Different Uptake of Tc-99m ECD and Tc-99m HMPAO in the Normal Brains: Analysis by Statistical Parametric Mapping

Euy-Neyng Kim, M.D., **Yong-An Jung**, M.D., **Hyung-Sun Sohn**, M.D., **Sung-Hoon Kim**, M.D., **Ie-Ryung Yoo**, M.D. and **Soo-Kyo Chung**, M.D.

Departments of Nuclear Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

정상 뇌 혈류 영상에서 방사성의약품에 따라 혈류 분포에 차이가 있는가: 통계적 파라미터 지도를 사용한 분석

가톨릭대학교 의과대학 방사선과학교실

김의녕 · 정용안 · 손형선 · 김성훈 · 유이령 · 정수교

목적: 이번 연구는 두 명의 경험 있는 핵의학과 의사에 의하여 정상이라고 판독된 뇌 혈류 단일광자방출전산화단층촬영 영상에서 사용한 방사성의약품에 따라 혈류 분포에 차이가 있는지를 통계적 파라미터 지도를 사용하여 분석하여 보았다. **대상 및 방법**: 정상이라고 판독된 뇌 혈류 단일광자방출전산화단층촬영 53 증례를 후향적으로 분석하였고, 그 중 32증례는 Tc-99m ECD를 방사성의약품으로 사용하였으며 나머지 21 증례는 Tc-99m HMPAO를 방사성의약품으로 사용하여 획득한 영상이었다. 모든 뇌 혈류 단일광자방출전산화단층촬영 영상은 통계적 파라미터 지도 분석에 적합하도록 미리 표준화 시킨 후 분석을 시행하였고 분석결과 통계적으로 두 그룹간에 corrected P value가 0.05 이하인 경우에 서로 의미 있는 차이라고 해석하였다. **결과**: 정상으로 판독된 뇌 혈류 단일광자방출전산화단층촬영 중에서도 방사성의약품을 어느것을 사용하느냐에 따라 분명한 혈류 분포의 차이를 나타내었다. Tc-99m ECD를 사용한 뇌 혈류 단일광자방출전산화단층촬영에서는 Tc-99m HMPAO를 사용하였을 때 보다 전두엽, 측두엽, 후두엽, 기저핵, 시상 및 소뇌의 상부 등 광범위한 부위에서 높은 혈류분포를 보였으며 반대로 Tc-99m HMPAO를 방사성의약품으로 사용한 경우에는 Tc-99m ECD를 사용하였을 경우보다 전두엽의 피질하 부위, 측두엽 일부 및 소뇌의 하부 등 국소적인 부위에서 상대적으로 증가된 혈류분포가 관찰되었다. **결론**: 통계적 파라미터 지도를 사용하여 분석하여 본 결과 정상으로 판독된 뇌 혈류 단일광자방출전산화단층촬영에서 사용된 방사성의약품에 따라 유의한 혈류분포의 차이를 나타내었다. 따라서 뇌 혈류를 평가하는데 있어서는 어떠한 방사성 의약품을 사용하였는가를 반드시 고려하여야 한다.**(대한핵의학회지 2002;36;244-54)**

Key Words: Tc-99m HMPAO, Tc-99m ECD, SPM

Received Dec 05, 2001; accepted Aug 12, 2002
Corresponding author: Hyung-Sun Sohn, M.D., Departments of Nuclear Medicine, St. Mary's Hospital, 62 Youido-Dong, Youngdeungpo-Gu, Seoul 150-713, Korea
Tel: 82-2-3779-1445, Fax: 82-2-769-1722, E-mail: hssohn@cmc.cuk.ac.kr
This study was supported by the clinical research fund of college of medicine, The catholic university of korea

