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Thallium-201 brain SPECT to diagnose aggressiveness of meningiomas

Keiko KINUYA,* Masahiro OHASHI,** Syotaro ITOH,** Sohtaro SAKAI,**
Kenji YAMAMOTO,** Kiyoshi KAKUDA,*** Koji NOBATA,***
Shintaro TERAHATA,**** Suzuka TAKI***** and Seigo KINUYA******

*Department of Nuclear Medicine, Tonami General Hospital
**Department of Neurosurgery, Tonami General Hospital
***Department of Radiology, Tonami General Hospital
****Department of Pathology, Tonami General Hospital
*****Department of Radiology, Kanazawa Medical University
******Department of Biotracer Medicine, Kanazawa University School of Medical Sciences

This investigation was conducted to determine the ability of ^{201}Tl brain SPECT with respect to pre-operative prediction of lesional aggressiveness of meningioma. Fifty-nine lesions in 42 patients were examined. Early (15 min) and late (3 h) SPECT were obtained. Early uptake ratio (ER; lesion to normal brain average count ratio), late uptake ratio (LR) and the ratio of LR to ER (L/E ratio) were calculated. Twenty-three lesions exhibited malignant features based on histologic or clinical course such as recurrence or skull invasion. Both ER and LR of malignant meningiomas were significantly higher than those in thirty-six benign lesions. Benign lesions were classified into two groups for further analysis: meningotheliomatous type, which is the most common histology, and benign lesions other than the meningotheliomatous (other benign) type. ER in other benign type was lower than the meningotheliomatous and the malignant type. LR afforded differentiation of the malignant type from the two benign types. These two benign types could be distinguished on the basis of the L/E ratio. These results indicate that high pre-operative ER and LR values in patients with meningioma are indicators of the aggressiveness of lesions, i.e., malignant meningioma, recurrence or skull invasion.

Key words: thallium-201 imaging, brain SPECT, meningioma

INTRODUCTION

MENINGIOMAS compromise approximately 20% of all primary tumors of the brain and meninges. They are typically hypervascular and clinically benign exhibiting slow growth. Twenty to thirty-two percent of meningiomas, however, recur following complete resection.[1,2] Existence of brain invasion and a high mitotic rate of ≥4 mitoses per 10 high-power fields were reported to function as satisfactory prognostic indicators of recurrence.[3] Higher recurrence rate also is associated with hyperosteosis, which is caused by skull invasion of meningioma cells.[1] Furthermore, malignant meningiomas are occasionally diagnosed and usually fatal with a median survival of 1.5 years.[4] Histological anaplasia and extracranial metastasis are common criteria of this malignancy. For instance, lesions characterized by anaplasia displaying a mitotic rate of ≥20 mitoses per 10 high-power fields or histology resembling carcinoma, sarcoma, or melanoma behave in a malignant fashion resulting in fatal outcomes in most cases.[4]

The extent of tumor extirpation most significantly correlates with long-term excess mortality[4,5]; however, complete removal of lesions may induce complications due to possible invasion of the bone, cerebral arteries, venous sinuses or cranial nerves.[5] Furthermore, conventional radiological methods, i.e., angiography, x-ray computed tomography or magnetic resonance imaging (MRI)

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For reprint contact: Keiko Kinuya, M.D., Department of Nuclear Medicine, Tonami General Hospital, 1–61 Shintomi-cho, Tonami, Toyama 939–1395, JAPAN.
E-mail: dinky@d9.dion.ne.jp

Table 1 Comparison of parameters between benign meningiomas and aggressive meningiomas

Group	Patient no.	Lesion no.	ER	LR	L/E ratio
Benign meningiomas	36	36	5.46 ± 2.15	2.62 ± 0.80	0.51 ± 0.15
Aggressive meningiomas	6	23	7.39 ± 3.14*	3.49 ± 1.19*	0.51 ± 0.20

ER, early uptake ratio; LR, late uptake ratio; L/E ratio, ratio of LR to ER. (mean ± s.d.) Aggressiveness was defined by high mitotic rate extracranial metastasis, skull invasion or recurrence. *, $p < 0.005$ vs. benign meningiomas.

