALS AND METHODS

Patient Selection

Twelve patients with meningiomas, six males and six females, aged 22 to 86 yr (median age 54 yr) were studied. All patients underwent angiographies and x-ray computed tomography (CT) scans with and without i.v. administration of contrast medium. Eleven patients underwent total resection of the tumors and their histologic diagnoses were confirmed. The remaining patient's diagnosis was made by x-ray CT scans and angiographies. All patients were awake, fully oriented, and cooperative.

Patients Preparation

Measurements of rCBF were performed with SPECT using xenon-133 (^{133}Xe) and [^{123}I]IMP. The patients were placed in a supine position in a quiet room with their eyes closed. At first they breathed ^{133}Xe gas at the concentration of 10 mCi/l for 1 min with a nose clamp and a rubber mouthpiece connected to the Ventil-Con spirometer. Then the spirometer was switched to open circuit and measurements continued for 9 min more. Iodine-123 IMP SPECT followed ^{133}Xe SPECT. Dynamic SPECT(D-SPECT) started immediately after i.v. injection of 3 mCi of [^{123}I]IMP which was free of ^{124}I and contained at most 4.5% of ^{125}I. Prior to injection the patients had been given iodine solution to block the thyroid. Data acquisition time of the D-SPECT was 20 min. And then static SPECT(S-SPECT) started 30 min after injection.

Data Acquisition and Analysis

This study was performed with a ring-type gamma camera (SET020 Shimazu Co.) which consists of a gantry assembly with 64 scanning detectors. This system has two rings and simultaneously acquires two parallel slices with a center-to-center interslice distance of 3.5 cm. A hypersensitive (HS) collimator was used in the D-SPECT and ^{133}Xe SPECT and a high-resolution (HR) one was done in the S-SPECT. The raw data were reconstructed by the method of filtered back-

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projection, using a Ramachandran-Butterworth filter. Reconstruction was performed using a Data General Eclipse S-120 processor for a 64 × 64 matrix image in the [^{123}I]IMP SPECT and a 32 × 32 one in the ^{133}Xe SPECT. Slice thickness were 24 and 16 mm in the HS and HR collimators respectively. In the ^{133}Xe SPECT the calculation of rCBF was performed by employing the Celsis modification of the Kanno and Lassen algorithm (*6,7*). In the D-SPECT the data acquisition was performed every 2 min for 20 min and ten serial images were obtained. The approximate number of counts were ~50,000–60,000 and 200,000–300,000 counts in the first and tenth images, respectively. In the S-SPECT the data acquisition lasted until 600,000 counts were collected. Data analysis was done without smoothing. A region of interest (ROI) of 1.75-cm diameter (4 × 4 matrix in the [^{123}I]IMP SPECT) was placed over the lesion. For comparison an equal size ROI was placed over the presumed normal region of the contralateral cerebral hemisphere, the symmetrical one if possible. And then ^{133}Xe rCBF of the two regions were calculated. In the D-SPECT time-activity curves (TACs) were constructed and the counting-rate ratio for the lesion to the contralateral presumed normal area (Lesion/Normal ratio, L/N ratio) was calculated in the first image. The vascularity of the tumor was graded to four grades by angiographical findings. Extremely hypervascular meningiomas with early venous filling and marked tumor stains were graded to Grade I, those with definite tumor stains to Grade II, those with minimal tumor stains to Grade III and hypovascular meningiomas without tumor stains to Grade IV. In the analysis of TACs filling time (time to the peak) and rapid washout time (time from the peak to the end of rapid washout phase) were evaluated (Fig. 1). Xenon-133 rCBF and L/N ratio were compared with angiographical grades and we investigated the usefulness of these SPECT studies in assessing the vascularity of meningiomas.

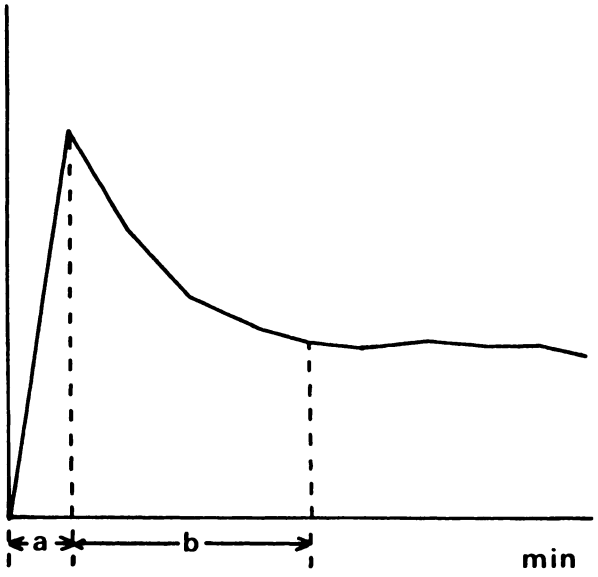

FIGURE 1
Filling time and rapid washout time. "a" indicates filling time (time to the peak) and "b" indicates rapid washout time (time from the peak to the end of rapid washout phase). The unit of the transversal axis is time (minutes) and that of the ordinate is number of counts in the ROI.