Introduction

The introduction of Tc-99m-labeled neuroperfusion tracers has enabled high-resolution SPECT imaging of the brain. Currently, Technetium-99m ethyl cysteinate dimer (Tc-99m ECD) and Tc-99m-hexamethylpropylene amine oxime (Tc-99m HMPAO) are commercially available for routine SPECT examinations of central nervous system disorders as a marker of regional cerebral blood flow (rCBF).[1-5] Both Tc-99m ECD and Tc-99m HMPAO are intravenously administered compounds that are highly lipophilic and quickly cross the blood-brain barrier. There have been several studies comparing the differences between Tc-99m ECD and Tc-99m HMPAO from the point of view of image quality and pharmacokinetics.[6-9] Recently, a software package known as Statistical Parametric Mapping (SPM) has been developed that not only spatially normalizes PET or SPECT images to a standardized stereotactic space, but can then also perform statistical analyses on groups of images.[10,11] This software allows for reliable, objective image handling and data analysis, which could definitely improve variability between studies due to the analytic process itself. Patterson et al. reported significant quantitative differences between Tc-99m ECD and Tc-99m HMPAO uptake in a side-by-side comparison and a SPM analysis.[12] Hyun et al. also reported differences between two tracers in the same brains using split-dose and sequential SPECT techniques for comparison using SPM.[13] Different tracer kinetics has been regarded as the main reason for differences in the uptake of Tc-99m ECD and Tc-99m HMPAO. Other investigators have examined intra-individual differences, but these studies were not performed using SPM methods and so were subject to the inherent inaccuracy of region of interest methods.[7,14] In this study, we used the SPM'99 software package in the normal brain to show the significant differences between these two common tracers used in SPECT brain mapping and to compare the results with previous reports.

Materials and Methods

1. Subjects

We analyzed retrospectively, age and sex, matching 53 cases of normal brain SPECT that performed for the one's health at our health promotion center. All of brain SPECTs were regarded as normal by the concordance of two readers with widely experience. SPECT measurement of brain perfusion was performed in 21 individuals who received Tc-99m HMPAO (11 women, 10 men; age 2175 years; mean age 4511 years) and in 32 who received Tc-99m ECD (16 women, 16 men; age 2274 years; mean age 4412 years). There was no abnormal finding on brain MRIs, which were performed on a 1.5-T MR imager (Vision plus; Siemens, Erlangen, Germany) with a standard birdcage head coil. Subjects with a history of psychotic or neurologic disorders, drug use, alcohol abuse, dementia, or head trauma were excluded.

2. SPECT

All SPECT imaging were initiated 20 minutes after intravenous injection of approximately 740~925 MBq of Tc-99m ECD or Tc-99m HMPAO using a multi-detector scanner (ECAM plus; Siemens, Erlangen, Germany) equipped with a low-energy, fan-beam collimator. The head unit consists of two rings of 59 probe-type detectors. Inside the right of crystals, there is a rotating collimator with septa varying from 0 degree to 35.2 degrees. Both the detector ring and the collimator rotate. Data was acquired on a 128×128 matrix with a 20% symmetric window at 140 keV. Continuous transaxial tomograms of the brain were reconstructed

after filtered backprojection with a Butterworth (cutoff frequency 0.4 cycles/pixel, order 5) to reduce statistical noise. Tc-99m ECD and Tc-99m HMPAO images were corrected for tissue attenuation using a standard commercial correction routine, which assumes uniform attenuation with the circular shape of the head.

3. Image formatting

All subsequent image manipulation and data analysis were performed on a personal computer using a WINDOWS 98 operating system (Microsoft, Redmond, Wash, USA). The software for image manipulation included Matlab, version 5.3 (Mathworks, Inc., Natick, MA) and SPM'99 (Institute of Neurology, University College of London, UK).[10]

The reconstructed SPECT data with attenuation and scatter correction were reformatted into Analyze (Mayo Foundation, Baltimore, Md., USA) header format. The header format of the SPECT data includes 348 bytes of header, 3.9 mm of x and y pixel size, and 3.9 mm of slice thickness. The SPECT images of Tc-99m ECD and Tc-99m HMPAO were separately co- registered to remove variations due to different sizes and shapes of individual brains. The parameters for co-registration were: intra- modality, linear algorithm, 12 affine parameter models for controlling the number of degrees of freedom used in registration, and tri-linear interpolation. All slices of brain images were then sampled and averaged to arrive at mean pixel intensity for that image. The intensity threshold was set at 80% of the whole-brain mean. This level eliminated low-intensity background noise inherent in the images and effectively removed brain-edge halo caused by partial-volume error, without losing any image data specific to the brain. The global cerebral blood flow rate was normalized to an arbitrary mean of 50 ml/100 ml per minute by a group-wise analysis of covariance (ANCOVA). The data were then normalized to a better resolution SPECT template (MNI template: Montreal Neurological Institution Template)[11] and smoothed with 8 mm FWHM prior to SPM statistical analysis. The final image format was 16-bit, with a size of $79\times95\times68$ and a voxel size of $2\times2\times2$ mm.