Table 2 Comparison of parameters among three types of meningiomas

Group	Patient no.	Lesion no.	ER	LR	L/E ratio
ME	19	19	6.40 ± 1.95	2.66 ± 0.76	0.43 ± 0.08****
Benign other than ME	17	17	4.41 ± 1.91**	2.57 ± 0.86	0.61 ± 0.16
Aggressive	6	23	7.39 ± 3.14	3.49 ± 1.19***	0.51 ± 0.20

ER, early uptake ratio; LR, late uptake ratio; L/E ratio, ratio of LR to ER. (mean ± s.d.) ME, meningotheliomatous type. Aggressiveness was defined by high mitotic rate extracranial metastasis, skull invasion or recurrence. *, $p < 0.005$ vs. benign meningiomas. **, $p < 0.0005$ vs. ME. ***, $p < 0.05$ vs. ME and $p < 0.005$ vs. benign other than ME. ****, $p < 0.005$ vs. benign other than ME.

may encounter difficulties with respect to pre-operative diagnosis of these types of lesional aggressiveness.[6–9]

Thallium-201 chloride (^{201}Tl) is a potassium analogue possessing an affinity for the sodium- and potassium-activated adenosine triphosphatase (Na^+-K^+ ATPase) pump.[10] ^{201}Tl uptake depends on regional blood flow, destruction of the blood-brain barrier (BBB), tissue viability, cellular activity and cell number.[11] Recent studies have demonstrated a potential role of ^{201}Tl single photon emission computed tomography (SPECT) in patients presenting with brain tumors. That is, this method provides information regarding characteristics of gliomas and enables the differential diagnosis between recurrence and scarring or radiation necrosis.[12–16] However, the usefulness of ^{201}Tl SPECT has not been elucidated fully in this regard in terms of meningiomas. Therefore, the objective of the current investigation was to determine the ability of pre-operative ^{201}Tl brain SPECT to predict these unfavorable qualities of meningiomas in comparison with biological behavior and histopathologic results.

SUBJECTS AND METHODS

Patient selection

Fifty-nine lesions in forty-two patients (15 men and 27 women, 60.3 ± 12.8 years of age) were examined. Histopathologic diagnosis was confirmed with surgical specimens for all lesions. Lesional aggressiveness or malignancy was defined by histological evidence, including a high mitotic rate, and clinical evidence of extracranial metastasis, skull invasion or recurrence. Follow-up duration following surgery was >3.5 years.

Data acquisition

Early (15 minutes post-injection) and late (3 hours) brain SPECT images were obtained using 111 MBq of ^{201}Tl. A single-head rotating gamma camera (GCA-901A, Toshiba Co., Tokyo, Japan) equipped with a low-energy high-resolution collimator, interfaced to a computer (GMS 550-U, Toshiba Co.), was employed. Images were acquired in a 64 × 64 pixel matrix with 60 angular steps over 360 degree at 30 seconds per step. Data were reconstructed utilizing the Butterworth prefilter and the filtered backprojection with the Ramp filter. Transverse, coronal and sagittal sections were reconstructed without attenuation correction or scatter correction. Slice thickness was 4 mm. The full-width at half-maximum (FWHM) of the system was 13.8 mm at the center of rotation when the rotation radius was set to 13 cm. All lesions were > 30 mm in diameter (greater than FWHM).