RESULTS

The clinical data of the 12 patients in this study are summarized in Table 1. These 12 meningiomas included two angioblastic types, two meningothelial ones, three transitional ones, and four fibroblastic ones. The other one (Case 3) did not undergo an operation because of his age and high vascularity of the tumor. In all patients CT scans revealed markedly enhanced tumor. In angiography two angioblastic meningiomas were graded to Grade I, five (two meningothelial, two transitional and an unverified one) to Grade II, three (a transitional and two fibroblastic ones) to Grade III and the other two small fibroblastic ones to Grade IV. Xenon-133 SPECT showed high blood flow areas corresponding to the tumors in all patients but three with fibroblastic meningiomas which were delineated as low or almost iso-blood flow areas. One of four fibroblastic meningiomas was delineated as a slightly high blood flow area in the ^{133}Xe SPECT. The blood flow of the meningiomas in the ^{133}Xe SPECT ranged between 44 ml/100g/min of a fibroblastic and a transitional one (Cases 8, 12) and 201 ml/100 g/min of an angioblastic one (Case 1). In only two patients (Cases 3, 4) did the S-SPECT delineate the lesion as a high uptake area. In almost all patients, the S-SPECT could not detect high blood flow of meningiomas. The first images of the D-SPECT, however, revealed high uptake areas in all patients but four with fibroblastic meningiomas.

L/N ratios ranged between 74% of a fibroblastic meningioma (Case 12) and 452% of an angioblastic one (Case 1). In two patients with angioblastic meningiomas the L/N ratios were 362% and 452%, respectively, while in four patients with fibroblastic ones they ranged between 74% and 105%. In the other five patients with meningothelial or transitional ones they ranged between 115% and 170%. In Case 3 histologic diagnosis was not confirmed by the L/N ratio suggested an angioblastic meningioma. The higher the L/N ratio was, the more hypervascular the tumor was. L/N ratio was more useful in assessing the blood flow of the tumor than that of ^{133}Xe rCBF. In Case 2 ^{133}Xe SPECT suggested a meningothelial or a transitional meningioma, whereas the D-SPECT suggested an angioblastic tumor. D-SPECT was more useful than ^{133}Xe SPECT also in Case 8 and Case 10. L/N ratio was very useful in assessing the vascularity of meningiomas, as was the angiographic grade.

TACs derived from the D-SPECT were classified into three types. Namely, type I is an initial high uptake and rapid washout type, type II is an initial high uptake and slow washout one and type III is an initial low uptake one (Figs. 2, 3, and 4). Of these 12 patients four belonged to type I, four did to type II, and four did to type III. All types of meningiomas except for fibroblastic

TABLE 1
Clinical Data

Case no.	Age (yr)	Sex	Histologic type	Angiographic grade	L/N ratio	^{133}Xe rCBF	TAC	Filling time	Rapid washout time
1	50	M	Angioblastic	I	452%	201/60 (335%)	Type I	≤2 min	8 min
2	60	F	Angioblastic	I	362%	70/40 (175%)	Type I	≤2 min	10 min
3	86	M	Unknown	II	255%	100/40 (250%)	Type II	4	—
4	59	M	Meningothelial	II	170%	49/39 (126%)	Type II	6	—
5	22	M	Meningothelial	II	120%	73/63 (116%)	Type I	≤2	2 min
6	77	M	Transitional	II	169%	63/35 (180%)	Type II	4	—
7	45	M	Transitional	II	115%	78/53 (147%)	Type I	≤2	2 min
8	51	F	Transitional	III	117%	44/43 (102%)	Type II	6	—
9	75	F	Fibroblastic	III	105%	61/57 (107%)	Type III	≥20	—
10	42	F	Fibroblastic	III	98%	55/43 (128%)	Type III	≥20	—
11	42	F	Fibroblastic	IV	95%	52/51 (102%)	Type III	≥20	—
12	42	F	Fibroblastic	IV	74%	44/47 (94%)	Type III	≥20	—