4. Image analysis

To examine images of specific regions for differences in perfusion between the two groups, the two groups were compared using contrasts. The first contrast examined areas of increased perfusion in one group, as compared to the other group, and the second contrast examined areas of decreased perfusion. After specifying the appropriate design matrix, differences of rCBF produced by the different subject groups were estimated according to the general linear model at each voxel. An ANCOVA model was fitted, and a t-statistic image (SPM [t]) for the contrast condition effect was constructed. The resulting set of voxel t-values constitutes the statistical parametric mapping SPM [t] with a threshold value of 4.80 (or p=0.05, corrected) and a minimal cluster size of 5 voxels. For visualization of the t-score statistics, the t-score voxel clusters were projected onto the standard high-resolution T1-weighted MRI data set, using the projection protocol, which additionally displays the Talairach coordinates, thus allowing anatomic identification with a hot (Tc-99m ECD>Tc-99m HMPAO) and blue (Tc-99m ECD<Tc-99m HMPAO) color map.

Results

SPM analysis showed significant differences in uptake between Tc-99m ECD and Tc-99m HMPAO images in the normal brains (Fig. 1). On the Tc-99m ECD SPECT images, relatively higher uptake was

observed in the frontal, parietal and occipital lobes, in the sensorimotor cortex, in the basal ganglia and thalamus and in the superior region of the cerebellum (Fig. 2, Table 1). On the Tc-99m HMPAO SPECT images, relatively higher uptake was observed in the subcortical area of the frontal region along the sub-gyral white matter, and small foci of the temporal lobe, and posterior portion of the inferior cerebellum (Fig. 2, Table 2).

Discussion

These data show that there are quantitative differences between the two radiotracers, Tc-99m ECD and Tc-99m HMPAO. The differences in pharmacokinetics between the two tracers could be a cause of the significant changes seen in this study. There are some possible explanations for this phenomenon. First, the accumulations of Tc-99m ECD and Tc-99m HMPAO are affected by nonspecific esterase and glutathione activity, respectively. The cortical distribution of these amino acids or enzymes is not uniform in the brain.[15] Thus, structural or functional heterogeneity of the brain might cause this phenomenon. Second, the contribution of regional metabolism to the accumulation of Tc-99m ECD and Tc-99m HMPAO might differ. The SPECT study of Oku et al. suggested that the accumulation of Tc-99m ECD was more sensitive to the level of metabolism than that of Tc-99m HMPAO.[14] Third, Tc-99m ECD shows a more linear relationship between rCBF and tracer uptake, and thus, back-diffusion of this tracer is not so significant.[16] This could be the causal factor of the large, numerous areas of apparently decreased flow of some cortical areas in the Tc-99m HMPAO group as compared to the Tc-99m ECD group. However, there are smaller areas of apparent increase in the Tc-99m HMPAO group. These areas are mainly subcortical areas.

As indicated above, significantly higher Tc- 99m ECD uptakes were exhibited in the frontal, parietal and occipital lobes, in the basal ganglia and thalamus and in the superior region of the cerebellum. On the other hand, Tc-99m HMPAO uptakes were significantly higher in the subcortical area of the frontal region along the sub-gyral white matter, and small foci of the temporal lobes and posterior portion of the inferior cerebellum. These findings, with some exceptions, are in agreement with previously published data (Table 3).[12-14,16] The reason of these exceptions is partly due to our usage of corrected p-value in SPM voxel [t] statistics rather than uncorrected p-value, that was used in other previous SPM users.[12,13]

The corrected and uncorrected p-values represent extremes along a continuum. If one has a prior hypothesis about one specific voxel in his SPM, which one is able to specify before his experiment, and this hypothesis was confirmed by the data, then one can legitimately quote the uncorrected p value. However, one is examining a very large number of voxels, and even on the null hypothesis, he would expect 5% of these to be significant at $p<0.05$ (that is, after all, what the p value means!). The 'corrected' p value takes into consideration the fact that one has made multiple comparisons, one for each voxel, over the whole brain. Thus, if the corrected p value is still $p<0.05$, then the result is still significant even taking into consideration the large number of comparisons that have been made. The corrected value is therefore the one that one should look at when one has no prior hypothesis about where the activation should be.