Analytical parameters

Regions of interest (ROIs) were manually drawn on the lesions on the slice which showed maximal diameters. Same ROIs were set both on early and late images. ROIs were also defined as references in the contralateral normal brain in the same slice. Average counts in ROIs were used for analyses. The early uptake ratio (ER, a lesion-to-reference count ratio in the early image), the late uptake ratio (LR, a count ratio in the late image) and the ratio of LR to ER (L/E ratio) were calculated. Feasibility with respect to differentiation of malignant lesions from benign lesions was assessed based on these parameters. Lesions were categorized into three groups for further evaluation: meningotheliomatous type, which is the most common histology, benign lesions other than the meningotheliomatous type, and malignant type as defined above. Results were analyzed by one-way analysis of variance (ANOVA) with Fisher's protected least significant difference (PLSD). The level of significance was set at 5%.

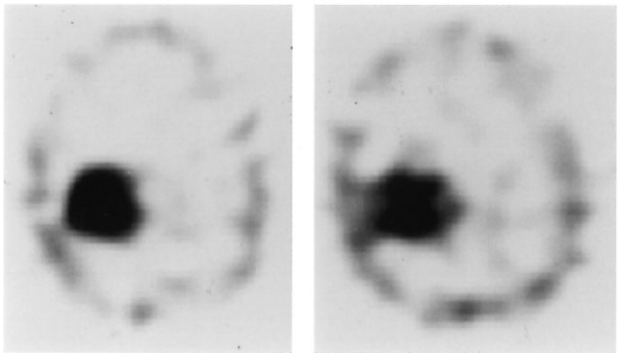

Fig. 1 ^{201}Tl early (*left*) and late (*right*) brain SPET in a 66-year-old man presenting with meningotheliomatous meningioma (4.5 cm in diameter). Early uptake ratio (ER), late uptake ratio (LR) and LR/ER ratio are 9.74, 3.80 and 0.39, respectively.

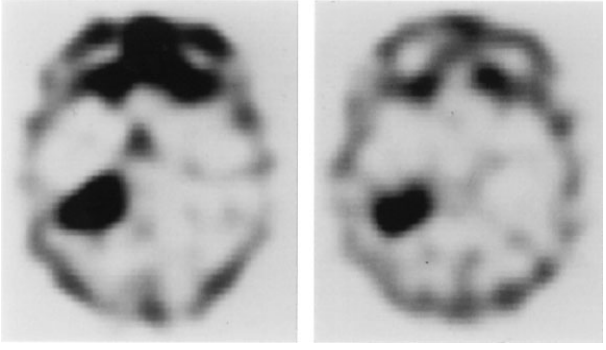

Fig. 2 ^{201}Tl early (*left*) and late (*right*) brain SPET in a 84-year-old woman presenting with psammomatous meningioma (6.0 cm in diameter). Early uptake ratio (ER), late uptake ratio (LR) and LR/ER ratio are 3.47, 2.26 and 0.65, respectively.

RESULTS

Thirty-six of 59 lesions were classified as benign meningiomas, including 19 cases of meningotheliomatous type, which is the most common histology, nine instances of psammomatous type, five examples of transitional type and three other benign types (clear cell, fibrous and fibroblastic types). Twenty-three lesions demonstrated aggressive features (5 men and a woman, age 54.7 ± 9.3 at initial diagnosis). Of those 23 lesions, 19 lesions in 4 men were diagnosed as malignant meningioma. Skin metastases were revealed in one of them and recurrences were revealed in three. Skull invasion with massive hematoma was revealed in one of them. Another man had three recurrent lesions without malignant histology. Skull invasion was seen in a woman without malignant histology or recurrence. Follow-up durations after operations were at least 3.5 years. No patient showed brain invasion.

All lesions were clearly delineated in both early and late images, irrespective of lesional characteristics; however, ER and LR values of malignant lesions were significantly higher than those in benign lesions ($p < 0.005$ and $p < 0.005$, respectively) (Table 1).