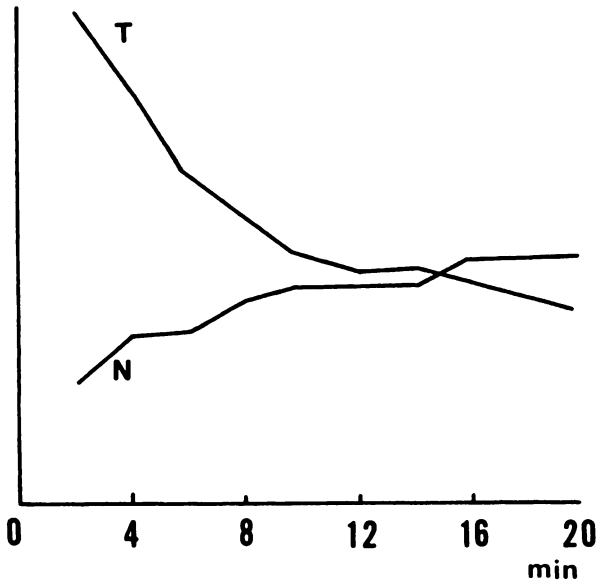

FIGURE 2
TAC of type I (Case 2) T; tumor, N; normal TAC of type I means initial higher uptake of [^{123}I]IMP in the tumor than the contralateral normal area and washout of [^{123}I]IMP in it within 20 min under normal level. In this case initial uptake of [^{123}I]IMP was extremely high and the L/N ratio was no less than 362%. The histologic diagnosis was an angioblastic meningioma.

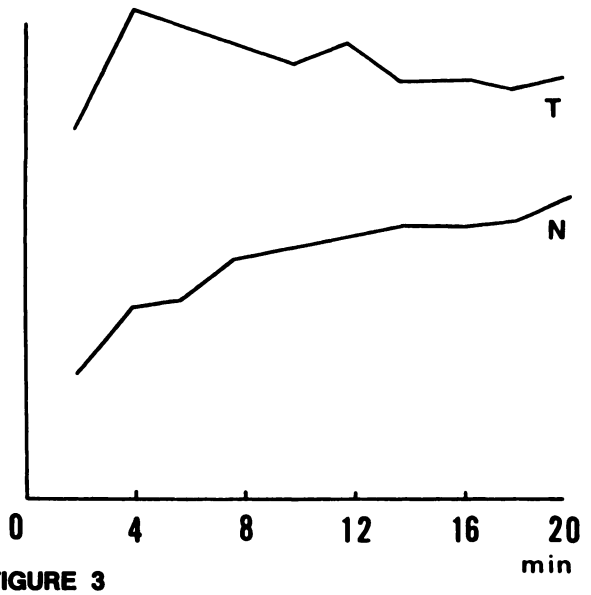

FIGURE 3
TAC of type II (Case 3) T; tumor, N; normal TAC of type II means initial higher uptake of [^{123}I]IMP in the tumor than the contralateral normal area and continuous higher level for 20 min without washout phase. In this case the L/N ratio was 255%. Though the histologic diagnosis was not confirmed, an angioblastic meningioma was suspected. Some retention mechanisms of [^{123}I]IMP in the tumor was suspected.

ones showed TACs of initial high uptake pattern, type I or type II, while all four fibroblastic meningiomas showed TACs of type III. In two of four meningiomas of type I [^{123}I]IMP had already been washed out in the second images of the D-SPECT. In the other two patients of type I (Case1,2) the uptake of [^{123}I]IMP was very high and its washout was slightly slow. Their histologic diagnosis was angioblastic meningiomas.

DISCUSSION

In 1980, Winchell et al. (*1*) first reported [^{123}I]IMP, a new radiopharmaceutical for rCBF imaging. Since then some hypotheses of mechanism for the retention of [^{123}I]IMP in the brain have been reported (*1,2,8*). A simple explanation such as lipophilicity is not sufficient. Yet, specific receptor binding theory could not be the explanation, either. "pH-shift" is a possible mechanism for the brain uptake and retention but this hypothesis cannot explain the long-term retention of [^{123}I]IMP (*9*). For example, N-t-butyl-o-iodobenzylamine having a partition coefficient and pH profile to the brain uptake and retention almost identical to those of IMP, washed out from the brain within an hour (*9*). In studies of synaptosomes in dogs and monkeys, Winchell et al. (*2*) found that uptakes of norepinephrine and especially serotonin were inhibited by IMP and both serotonin and dopamine were released or displaced by IMP. These findings suggested that IMP bound to "non-specific, high capacity binding sites for amines."