Heiss et al. described higher Tc-99m HMPAO uptake in the cerebellum owing to higher capillary density.[17] However, the results of our SPM analysis showed that Tc-99m ECD uptake was relatively higher than Tc-99m HMPAO uptake in the large area of superior region of the cerebellum. This is at

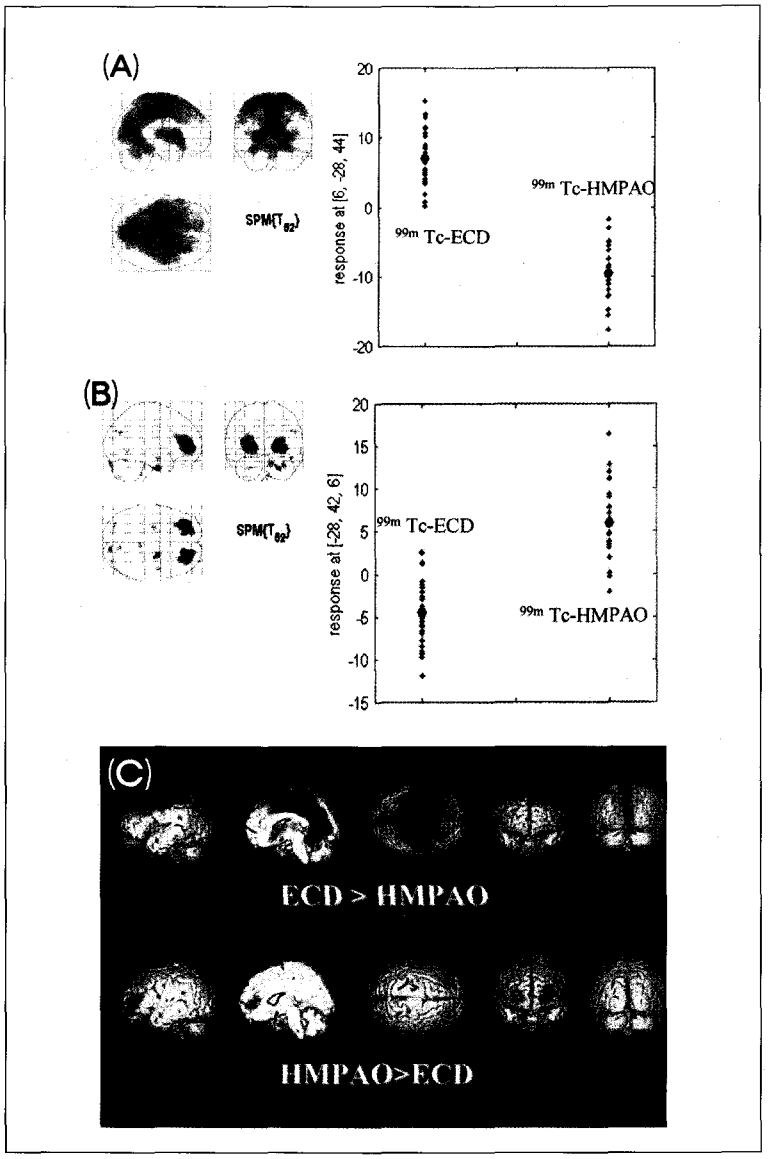

Fig. 1. Apparent increases in brain perfusion of subjects in (A) Tc-99m ethyl cysteinate dimer (ECD) (Tc-99m ECD>Tc-99m HMPAO), (B) Tc-99m hexamethyl propylene amine oxime (HMPAO) (Tc-99m ECD < Tc-99m HMPAO), and (C) rendering images. (A) On the Tc-99m ECD SPECT images, relatively increased areas were observed in the frontal, parietal and occipital lobes, in the sensorimotor cortex, in the basal ganglia and thalamus, and in the superior region of the cerebellum. (B) On the Tc-99m HMPAO SPECT images, relatively increased uptake areas were observed in the subcortical area of the frontal region along the sub-gyral white matter, and small foci of the temporal region, and posterior portion of the inferior cerebellum. The left panel shows a tree-way glass brain view of all the apparent increases seen, where as the right panel shows the plots of two radiotracers at given points (small red mark) among the two groups.