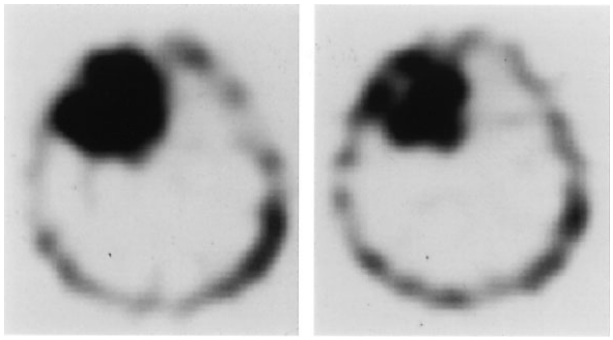

Fig. 3 ^{201}Tl early (*left*) and late (*right*) brain SPET in a 46-year-old man representing with malignant meningioma (7.0 cm in diameter). Early uptake ratio (ER), late uptake ratio (LR) and LR/ER ratio are 8.25, 5.12 and 0.62, respectively.

ER values of benign lesions other than the meningotheliomatous (other benign) type were significantly lower than those of the meningotheliomatous type ($p < 0.05$) and malignant lesions ($p < 0.0005$) (Table 2 and Figs. 1–3). LR readings of the malignant lesions were significantly higher than those of the meningotheliomatous ($p < 0.01$) and other benign types ($p < 0.005$). The L/E ratio of the meningotheliomatous type was significantly lower than that of other benign types ($p < 0.005$). The L/E ratio of the meningotheliomatous type tended to be lower than that of malignant lesions ($p = 0.07$).

DISCUSSION

The current investigation demonstrates the feasibility of ^{201}Tl brain SPECT in terms of characterization of meningioma lesions: both high ER and LR would serve as markers of meningioma aggressiveness. Furthermore, meningotheliomatous meningioma, which is the most common cell type of meningioma, could be differentiated from other benign types by ^{201}Tl SPECT: lesions displaying high ER with rapid lesional clearance are likely meningotheliomatous meningioma, whereas lesions exhibiting both low ER and low LR are other benign types. These results confirm those of a previous preliminary report concerning a small patient population.[17]

Lesional vascularity may be an important determinant for ^{201}Tl accumulation in individual meningiomas: previous investigations indicated the relationship between early ^{201}Tl uptake and the lesional vascularity on angiography[18] or the degree of contrast enhancement on MRI.[19] Furthermore, a dynamic SPECT study by Tedeschi et al.[20] demonstrated that higher ^{201}Tl accumulation occurred in malignant or recurrent meningiomas in comparison to non-aggressive meningiomas 2–4 min after tracer injection when the tracer distribution might be associated with tissue perfusion. On the other hand, several reports

indicated that vascularity itself would not correlate with histologic type or malignancy grade, which suggested that factors other than lesional vascularity were involved.[21,22]

Mitotic or proliferation rate would be a factor regulating lesional ^{201}Tl accumulation. For instance, growth rates of distinct kinds of cell lines reportedly correlated to cellular Na^+-K^+ ATPase activity,[23,24] which is believed to function as an important uptake mechanism for ^{201}Tl. In addition, intensity of MIB-1, which recognizes the Ki-67 antigen and has been cited as supportive information in histological grading of meningiomas, is a parameter for the proliferation ability. Its high labeling index in meningiomas has been documented to associate with aggressiveness, poor prognosis, and/or residual tumor growth.[25–31] p53 nuclear protein expression, which plays an important role in cell-cycle control, cell differentiation, maintenance of genomic stability, cellular senescence and apoptosis, also displays a significant correlation with the histological grade of meningioma.[25,29,32–34] Consequently, information regarding these markers may correlate with ^{201}Tl uptake.

In general, tracer clearance from tissues depends on tissue blood flow, which may affect changes in ^{201}Tl radioactivity between the early and late images as represented by the L/E ratio. On the other hand, the results of Ueda et al.[35] suggest that factors other than tissue vascularity must also be involved in ^{201}Tl clearance: its clearance from malignant brain tumors is slow despite the hypervascular nature of the lesions.

In conclusion, despite possible multifactorial uptake mechanisms, pre-operative ^{201}Tl SPECT can provide information related to the aggressiveness of meningiomas, demonstration of which is difficult via other imaging methods.

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