In brain tumors, even in hypervascular lesions such as meningiomas [^{123}I]IMP is distributed proportionally

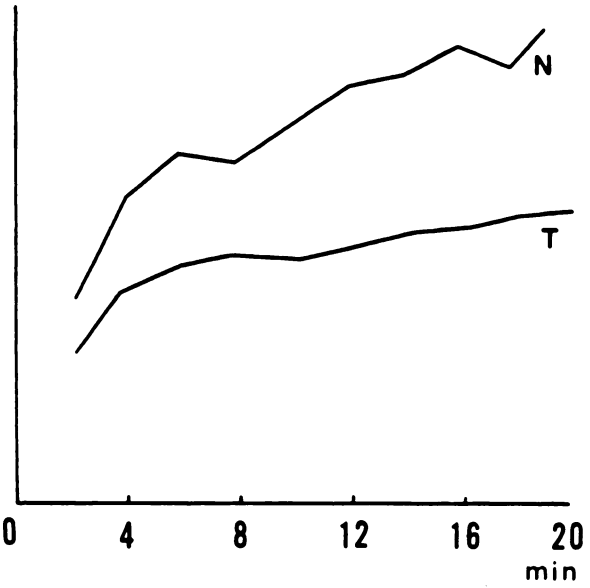

FIGURE 4
TAC of type III (Case 12) T; tumor, N; normal TAC of type III means continuous lower uptake of [^{123}I]IMP in the tumor than the contralateral normal area for 20 min and gradual increase of [^{123}I]IMP uptake in it without washout phase. In this case the L/N ratio was only 74% and the histologic diagnosis was a fibroblastic meningioma.

to blood flow but there is no [^{123}I]IMP uptake in the S-SPECT regardless of the tumor type, blood flow or blood-brain-barrier damage (*3–5*). This may reflect a lack of binding sites for [^{123}I]IMP in them. Probably it had been washed out rapidly. We tried to detect the intravascular blood flow of the hypervascular lesions with the D-SPECT.

Mizukawa et al. (*10*) reported that the concentration of [^{123}I]IMP in the arterial blood reached to the peak 20 sec after i.v. bolus injection and decreased rapidly within a few minutes. Rapin et al. (*11*) also reported that arterial radioactivity declined sharply during the first 5 min after intravenous injection. Thus, it is necessary to perform SPECT scans at least within a few minutes after intravenous injection of [^{123}I]IMP in order to detect the intravascular high blood flow of meningiomas. Kuhl et al. (*12*) have shown a good correlation between [^{123}I]IMP deposition at 5 min after i.v. injection and rCBF measured by microsphere extraction in normal dogs. Some authors (*3,12–15*) have stressed that [^{123}I]IMP SPECT should be taken within the first 10–30 min after intravenous injection to evaluate rCBF. We agree with them in evaluating the ischemic lesions. However, in hypervascular lesions [^{123}I]IMP was washed out more rapidly. We stress that it should be taken within a few minutes after intravenous injection in evaluating the intravascular blood flow of the hypervascular lesions. Hypervascular meningiomas including angioblastic, meningothelial and transitional ones showed TACs of initial high uptake pattern, type I or type II, while all four fibroblastic ones showed TACs of type III, four meningiomas showing TACs of type II were suspected to have some retention mechanisms of [^{123}I]IMP. Unlike many other tumors, meningiomas often showed TACs of type II. "pH-shift" mechanism or some chemical reactions inducing lipophobic metabolites of [^{123}I]IMP in the tumor were suspected.

In the analysis of TACs, filling time and rapid washout time reflect the speed of [^{123}I]IMP influx in the tumor and the transit time respectively. TACs of angioblastic meningiomas showed short filling time and slightly prolonged rapid washout time. Of course short filling time indicates high speed of [^{123}I]IMP influx in the tumor. Their rapid washout time is too long to be explained by only prolonged transit time and some short term retention mechanisms of [^{123}I]IMP in them is suspected, while TACs of all four fibroblastic meningiomas showed gradual increase of radioactivity without peak and washout phase. This may reflect not only low speed of [^{123}I]IMP influx but also prolonged transit time and some retention mechanism of [^{123}I]IMP in them.

Angiographies have been used to evaluate the blood flow of meningiomas. We graded the vascularity of meningiomas to four grades by angiographical findings and compared them with L/N ratios. L/N ratios of angioblastic meningiomas were over 300%, while those of many fibroblastic ones were under 100%. Those of meningothelial or transitional ones ranged 115% and 170%. L/N ratios of meningiomas with angiographical Grade I were more than 300%, while those with Grade III or IV ranged 74% and 117%. Thus L/N ratios were very useful in evaluating the vascularity of meningiomas.