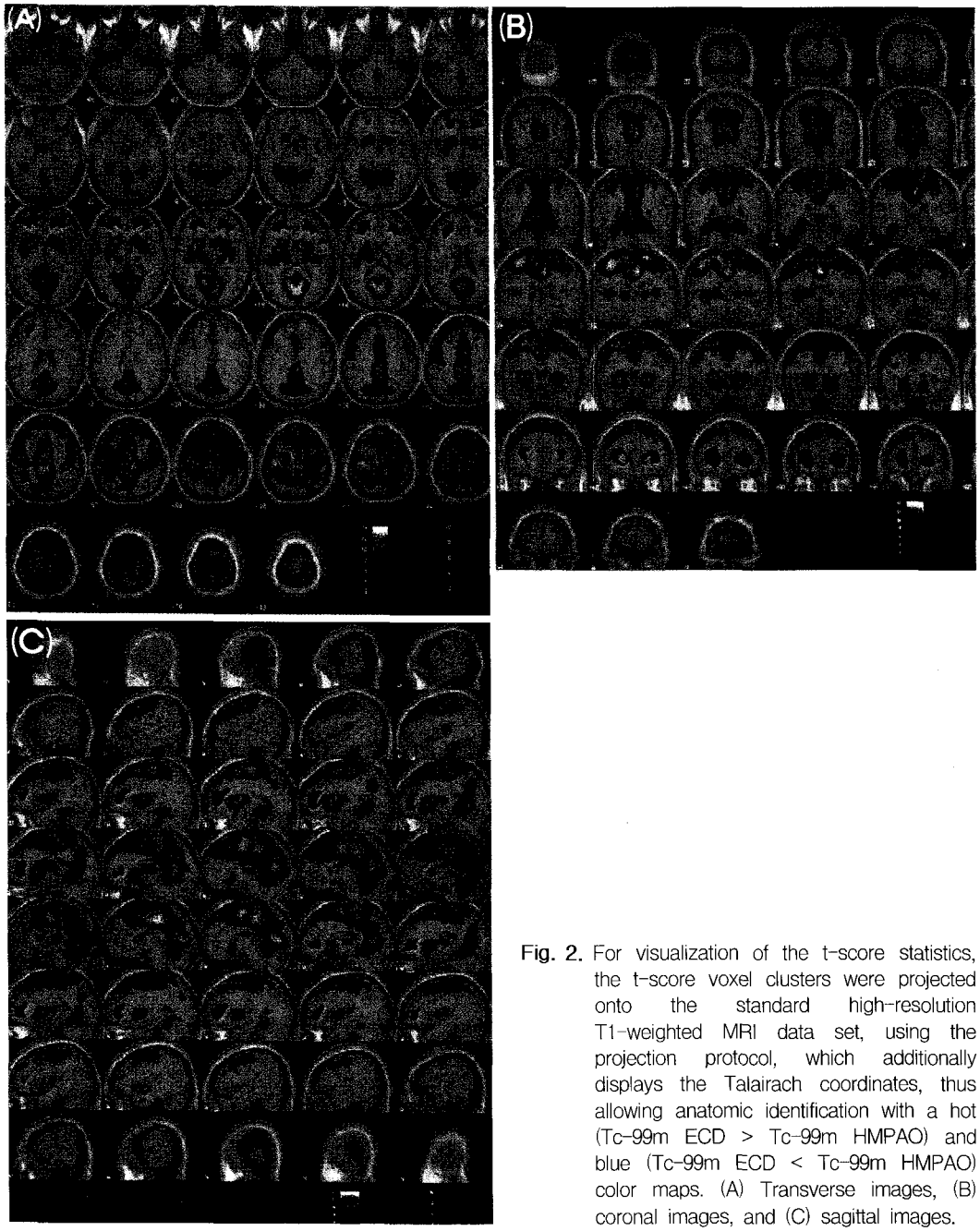

Fig. 2. For visualization of the t-score statistics, the t-score voxel clusters were projected onto the standard high-resolution T1-weighted MRI data set, using the projection protocol, which additionally displays the Talairach coordinates, thus allowing anatomic identification with a hot (Tc-99m ECD > Tc-99m HMPAO) and blue (Tc-99m ECD < Tc-99m HMPAO) color maps. (A) Transverse images, (B) coronal images, and (C) sagittal images.

variance with the results of previous studies.[12,17,18] but in concordance with Hyun at al.[13] Hyun et al. described higher uptake of Tc-99m ECD in the superior region of the cerebellum as contaminated pseudo-activity by the high activity of the neighboring occipital cortex. But in this study, we used an 8-mm FWHM kernel for smoothing rather than the 18mm used by Hyun et al. and there was obvious breakage of activity between the occipital high activity and superior region of the cerebellum