Xenon-133 rCBF calculated by the Celsis modification of the Kanno and Lassen algorithm could not reflect the vascularity of meningiomas well because ^{133}Xe SPECT could not provide correct rCBF values of intravascular shunt flow. Furthermore, [^{123}I]IMP SPECT images had better spatial resolution than ^{133}Xe SPECT and had an advantage in detecting the lesions of the lower part of the frontal lobe which ^{133}Xe SPECT could not delineate well because of ^{133}Xe gas in the paranasal sinuses (*15*). Thus the D-SPECT is the examination of choice in evaluating hypervascular lesions, and in a patient with a fibroblastic meningioma without attachment to major vessels such as the superior sagittal sinus the diagnosis can be made by CT scan and its low vascularity can be assessed by the D-SPECT and angiography is therefore not necessary.

REFERENCES

1. Winchell HS, Baldwin RM, Lin TH. Development of I-123-labeled amines for brain studies: localization of I-123 iodophenylalkyl amines in rat brain. *J Nucl Med* 1980; 21:940–946.
2. Winchell HS, Horst WP, Braun L, et al. N-isopropyl-[^{123}I]p-iodoamphetamine: single-pass brain uptake and washout; binding to brain synaptosomes; and localization in dog and monkey brain. *J Nucl Med* 1980; 21:947–952.
3. Creutzig H, Schober O, Gielow P, et al. Cerebral dynamics of N-isopropyl-[^{123}I]iodoamphetamine. *J Nucl Med* 1986; 27:178–183.
4. LaFrance ND, Wagner HN, Whitehouse JP, et al. Decreased accumulation of isopropyl-iodoamphetamine(I-123) in brain tumors. *J Nucl Med* 1981; 22:1081–1083.
5. Moretti JL, Askienazy S, Raynaud C, et al. ^{123}I-p-iodoisopropyl amphetamine for brain tumor diagnosis. In Biersack HJ and Winkler C (eds). Amphetamines and ph-shift agent for brain imaging, basic research and clinical results. New York: Walter de Gruyter, 1986: 167–170.
6. Celsis P, Goldman T, Henriksen L, et al. A method for calculating regional cerebral blood flow from emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr* 1981; 5:641–645.
7. Kanno I, Lassen NA. Two methods for calculating regional cerebral blood flow from emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr* 1979; 3:71–76.
8. Tramposch KM, Kung HF, Blau M. Brain imaging with ^{123}I labeled diamines: a kit preparation suitable for routine clinical use. *J Nucl Med* 1981; 22:12.
9. Baldwin RM, Lin TH, Wu JL, et al. Receptors for amines. In: Biersack HJ, Winkler C, eds. Ampheta-

mines and pH-shift agent for brain imaging, basic research and clinical results. New York: Walter de Gruyter, 1986: 19–23.
10. Mizukawa N, Toho H, Uchibori M, et al. Single photon emission tomography (SPECT) study of the patients with cerebrovascular disease using N-isopropyl-p-[^{123}I] iodoamphetamine (IMP). *J Kyoto Pref Univ Med* 1985; 94:521–532.
11. Rapin JR, Le Poncin-Lafitte M, Duterte D, et al. Iodoamphetamine as a new tracer for local cerebral blood flow in the rat: comparison with isopropyl-iodoamphetamine. *J Cereb Blood Flow Metab* 1984; 4:270–274.
12. Kuhl DE, Barrio JR, Huang S-C, et al. Quantifying local cerebral blood flow by N-isopropyl-p-[^{123}I]iodoamphetamine (IMP) tomography. *J Nucl Med* 1982; 23:196–203.
13. Buell U, Krappel W, Schmiedek P, et al. Regional iodoamphetamine (^{123}I-IMP) uptake (SPECT) and regional cerebral blood flow (^{133}Xe-DSPECT). In Biersack HJ and Winkler C (eds). Amphetamines and pH-shift agent for brain imaging, basic research and clinical results. New York: Walter de Gruyter, 1986: 127–137.
14. Holman BL, Zimmerman RE, Schapiro JR, et al. Biodistribution and dosimetry of N-isopropyl-p-[^{123}I] iodoamphetamine in the primate. *J Nucl Med* 1983; 24:922–931.
15. Lassen NA, Henriksen L, Holm S, et al. Cerebral blood-flow tomography: xenon-133 compared with isopropyl-amphetamine-iodine-123: concise communication. *J Nucl Med* 1983; 24:17–21.