Table 1. Areas of Increased Regional Cerebral Blood Flow (rCBF) in Tc-99m Ethyl Cysteinate Dimer (ECD) Compared to Tc-99m Hexamethylpropylene Amine Oxime (HMPAO)

Regions	Voxel T Value	X	Y	Z
Right				
Frontal lobe				
Medial Frontal Gyrus, Brodmann area 6	14.48	6	0	52
Middle Frontal Gyrus	12.33	32	0	62
Middle Frontal Gyrus, Brodmann area 8	6.49	54	10	38
Precentral Gyrus, Brodmann area 6	8.92	44	-10	58
Precentral Gyrus, Brodmann area 4	8.75	48	-10	54
Superior Frontal Gyrus, Brodmann area 8	8.21	30	32	52
Superior Frontal Gyrus, Brodmann area 8	6.62	12	40	52
Other	10.82	14	-32	72
	9.49	30	20	62
	9.23	12	18	64
Insula	6.61	38	-18	12
Parietal lobe				
Postcentral Gyrus	10.20	30	-28	66
Other	15.61	6	-28	44
	6.39	22	-60	64
Occipital lobe				
Cuneus, White Matter	11.20	8	-74	8
Cuneus, White Matter	11.08	10	-62	8
Cerebellum				
Anterior Lobe, Culmen	10.27	20	-46	-12
Deep Nuclei				
Putamen	11.15	20	16	0
Putamen	10.94	26	6	4
Caudate	10.93	14	20	-6
Thalamus, Ventral Posterior Lateral Nucleus	7.34	18	-18	4
Left				
Frontal lobe				
Medial Frontal Gyrus	13.07	-6	-2	50
Medial Frontal Gyrus	12.34	-10	0	60
Middle Frontal Gyrus	7.13	-42	30	42
Middle Frontal Gyrus, Brodmann area 9	7.93	-54	18	34
Precentral Gyrus	12.05	-38	-22	60
Precentral Gyrus, Brodmann area 4	11.72	-38	-20	54
Precentral Gyrus, Brodmann area 4	5.67	-62	-12	30
Precentral Gyrus, Brodmann area 4	5.67	-60	-12	36
Cingulate Gyrus, Brodmann area 9	6.66	-6	28	32
Cingulate Gyrus, Brodmann area 32	6.56	-6	24	36
Sub-Gyral, White Matter	9.23	-16	22	-14
Other	11.55	-10	-14	70
	10.93	-8	-34	74
	10.57	-36	6	58

	9.03	-10	30	60
	7.11	-10	54	40
	6.66	-16	44	50
	5.32	-34	56	28
	5.28	-32	54	32
Parietal lobe				
Paracentral lobule	13.93	-8	-32	50
Limbic Lobe, Posterior Cingulate, Brodmann area 30	12.26	-14	-62	12
Inferior Parietal Lobule, Gray Matter, Brodmann area 40	6.86	-38	-48	48
Occipital lobe				
Cuneus, Brodmann area 18	11.47	-2	-74	16
Temporal lobe				
Fusiform Gyrus	10.22	-36	-34	-16
Transverse Temporal Gyrus, Brodmann area 41	6.66	-44	-22	10
Cerebellum				
Anterior Lobe Culmen	9.17	0	-52	-14
Deep Nuclei				
Putamen	12.66	-22	14	2
Putamen	12.39	-30	0	6
Thalamus, Ventral Posterior Lateral Nucleus	8.99	-14	-16	8
Thalamus, Ventral Lateral Nucleus	8.85	-14	-10	12

Table 2. Areas of Increased rCBF in Tc-99m HMPAO Compared to Tc-99m ECD

Regions	Voxel Equivalent Z	X	Y	Z
Right				
Frontal Lobe				
Sub-Gyral, White Matter	7.88	26	38	12
Sub-Gyral, White Matter	7.57	18	42	2
Superior Frontal Gyrus, White Matter	7.23	20	54	0
Temporal Lobe	7.26	22	-4	-34
Inferior Temporal Gyrus, Brodmann area 37	5.52	62	-60	6
Sub-Gyral, White Matter	5.54	46	-4	-16
Parietal Lobe	6.21	54	-70	28
	5.56	46	-78	32
Cerebellum	5.71	8	-72	-50
Posterior Lobe, Uvula	6.96	10	-88	-26
Posterior Lobe, Tuber	6.19	34	-86	-30
Left				
Frontal Lobe				
Sub-Gyral, White Matter	9.38	-28	42	6
Sub-Gyral, White Matter	7.80	-18	42	2
Temporal Lobe	6.08	-24	-12	-32
Cerebellum	5.34	-32	-80	-50

Table 3. Comparison of This Study with Previous Studies Using SPM Concerning Different Uptakes of Tc-99m HMPAO and Tc-99m ECD

Study	Tc-99m ECD > Tc-99m HMPAO	Tc-99m ECD < Tc-99m HMPAO
Patterson JC. et al.[10]	Large areas of parietal, occipital and superior temporal cortex	Subcortical nuclei, brain stem, hippocampus, and small areas of the cerebellum
Hyun IY. et al.[11]	Frontal, parietal and occipital lobes, in the left superior temporal lobe and in the superior region of the cerebellum	Medial temporal lobes, thalami, periventricular white matter and brain stem
Asenbaum S. et al.[17]	Occipital, supratemporal/inferior parietal and parietal cortex	Right cerebellum, brain stem, mediotemporal regions, right basal ganglia and thalamus
This study	Frontal, parietal, occipital lobes, basal ganglia, thalamus and in the superior region of the cerebellum	Frontal sub-gyral white matter, Small areas of frontal, temporal, parietal lobes and cerebellum

on the sagittal reformatted image (Fig. 3C). By these facts, the visualized high uptake in the superior region of the cerebellum on Tc-99m ECD is thought to be true activity rather than pseudo-activity due to high activity of the neighboring occipital cortex.

Patterson et al.[12] and Hyun et al.[13] postulated that there are relatively large areas of higher Tc-99m HMPAO uptake in the medial temporal lobes. But, in this study, there are only small areas of higher Tc-99m HMPAO uptake in the medial temporal lobe (Fig. 3). The main reason is probably due to our usages of stricter thresholds or corrected p-values rather than a placid, uncorrected p-value.

Koyama et al. described higher Tc-99m HMPAO uptake in the thalamic area.[18] However, the results of our SPM analysis showed that Tc-99m ECD uptake was relatively higher than the Tc-99m HMPAO uptake in the deep nuclei. This is at variance with the results of previous studies.[12,13] Further investigation is necessary to determine which is accurate.

This study compared Tc-99m ECD and Tc-99m HMPAO uptake in the normal-looking brains. SPM analysis demonstrated significant quantitative differences in the regional tracer distribution between Tc-99m HMPAO and Tc-99m ECD, probably caused by different tracer kinetics. The results indicate that direct comparison of studies performed with Tc-99m HMPAO and Tc-99m ECD is not possible and the use of either tracer can be favorable in different clinical questions. Further investigation is necessary to determine which tracer is more accurate for diagnosing different clinical conditions.

Abstract

Purpose: This study investigated the differences between technetium-99m ethyl cysteinate dimer (Tc-99m ECD) and technetium-99m hexamethylpropylene amine oxime (Tc-99m HMPAO) uptake in the normal brain by means of statistical parametric mapping (SPM) analysis. **Materials and Methods:** We retrospectively analyzed age and sex matched 53 cases of normal brain SPECT. Thirty-two cases were obtained with Tc-99m ECD and 21 cases with Tc-99m HMPAO. There were no abnormal findings on brain MRIs. All of the SPECT images were spatially transformed to standard space,

smoothed and globally normalized. The differences between the Tc-99m ECD and Tc-99m HMPAO SPECT images were statistically analyzed using statistical parametric mapping (SPM'99) software. The differences between the two groups were considered significant at a threshold of corrected P values less than 0.05. **Results:** SPM analysis revealed significantly different uptakes of Tc-99m ECD and Tc-99m HMPAO in the normal brains. On the Tc-99m ECD SPECT images, relatively higher uptake was observed in the frontal, parietal and occipital lobes, in the basal ganglia and thalamus, and in the superior region of the cerebellum. On the Tc-99m HMPAO SPECT images, relatively higher uptakes was observed in subcortical areas of the frontal region, temporal lobe, and posterior portion of inferior cerebellum. **Conclusion:** Uptake of Tc-99m ECD and Tc-99m HMPAO in the normal-looking brain was significantly different on SPM analysis. The selective use of Tc-99m ECD or Tc-99m HMPAO in brain SPECT imaging appears especially valuable for the interpretation of cerebral perfusion. Further investigation is necessary to determine which tracer is more accurate for diagnosing different clinical conditions.

References

1) Greenberg JH, Lassen NA. Characterization of Tc-99m bicisate as an agent for the measurement of cerebral blood flow with SPET. *J Cereb Blood Flow Metab* 1994;14: S36-43.
2) Walovitch RC, Hill TC, Garrity ST, Cheesman EH, Burgess BA, O'Leary DH, et al: Characterization of Tc-99m-L,L-ECD for brain perfusion imaging. Part 1. Pharmacology of Tc-99m-ECD in nonhuman primates. *J Nucl Med* 1989;30:1902-10.
3) Van Dyck CH, Lin CH, Smith EO, Wisniewski G, Cellar J, Robinson R, et al. Comparison of Tc-99m-HMPAO and Tc-99m-ECD cerebral SPET images in Alzheimer's disease. *J Nucl Med* 1996;37:1749-55.
4) Rieck H, Adelwohrer C, Lungenschmid K, Deisenhammer E. Discordance of Tc-99m-HMPAO and Tc-99m-ECD SPET in herpes simplex encephalitis. *J Nucl Med* 1998;39: 1508-10.
5) Lee JD, Kim DI, Ryu YH, Whang GJ, Park CI, Kim DG, et al. Tc-99m-ECD brain SPET in cerebral palsy: comparison with MRI. *J Nucl Med* 1998;39:619-23.
6) Friberg L, Andersen AR, Lassen NA, Holm S, Dam M. Retention of Tc-99m bicisate in the human brain after intracarotid injection. *J Cereb Blood Flow Metab* 1994;14:S19-27.
7) Leveille J, Demonceau G, Walovitch RC. Intrasubject comparison between Tc-99m- ECD and Tc-99m-HMPAO in healthy human subjects. *J Nucl Med* 1992;33:480-4.
8) Pupi A, Castagnoli A, De Cristofaro MT, Bacciottini L, Petti AR. Quantitative comparison between Tc-99m HMPAO and Tc-99m ECD: measurement of arterial input and brain retention. *Eur J Nucl Med* 1994;21:124-30.
9) Matsuda H, Li YM, Higashi S, Sumiya H, Tsuji S, Kinuya K et al. Comparative SPECT study of stroke using Tc-99m ECD, 123 I-IMP and Tc-99m HMPAO. *Clin Nucl Med* 1993;18:754-8.
10) Friston KJ, Holmes AP, Worsley KJ. Statistical parametric maps in functional imaging: a general linear approach. *Human Brain Mapping* 1995;2: 190-210.
11) Friston KJ, Ashburner CD, Frith CD. Spatial registration and normalization of images. *Human Brain Mapping* 1995:3;165- 89.
12) Patterson JC, Early TS, Martin A, Walker MZ, Russell JM, Villanueva-Meyer H, et al. SPET image analysis using statistical parametric mapping: comparison of Tc-99m- HMPAO and

Tc-99m-ECD. *J Nucl Med* 1997;38:1721-5.

13) Hyun IY, Lee JS, Rha JH, Lee IK, Ha CK, Lee DS. Different uptake of Tc-99m ECD and Tc-99m HMPAO in the same brains: analysis by statistical parametric mapping. *Eur J Nucl Med* 2001;28:191-7.

14) Oku N, Matsumoto M, Hashikawa K, Moriwaki H, Ishida M, Seike Y, et al. Intra-individual differences between Tc-99m-HMPAO and Tc-99m-ECD in the normal medial temporal lobe. *J Nucl Med* 1997;28:1109-11.

15) Perry TL, Berry K, Hansen S, Diamond S, Mok C. Regional distribution of amino acids in human brain obtained at autopsy. *J Neurochem* 1971;18:513-9.

16) Asenbaum S, Brucke T, Pirker W, Pietrzyk U, Podreka I. Imaging of cerebral blood flow with Tc-99m-HMPAO and Tc--99m-ECD: a comparison. *J Nucl Med* 1998;39:613-8.

17) Heiss WD, Herholz K, Podreka I, Neubauer I, Pietrzyk U. Comparison of [^{99m} Tc] HMPAO SPET with [^{18} F]fluoromethane PET in cerebrovascular disease. *J Cereb Blood Flow Metab* 1990;10:687-97.

18) Koyama M, Kawashima R, Ito H, Ono S, Sato K, Goto R, et al. SPECT imaging of normal subjects with technetium-99m- HMPAO and technetium-99m-ECD. *J Nucl Med* 1997;38: 587-92.